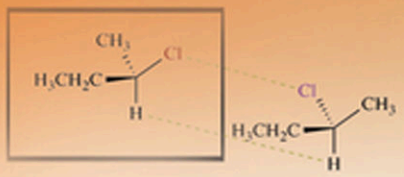
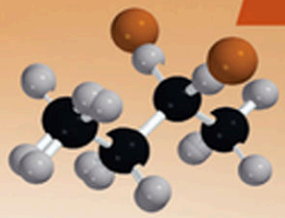
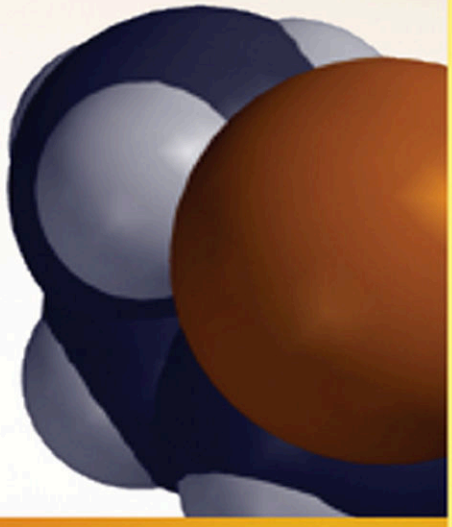
7th Edition

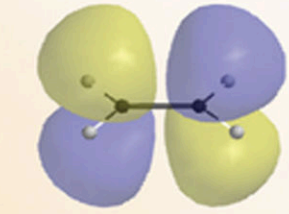


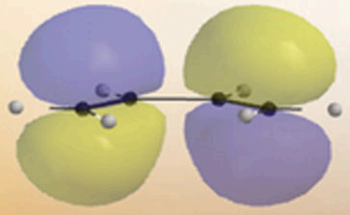


March's Advanced Organic Chemistry

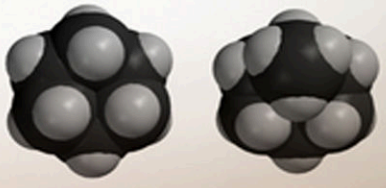


Reactions, Mechanisms, and Structure





Michael B. Smith



WILEY

MARCH'S ADVANCED ORGANIC CHEMISTRY

MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

SEVENTH EDITION

Michael B. Smith
Professor of Chemistry

WILEY

Copyright © 2013 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at http://www.wiley.com/go/permission.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Smith, Michael, 1946 Oct. 17- March's Advanced Organic Chemistry : Reactions, Mechanisms, and Structure. – 7th Edition / Michael B. Smith, Professor of Chemistry.
pages cm
Includes index.
ISBN 978-0-470-46259-1 (cloth)
1. Chemistry, Organic. I. Title. II. Title: Advanced organic chemistry.
QD251.2.M37 2013
547—dc23

2012027160

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTENTS

PREFACE xiii

COMMON ABBREVIATIONS xxi

BIOGRAPHICAL STATEMENT xxv

PART I INTRODUCTION 1

1. Localized Chemical Bonding 3

1.A. Covalent Bonding 3
1.B. Multiple Valence 6
1.C. Hybridization 7
1.D. Multiple Bonds 9
1.E. Photoelectron Spectroscopy 11
1.F. Electronic Structures of Molecules 14
1.G. Electronegativity 15
1.H. Dipole Moment 18
1.I. Inductive and Field Effects 19
1.J. Bond Distances 21
1.K. Bond Angles 25
1.L. Bond Energies 27

2. Delocalized Chemical Bonding 31

2.A. Molecular Orbitals 32
2.B. Bond Energies and Distances in Compounds Containing Delocalized Bonds 35
2.C. Molecules that have Delocalized Bonds 37
2.D. Cross-Conjugation 42
2.E. The Rules of Resonance 43
2.F. The Resonance Effect 45
2.G. Steric Inhibition of Resonance and the Influences of Strain 46
2.H. $p\pi$–$d\pi$ Bonding. Ylids 49
2.I. Aromaticity 50
2.I.i. Six-Membered Rings 54
2.I.ii. Five, Seven, and Eight-Membered Rings 57
2.I.iii. Other Systems Containing Aromatic Sextets 62
2.J. Alternant and Nonalternant Hydrocarbons 63

2.K. Aromatic Systems with Electron Numbers other than Six 65
2.K.i. Systems of Two Electrons 66
2.K.ii. Systems of Four Electrons: Antiaromaticity 67
2.K.iii. Systems of Eight Electrons 71
2.K.iv. Systems of Ten Electrons 72
2.K.v. Systems of more than Ten Electrons: $4n + 2$ Electrons 74
2.K.vi. Systems of more than 10 Electrons: $4n$ Electrons 79
2.L. Other Aromatic Compounds 82
2.M. Hyperconjugation 85
2.N. Tautomerism 89
2.N.i. Keto–Enol Tautomerism 89
2.N.ii. Other Proton-Shift Tautomerism 92

3. Bonding Weaker Than Covalent 96

3.A. Hydrogen Bonding 96
3.B. π–π Interactions 103
3.C. Addition Compounds 104
3.C.i. Electron Donor–Acceptor Complexes 104
3.C.ii. Crown Ether Complexes and Cryptates 108
3.C.iii. Inclusion Compounds 113
3.C.iv. Cyclodextrins 116
3.D. Catenanes and Rotaxanes 118
3.E. Cucurbit[*n*]Uril-Based Gyroscane 121

4. Stereochemistry and Conformation 122

4.A. Optical Activity and Chirality 122
4.A.i. Dependence of Rotation on Conditions of Measurement 124
4.B. What Kinds of Molecules Display Optical Activity? 125
4.C. The Fischer Projection 136
4.D. Absolute Configuration 137
4.D.i. The CAHN–INGOLD–PRELOG System 138
4.D.ii. Methods of Determining Configuration 141
4.E. The Cause of Optical Activity 145
4.F. Molecules with more than One Stereogenic Center 146
4.G. Asymmetric Synthesis 149
4.H. Methods of Resolution 154
4.I. Optical Purity 160
4.J. *cis–trans* Isomerism 162
4.J.i. *cis-trans* Isomerism Resulting from Double Bonds 162
4.J.ii. *cis–trans* Isomerism of Monocyclic Compounds 165
4.J.iii. *cis–trans* Isomerism of Fused and Bridged Ring Systems 167
4.K. Out–In Isomerism 168
4.L. Enantiotopic and Diastereotopic Atoms, Groups, and Faces 170
4.M. Stereospecific and Stereoselective Syntheses 173
4.N. Conformational Analysis 173
4.N.i. Conformation in Open-Chain Systems 175

4.N.ii. Conformation in Six-Membered Rings 180
4.N.iii. Conformation in Six-Membered Rings Containing Heteroatoms 186
4.N.iv. Conformation in Other Rings 188
4.O. Molecular Mechanics 190
4.P. STRAIN 192
4.P.i. Strain in Small Rings 193
4.P.ii. Strain in Other Rings 199
4.P.iii. Unsaturated Rings 201
4.P.iv. Strain Due to Unavoidable Crowding 204

5. Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes 208

5.A. Carbocations 208
5.A.i. Nomenclature 208
5.A.ii. Stability and Structure of Carbocations 209
5.A.iii. The Generation and Fate of Carbocations 218
5.B. Carbanions 221
5.B.i. Stability and Structure 221
5.B.ii. The Structure of Organometallic Compounds 228
5.B.iii. The Generation and Fate of Carbanions 233
5.C. Free Radicals 234
5.C.i. Stability and Structure 234
5.C.ii. The Generation and Fate of Free Radicals 245
5.C.iii. Radical Ions 248
5.D. Carbenes 249
5.D.i. Stability and Structure 249
5.D.ii. The Generation and Fate of Carbenes 253
5.E. Nitrenes 257

6. Mechanisms and Methods of Determining them 261

6.A. Types of Mechanism 261
6.B. Types of Reaction 262
6.C. Thermodynamic Requirements for Reaction 264
6.D. Kinetic Requirements for Reaction 266
6.E. The Baldwin Rules for Ring Closure 270
6.F. Kinetic and Thermodynamic Control 271
6.G. The Hammond Postulate 272
6.H. Microscopic Reversibility 273
6.I. Marcus Theory 273
6.J. Methods of Determining Mechanisms 275
6.J.i. Identification of Products 275
6.J.ii. Determination of the Presence of an Intermediate 275
6.J.iii. The Study of Catalysis 277
6.J.iv. Isotopic Labeling 277
6.J.v. Stereochemical Evidence 278
6.J.vi. Kinetic Evidence 278
6.J.vii. Isotope Effects 285

7. Irradiation Processes in Organic Chemistry **289**

7.A. Photochemistry 289
7.A.i. Excited States and the Ground State 289
7.A.ii. Singlet and Triplet States: "Forbidden" Transitions 291
7.A.iii. Types of Excitation 292
7.A.iv. Nomenclature and Properties of Excited States 294
7.A.v. Photolytic Cleavage 295
7.A.vi. The Fate of the Excited Molecule: Physical Processes 296
7.A.vii. The Fate of the Excited Molecule: Chemical Processes 301
7.A.viii. The Determination of Photochemical Mechanisms 306
7.B. Sonochemistry 307
7.C. Microwave Chemistry 309

8. Acids and Bases **312**

8.A. Brønsted Theory 312
8.A.i. Brønsted Acids 313
8.A.ii. Brønsted Bases 320
8.B. The Mechanism of Proton-Transfer Reactions 323
8.C. Measurements of Solvent Acidity 324
8.D. Acid and Base Catalysis 327
8.E. Lewis Acids and Bases 330
8.E.i. Hard–Soft Acids–Bases 331
8.F. The Effects of Structure on the Strengths of Acids and Bases 334
8.G. The Effects of the Medium on Acid and Base Strength 343

9. Effects of Structure and Medium on Reactivity **347**

9.A. Resonance and Field Effects 347
9.B. Steric Effects 349
9.C. Quantitative Treatments of the Effect of Structure on Reactivity 352
9.D. Effect of Medium on Reactivity and Rate 361
9.D.i. High Pressure 362
9.D.ii. Water and Other Non-Organic Solvents 363
9.D.iii. Ionic Solvents 364
9.D.iv. Solventless Reactions 366

PART II INTRODUCTION **367**

10. Aliphatic Substitution, Nucleophilic and Organometallic **373**

10.A. Mechanisms 373
10.A.i. The S_N2 Mechanism 374
10.A.ii. The S_N1 Mechanism 379
10.A.iii. Ion Pairs in the S_N1 Mechanism 383
10.A.iv. Mixed S_N1 and S_N2 Mechanisms 387
10.B. SET Mechanisms 389

10.C. The Neighboring-Group Mechanism 391
10.C.i. Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations 394
10.D. The S_Ni Mechanism 408
10.E. Nucleophilic Substitution at an Allylic Carbon: Allylic Rearrangements 409
10.F. Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism 413
10.G. Reactivity 417
10.G.i. The Effect of Substrate Structure 417
10.G.ii. The Effect of the Attacking Nucleophile 426
10.G.iii. The Effect of the Leaving Group 432
10.G.iv. The Effect of the Reaction Medium 435
10.G.v. Phase-Transfer Catalysis 442
10.G.vi. Influencing Reactivity by External Means 445
10.G.vii. Ambident (Bidentant) Nucleophiles: Regioselectivity 446
10.G.viii. Ambident Substrates 450
10.H. Reactions 451
10.H.i. Oxygen Nucleophiles 451
10.H.ii. Attack by OR at an Alkyl Carbon 459
10.H.iii. Sulfur Nucleophiles 475
10.H.iv. Nitrogen Nucleophiles 481
10.H.v. Halogen Nucleophiles 498
10.H.vi. Carbon Nucleophiles 510

11. Aromatic Substitution, Electrophilic 569

11.A. Mechanisms 569
11.A.i. The Arenium Ion Mechanism 570
11.A.ii. The S_E1 Mechanism 576
11.B. Orientation and Reactivity 576
11.B.i. Orientation and Reactivity in Monosubstituted Benzene Rings 576
11.B.ii. The Ortho/Para Ratio 580
11.B.iii. Ipso Attack 581
11.B.iv. Orientation in Benzene Rings with More Than One Substituent 583
11.B.v. Orientation in Other Ring Systems 584
11.C. Quantitative Treatments of Reactivity in the Substrate 586
11.D. A Quantitative Treatment of Reactivity of the Electrophile: The Selectivity Relationship 588
11.E. The Effect of the Leaving Group 591
11.F. Reactions 591
11.F.i. Hydrogen as the Leaving Group in Simple Substitution Reactions 592
11.F.ii. Hydrogen as the Leaving Group in Rearrangement Reactions 635
11.F.iii. Other Leaving Groups 641

12. Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic **649**

12.A. Mechanisms 650
12.A.i. Bimolecular Mechanisms: S_E2 and S_Ei 650
12.A.ii. The S_E1 Mechanism 654
12.A.iii. Electrophilic Substitution Accompanied by Double-Bond Shifts 657
12.A.iv. Other Mechanisms 658
12.B. Reactivity 658
12.C. Reactions 660
12.C.i. Hydrogen as Leaving Group 660
12.C.ii. Metals as Leaving Groups 698
12.C.iii. Halogen as Leaving Group 713
12.C.iv. Carbon Leaving Groups 718
12.C.v. Electrophilic Substitution at Nitrogen 727

13. Aromatic Substitution: Nucleophilic and Organometallic **732**

13.A. Mechanisms 732
13.A.i. The S_NAr Mechanism 732
13.A.ii. The S_N1 Mechanism 735
13.A.iii. The Benzyne Mechanism 737
13.A.iv. The $S_{RN}1$ Mechanism 739
13.A.v. Other Mechanisms 740
13.B. Reactivity 741
13.B.i. The Effect of Substrate Structure 741
13.B.ii. The Effect of the Leaving Group 744
13.B.iii. The Effect of the Attacking Nucleophile 745
13.C. Reactions 745
13.C.i. All Leaving Groups Except Hydrogen and N_2^+ 746
13.C.ii. Hydrogen as Leaving Group 784
13.C.iii. Nitrogen as Leaving Group 788
13.C.iv. Rearrangements 797

14. Substitution Reactions: Radical **803**

14.A. Mechanisms 803
14.A.i. Radical Mechanisms in General 803
14.A.ii. Free Radical Substitution Mechanisms 807
14.A.iii. Mechanisms at an Aromatic Substrate 809
14.A.iv. Neighboring-Group Assistance in Free Radical Reactions 810
14.B. Reactivity 812
14.B.i. Reactivity for Aliphatic Substrates 812
14.B.ii. Reactivity at a Bridgehead 817
14.B.iii. Reactivity in Aromatic Substrates 818
14.B.iv. Reactivity in the Attacking Radical 819
14.B.v. The Effect of Solvent on Reactivity 820

14.C. Reactions 821
14.C.i. Hydrogen as a Leaving Group 821
14.C.ii. N_2 as Leaving Group 846
14.C.iii. Metals as Leaving Groups 849
14.C.iv. Halogen as Leaving Group 851
14.C.v. Sulfur as Leaving Group 851
14.C.vi. Carbon as Leaving Group 853

15. Addition to Carbon–Carbon Multiple Bonds 859

15.A. Mechanisms 859
15.A.i. Electrophilic Addition 859
15.A.ii. Nucleophilic Addition 865
15.A.iii. Free Radical Addition 867
15.A.iv. Cyclic Mechanisms 869
15.A.v. Addition to Conjugated Systems 869
15.B. Orientation and Reactivity 871
15.B.i. Reactivity 871
15.B.ii. Orientation 874
15.B.iii. Stereochemical Orientation 877
15.B.iv. Addition to Cyclopropane Rings 879
15.C. Reactions 881
15.C.i. Isomerization of Double and Triple Bonds 881
15.C.ii. Reactions in which Hydrogen Adds to One Side 883
15.C.iii. Reactions in which Hydrogen Adds to Neither Side 981
15.C.iv. Cycloaddition Reactions 1014

16. Addition to Carbon–Hetero Multiple Bonds 1067

16.A. Mechanism and Reactivity 1067
16.A.i. Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism 1069
16.B. Reactions 1075
16.B.i. Reactions in which Hydrogen or a Metallic Ion Adds to the Heteroatom 1075
16.B.ii. Acyl Substitution Reactions 1189
16.B.iii. Reactions in which Carbon Adds to the Heteroatom 1239
16.B.iv. Addition to Isocyanides 1246
16.B.v. Nucleophilic Substitution at a Sulfonyl Sulfur Atom 1248

17. Eliminations 1253

17.A. Mechanisms and Orientation 1253
17.A.i. The E2 Mechanism 1254
17.A.ii. The E1 Mechanism 1261
17.A.iii. The E1cB Mechanism 1262
17.A.iv. The E1–E2–E1cB Spectrum 1267
17.A.v. The E2C Mechanism 1268
17.B. Regiochemistry of the Double Bond 1269

17.C. Stereochemistry of the Double Bond 1273
17.D. Reactivity 1274
17.D.i. Effect of Substrate Structure 1274
17.D.ii. Effect of the Attacking Base 1276
17.D.iii. Effect of the Leaving Group 1276
17.D.iv. Effect of the Medium 1277
17.E. Mechanisms and Orientation in Pyrolytic Eliminations 1278
17.E.i. Mechanisms 1278
17.E.ii. Orientation in Pyrolytic Eliminations 1281
17.E.iii. 1,4-Conjugate Eliminations 1282
17.F. Reactions 1282
17.F.i. Reactions in which C=C and C≡C Bonds are Formed 1282
17.F.ii. Fragmentations 1307
17.F.iii. Reactions in which C≡N or C=N Bonds are Formed 1310
17.F.iv. Reactions in which C=O Bonds are Formed 1314
17.F.v. Reactions in which N=N Bonds are Formed 1315
17.F.vi. Extrusion Reactions 1316

18. Rearrangements 1321

18.A. Mechanisms 1322
18.A.i. Nucleophilic Rearrangements 1322
18.A.ii. The Actual Nature of the Migration 1324
18.A.iii. Migratory Aptitudes 1328
18.A.iv. Memory Effects 1330
18.B. Longer Nucleophilic Rearrangements 1331
18.C. Free Radical Rearrangements 1333
18.D. Carbene Rearrangements 1337
18.E. Electrophilic Rearrangements 1337
18.F. Reactions 1337
18.F.i. 1,2-Rearrangements 1338
18.F.ii. Non-1,2 Rearrangements 1380

19. Oxidations and Reductions 1433

19.A. Mechanisms 1434
19.B. Reactions 1436
19.B.i. Oxidations 1437
19.B.ii. Reductions 1497

APPENDIX A: THE LITERATURE OF ORGANIC CHEMISTRY 1569

APPENDIX B: CLASSIFICATION OF REACTIONS BY TYPE OF COMPOUNDS SYNTHESIZED 1605

INDEXES

AUTHOR INDEX 1631
SUBJECT INDEX 1835

PREFACE

This seventh edition of *March's Advanced Organic Chemistry* has been thoroughly updated to include new advances in areas of Organic chemistry published between 2005 and 2010. Every topic retained from the sixth edition has been brought up to date if there was activity in that area during that five year period. Changes also include a significant rewrite of most of the book. More than 5500 new references have been added for work published since 2005. As with the sixth edition, many older references were deleted to make room for new ones, and in cases where a series of papers by the same principal author were cited, all but the most recent were deleted. The older citations are usually found by referring to the more recent publication(s). Many of the figures relating to molecular orbitals dated to the 1960s. In all cases possible, they have been replaced by molecular orbitals drawings using Spartan software from Wavefunction, Inc. The fundamental structure of the seventh edition is essentially the same as that of all previous ones.

The goal, as in previous editions is to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern organic chemistry. Major special areas of organic chemistry: terpenes, carbohydrates, proteins, many organometallic reagents, combinatorial chemistry, polymerization and electrochemical reactions, steroids, and so on, have been treated lightly or ignored completely. The use of this book in the first year of graduate study should help master the fundamentals. It is hoped that this book will lead a student to consult the many excellent books and review articles cited for various topics in order to understand the subject in more detail. Indeed, many of these topics are so vast, they cannot be explained completely in this book.

The organization is based on reaction types, and a relatively few principles suffice to explain nearly all of them despite the large number of organic reactions. Accordingly, the reactions-mechanisms section of this book (Part II) is divided into 10 chapters (10–19), each concerned with a different type of reaction. In the first part of each chapter, the appropriate basic mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. Numbered sections are used for the reactions and are set in boldface. Since the methods for the preparation of individual classes of compounds (ketones, nitriles, etc.) are not treated all in one place, an updated and revised index has been provided (Appendix B) by use of which the synthesis of a given type of compound will be found. It is important to note that the numbers for each reaction in the 7th edition are *different* from editions 1–5 in many cases, but are the same as found in the 6th edition. For this reason, a correlation table is included at the end of this Preface that directly correlates the sections found in the 5th edition with the new ones in both the 6th and 7th editions.

The structure of organic compounds is discussed in Chapters 1–5 (Part I). This section provides a necessary background for understanding mechanisms and is also important in its own right. The discussion begins with chemical bonding (Chapt. 1) and ends with a chapter on stereochemistry (Chapt. 4). Two chapters follow (Chapt 6–7) on reaction mechanisms in general, one for ordinary reactions and the other for photochemical reactions. Part 1 concludes with two more chapters (Chapt 8 and 9) that give further background to the study of mechanisms.

The IUPAC names for many organic transformations are included, first introduced in the 3rd edition. Since then the rules have been broadened to cover additional cases; hence more such names are given in this edition. Furthermore, International Union of Pure and Applied Chemistry (IUPAC) has now published a system for designating reaction mechanisms, and some of the simpler designations are included.

Appendix A is devoted to the literature of organic chemistry.

In treating subjects as broad as structure, reactions, and mechanisms of organic chemistry, it is impossible to cover each topic in great depth, and this would not be desirable even if possible. This book is intended to point the reader to the primary literature of the areas it covers. To this end, there are >20,000 references to original papers. Secondary literature sources including reviews, books, and monographs have been included as well. Appendix A provides a brief introduction to using computer-based search engines (e.g., *Reaxys*® and *SciFinder*®).

Although basically designed as a reference text for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses, but only after completion of a one-year course in organic chemistry. A one year course in both inorganic and physical chemistry would be most helpful. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material and greatly profit from a representation of the material if it is easily accessible. The material in the first nine chapters, particularly Chapters 1, 2, 4, 6, and 8 may be helpful for reviewing such material when this book is used in connection with a course.

This book is probably most valuable as a reasonably up-to-date reference work. Students preparing for qualifying examinations and practicing organic chemists will find that Part II contains a survey of what is known about the mechanism and scope of a large number of reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed.

For units of energy, IUPAC mandates joules, and many journals do use this unit exclusively. However, organic chemists who publish in United States journals commonly use calories. Virtually all energy values are presented in both calories and joules. Although IUPAC does not recommend angstrom units for bond distances, but rather picometers (pm), a vast number of bond distances published in the literature are in angstrom units, and this book therefore uses angstrom units.

I would like to acknowledge the contributions of those chemists cited and thanked by Professor March in the first-four editions, and those I thanked in the 5th and 6th editions. This book would not be possible without their contributions. For the 7th edition, I thank Lou Allinger for pointing out the deficiencies in the hyperconjugation section, and graciously helping me write the new section appearing in this new edition. I thank Warren Hehre for his invaluable help in calculating and presenting the molecular orbital drawings using Spartan. I also thank Adrian Shell (Elsevier) for facilitating the transfer of material relating to the program *Reaxys*, discussed in Appendix A. I thank the many people who have contributed comments or have pointed out errors in the 6th edition that were

invaluable to putting together the 7th edition. I thank Warren Hehre and Sean Ohlinger of Wavefunction, Inc., Irvine, CA (www.wavefun.com) for providing Spartan 10 Macintosh (v. 1.0.1), allowing the incorporation of Spartan models for selected molecules and intermediates. All structures and line drawings in this book were done using ChemDraw® Ultra 11.0.1 (350440), graciously provided by CambridgeSoft Corporation, Cambridge, MA (www.cambridgesoft.com).

Special thanks are due to the Interscience division of John Wiley & Sons and to Jonathan Rose. Special thanks are also given to Kristen Parrish and Amanda Amanullah, at Wiley for their fine work as editors in turning the manuscript into the finished book as well as Sanchari Sil of Thomson Digital. I also thank Jeanette Stiefel for an excellent job of copy editing the manuscript.

With gratitude, I acknowledge the work of Jerry March, upon whose work this new edition is built, and who is responsible for the concept of this book and for carrying it through four very successful editions. I used Jerry's book as a student and it is an honor to continue this tradition.

I encourage those who read and use the 7th edition to contact me directly with comments, errors, and with publications that might be appropriate for future editions. I hope that this new edition will due justice to the tradition that Professor March began with the first edition.

My Email address is michael.smith@uconn.edu
and my homepage is http://orgchem.chem.uconn.edu/home/mbs-home.html

Finally, I want to thank my wife Sarah for her patience and understanding during the preparation of this manuscript. I also thank my son Steven for his support. Without their support, this work would not have been possible.

MICHAEL B. SMITH
May, 2012

Correlation Table
5th edition → 7th edition Reactions

10-1 → 10-1	**10-18 → 10-14**	**10-35 → 16-68**
10-2 → 10-2	**10-19 → 10-15**	**10-36 → 10-24**
10-3 → 10-3	**10-20 → 10-16**	**10-37 → 10-25**
10-4 → 10-4	**10-21 → 16-61**	**10-38 → 10-26**
10-5 → 10-5	**10-22 → 16-62**	**10-39 → 16-69**
10-6 → 10-6	**10-23 → 16-63**	**10-40 → 10-27**
10-7 → 10-7	**10-24 → 16-64**	**10-41 → 10-28**
10-8 → 16-57	**10-25 → 16-65**	**10-42 → 10-29**
10-9 → 16-58	**10-26 → 10-17**	**10-43 → 10-30**
10-10 → 16-59	**10-27 → 10-18**	**10-44 → 10-31**
10-11 → 16-60	**10-28 → 10-19**	**10-46 → 10-32**
10-12 → 10-8	**10-29 → 16-66**	**10-47 → 10-33**
10-13 → 10-9	**10-30 → 16-67**	**10-48 → 16-70**
10-14 → 10-10	**10-31 → 10-20**	**10-49 → 10-34**
10-15 → 10-11	**10-32 → 10-21**	**10-50 → 10-35**
10-16 → 10-12	**10-33 → 10-22**	**10-51 → 10-37**
10-17 → 10-13	**10-34 → 10-23**	**10-52 → 10-38**

10-53 → 10-39
10-54 → 10-40
10-55 → 16-72
10-56 → 16-73
10-57 → 16-74
10-58 → 16-75
10-59 → 16-76
10-60 → 16-77
10-61 → 10-41
10-62 → 10-42
10-63 → 10-36
10-64 → 10-42
10-65 → 10-43
10-66 → 10-44
10-67 → 10-45
10-68 → 10-46
10-69 → 10-47
10-70 → 10-48
10-71 → 10-49
10-72 → 10-50
10-73 → 10-51
10-74 → 10-52
10-75 → 10-53
10-76 → 10-54
10-77 → 16-79
10-78 → 16-80
10-79 → 19-53
10-80 → 19-57
10-81 → 19-54
10-82 → 19-58
10-83 → 19-66
10-84 → 19-56
10-85 → 19-35
10-86 → 19-59
10-87 → 19-67
10-88 → 19-70
10-89 → 19-39
10-90 → 19-40
10-91 → 19-41
10-92 → 10-55
10-93 → 10-56
10-94 → 10-57
10-95 → 10-58
10-96 → 10-59
10-98 → 10-61
10-99 → 10-63
10-100 → 10-60
10-101 → 10-64
10-102 → 10-65
10-103 → 10-66
10-104 → 10-67
10-105 → 10-68
10-106 → 10-70
10-107 → 10-71
10-108 → 10-72
10-109 → 10-73
10-110 → 10-74
10-111 → 10-75
10-112 → 10-76
10-113 → 10-77
10-114 → 16-81
10-115 → 16-82
10-116 → 16-83
10-117 → 16-84
10-118 → 16-85
10-119 → 16-86
10-120 → 16-87
10-121 → 16-88
10-122 → 16-89
10-123 → 16-90
10-124 → 16-100
10-125 → 16-101
10-126 → 16-102
10-127 → 16-103
10-128 → 16-104
10-129 → 16-105

11-1 → 11-1
11-2 → 11-2
11-3 → 11-3
11-4 → 11-4
11-5 → 11-5
11-6 → 11-6
11-7 → 11-7
11-8 → 11-8
11-9
11-10 → 11-9
11-11 → 11-10
11-12 → 11-11
11-13 → 11-15
11-14 → 11-17
11-15 → 11-18
11-16 - deleted
11-17 - deleted
11-18 - deleted
11-19 → 11-19
11-20 → 11-20
11-21 → 11-21
11-22 → 11-12
11-23 → 11-13
11-24 → 11-14
11-25 → 11-22
11-26 → 11-23
11-27 → 11-24
11-28 → 11-25
11-29 → 11-26
11-30 → 11-27
11-31 → 11-28
11-32 → 11-29
11-33 → 11-30
11-34 → 11-31
11-35 → 11-32
11-36 → 11-33
11-37 → 11-34
11-38 → 11-35
11-39 → 11-36
11-40 → 11-37
11-41 → 11-38
11-42 → 11-39
11-43 → 11-40
11-44 → 11-41

12-1 → 12-1
12-2 → 12-2
12-3 → 12-3
12-4 → 12-4
12-5 → 12-5
12-6 → 12-6
12-7 → 12-7
12-8 → 12-8
12-9 → 12-10
12-10 → 12-11
12-11 → 12-12
12-12 → 12-13
12-13 → 12-14
12-14 → 12-16
12-15 → 12-18
12-16 → 12-19
12-17 → 12-20
12-18 → 10-69
12-19 → 12-21

12-20 → **12-22**
12-21 → **12-23**
12-22 → **12-17**
12-23 → **12-24**
12-24 → **12-25**
12-25 → **12-26**
12-26 → **12-27**
12-27 → **12-30**
12-28 → **12-31**
12-29 → **12-32**
12-30 → **12-33**
12-31 → **12-34**
12-32 → **12-35**
12-33 → **12-36**
12-34 → **12-37**
12-35 deleted
12-36 → **12-38**
12-37 → **12-39**
12-38 → **12-40**
12-39 → **12-41**
12-40 → **12-42**
12-41 → **12-43**
12-42 → **12-44**
12-43 → **12-45**
12-44 → **12-46**
12-45 → **12-47**
12-46 → **12-48**
12-47 → **13-19**
12-48 → **12-49**
12-49 → **12-50**
12-50 → **13-24**
12-51 → **12-51**
12-52 → **12-52**
12-53 → **12-53**

13-1 → **13-1**
13-2 → **13-2**
13-3 → **13-3**
13-4 → **13-4**
13-5 → **13-5**
13-6 → **13-6**
13-7 → **13-7**
13-8 → **19-55**
13-9 deleted
13-10 → **13-8**
13-11 → **13-9**
13-12 → **13-14**
13-13 → **13-15**
13-14 → **13-11**
13-15 → **13-17**
13-16 → **13-18**
13-17 → **13-20**
13-18 → **13-21**
13-19 → **13-22**
13-20 → **13-23**
13-21 → **13-30**
13-22 → **13-31**
13-23 → **13-32**
13-24 → **13-33**

14-1 → **14-1**
14-2 → **14-3**
14-3 → **14-4**
14-4 → **19-14**
14-5 → **14-5**
14-6 → **19-23**
14-7 → **14-6**
14-8 → **14-7**
14-9 → **14-8**
14-10 → **14-9**
14-11 → **14-10**
14-12 → **12-9**
14-13 → **14-11**
14-14 → **14-12**
14-15 → **14-14**
14-16 → **14-16**
14-17 → **13-27**
14-18 → **13-26**
14-19 → **13-10**
14-20 → **12-15**
14-21 → **14-17**
14-22 → **14-18**
14-23 → **14-19**
14-24 → **19-69**
14-25 → **14-20**
14-26 → **14-21**
14-27 → **14-22**
14-28 → **13-28**
14-29 → **13-25**
14-30 → **14-23**
14-31 → **14-24**
14-32 → **14-26**
14-33 → **14-25**
14-34 → **14-27**
14-35 → **14-28**
14-36 → **14-29**
14-37 → **14-30**
14-38 → **14-31**
14-39 → **14-32**

15-1 → **15-1**
15-2 → **15-2**
15-3 → **15-3**
15-4 → **15-4**
15-5 → **15-5**
15-6 → **15-6**
15-7 → **15-7**
15-8 → **15-8**
15-9 → **15-9**
15-10 → **15-10**
15-11 → **15-11**
15-12 → **15-12**
15-13 → **15-14**
15-14 → **15-13**
15-15 → **15-15**
15-16 → **15-16**
15-17 → **15-17**
15-18 → **15-18**
15-19 → **15-20**
15-20 → **15-23**
15-21 → **15-24**
15-22 → **15-21**
15-23 → **15-22**
15-24 → **15-25**
15-25 → **15-27**
15-26 → **15-28**
15-27 → **15-32**
15-28 → **15-33**
15-29 → **15-36**
15-30 → **15-35**
15-31 → **15-37**
15-32 → **15-34**
15-33 → **15-38**
15-34 → **15-19**
15-35 → **15-29**
15-36 → **15-30**
15-37 → **15-39**
15-38 → **15-41**
15-39 → **15-40**
15-40 → **15-42**
15-41 → **15-43**
15-42 → **15-44**
15-43 → **15-45**
15-44 → **15-46**

15-45 → **15-47**
15-46 → **15-48**
15-47 → **15-49**
15-48 → **15-50**
15-49 → **15-62**
15-50 → **15-51**
15-51 → **15-52**
15-52 → **15-53**
15-53 → **15-54**
15-54 → **15-55**
15-55 → **15-56**
15-56 → **15-57**
15-57 → **15-58**
15-58 → **15-60**
15-59 → **15-61**
15-60 → **15-59**
15-61 → **15-63**
15-62 → **15-64**
15-63 → **15-65**
15-64 → **15-66**

16-1 → **16-1**
16-2 → **16-2**
16-3 → **16-3**
16-4 → **16-4**
16-5 → **16-5**
16-6 → **16-7**
16-7 → **16-8**
16-8 → **16-9**
16-9 → **16-10**
16-10 → **16-11**
16-11 → **16-12**
16-12 → **16-13**
16-13 → **16-18**
16-14 → **16-17**
16-15 → **16-19**
16-16 → **16-20**
16-17 → **16-21**
16-18 → **16-22**
16-19 → **16-14**
16-20 → **16-15**
16-21 → **16-16**
16-22 → **16-23**
16-23 → **19-36**
16-24 → **19-42**
16-25 → **19-43**
16-26 → **19-44**
16-27 → **16-24**
16-28 → **16-25**
16-29 → **16-26**
16-30 → **16-27**
16-31 → **16-28**
16-32 → **16-29**
16-33 deleted
combined
with **10-115**
16-34 → **16-30**
16-35 → **16-31**
16-36 → **16-32**
16-37 → **16-33**
16-38 → **16-34**
16-39 → **16-35**
16-40 → **16-36**
16-41 → **16-38**
16-42 → **16-41**
16-43 → **16-42**
16-44 → **16-39**
16-45 → **16-40**
16-46 → **16-43**
16-47 → **16-44**
16-48 → **16-45**
16-49 → **16-50**
16-50 → **16-51**
16-51 → **16-52**
16-52 → **16-53**
16-53 → **16-54**
16-54 → **16-55**
16-55 → **16-56**
16-56 → **16-91**
16-57 → **16-6**
16-58 → **16-92**
16-59 → **16-93**
16-60 → **16-94**
16-61 → **16-46**
16-62 → **16-48**
16-63 → **16-95**
16-64 → **16-96**
16-65 → **16-97**
16-66 → **16-98**
16-67 → **16-99**

17-1 → **17-1**
17-2 → **17-2**
17-3 → **17-4**
17-4 → **17-5**
17-5 → **17-6**
17-6 → **17-7**
17-7 → **17-8**
17-8 → **17-9**
17-9 → **17-10**
17-10 → **17-11**
17-11 → **17-12**
17-12 → **17-13**
17-13 → **17-14**
17-14 → **17-15**
17-15 → **17-16**
17-16 → **17-17**
17-17 → **17-18**
17-18 → **17-19**
17-19 → **17-3**
17-20 → **17-20**
17-21 → **17-21**
17-22 → **17-22**
17-23 → **17-23**
17-24 → **17-24**
17-25 → **17-25**
17-26 deleted
combined
with **17-25**
17-27 → **17-26**
17-28 → **17-27**
17-29 → **17-28**
17-30 → **17-29**
17-31 deleted
combined
with **17-30**
17-32 → **17-30**
17-33 → **17-31**
17-34 → **17-32**
17-35 → **17-33**
17-36 → **17-34**
17-37 → **17-35**
17-38 → **17-36**
17-39 → **17-37**
17-40 → **17-38**

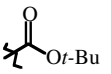
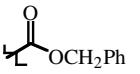
18-1 → **18-1**
18-2 → **18-2**
18-3 → **18-3**
18-4 → **18-4**
18-5 → **18-5**

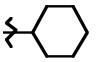
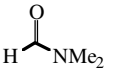
18-6 → **18-6**
18-7 → **18-7**
18-8 → **18-8**
18-9 → **18-9**
18-10 → **18-10** .
18-11 → **18-11**
18-12 → **18-12**
18-13 → **18-13**
18-14 → **18-14**
18-15 → **18-15**
18-16 → **18-16**
18-17 → **18-17**
18-18 → **18-18**
18-19 → **18-19**
18-20 → **18-20**
18-21 → **18-21**
18-22 → **18-22**
18-23 → **18-23**
18-24 → **18-24**
18-25 → **18-25**
18-26 → **18-26**
18-27 → **18-27**
18-28 → **18-28**
18-29 → **18-29**
18-30 → **18-30**
18-31 → **18-31**
18-32 → **18-32**
18-33 → **18-33**
18-34 → **18-34**
18-35 → **18-35**
18-36 → **18-36**
18-37 → **18-37**
18-38 → **18-38**
18-39 → **18-39**
18-40 → **18-40**
18-42 → **18-42**
18-43 → **18-43**
18-44 → **18-44**

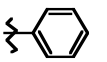
19-1 → **19-1**
19-2 → **19-2**
19-3 → **19-3**
19-4 → **19-4**
19-5 → **19-5**
19-6 → **19-6**
19-7 → **19-7**
19-8 → **19-8**
19-9 → **19-9**
19-10 → **19-10**
19-11 → **19-11**
19-12 → **19-12**
19-13 → **19-13**
19-14 → **19-17**
19-15 → **19-15**
19-16 → **19-18**
19-17 deleted
incorporated
in **19-14**
19-18 → **19-19**
19-19 → **19-20**
19-20 → **19-21**
19-21 → **19-22**
19-22 → **19-25**
19-23 → **19-27**
19-24 → **19-28**
19-25 → **19-30**
19-26 → **19-26**
19-27 → **19-29**
19-28 → **19-31**
19-29 → **19-24**
19-30 → **19-32**
19-31 → **19-33**
19-32 → **19-34**
19-33 → **19-61**
19-34 → **19-37**
19-35 → **19-64**
19-36 → **19-62**
19-37 → **19-63**
19-38 → **19-38**
19-39 → **19-65**
19-40 deleted
incorporated
into **10-85**
19-41 → **19-45**
19-42 → **19-46**
19-43 → **19-47**
19-44 → **19-48**
19-45 → **19-50**
19-46 → **19-51**
19-47 → **19-71**
19-48 → **19-68**
19-49 → **19-72**
19-50 → **19-60**
19-51 → **19-49**
19-52 → **19-73**
19-53 → **19-74**
19-54 → **19-75**
19-55 → **19-76**
19-56 → **19-77**
19-57 → **19-78**
19-58 → **19-79**
19-59 → **19-80**
19-60 → **19-81**
19-61 → **19-82**
19-62 → **19-83**
19-63 → **19-84**

COMMON ABBREVIATIONS

Other, less common abbreviations are given in the text when the term is used.

Ac	Acetyl	
acac	Acetylacetonate (ligand)	
AIBN	Azobisisobutyronitrile	
aq	Aqueous	
ARC	Anion relay chemistry	
Ax	Axial	
	9-Borabicyclo[3.3.1]nonylboryl	
9-BBN	9-Borabicyclo[3.3.1]nonane	
BDE	Bond dissociation energy	
BER	Borohydride exchange resin	
BINAP	(*2R*,*3S*)-2,2′-bis-(diphenylphosphino)-1,1′-binapthyl	
BINOL	1,1′-Bi-2-naphthol	
BMS	Borane methyl sulfide	
Bn	Benzyl	$-CH_2Ph$
Boc	*tert*-Butoxycarbonyl	
Bpy (Bipy)	2,2′-Bipyridyl	
BSA	*N*-*O*-Bis(trimethylsily)acetamide	
Bu	*n*-Butyl	$-CH_2CH_2CH_2CH_3$
Bs	Brosylate, *O*-(4-Bromophenyl) sulfenate	
Bz	Benzoyl	
CAN	Ceric ammonium nitrate	$(NH_4)_2Ce(NO_3)_6$
cat	Catalytic	
Cbz	*N*-Carbobenzyloxy	
CD	Circular dichroism	
Chap	Chapter(s)	
Chirald	(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol	
CIDNIP	Chemically induced dynamic nuclear polarization	
CIP	Cahn–Ingold–Prelog	
CNDO	Complete Neglect of Differential Overlap	
cod	1,5-Cyclooctadienyl (ligand)	

cot	1,3,5-Cyclooctatrienyl (ligand)	
Cp	Cyclopentadienyl	
Cy	Cyclohexyl	
°C	Temperature in degrees Celcius	
3D	Three dimensional	
DABCO	1,4-Diazabicyclo[2.2.2]octane	
DAST	Diethylammoniumsulfer trifluoride	Et_2NSF_3
dba	Dibenzylidene acetone	
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene	
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	
DCC	1,3-Dicyclohexylcarbodiimide	$c\text{-}C_6H_{11}\text{—N=C=N—}c\text{-}C_6H_{11}$
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
DDT	1,1,1-Trichloro-2,2′-bis(*p*-chlorophenyl)ethane	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DEAD	Diethylazodicarboxylate	$EtO_2C\text{—N=N}CO_2Et$
DHAD	Dihydroquinidine	
DHU	Dicyclohexylurea	
DIAD	Diisopropylazodicarboxylate	
Dibal-H	Diisobutylaluminum hydride	$(Me_2CHCH_2)_2AlH$
DMA	Dimethylacetamide	
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	$MeOCH_2CH_2OMe$
DMEAD	Di-2-methoxyethyl azodicarboxylate	
DMF	*N*,*N*′-Dimethylformamide	
DMS	Dimethyl sulfide	
DMSO	Dimethyl sulfoxide (ligand)	
DNA	Deoxyribonucleic acid	
DOSY	Diffusion-ordered NMR Spectroscopy	
dppb	1,4-Bis-(Diphenylphosphino) butane	$Ph_2P(CH_2)_4PPh_2$
dppe	1,2-Bis-(Diphenylphosphino)ethane; see also Diphos	$Ph_2PCH_2CH_2PPh_2$
dppf	Bis(Diphenylphosphino)ferrocene	
dpm	1,1-Bis(diphenylphosphino)methane	
dppp	1,3-Bis(Diphenylphosphino)propane	$Ph_2P(CH_2)_3PPh_2$
$\mathbf{e}^-$	Transfer of electrons	
% ee	% Enantiomeric excess	
EE	1-Ethoxyethoxy	$EtO(Me)CH\text{—}\text{—}CH_2CH_3$
Et	Ethyl	
EDA	Electron donor–acceptor orbital	
EDTA	Ethylenediaminetetraacetic acid	
Equiv	Equivalent(s)	
EPR	Electron paramagnetic resonance spectroscopy	
ESR	Electron spin resonance spectroscopy	
FMO	Frontier molecular orbital	
FVP	Flash vacuum pyrolysis	
GC	Gas chromatography	
h	Hour (hours)	
$h\nu$	Irradiation with light	
HF	Hartree–Fock	

HMO	Hückel molecular orbital	
HMPA	Hexamethylphosphoramide	$(Me_2N)_3P{=}O$
HMPT	Hexamethylphosphorus triamide	$(Me_2N)_3P$
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy	
HOMO	Highest occupied molecular orbital	
HPLC	High-performance liquid chromatography	
HSAB	Hard–Soft Acid–Base	
IBX	*o*-Iodoxybenzoic acid	
i-Pr	Isopropyl	$-CH(Me)_2$
IR	Infrared spectroscopy	
IUPAC	International Union of Pure and Applied Chemistry	
ISC	Intersystem crossing	
LCAO	Linear combination of atomic orbitals	
LICA (LIPCA)	Lithium *N*-isopropyl-*N*-cyclohexylamide	
LDA	Lithium diisopropylamide	$LiN(i\text{-}Pr)_2$
LHMDS	Lithium hexamethyl disilazide	$LiN(SiMe_3)_2$
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
LUMO	Lowest unoccupied molecular orbital	
Mcpba	*m*-Chloroperoxybenzoic acid	
Me	Methyl	$-CH_3$ or Me
MEM	β-Methoxyethoxymethyl	$MeOCH_2CH_2OCH_2$-
Mes	Mesityl	2,4,6-tri-Me–C_6H_2
min	minutes	
MMPP	Magnesium monoperoxyphthalate	
MO	Molecular Orbital	
MOM	Methoxymethyl	$MeOCH_2-$
Ms	Methanesulfonyl	$MeSO_2-$
MTO	Methyl trioxorhenium	
NBS	*N*-Bromosuccinimide	
NCS	*N*-Chlorosuccinimide	
NHS	*N*-Hydroxysuccinimide	
NIS	*N*-Iodosuccinimide	
NMO	*N*-Methylmorpholine *N*-oxide	
NMP	*N*-Methylpyrrolidinone	
NMR	Nuclear magnetic resonance	
NOESY	Nuclear overhauser effect spectroscopy	
NOE	Nuclear overhauser effect	
Nu (Nuc)	Nucleophile	
OBs	*O*-(4-Bromophenyl)sulfinate	
Oxone®	2 $KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$	
	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	
PES	Photoelectron spectroscopy	
Ph	Phenyl	
PhH	Benzene	
PhMe	Toluene	

PIFA	Phenyliodine (III)-bis-(trifluoroacetate)	
PPHF	Pyridinium poly(hydrogen fluoride)	
PMHS	Polymethylhydrosiloxane	
Pr	*n*-Propyl	—$CH_2CH_2CH_3$
Py	Pyridine	
Quant	Quantitative yield	
Red-Al	$[(MeOCH_2CH_2O)2AlH_2]Na$	
ROESY	Rotating-frame NOE spectroscopy	
rt	Room temperature	
*s*BuLi	*sec*-Butyllithium	$CH_3CH_2CH(Li)CH_3$
s	seconds	
salen	Bis (salicylidene) ethylenediamine	
sc CO_2	supercritical CO_2	
SCF	self-consistant field	
SDS	Sodium dodecyl sulfate	
Sec.	Section(s)	
SET	Single electron transfer	
Siamyl		
$(Sia)_2BH$	Disiamylborane *sec*-Isoamyl	
SOMO	Singly occupied molecular orbital	
Tr	Tritium	
TBAF	Tetrabutylammonium fluoride	$n\text{-}Bu_4N^+ F^-$
t-Bu	*tert*-Butyl	—CMe_3
TEAB	Tetraethylammonium bromide	
TEBA	Triethylbenzylammonium	$Bn(Et_3)_3N^+$
TED	Tetraethylenediamine	
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy free radical	
TFA	Trifluoroacetic acid (solvent)	CF_3COOH
tfa	Trifluoroacetic acid (ligand)	$(CF_3CO)_2O$
Tf (OTf)	Triflate	—SO_2CF_3 (—OSO_2CF_3)
THF	Tetrahydrofuran (solvent)	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
TMS	Trimethylsilyl or tetramethylsilane	—$Si(CH_3)_3$
Tol	Tolyl	4-(Me)C_6H_4
TOSMIC	Toluenesulfonylmethyl isocyanide	
TPAP	Tetrapropylammonium perruthenate	$Pr_4N^+RuO_4^-$
TPP	Triphenylphosphine (solvent)	
tpp	Triphenylphosphine (ligand)	pPh_3
Ts(Tos)	Tosyl = *p*-Toluenesulfonyl	4-(Me)$C_6H_4SO_2$
UV	Ultraviolet spectroscopy	
VCD	Vibrational circular dichroism	
VDW	van der Walls	
vis	Visible	
XPS	X-ray photoelectron spectroscopy	

BIOGRAPHICAL STATEMENT

Professor Michael B. Smith was born in Detroit, Michigan in 1946. In 1957, he and his family moved to Madison Heights, Virginia. After graduation from Amherst County high school, he entered Ferrum Jr. College and graduated with an A.A. Professor Smith transferred to Virginia Polytechnic Institute (Virginia Tech), where he did undergraduate research with Professor Harold Bell, and graduated with a B.S in chemistry in 1969. After working as an analytical chemist at the Newport News Shipbuilding and Dry Dock Co. (Tenneco) in Newport News, Virginia for three years, he began graduate studies at Purdue University under the mentorship of Professor Joseph Wolinsky. Professor Smith graduated with a Ph.D. in Organic chemistry in 1977. He spent one year as a faculty research associate at the Arizona State University in the Cancer Research Institute, directed by Professor George R. Pettit, and a second year doing postdoctoral work at the Massachusetts Institute of Technology under the mentorship of Professor Sidney Hecht. In 1979 he began his independent academic career, where he now holds the rank of full professor.

Professor Smith is the author of approximately 90 independent research articles, and 20 published books. The books include the 5th and 6th edition of *March's Advanced Organic Chemistry* (Wiley), volumes 6–12 of the *Compendium of Organic Synthetic Methods* (Wiley), *Organic Chemistry a Two Semester Course* (HarperCollins) into its 2nd edition, and *Organic Synthesis* (Elsevier) in its 3rd edition. A new undergraduate organic chemistry book, *Organic Chemistry: An Acid-Base Approach*, was published in 2011 by the CRC Press.

Professor Smith's current research involves the synthesis and structural verification of lipids obtained from the dental pathogen *Porphyromonas gingivalis*, which show inflammatory activity, induce bone degeneration and are involved in triggering multiple sclerosis. A main area of research is the synthesis of fluorescent dye-heterocyclic conjugates that target hypoxic cancerous tumors, allowing non-invasive fluorescence imaging in the near IR. The synthesis of anti-cancer alkaloids is also ongoing.

PART I

INTRODUCTION

This book contains 19 chapters. Chapters 1–9 may be thought of as an introduction to Part II. The first-five chapters deal with the structure of organic compounds. These chapters discuss the kinds of bonding important in organic chemistry, the fundamental principles of conformation and stereochemistry of organic molecules, and reactive intermediates in organic chemistry. Chapters 6–9 are concerned with general principles of mechanism in organic chemistry, including acids and bases, photochemistry, sonochemistry and microwave irradiation, and finally the relationship between structure and reactivity.

Chapters 10–19, which make up Part II, are directly concerned with the nature and the scope of organic reactions and their mechanisms.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

CHAPTER 1

Localized Chemical Bonding

Localized chemical bonding may be defined as bonding in which the electrons are shared by two and only two nuclei. Such bonding is the essential feature associated with the structure of organic molecules.[1] Chapter 2 will discuss *delocalized bonding*, in which electrons are shared by more than two nuclei.

1.A. COVALENT BONDING[2]

Wave mechanics is based on the fundamental principle that electrons behave as waves (e.g., they can be diffracted). Consequently, a wave equation can be written for electrons, in the same sense that light waves, sound waves, and so on, can be described by wave equations. The equation that serves as a mathematical model for electrons is known as the *Schrödinger equation*, which for a one-electron system is

$$\frac{\delta^2\psi}{\delta x^2}+\frac{\delta^2\psi}{\delta y^2}+\frac{\delta^2\psi}{\delta z^2}+\frac{8\pi^2 m}{h^2}(\mathrm{E}-\mathrm{V})\psi=0$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function (Ψ) expresses the square root of the probability of finding the electron at any position defined by the coordinates x, y, and z, where the origin is at the nucleus. For systems containing more than one electron, the equation is similar, but more complicated.

The Schrödinger equation is a differential equation, so solutions to it are themselves equations, but the solutions are not differential equations. They are just simple equations for which graphs can be drawn. Such graphs are essentially three-dimensional (3D)

[1] See Hoffmann, R.; Schleyer, P.v.R.; Schaefer, III, H.F. *Angew. Chem. Int. Ed. (Engl.)* ***2008***, *47*, 7164.

[2] This treatment of orbitals is simplified by necessity. For more detailed treatments of orbital theory, as applied to organic chemistry, see Matthews, P.S.C. *Quantum Chemistry of Atoms and Molecules*, Cambridge University Press, Cambridge, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***; Albright, T.A.; Burdett, J.K.; Whangbo, M. *Orbital Interactions in Chemistry*, Wiley, NY, ***1985***; MacWeeny, R.M. *Coulson's Valence*, Oxford University Press, Oxford, ***1980***; Murrell, J.N.; Kettle, S.F.A; Tedder, J.M. *The Chemical Bond*, Wiley, NY, ***1978***; Dewar, M.J.S.; Dougherty. R.C. *The PMO Theory of Organic Chemistry*, Plenum, NY, ***1975***; Zimmerman, H.E. *Quantum Mechanics for Organic Chemists*, Academic Press, NY, ***1975***; Borden, W.T. *Modern Molecular Orbital Theory for Organic Chemists*, Prentice-Hall, Englewood Cliffs, NJ, ***1975***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

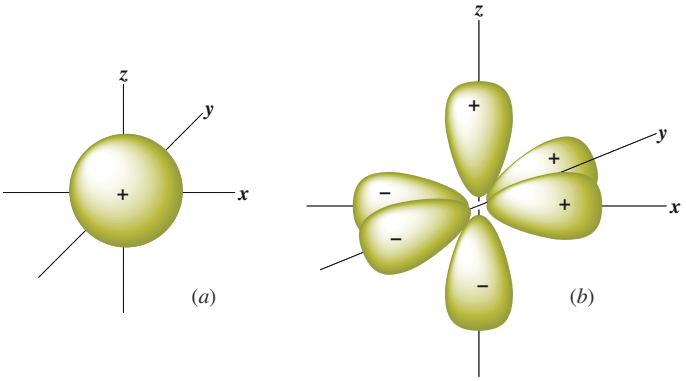


FIG. 1.1. (*a*) The 1s orbital. (*b*) The three 2*p* orbitals.

pictures that show the electron density, and these pictures are called *orbitals* or electron clouds. Most students are familiar with the shapes of the *s* and *p* atomic orbitals (Fig. 1.1). Note that each *p* orbital has a *node*: A region in space where the probability of finding the electron is extremely small.[3] Also note that in Fig. 1.1 some lobes of the orbitals are labeled + and others −. These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged. They are the signs of the wave function Ψ. When a node separates two parts of an orbital, a point of zero electron density, Ψ always has opposite signs on the two sides of the node. According to the *Pauli exclusion principle*, no more than two electrons can be present in any orbital, and they must have opposite spins.

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron systems (e.g., the hydrogen atom). If it could be solved exactly for molecules containing two or more electrons,[4] a precise picture of the shape of the orbitals available to each electron (especially for the important ground state) would become available, as well as the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief general methods of approximation: the molecular orbital (MO) method and the valence bond method.

In the MO method, bonding is considered to arise from the overlap of atomic orbitals. When any number of atomic orbitals overlap, they combine to form an equal number of new orbitals, called *molecular orbitals*. Molecular orbitals differ from atomic orbitals in that an electron cloud effectively surrounds the nuclei of two or more atoms, rather than just one atom. In other words, the electrons are shared by two atoms rather than being localized on one atom. In localized bonding for a single covalent bond, the number of atomic orbitals that overlap is two (each containing one electron), so that two molecular orbitals are generated. One of these, called a *bonding orbital*, has a lower energy than the original atomic orbitals (otherwise a bond would not form), and the other, called an *antibonding orbital*, has a higher

[3] When wave mechanical calculations are made according to the Schrödinger equation, the probability of finding the electron in a node is zero, but this treatment ignores relativistic considerations. When such considerations are applied, Dirac has shown that nodes do have a very small electron density: Powell, R.E. *J. Chem. Educ.* ***1968***, *45*, 558. See also, Ellison, F.O.; Hollingsworth, C.A. *J. Chem. Educ.* ***1976***, *53*, 767; McKelvey, D.R. *J. Chem. Educ.* ***1983***, *60*, 112; Nelson, P.G. *J. Chem. Educ.* ***1990***, *67*, 643. For a general review of relativistic effects on chemical structures, see Pyykkö, P. *Chem. Rev.* ***1988***, *88*, 563.

[4] See Roothaan, C.C.J.; Weiss, A.W. *Rev. Mod. Phys.* ***1960***, *32*, 194; Kolos, W.; Roothaan, C.C.J. *Rev. Mod. Phys.* ***1960***, *32*, 219. For a review, see Clark, R.G.; Stewart, E.T. *Q. Rev. Chem. Soc.* ***1970***, *24*, 95.

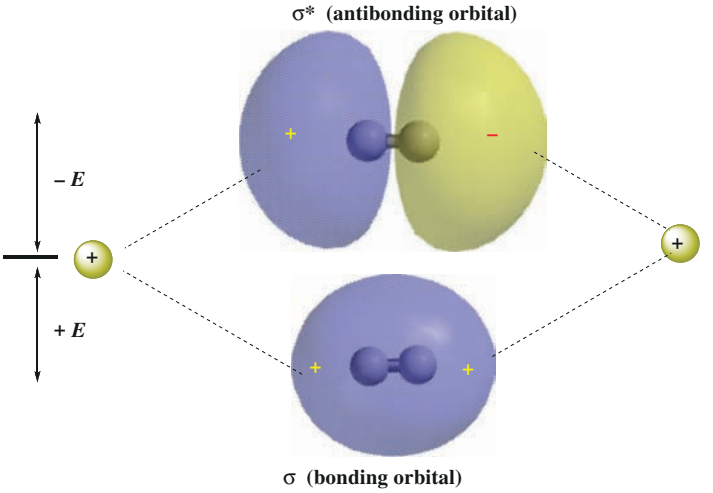


FIG. 1.2. Overlap of two 1*s* orbitals gives rise to a σ and a σ* orbital.

energy. Orbitals of lower energy fill first. Since the two original atomic orbitals each held one electron, both of these electrons will reside in the new molecular *bonding* orbital, which is lower in energy. Remember that any orbital can hold two electrons. The higher energy antibonding orbital remains empty in the ground state.

The strength of a bond is determined by the amount of electron density that resides between the two nuclei. The greater the overlap of the orbitals, the stronger the bond, but total overlap is prevented by repulsion between the nuclei. Figure 1.2 shows the bonding and antibonding orbitals that arise by the overlap of two 1*s* electrons. Note that since the antibonding orbital has a node between the nuclei, there is practically no electron density in that area, so that this orbital cannot be expected to bond very well. When the centers of electron density are on the axis common to the two nuclei, the molecular orbitals formed by the overlap of two atomic orbitals are called σ (*sigma*) orbitals, and the bonds are called σ bonds. The corresponding antibonding orbitals are designated σ*. Sigma orbitals may be formed by the overlap of any of the atomic orbital (*s, p, d,* or *f*) whether the same or different, not only by the overlap of two *s* orbitals. However, the two lobes that overlap must have the same sign: A positive *s* orbital can form a bond only by overlapping with another positive *s* orbital or with a positive lobe of a *p, d,* or *f* orbital. Any *σ* molecular orbital may be represented as approximately ellipsoidal in shape.

Orbitals are frequently designated by their symmetry properties. The σ orbital of hydrogen is often written ψ_g. The *g* stands for *gerade*. A *gerade* orbital is one in which the sign on the orbital does not change when it is inverted through its center of symmetry. The σ* orbital is *ungerade* (designated ψ_u). An *ungerade* orbital changes sign when inverted through its center of symmetry.

In MO calculations, the *linear combination of atomic orbitals* (known as LCAO) generates a wave function from a linear combination of overlapped atomic orbitals. Addition of the atomic orbitals gives the bonding MO:

$$\psi = c_A\psi_A + c_B\psi_B \tag{1-1}$$

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors. Subtraction is also a linear combination:

$$\psi = c_A\psi_A - c_B\psi_B \tag{1-2}$$

This gives rise to the antibonding molecular orbital.

In the valence bond method, a wave equation is written for each of various possible electronic structures that a molecule may have (each of these is called a *canonical form*), and the total ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\psi = c_1\psi_1 + c_2\psi_2 + \cdots \tag{1-3}$$

This resembles Eq. (1-1), but here each ψ represents a wave equation for an imaginary canonical form and each c is the amount contributed to the total picture by that form. For example, a wave function can be written for each of the following canonical forms of the hydrogen molecule[5]:

$$\mathrm{H{-}H} \qquad \mathrm{H{:}^-\ \ H^+} \qquad \mathrm{{}^+H\ \ H{:}^-}$$

Values for c in each method are obtained by solving the equation for various values of each c, and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules that contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2. Note that orbital functions can indeed be reconstructed from measured data using several different approaches. Often, however, the results are still less accurate than those achieved with purely theoretical methods.[6]

1.B. MULTIPLE VALENCE

A univalent atom has only one orbital available for bonding. But atoms with a valence of 2 or more must form bonds by using at least two orbitals. An oxygen atom has two half-filled orbitals, giving it a valence of 2. It forms single bonds by the overlap of these with the orbitals of two other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are p orbitals, which are perpendicular. If this is correct, nitrogen, which has three mutually perpendicular p orbitals, would have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond angles in water are,[7] 104°27′, and in ammonia, 106°46′. For alcohols and ethers, the angles are even larger (see Sec. 1.K). A discussion of this will be deferred to Section 1.K, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating, the mean position is the same for each molecule of a given compound.

[5] In this book, a pair of electrons in a bond is represented by two dots.

[6] Schwarz, W.H.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1508. For the ball-in-box model, see Pierrefixe, S.C.A.H.; Guerra, C.F.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2008***, *14*, 819; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A.* ***2008***, *112*, 12816.

[7] Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, 277.

1.C. HYBRIDIZATION

Consider the case of mercury. Its electronic structure is

$$[\mathbf{Xe}\,\text{core}]4f^{14}5d^{10}6s^2$$

Although it has no half-filled orbitals, it has a valence of 2 and forms two covalent bonds. This result can be explained by imagining that one of the 6*s* electrons is promoted to a vacant 6*p* orbital to give the excited configuration

$$[\mathbf{Xe}\,\text{core}]4f^{14}5d^{10}6s^16p^1$$

In this state, the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by the overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent. The bond formed from the 6*p* orbital would be more stable than the one formed from the 6*s* orbital, since a larger amount of overlap is possible with the former. A more stable situation is achieved when, in the course of bond formation, the 6*s* and 6*p* orbitals combine to form two new orbitals that *are* equivalent; these are shown in Fig. 1.3.

The new molecular orbitals are a mixture of the two original orbitals, so they are called *hybrid orbitals*. Each orbital is a merger of an *s* and *p* orbital and is called an *sp* orbital. The *sp* orbitals, each of which consists of a large lobe and a very small one, arise only in the bonding process and do not represent a possible structure for the free atom. A mercury atom forms its two bonds by overlapping each of the large lobes shown in Fig. 1.3 with an orbital from an external atom. The orbital of this external atom may be any of the atomic orbitals previously considered (*s, p, d,* or *f*), or it may be another hybrid orbital. Note that only lobes of the same sign can overlap. In any of these cases, the molecular orbital that arises is called a σ orbital since it fits the previous definition of a σ orbital.

In general, equivalent orbitals lie as far away from each other as possible because of mutual repulsion, so two *sp* orbitals form an angle of 180°. In other words, an atom that forms only two σ bonds uses two *sp* orbitals so $HgCl_2$, for example, should be a linear molecule, and it is. This kind of hybridization is called *digonal hybridization*. An *sp* hybrid orbital forms a stronger covalent bond than either an *s* or a *p* orbital because it extends out in space in the direction of the other atom's orbital farther than the *s* or the *p* and permits

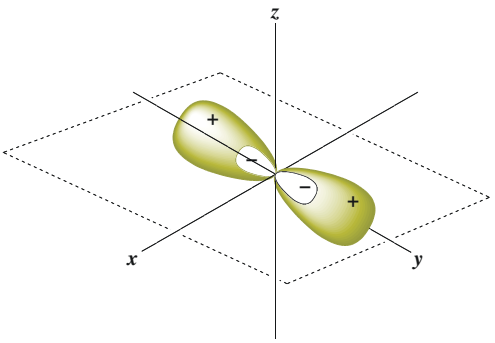


FIG. 1.3. The two *sp* orbitals formed by mercury.

greater overlap. Compare $HgCl_2$ with water (OH_2). It is known that the shape of $HgCl_2$ is linear, but water is angular. This fact suggests that the hybrid orbitals utilized by oxygen in water is different from those used by mercury in $HgCl_2$.

Many other kinds of hybridization are possible. Consider boron, which has the electronic configuration $1s^2 2s^2 2p^1$ yet has a valence of 3. To begin, boron has only three valence electrons available to form bonds, hence the valence of three. Any hybridization model must take this into account. As before, imagine promotion of an electron and hybridization:

$$1s^2 2s^2 2p^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 \xrightarrow{\text{hybridization}} 1s^2 (2s^2)^3$$

In this case, there are three equivalent hybrid orbitals, each called sp^2 (*trigonal hybridization).* This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but keep in mind that *each* of the three orbitals is called sp^2. The key is to understand that the atom forms two σ bonds for *sp* hybridization and three σ bonds for sp^2 hybridization. The sp^2 hybrid orbitals just noted are shown in Fig. 1.4. The three axes are all in one plane and point to the corners of an equilateral triangle. This accords with the known structure of BF_3, a planar molecule with angles of 120°.

Another type of hybrid orbital is possible, formed by atoms that can form four σ bonds. Carbon is an important atom that can form four single bonds (four σ bonds). Imagine promotion of an electron and hybridization that leads to

$$1s^2 2s^2 2p_x^1 2p_y^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1 \xrightarrow{\text{hybridization}} 1s^2 (2sp^3)^4$$

There are four equivalent molecular orbitals, each called sp^3, and electron repulsion leads to a shape in which the orbitals point to the corners of a regular tetrahedron (Fig. 1.4). A typical molecule is methane (CH_4) and assuming that carbon forms four bonds with sp^3 hybrid orbitals, the bond angles of methane would thus be expected to be 109°28′, which is the angle for a regular tetrahedron. In reality, electrons are not "promoted" in atomic orbitals, but atomic orbitals are different from molecular orbitals (e.g., those found in methane). The model of promoting an electron is a mathematical device to describe molecular orbitals using the atomic orbitals.

The hybrid orbitals discussed in this section stem from only one possible approximate solution of the Schrödinger equation. The *s* and the three *p* atomic orbitals used to form sp^3 orbitals, for example, can be combined in other equally valid ways. As will be seen in Section 1.E, the four C—H bonds of methane do not always behave as if they are

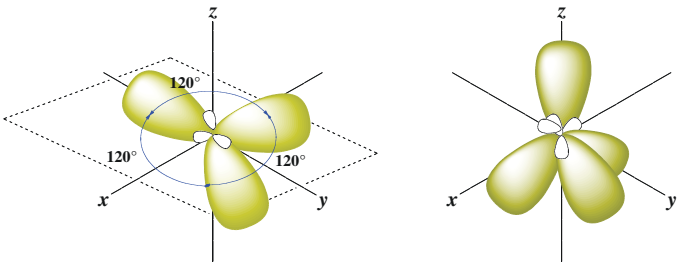


FIG. 1.4. The three sp^2 and the four sp^3 orbitals.

equivalent. Bickelhaupt[6] has proposed an alternative approach to the bonding in carbon suggesting that the maximum coordination number of carbn cannot exceed four because it is too small to allow more than four substituents approach and form the appropriate bonds.

1.D. MULTIPLE BONDS

If ethylene ($H_2C{=}CH_2$) is examined in terms of the MO concepts discussed so far, each carbon has three σ bonds, one to each of the three atoms. Therefore, sp^2 orbitals are used to form those three bonds. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x{}^1$, and $2p_y{}^1$ electrons after promotion of electrons (Sec. 1.C). In general, any carbon atom that is bonded to only three different atoms uses sp^2 orbitals for this bonding. The three σ bonds of ethylene are one to each of two hydrogen atoms and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital that is perpendicular to the plane of the sp^2 orbitals. The two parallel $2p_z$ orbitals, one on each of the two adjacent carbon atoms, can overlap sideways to generate a bonding and an antibonding orbital (Fig. 1.5). In the ground state, both electrons go into the bonding orbital and the antibonding orbital remains vacant. In other words, a new bond is formed, but it is formed by sideways overlap of adjacent *p* orbitals rather than direct overlap of σ orbitals. Molecular orbitals formed by the overlap of atomic

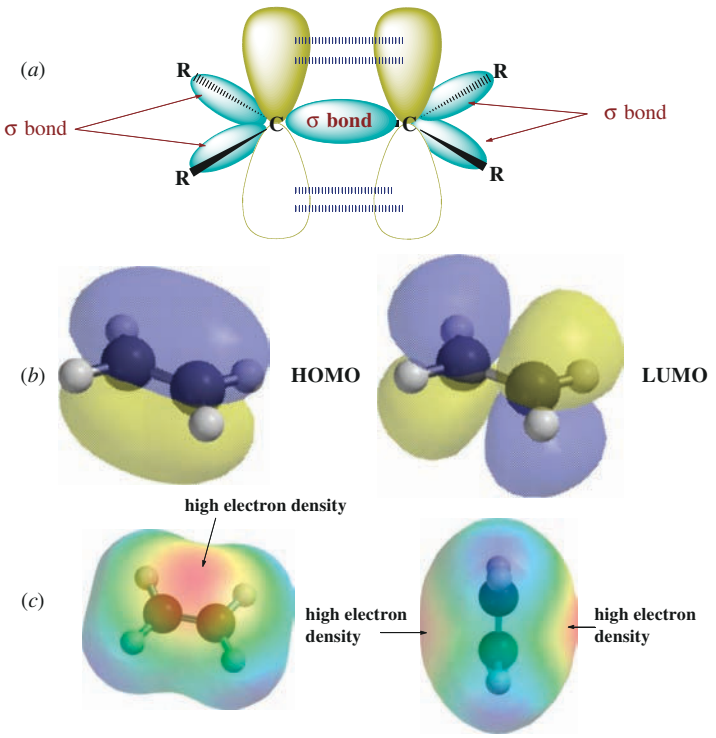


FIG. 1.5. (*a*) Overlapping *p* orbitals form a π and a π* orbital. The σ orbitals are shown in (*a*). The π orbitals are shown in (*b*) as the highest occupied molecular orbital (HOMO) (on the left) and the LUMO. In (*c*), the electron potential map of ethylene shows the concentration of electron density above and below the plane of the atoms, consistent with a π bond.

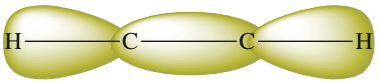


FIG. 1.6. The σ orbitals of acetylene.

orbitals whose axes are parallel are called π *orbitals* if they are bonding and π* if they are antibonding.

In this picture of ethylene, there are two bonds connecting the adjacent carbon atoms, but the two orbitals that make up the double bond are not equivalent.[8] This means that the two bonds are different one from the other. The σ orbital is ellipsoidal and symmetrical about the C—C axis, and this is the familiar σ bond. The π orbital is in the shape of two ellipsoids, one above the plane and one below, and forms the second bond, a π bond. The plane itself represents a node for the π orbital. In order for the *p* orbitals to maintain maximum overlap, they must be parallel. Since both a σ bond and the π bond connect the two carbon atoms, free rotation is not possible about the double bond. In other words, the two *p* orbitals would have to reduce their overlap to allow one H—C—H plane to rotate with respect to the other (i.e., the π bond would have to disappear). With two sp^2 hybrid carbon atoms in ethylene, the six atoms associated with the double bond ($H_2C{=}CH_2$) are in a plane with angles that should be ∼120°. Double bonds are shorter than the corresponding single bonds because maximum stability is obtained when the *p* orbitals overlap as much as possible (see Sec. 1.J). Double bonds between carbon and oxygen (C=O) or nitrogen (C=N) similarly consist of one σ and one π orbital.

When carbon is connected to another carbon atom by a triple bond, as in acetylene (HC≡CH), each carbon is connected to only two other atoms by a σ bond, and hence uses *sp* hybridization. This fact requires that the four atoms of acetylene (2H and 2C) are in a straight line (Fig. 1.6).[9] Each carbon has two *p* orbitals remaining, with one electron in each. These orbitals are perpendicular to each other and also to the C—C axis. They overlap in the manner shown in Fig. 1.7 to form two π orbitals. A triple bond is thus composed of one σ and two π orbitals. Triple bonds between carbon and nitrogen can be represented in a similar manner, C≡N.

For most organic molecules, double and triple bonds typically involve the first-row elements carbon, nitrogen, and oxygen.[10] Second-row elements tend to form weaker π bonds than do the first-row elements,[11] so multiple bonds are less common and compounds containing them are generally less stable.[12] Compounds with C=S bonds are known, for example, and C=S compounds are generally much less stable than the corresponding C=O compounds (however, see *pπ–dπ* bonding in Sec. 2.H). Stable compounds with

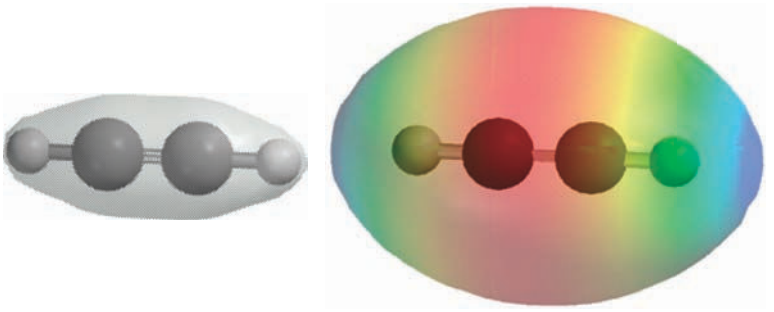
[8] For an alternative representation, see Pauling, L. *Theoretical Organic Chemistry*, *The Kekulé Symposium*, Butterworth, London, ***1959***, pp. 2–5; Palke, W.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6543.

[9] See Simonetta, M.; Gavezzotti, A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 1–56; Dale, J., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 3–96.

[10] For a review of metal–metal multiple bonds, see Cotton, F.A. *J. Chem. Educ.* ***1983***, *60*, 713.

[11] For discussions, see Schmidt, M.W.; Truong, P.N.; Gordon, M.S. *J. Am. Chem. Soc.* ***1987***, *109*, 5217; Schleyer, P. von R.; Kost, D. *J. Am. Chem. Soc.* ***1988***, *110*, 2105.

[12] For double bonds between carbon and elements other than C, N, S, or O, see Jutzi, P. *Angew. Chem. Int. Ed.* ***1975***, *14*, 232; Raabe, G.; Michl, J. *Chem. Rev.* ***1985***, *85*, 419 (Si only); Wiberg, N. *J. Organomet. Chem.* ***1984***, *273*, 141 (Si only); Gordon, M.S. *Mol. Struct. Energ.* ***1986***, *1*, 101. For reviews of C=P and C≡P bonds, see Regitz, M. *Chem. Rev.* ***1990***, *90*, 191; Appel, R.; Knoll, F. *Adv. Inorg. Chem.* ***1989***, *33*, 259; Markovski, L.N.; Romanenko, V.D. *Tetrahedron* ***1989***, *45*, 6019.



(*a*) (*b*)

FIG. 1.7. (*a*) The electron density map of acetylene. Note the concentration of electron density along a line between the nuclei of each atom, consistent with overlap of σ orbitals in a triple bond. (*b*) Electron potential map of acetylene showing the concentration of electron density between the carbon atoms, consistent with two orthogonal π bonds.

Si=C and Si=Si bonds are rare, but examples have been reported,[13] including a pair of cis and trans Si=Si isomers.[14]

There is at least one report of a so-called two-electron, four-center C—C bond for the dimer of tetracyanoethylene.[15] While such multi-center bonding is not formally an example of the multiple bonding described in this section, it constitutes a different type of bonding when compared to the simple C—C bonds described earlier.

1.E. PHOTOELECTRON SPECTROSCOPY

Based on the hybridization model, methane is expected to have four equivalent σ bonds. Indeed, the four bonds of methane are equivalent according to most physical and chemical methods of detection. The *nuclear magnetic resonance* (NMR) and the *infrared* (IR) spectrum of methane show *no* peaks that can be attributed to different kinds of C—H bonds. However, there is one physical technique showing that the eight valence electrons of methane can be differentiated. In this technique, called *photoelectron spectroscopy* (PES),[16] a molecule or free atom is bombarded with vacuum *ultraviolet* (UV) radiation, causing an electron to be ejected. The energy of the ejected electron can be measured, and the difference between the energy of the radiation used and that of the ejected electron is

[13] For Si=C bonds, see Fink, M.J.; DeYoung, D.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 1070; Fink, M.J.; Michalczyk, M.J.; Haller, K.J.; West, R.; Michl, J. *Organometallics* ***1984***, *3*, 793; West, R. *Pure Appl. Chem.* ***1984***, *56*, 163; Masamune, S.; Eriyama, Y.; Kawase, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 584; Shepherd, B.D.; Campana, C.F.; West, R. *Heteroat. Chem.* ***1990***, *1*, 1.

[14] Michalczyk, M.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1984***, *106*, 821, *Organometallics* ***1985***, *4*, 826.

[15] Miller, J.S.; Novoa, J.J. *Acc. Chem. Res*. ***2007***, *40*, 189.

[16] See Ballard, R.E. *Photoelectron Spectroscopy and Molecular Orbital Theory*, Wiley, NY, ***1978***; Rabalais, J.W. *Principles of Ultraviolet Photoelectron Spectroscopy*, Wiley, NY, ***1977***; Baker, A.D.; Betteridge, D. *Photoelectron Spectroscopy*, Pergamon, Elmsford, NY, ***1972***; Turner, D.W.; Baker, A.D.; Baker, C.; Brundle, C.R. *High Resolution Molecular Photoelectron Spectroscopy*, Wiley, NY, ***1970***. For reviews, see Westwood, N.P.C. *Chem. Soc. Rev*. ***1989***, *18*, 317; Baker, C.; Brundle, C.R.; Thompson, M. *Chem. Soc. Rev*. ***1972***, *1*, 355; Bock, H.; Ramsey, B.G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 734; Turner, D.W. *Adv. Phys. Org. Chem*. ***1966***, *4*, 31. For the IUPAC descriptive classification of various electron spectroscopy techniques, see Porter, H.Q.; Turner, D.W. *Pure Appl. Chem.* ***1987***, *59*, 1343.

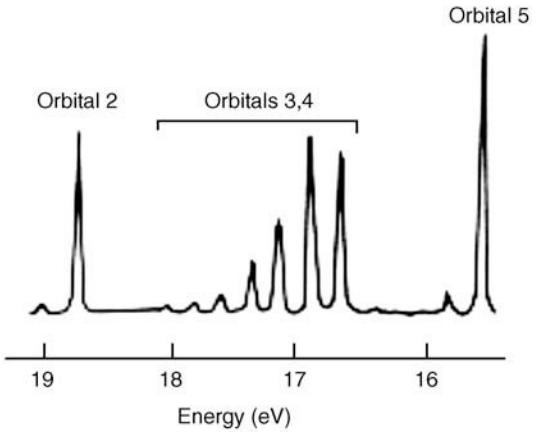


FIG. 1.8. Photoelectron spectrum of N_2.[18] [Reprinted with permission from Brundle, C.R.; Robin, M.B. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1971***, p. 18. Copyright © 1971, with permission from Elsevier Science. With permission of C. Richard Brundle, 2012.]

the *ionization potential* of that electron. A molecule that contains several electrons of differing energies can lose any one of them as long as its ionization potential is less than the energy of the radiation used. A single molecule loses only one electron; the loss of two electrons by any individual molecule almost never occurs. Since electrons reside in orbitals, a photoelectron spectrum consists of a series of bands, each corresponding to an orbital of a different energy. The spectrum gives a direct experimental picture of all orbitals that are present, and they are ejected in ascending order of their energies, provided that radiation of sufficiently high energy is used.[17] Broad bands usually correspond to strongly bonding electrons and narrow bands to weakly bonding or nonbonding electrons.

Using PES, it is possible to probe the validity of the hybridization model for bonding. Dinitrogen (N_2) is a typical diatomic molecule and is shown in Fig. 1.8.[18] The N_2 molecule has the electronic structure shown in Fig. 1.9: The two 2*s* orbitals of the nitrogen atoms combine to give the two orbitals marked 1 (bonding) and 2 (antibonding), while the six 2*p* orbitals combine to give six orbitals, three of which (marked 3, 4, and 5) are bonding. The three antibonding orbitals (not indicated in Fig. 1.9) are unoccupied. Electrons ejected from orbital 1 are not found in Fig. 1.8 because the ionization potential of these electrons is greater than the energy of the light used (they can be seen when higher energy light is used). The broad band in Fig. 1.8 corresponds to the four electrons in the degenerate orbitals 3 and 4. The individual peaks within this band are caused by different vibrational levels (see Chap. 7). The triple bond of N_2 is therefore composed of these two orbitals and orbital 1. The bands corresponding to orbitals 2 and 5 are narrow; hence these orbitals contribute little to the bonding and may be regarded as the two unshared pairs of $\ddot{N} \equiv \ddot{N}$. Note that this result is contrary to that expected from a naive consideration of orbital overlaps, where it

[17] The correlation is not perfect, but the limitations do not seriously detract from the usefulness of the method. The technique is not limited to vacuum UV radiation. Higher energy radiation can also be used.

[18] From Brundle, C.R.; Robin, M.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, p. 18.

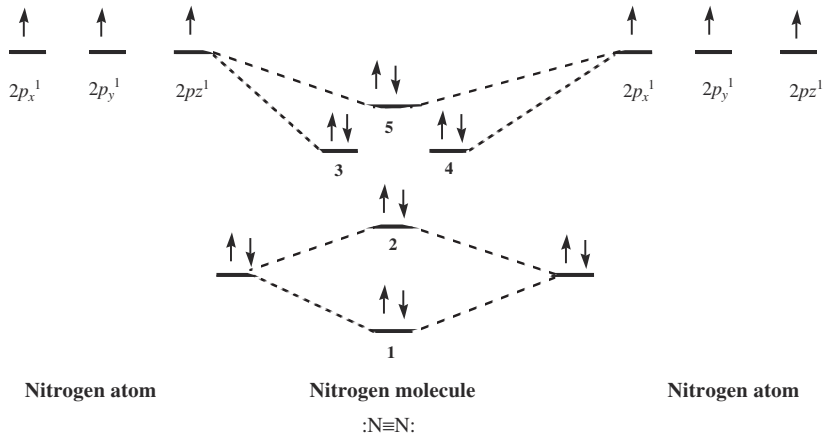


FIG. 1.9. Electronic structure of N_2 (inner-shell electrons omitted).

would be expected that the two unshared pairs would be those of orbitals 1 and 2, resulting from the overlap of the filled 2*s* orbitals. In addition, the triple bond would be composed of orbitals 3, 4, and 5, resulting from overlap of the *p* orbitals. This example is one illustration of the value of PES.

The photoelectron spectrum of methane[19] in Fig. 1.10 shows two bands,[20] at ∼23 and 14 eV, and not the single band expected from the equivalency of the four C—H bonds. Indeed, Fig. 1.10 suggests that carbon uses the available orbitals to form four bonds and the electrons in the bonds are distributed between carbon and the four atoms involved in the bonds. Remember that the hybridization model predicts four identical σ bonds made by overlap of four identical hybrid orbitals. The band at 23 eV comes from two electrons in a low-energy

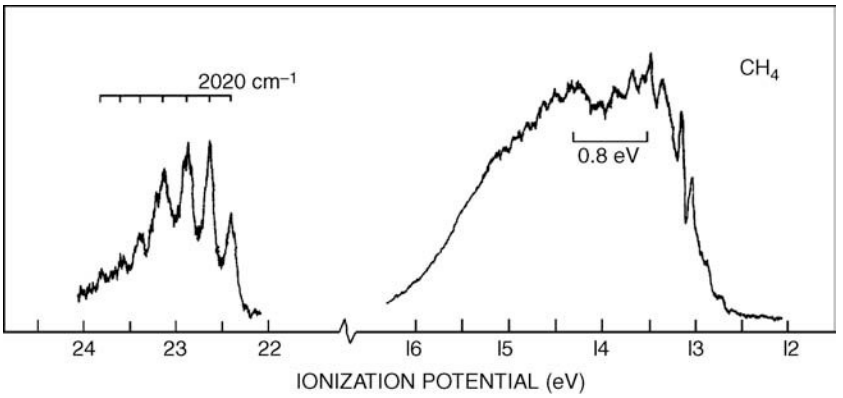


FIG. 1.10. Photoelectron spectroscopy scan of methane. [Reprinted with permission from Brundle, C.R.; Robin, M.B. *J. Chem. Phys.* ***1970*** *, 53*, 2196. Copyright © 1970, American Institute of Physics.]

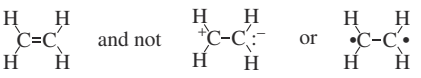
[19] Brundle, C.R.; Robin, M.B.; Basch, H. *J. Chem. Phys.* ***1970***, *53*, 2196; Baker, A.D.; Betteridge, D.; Kemp, N.R.; Kirby, R.E. *J. Mol. Struct.* ***1971***, *8*, 75; Potts, A.W.; Price, W.C. *Proc. R. Soc. London*, *Ser, A* ***1972***, *326*, 165.
[20] A third band, at 290 eV, caused by the 1*s* electrons of carbon, can also be found if radiation of sufficiently high energy is used.

level (called the a_1 level), which can be regarded as arising from a combination of the 2*s* orbital of carbon with an appropriate combination of hydrogen 1*s* orbitals. The band at 14 eV comes from six electrons in a triply degenerate level (the t_2 level), arising from a combination of the three 2*p* orbitals of carbon with other combinations of 1*s* hydrogen orbitals. As mentioned above, most physical and chemical processes cannot distinguish these levels, but PES can. The photoelectron spectra of many other organic molecules are known as well,[21] including monocyclic alkenes, in which bands < 10 eV are due to π-orbital ionization and those > 10 eV originate from ionization of σ orbitals only.[22] Note that ordinary sp^3 hybridization is not adequate to explain phenomena involving ionized molecules (e.g., the $CH_4^{\bullet+}$ radical ion, which is left behind when an electron is ejected from methane). For these phenomena, it is necessary to use other combinations of atomic orbitals (see Sec. 1.C).

1.F. ELECTRONIC STRUCTURES OF MOLECULES

For each molecule, ion, or free radical that has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure*, which shows the location of these electrons. Only the valence electrons are shown. Valence electrons may be found in covalent bonds connecting two atoms or they may be unshared.[23] Drawing these structures correctly is essential, since the position of electrons changes in the course of a reaction, and it is necessary to know where the electrons are initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons "contributed" to the molecule by each atom plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4, there are 2 (one for each hydrogen) + 6 (for the sulfur) + 24 (6 for each oxygen) = 32; while for SO_4^{2-}, the number is also 32, since each atom "contributes" 6 plus 2 for the negative charge.
2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons*, and usually have this number, although some cases are known where a first-row atom has only six or seven. Where there is a choice between a structure that has six or seven electrons around a first-row atom and one in which all such atoms have an octet, the structure based on the octet is generally lower in energy than the one that is observed. For example, ethylene is

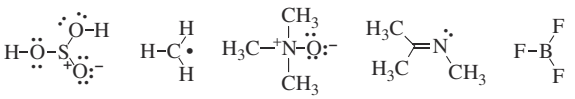


[21] See Robinson, J.W., *Practical Handbook of Spectroscopy*, CRC Press, Boca Raton, FL, ***1991***, p. 178.
[22] Novak, I.; Potts, A.W. *Tetrahedron* ***1997***, *53*, 14713.
[23] It has been argued that although the Lewis picture of two electrons making up a covalent bond may work well for organic compounds, it cannot be successfully applied to the majority of inorganic compounds: Jørgensen, C.K. *Top. Curr. Chem.* ***1984***, *124*, 1.

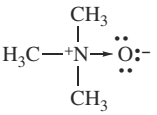
There are a few exceptions. For the molecule O_2, the structure $\dot{O}—\dot{O}$: has a lower energy than Ö=Ö:. Although first-row atoms are limited to 8 valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12 because empty *d* orbitals may be utilized.[24] For example, PCl_5 and SF_6 are stable compounds, and the hybridization model can be used to explain this fact. In SF_6, one *s* and one *p* electron from the ground state $3s^2 3p^4$ of the sulfur are promoted to empty *d* orbitals, and the six orbitals hybridize to give six sp^3d^2 orbitals, which point to the corners of a regular octahedron.

3. It is customary to show the formal charge on each atom. For this purpose, an atom is considered to "own" all unshared electrons, but only *one-half of the electrons in covalent bonds*. The sum of electrons that thus "belong" to an atom is compared with the number "contributed" by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. Note that the counting procedure is not the same for determining formal charge as for determining the number of valence electrons. For both purposes, an atom "owns" all unshared electrons, but for outer-shell purposes it "owns" both the electrons of the covalent bond, while for formal-charge purposes it "owns" only one-half of these electrons.

Examples of electronic structures are



A coordinate-covalent bond (sometimes called a dative bond), represented by an arrow, is one in which both electrons come from the same atom; that is, the bond can be regarded as being formed by the overlap of an orbital containing two electrons with an empty one. Thus trimethylamine *N*-oxide would be represented:



For a coordinate-covalent bond, the rule concerning formal charge is amended so that both electrons count for the donor and neither for the recipient. Thus the nitrogen and oxygen atoms of trimethylamine oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine *N*-oxide given just above, and there is a choice of drawing an arrowhead or a charge separation. Some compounds (e.g., amine *N*-oxides) must be drawn one way or the other. It is usually simpler to use charge separation.

1.G. ELECTRONEGATIVITY

The electron cloud that bonds two atoms is not symmetrical (with respect to the plane that is the perpendicular bisector of the bond) except when the two atoms are the same and have the same substituents. A symmetrical electron cloud typically occurs when there is a bond

[24] For a review concerning sulfur compounds with a valence shell larger than eight, see Salmond, W.G. *Q. Rev. Chem. Soc.* ***1968***, *22*, 235.

between two identical atoms, and an unsymmetrical electron cloud occurs when there are two different atoms. When there are two different atoms, and one is more electronegative than the other, the electron cloud is necessarily distorted toward one side of the bond or the other, depending on which atom (nucleus plus electrons) maintains the greater attraction for the cloud. This attraction is called *electronegativity;*[25] and it is greatest for atoms in the upper-right corner of the periodic table and lowest for atoms in the lower-left corner. Thus a bond between fluorine and carbon (C—F) shows distortion of the electron cloud associated with the bond, so that there is a higher probability of finding the electrons near the fluorine than near the carbon. Such a bond is said to be *polarized*, and the C—F bond is an example of a polarized covalent bond. The polarization gives the fluorine a partial negative charge (δ^-) and the carbon a partial positive charge (δ^+).

A number of attempts have been made to set up quantitative tables of electronegativity that will indicate the direction and extent of electron-cloud distortion for a bond between any pair of atoms. The most popular of these scales, devised by Pauling, is based on bond energies (see Sec. 1.L) of diatomic molecules. It is rationalized that if the electron distribution were symmetrical in a molecule A—B, the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), it is the result of the partial charges (the charges attract each other and make a stronger bond, which requires more energy to break). It is necessary to assign a value to one element arbitrarily (F = 4.0). Then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}}$$

where x_A and x_B are the electronegativities of the known and unknown atoms and 23.06 is an arbitrary constant. Part of the scale derived from this treatment is shown in Table 1.1.[26,27]

Other treatments[28] have led to scales that are based on different principles, for example, the average of the ionization potential and the electron affinity,[29] the average one-electron energy of valence-shell electrons in ground-state free atoms,[30] or the "compactness" of an atom's electron cloud.[24] In some of these treatments, electronegativities can be calculated for different valence states, for different hybridizations (e.g., *sp* carbon atoms are more electronegative than sp^2, which are still more electronegative than sp^3),[31] and even

[25] For a collection of articles on this topic, see Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***. For a review, see Batsanov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 332.

[26] Taken from Pauling, L. *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, ***1960***, p. 93, except for the value for Na, which is from Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[27] See Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[28] See Huheey, J.E. *Inorganic Chemistry*, 3rd ed., Harper and Row, NY, ***1983***, pp. 146–148; Mullay, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, p. 9.

[29] Hinze, J.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1962***, *84*, 540; Rienstra-Kiracofe, J.C.; Tschumper, G.S.; Schaefer, III, H.F.; Nandi, S.; Ellison, G.B. *Chem. Rev.* ***2002***, *102*, 231.

[30] Allen, L.C. *J. Am. Chem. Soc.* ***1989***, *111*, 9003.

[31] Walsh, A.D. *Discuss. Faraday Soc.* ***1947***, *2*, 18; Bergmann, D.; Hinze, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, pp. 146–190.

TABLE 1.1 Electronegativities of Some Atoms on the Pauling[26] and Sanderson[27] Scales

Element	Pauling	Sanderson	Element	Pauling	Sanderson
F	4.0	4.000	H	2.1	2.592
O	3.5	3.654	P	2.1	2.515
Cl	3.0	3.475	B	2.0	2.275
N	3.0	3.194	Si	1.8	2.138
Br	2.8	3.219	Mg	1.2	1.318
S	2.5	2.957	Na	0.9	0.835
I	2.5	2.778	Cs	0.7	0.220
C	2.5	2.746			

[Adapted material from *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, 3rd edition, edited by Linus Pauling. Copyright © 1960 by Cornell University. Used by permission of the publisher, Cornell University Press. Reprinted with permission Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259. Copyright © 1983 American Chemical Society.]

TABLE 1.2 Some Group Electronegativities Relative to H = 2.176[32]

CH_3	2.472	CCl_3	2.666
CH_3CH_2	2.482	C_6H_5	2.717
CH_2Cl	2.538	CF_3	2.985
CBr_3	2.561	$C{\equiv}N$	3.208
$CHCl_2$	2.602	NO_2	3.421

[Reprinted with permission from Inamoto, N.; Masuda, S. *Chem. Lett*. ***1982***, 1003. Copyright © 1982 The Chemical Society of Japan.]

differently for primary, secondary, and tertiary carbon atoms. Also, electronegativity values can be calculated for groups rather than atoms (Table 1.2).[32]

Electronegativity information can be obtained from NMR spectra. In the absence of a magnetically anisotropic group[33] the chemical shift of a ^1H or a ^{13}C nucleus is approximately proportional to the electron density around it, and hence to the electronegativity of the atom or group to which it is attached. The greater the electronegativity of the atom or group, the lower the electron density around the proton, and the further downfield the chemical shift [relative to tetramethylsilane (TMS) as zero ppm]. An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series toluene, ethylbenzene, isopropylbenzene, and *tert*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). The electron density surrounding the ring protons decreases[34] in the order given.[35] However, this type of correlation is by no means perfect, since all the measurements are made in a powerful field, which itself may affect the electron density distribution.

[32] Inamoto, N.; Masuda, S. *Chem. Lett*. ***1982***, 1003. See also, Bratsch, S.G. *J. Chem. Educ.* ***1988***, *65*, 223; Mullay, J. *J. Am. Chem. Soc.* ***1985***, *107*, 7271; Zefirov, N.S.; Kirpichenok, M.A.; Izmailov, F.F.; Trofimov, M.I. *Dokl. Chem.* ***1987***, *296*, 440; Boyd, R.J.; Edgecombe, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4182.

[33] A magnetically anisotropic group is one that is not equally magnetized along all three axes. The most common such groups are benzene rings (see Sec. 2.I) and triple bonds.

[34] This order is opposite to that expected from the field effect (Sec. 1.I). It is an example of the *Baker–Nathan order* (Sec. 2.M).

[35] Moodie, R.B.; Connor, T.M.; Stewart, R. *Can. J. Chem.* ***1960***, *38*, 626.

Coupling constants between the two protons of a system —CH—CH—X have also been found to depend on the electronegativity of X.[36]

When the difference in electronegativities is great, the electron density in an orbital may be effectively localized on only one nucleus. This is an *ionic bond*, which is seen to arise naturally out of the previous discussion. It is possible to view polarized covalent bonds as intermediates between ionic and covalent bonds. With this view, the extent of electron-cloud distortion is expressed as the percent ionic character of a bond. In this model, there is a continuous gradation from ionic to covalent bonds.

1.H. DIPOLE MOMENT

The *dipole moment* is a property of a molecule that results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule. Only the total moment of the molecule may be measured, and it is the vectorial sum of the individual bond moments.[37] These individual moments are roughly the same from molecule to molecule,[38] but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Fig. 1.11)[39] the moment of *p*-nitrotoluene is predicted to be ~4.36 D. The actual value 4.39 D is reasonable. However, the moment of

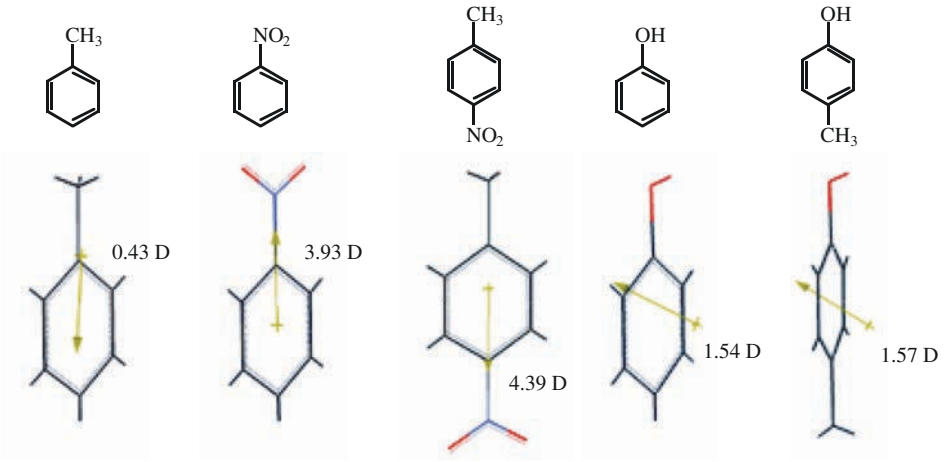


FIG. 1.11. Some dipole moments, in Debye units, measured in benzene. In the 3D model, the arrow indicates the direction of the dipole moment for the molecule, pointing to the negative part of the molecule.[39]

[36] Williamson, K.L. *J. Am. Chem. Soc.* ***1963***, *85*, 516; Laszlo, P.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 2709; Niwa, J. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2192.

[37] See Exner, O. *Dipole Moments in Organic Chemistry*, Georg Thieme Publishers, Stuttgart, ***1975***; McClellan, A. L. *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, ***1963***; Vol. 2, Rahara Enterprises, El Cerrito, CA, ***1974***.

[38] For example, see Koudelka, J.; Exner, O. *Collect. Czech. Chem. Commun.* ***1985***, *50*, 188, 200.

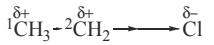
[39] The values for toluene, nitrobenzene, and *p*-nitrotoluene are from MacClellan, A.L., *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman: San Francisco, ***1963***; Vol. 2, Rahara Enterprises, El Cerrito, CA, ***1974***. The values for phenol and *p*-cresol were determined by Goode, E.V.; Ibbitson, D.A. *J. Chem. Soc.* ***1960***, 4265.

p-cresol (1.57 D) is quite far from the predicted value of 1.11 D. In some cases, molecules may have substantial individual bond moments, but no total moments at all because the individual moments are canceled out by the overall symmetry of the molecule. Some examples are CCl_4, *trans*-1,2-dibromoethene, and *p*-dinitrobenzene.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D[40] and that of propane is 0.085 D.[41] Of course, methane and ethane, because of their symmetry, have no dipole moments.[42] Few organic molecules have dipole moments > 7 D.

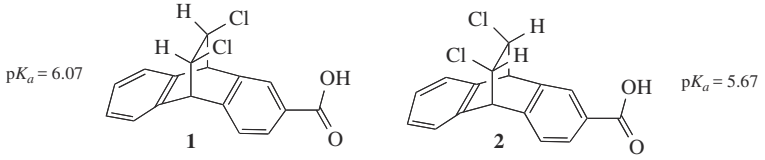
1.I. INDUCTIVE AND FIELD EFFECTS

The C—C bond in ethane has no polarity because it connects two equivalent atoms, with identical electronegativities. The presence of a more electronegative atom attached to one of the carbon atoms will lead to bond polarization, however, in what is known as an induced dipole. The C—C bond in chloroethane, for example, is polarized by the presence of the electronegative chlorine atom. This polarization is actually the sum



of two effects. In the first of these, the C-1 atom is deprived of some of its electron density by the greater electronegativity of Cl, and this effect is partially compensated by drawing the C—C electrons closer to itself. The result is a polarization of this bond and a slightly positive charge on the C-2 atom: an induced dipole. This polarization of one bond caused by the polarization of an adjacent bond is known as an *inductive effect*. The effect is greatest for adjacent bonds but may also be felt farther away; thus the polarization of the C—C bond causes a (slight) polarization of the three methyl C—H bonds. As a practical matter, the effect is negligible if the polarizing group is more than three bonds away.

The other effect operates not through bonds, but directly through space or solvent molecules, and is called a *field effect*.[43] It is often very difficult to separate the two kinds of effect, but a number of cases have been reported. This is generally accomplished by taking advantage of the fact that the field effect depends on the geometry of the molecule, but the inductive effect depends only on the nature of the bonds. For example, in isomers, **1** and **2**[44] the inductive effect of the chlorine atoms on the position of the electrons in the COOH group (and hence on the



[40] Lide Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *29*, 914.
[41] Muenter, J.S.; Laurie, V.W. *J. Chem. Phys.* ***1966***, *45*, 855.
[42] Actually, symmetrical tetrahedral molecules like methane do have extremely small dipole moments, caused by centrifugal distortion effects; these moments are so small that they can be ignored for all practical purposes. For CH4, μ is $\sim 5.4 \times 10^{-6}$ *D*: Ozier, I. *Phys. Rev. Lett.* ***1971***, *27*, 1329; Rosenberg, A.; Ozier, I.; Kudian, A.K. *J. Chem. Phys.* ***1972***, *57*, 568.
[43] Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* ***1953***, *75*, 2167.
[44] This example is from Grubbs, E.J.; Fitzgerald, R.; Phillips, R.E.; Petty, R. *Tetrahedron* ***1971***, *27*, 935.

acidity, see Chap. 8) should be the same since the same bonds intervene. The field effect is different, however, because the chlorine atoms are closer in space to the COOH in **1** than they are in **2**. Thus, a comparison of the acidity of **1** and **2** should reveal whether a field effect is truly operating. The evidence obtained from such experiments is overwhelming that field effects are much more important than inductive effects.[45] In most cases, the two types of effect are considered together; in this book, they will not be separated but will use the name *field effect* to refer to their combined action.[46] Note that the field effect for **1** may be viewed as internal hydrogen bonding (see Sec. 3.A).

Functional groups can be classified as electron withdrawing ($-I$) or electron donating ($+I$) groups relative to hydrogen. This means, for example, that NO_2, a $-I$ group, will draw electrons to itself more than a hydrogen atom would if it occupied the same position in the molecule.

$$O_2N \leftarrow\!\leftarrow CH_2 \leftarrow Ph$$

$$H—CH_2—Ph$$

Thus, in α-nitrotoluene, the electrons in the N—C bond are farther away from the carbon atom than the electrons in the H—C bond of toluene. Similarly, the electrons of the C—Ph bond are farther away from the ring in α-nitrotoluene than they are in toluene. Field effects are always comparison effects. For example, compare the $-I$ or $+I$ effect of one group with another (usually hydrogen). Therefore, it may be said that, compared with hydrogen, the NO_2 group is electron withdrawing and the O^- group is electron donating or electron releasing. However, there is no actual donation or withdrawal of electrons, but rather electron distortion or electron redistribution. While withdrawing and releasing terms are convenient to use, the terms merely represent a difference in the position of electrons due to the difference in electronegativity between H and NO_2 or between H and O^-.

Table 1.3 lists a number of the most common $-I$ and $+I$ groups.[47] It can be seen that compared with hydrogen, most groups are electron withdrawing. The only electron-donating groups are those with a formal negative charge (but not even all these), atoms of low electronegativity (Si,[48] Mg, etc., and perhaps alkyl groups). Alkyl groups[49] were formerly regarded as electron donating, but many examples of behavior have been found that can be interpreted only by the conclusion that alkyl groups are electron withdrawing compared with hydrogen.[50] In accord with this is the value of 2.472 for the group electronegativity of CH_3 (Table 1.2) compared with 2.176 for H. When an alkyl group is attached to an unsaturated or trivalent carbon (or other atom), its behavior is best explained by assuming it is $+I$ (see, e.g., Sec. 5.A.ii, 5.B.i, 8.E, 11.B.i), but when it is

[45] See Schneider, H.; Becker, N. *J. Phys. Org. Chem.* ***1989***, *2*, 214; Bowden, K.; Ghadir, K.D.F. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1333. Also see Exner, O.; Fiedler, P. *Collect. Czech. Chem. Commun.* ***1980***, *45*, 1251; Li, Y.; Schuster, G.B. *J. Org. Chem.* ***1987***, *52*, 3975.

[46] There has been some question as to whether it is even meaningful to maintain the distinction between the two types of effect: see Grob, C.A. *Helv. Chim. Acta* ***1985***, *68*, 882; Lenoir, D.; Frank, R.M. *Chem. Ber.* ***1985***, *118*, 753; Sacher, E. *Tetrahedron Lett.* ***1986***, *27*, 4683.

[47] See also, Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* ***1973***, 3627.

[48] For a review of field and other effects of silicon-containing groups, see Bassindale, A.R.; Taylor. P.G., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, ***1989***, pp. 893–963.

[49] See Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* ***1976***, *12*, 119.

[50] See Sebastian, J.F. *J. Chem. Educ.* ***1971***, *48*, 97.

TABLE 1.3 Field Effects of Various Groups Relative to Hydrogen[a]

+I		*−I*	
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	C≡CR
D	SO_2Ar	COOR	Ar
			$C{\equiv}CR_2$

[a]The groups are listed approximately in order of decreasing strength for both −I and +I groups. [Reprinted with permission from Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* ***1973***, 3627. Copyright © 1973, with permission from Elsevier Science.]

connected to a saturated atom, the results are not as clear, and alkyl groups seem to be $+I$ in some cases and $-I$ in others[51] (see also, Sec. 8.F). When connected to a positive carbon, alkyl groups are clearly electron releasing.

It is clear that the field-effect order of alkyl groups attached to unsaturated systems is tertiary > secondary > primary > CH_3, but this order is not always maintained when the groups are attached to saturated systems. Deuterium is electron donating with respect to hydrogen.[52] Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with sp^2 bonding, which in turn have more electron-withdrawing power than those with sp^3 bonding.[53] This accounts for the fact that aryl, vinylic, and alkynyl groups are $-I$. Field effects always decrease with increasing distance, and in most cases (except when a very powerful +I or $-I$ group is involved), cause very little difference in a bond four bonds away or more. There is evidence that field effects can be affected by the solvent.[54]

For discussions of field effects on acid and base strength and on reactivity, see Chapters 8 and 9, respectively.

1.J. BOND DISTANCES[55]

The distances between atoms in a molecule are characteristic properties of the molecule and can give information if compared with the same bond in different molecules. The chief methods of determining bond distances and angles are X-ray diffraction (only for solids),

[51] See Wahl, Jr., G.H.; Peterson, Jr., M.R. *J. Am. Chem. Soc.* ***1970***, *92*, 7238; Minot, C.; Eisenstein, O.; Hiberty, P. C.; Anh, N.T. *Bull. Soc. Chim. Fr.* ***1980***, II-119.

[52] Streitwieser, Jr., A.; Klein, H.S. *J. Am. Chem. Soc.* ***1963***, *85*, 2759.

[53] Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, p. 281.

[54] See Laurence, C.; Berthelot, M.; Lucon, M.; Helbert, M.; Morris, D.G.; Gal, J. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 705.

[55] For tables of bond distances and angles, see Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1–S19 (follows p. 1914); Tables of Interatomic Distances and Configurations in Molecules and Ions *Chem. Soc. Spec. Publ.* No. 11, ***1958***; Interatomic Distances Supplement *Chem. Soc. Spec. Publ.* No. 18, ***1965***; Harmony, M.D.; Laurie, V.W.; Kuczkowski, R.L.; Schwendeman, R.H.; Ramsay, D.A.; Lovas, F.J.; Lafferty, W.J.; Maki, A.G. *J. Phys. Chem. Ref. Data* ***1979***, *8*, 619–721. See Lathan, W.A.; Curtiss, L.A.; Hehre, W.J.; Lisle, J.B.; Pople, J.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 175; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 85.

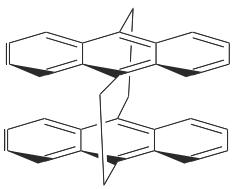
TABLE 1.4 Bond Lengths between sp^3 Carbons in Some Compounds

C—C Bond in	Reference	Bond Length (Å)
Diamond	58	1.544
C_2H_6	59	1.5324 ± 0.0011
C_2H_5Cl	60	1.5495 ± 0.0005
C_3H_8	61	1.532 ± 0.003
Cyclohexane	62	1.540 ± 0.015
tert-Butyl chloride	63	1.532
n-Butane to *n*-heptane	64	1.531–1.534
Isobutane	65	1.535 ± 0.001

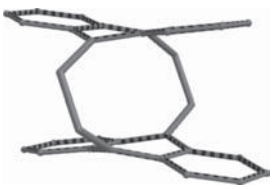
electron diffraction (only for gases), and spectroscopic methods, especially microwave spectroscopy. The distance between the atoms of a bond is not constant, since the molecule is always vibrating; the measurements obtained are therefore average values, so that different methods give different results.[56] However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next. While exceptions are known,[57] the variation is generally $< 1\%$. Table 1.4 shows distances for single bonds between two sp^3 carbons.[58–65] However, an analysis of C—OR bond distances in >2000 ethers and carboxylic esters (all with sp^3 carbon) shows that this distance increases with increasing electron withdrawal in the R group and as the C changes from primary to secondary to tertiary.[66] For these compounds, mean bond lengths of the various types ranged from 1.418 to 1.475 Å. Certain substituents can also influence bond length. The presence of a silyl substituent β^- to a C—O (ester) linkage can lengthen the C—O, thereby weakening it.[67] This finding is believed to result from σ–σ^* interactions in which the C—Si σ bonding orbital acts as the donor and the C—O σ^* orbitals acts as the receptor.

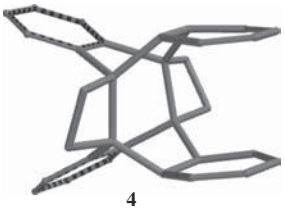
[56] Burkert, U.; Allinger, N.L. *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, ***1982***, pp. 6–9; Whiffen, D.H. *Chem. Ber.* ***1971***, *7*, 57–61; Stals, J. *Rev. Pure Appl. Chem.* ***1970***, *20*, 1, pp. 2–5.
[57] Schleyer, P.v.R.; Bremer, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1226.
[58] Lonsdale, K. *Philos. Trans. R. Soc. London* ***1947***, *A240*, 219.
[59] Bartell, L.S.; Higginbotham, H.K. *J. Chem. Phys.* ***1965***, *42*, 851.
[60] Wagner, R.S.; Dailey, B.P. *J. Chem. Phys.* ***1957***, *26*, 1588.
[61] Iijima, T. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1291.
[62] Tables of Interatomic Distances, Ref. 55.
[63] Momany, F.A.; Bonham, R.A.; Druelinger, M.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3075. Also see, Lide, Jr., D.R.; Jen, M. *J. Chem. Phys.* ***1963***, *38*, 1504.
[64] Bonham, R.A.; Bartell, L.S.; Kohl, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4765.
[65] Hilderbrandt, R.L.; Wieser, J.D. *J. Mol. Struct.* ***1973***, *15*, 27.
[66] Allen, F.H.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6197; Jones, P.G.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6207.
[67] White, J.M.; Robertson, G.B. *J. Org. Chem.* ***1992***, *57*, 4638.



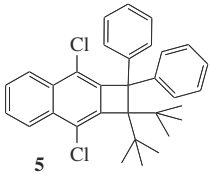
3A



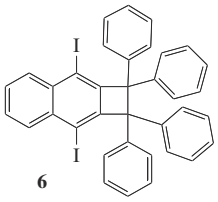
3B



4



5



6

Bond distances for some important bond types are given in Table 1.5.[68] Although a typical carbon–carbon single bond has a bond length of ~1.54 Å, certain molecules are known that have significantly longer bond lengths.[69] Calculations have been done for unstable molecules that showed them to have long bond lengths, and an analysis of the X-ray structure for a photoisomer (**4**) of [2.2]-tetrabenzoparacyclophane, **3A** (also see Sec. 2.G), showed a C—C bond length of 1.77 Å.[69,70] Note that **3A** is shown as the molecular model **3B** for comparison with photoisomer **4**, which has the two four-membered ring moieties. Long bond lengths have been observed in stable molecules (e.g., benzocyclobutane derivatives).[71] A bond length of 1.729 Å was reliably measured in 1,1-di-*tert*-butyl-2,2-diphenyl-3,8-dichlorocyclobutan[*b*] naphthalene, **5**.[72] X-ray analysis of several of these derivations confirmed the presence of long C—C bonds, with **6** having a confirmed bond length of 1.734 Å.[73]

A theoretical study has been reported, using computer simulation to apply encapsulation, strapping back, and stiffening to "squeeze" C—C bonds, leading to shorter bonds than would be observed if hybridization and conjugative effects operated alone.[74] The additional strain caused by threefold symmetric geometry constraints is believed responsible for this effect rather than changes in hybridization alone, as postulated by others.[75–82]

[68] Except where noted, values are from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1–S19 (follows p. 1914). In this source, values are given to three significant figures.

[69] Kaupp, G.; Boy, J *Angew. Chem. Int. Ed.* ***1997***, *36*, 48.

[70] Ehrenberg, M. *Acta Crystallogr.* ***1966***, *20*, 182.

[71] Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *Acta Crystallogr., Sect. C* ***1996***, *52*, 177.

[72] Toda, F.; Tanaka, K.; Watanabe, M.; Taura, K.; Miyahara, I.; Nakai, T.; Hirotsu, K. *J. Org. Chem.* ***1999***, *64*, 3102.

[73] Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* ***2001***, *57*, 3761.

[74] Huntley, D.R.; Markopoulos, G.; Donovan, P.M.; Scott, L.T.; Hoffmann, R. *Angew. Chem. Int. Ed.* ***2005***, *44*, 7549.

[75] See Tanaka, M; Sekiguchi, A. *Angew. Chem. Int. Ed.* ***2005***, *44*, 5821–5823.

[76] Costain, C.C.; Stoicheff, B.P. *J. Chem. Phys.* ***1959***, *30*, 777.

[77] For a full discussion of alkyne bond distances, see Simonetta, M.; Gavezzotti, A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***.

[78] See Henry, B.R. *Acc. Chem. Res.* ***1987***, *20*, 429.

[79] Bartell, L.S.; Roth, E.A.; Hollowell, C.D.; Kuchitsu, K.; Young, Jr., J.E. *J. Chem. Phys.* ***1965***, *42*, 2683.

[80] For reviews of carbon–halogen bonds, see Trotter, J. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley, NY, ***1973***, pp. 49–62; Mikhailov, B.M. *Russ. Chem. Rev.* ***1971***, *40*, 983.

[81] Lide, Jr., D.R. *Tetrahedron* ***1962***, *17*, 125.

[82] Rajput, A.S.; Chandra, S. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1854.

TABLE 1.5 Bond Distances[a]

Bond Type	Length (Å)	Typical Compounds
C—C		
sp^3–sp^3	1.53	
sp^3–sp^2	1.51	Acetaldehyde, toluene, propene
sp^3–sp	1.47	Acetonitrile, propyne
sp^2–sp^2	1.48	Butadiene, glyoxal, biphenyl
sp^2–sp	1.43	Acrylonitrile, vinylacetylene
sp–sp	1.38	Cyanoacetylene, butadiyne
C=C		
sp^2–sp^2	1.32	Ethylene
sp^2–sp	1.31	Ketene, allenes
sp–sp[76]	1.28	Butatriene, carbon suboxide
C≡C[77]		
sp–sp	1.18	Acetylene
C—H[78]		
sp^3–**H**	1.09	Methane
sp^2–**H**	1.08	Benzene, ethylene
sp–**H**[79]	1.08	**HCN**, acetylene
C—O		
sp^3–**O**	1.43	Dimethyl ether, ethanol
sp^2–**O**	1.34	Formic acid
C=O		
sp^2–**O**	1.21	Formaldehyde, formic acid
sp–**O**[62]	1.16	**CO_2**
C—N		
sp^3–**N**	1.47	Methylamine
sp^2–**N**	1.38	Formamide
C=N		
sp^2–**N**	1.28	Oximes, imines
C≡N		
sp–**N**	1.14	**HCN**
C—S		
sp^3–**S**	1.82	Methanethiol
sp^2–**S**	1.75	Diphenyl sulfide
sp–**S**	1.68	CH_3SCN
C=S		
sp–**S**	1.67	**CS_2**

C–halogen[80]	F	Cl	Br	I
sp^3–halogen	1.40	1.79	1.97	2.16
sp^2–halogen	1.34	1.73	1.88	2.10
sp–halogen	1.27[81]	1.63	1.79[82]	1.99[82]

[a]The values given are average lengths and do not necessarily apply exactly to the compounds mentioned.[80] [Reproduced from Allen F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1–S19 with permission from the Royal Society of Chemistry.]

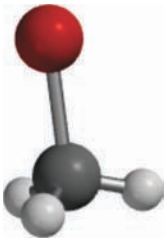
There are indications that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C_2H_6 and C_2D_6 showed a C—H bond distance of 1.1122 ± 0.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.[59]

As seen in Table 1.5, carbon bonds are shortened by increasing *s* character. This is most often explained by the fact that, as the percentage of *s* character in a hybrid orbital

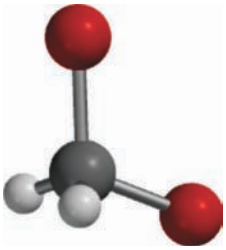
increases, the orbital becomes more like an *s* orbital and hence is held more tightly by the nucleus than an orbital with less *s* character. However, other explanations have also been offered (see Sec. 2.C), and the matter is not completely settled. In general, molecules with one π bond (X=X) have shorter bond distances when compared to single bonds, X—X, and molecules with two π bonds (X≡X) have even shorter bond lengths. Indeed, the bond length clearly decreases in the molecules $H_3C—CH_3$, $H_2C=CH_2$, and HC≡CH: C—C bond lengths of 1.538, 1.338, and 1.203 Å.[83] There is work that suggests the absence of σ bonds may play a role in producing short bond distances in molecules that contain only π bonds.[84] This suggests that σ bonds prevent π bonds from adopting their optimal shorter distances. Such bonds occur in some organometallic compounds.



7



8



9

1.K. BOND ANGLES

The bond angles of sp^3 carbon should be the tetrahedral angle 109°28′ when the four atoms or groups are relatively small and identical, as in methane, neopentane, or carbon tetrachloride. As atoms or groups become larger, bond angles are distorted to accommodate the larger size of the attached units. In most cases, the angles deviate a little from the pure tetrahedral value unless two or more units are very large. Molecular models **7–9** illustrate this phenomenon. The H—C—H bond angles in methane (**7**) are calculated for the model to be 109°47′, whereas the Br—C—H bond angle in **8** is calculated to be 108.08° and the Br—C—Br bond angle in **9** is calculated to be 113.38°. Note that the C—Br bond length is longer than the C—H bond lengths. As the bond angles expand to accommodate the larger atoms, the H—C—H bond angles in **8** and **9** must compress to a smaller angle. In 2-bromopropane, the bromine atom also has a methyl group (compare with bromomethane **8** where Br competes with H) and, the C—C—Br angle in 2-bromopropane is 114.2°.[85]

Variations are generally found from the ideal values of 120° and 180° for sp^2 and *sp* carbon, respectively. These deviations occur because of slightly different hybridizations; that is, a carbon bonded to four other atoms hybridizes one *s* and three *p* orbitals, but the four hybrid orbitals thus formed are generally not exactly equivalent, nor does each contain exactly 25% *s* and 75% *p* character. Because the four atoms have (in the most general case) different electronegativities, each makes its own demand for electrons from the carbon atom.[86] The carbon atom supplies more *p* character when it is bonded to more

[83] Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B* ***1978***, *B34*, 1947; Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B*, ***1979***, *B35*, 2593; Mcmullan, R.K.; Kvick, A. *Acta Crystallogr. Sect. B*, ***1992***, *B48*, 726.
[84] Jemmis, E.D.; Pathak, B.; King, R.B.; Schaefer, III, H.F. *Chem. Commun.* ***2006***, 2164.
[85] Schwendeman, R.H.; Tobiason, F.L. *J. Chem. Phys.* ***1965***, *43*, 201.
[86] For a review of this concept, see Bingel, W.A.; Lüttke, W. *Angew. Chem. Int. Ed.* ***1981***, *20*, 899.

TABLE 1.6 Oxygen, Sulfur, and Nitrogen Bond Angles in Some Compounds

Angle	Value	Compound	Reference
H—O—H	104°27′	Water	7
C—O—H	107–109°	Methanol	62
C—O—C	111°43′	Dimethyl ether	88
C—O—C	124° ± 5°	Diphenyl ether	89
H—S—H	92.1°	Hydrogen sulfide	82
C—S—H	99.4°	Methanethiol	82
C—S—C	99.1°	Dimethyl sulfide	90
H—N—H	106°46′	Ammonia	7
H—N—H	106°	Methylamine	91
C—N—H	112°	Methylamine	83
C—N—C	108.7°	Trimethylamine	92

electronegative atoms, so that in chloromethane, for example, the bond to chlorine has somewhat > 75% *p* character, which of course requires that the other three bonds have somewhat less, since there are only three *p* orbitals (and one *s*) to be divided among the four hybrid orbitals.[87] Of course, in strained molecules (e.g., **3–6**), the bond angles may be greatly distorted from the ideal values (also see Sec. 4.Q).

For molecules that contain oxygen and nitrogen, angles of 90° are predicted from p^2 bonding. However, as seen in Section 1.B, the angles of water and ammonia are much larger than this, as are the angles of other organic molecules that contain oxygen and nitrogen (Table 1.6).[88–92] In fact, they are much closer to the tetrahedral angle of 109°28′ than to 90°. These facts have led to the suggestion that in these compounds oxygen and nitrogen use sp^3 bonding. Using the hybridization model, these atoms are said to form bonds by the overlap of two (or three) *p* orbitals with 1*s* orbitals of the hydrogen atoms, which means that they hybridize their 2*s* and 2*p* orbitals to form four sp^3 orbitals and then use only two (or three) of these for bonding with hydrogen, the others remaining occupied by unshared pairs (also called *lone pairs*). If this description is valid, and it is generally accepted by most chemists today,[93] it becomes necessary to explain why the angles of these two compounds are in fact not 109°28′ but a few degrees smaller. One explanation that has been offered is that the unshared electron pair actually has a greater steric requirement (see Sec. 4.Q) than the electrons in a bond, since there is no second nucleus to draw away some of the electron density and the bonds are thus crowded together. However, most evidence is that unshared pairs have smaller steric requirements than bonds[94] and the explanation most commonly

[87] This assumption has been challenged: see Pomerantz, M.; Liebman, J.F. *Tetrahedron Lett*. ***1975***, 2385.
[88] Blukis, V.; Kasai, P.H.; Myers, R.J. *J. Chem. Phys.* ***1963***, *38*, 2753.
[89] Abrahams, S.C. *Q. Rev. Chem. Soc.* ***1956***, *10*, 407.
[90] Iijima, T.; Tsuchiya, S.; Kimura, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2564.
[91] Lide, Jr., D.R. *J. Chem. Phys.* ***1957***, *27*, 343.
[92] Lide, Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *28*, 572.
[93] The O—H bonding is between 2 H 1*s* and 2 O *p* orbitals, and that the increased angles come from repulsion of the hydrogen or carbon atoms. See Laing, M., *J. Chem. Educ.* ***1987***, *64*, 124.
[94] See Blackburne, I.D.; Katritzky, A.R.; Takeuchi, Y. *Acc. Chem. Res.* ***1975***, *8*, 300; Aaron, H.S.; Ferguson, C.P. *J. Am. Chem. Soc.* ***1976***, *98*, 7013; Anet, F.A.L.; Yavari, I. *J. Am. Chem. Soc.* ***1977***, *99*, 2794; Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.* ***1979***, *44*, 1081; Gust, D.; Fagan, M.W. *J. Org. Chem.* ***1980***, *45*, 2511. For other views, see Lambert, J.B.; Featherman, S.I. *Chem. Rev.* ***1975***, *75*, 611; Breuker, K.; Kos, N.J.; van der Plas, H.C.; van Veldhuizen, B. *J. Org. Chem.* ***1982***, *47*, 963.

accepted is that the hybridization is not pure sp^3. As seen above, an atom supplies more p character when it is bonded to more electronegative atoms. An unshared pair may be considered to be an "atom" of the lowest possible electronegativity, since there is no attracting power at all. Consequently, the unshared pairs have more s and the bonds more p character than pure sp^3 orbitals, making the bonds somewhat more like p^2 bonds and reducing the angle. However, these arguments ignore the steric effect of the atoms or groups attached to oxygen or nitrogen. As seen in Table 1.6, oxygen, nitrogen, and sulfur angles generally increase with decreasing electronegativity of the substituents. Note that the explanation given above cannot explain why some of these angles are *greater* than the tetrahedral angle.

1.L. BOND ENERGIES[95]

There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation energy* (D). For example, D for $H_2O \rightarrow HO + H$ is 118 kcal mol^{-1} (494 kJ mol^{-1}). However, this is not taken as the energy of the O—H bond in water, since D for H—O → H + O is 100 kcal mol^{-1} (418 kJ mol^{-1}). The average of these two values, 109 kcal mol^{-1} (456 kJ mol^{-1}), is taken as the *bond energy* (E). In diatomic molecules, of course, $D = E$.

The D values may be easy or difficult to measure. They can be estimated by various techniques.[96] When properly applied, "Pauling's original electronegativity equation accurately describes homolytic bond dissociation enthalpies of common covalent bonds, including highly polar ones, with an average deviation of (1.5 kcal mol^{-1} (~6.3 kJ mol^{-1}) from literature values)".[97] Whether measured or calculated, there is no question as to what D values mean. With E values the matter is not so simple. For methane, the total energy of conversion from CH_4 to C + 4H (at 0 K) is 393 kcal mol^{-1} (1644 kJ mol^{-1}).[98] Consequently, E for the C—H bond in methane is 98 kcal mol^{-1} (411 kJ mol^{-1}) at 0 K. The more usual practice is not to measure the heat of atomization (i.e., the energy necessary to convert a compound to its atoms) directly, but to calculate it from the heat of combustion. Such a calculation is shown in Fig. 1.12.

Heats of combustion are very accurately known for hydrocarbons.[99] For methane, the value at 25 °C is 212.8 kcal mol^{-1} (890.4 kJ mol^{-1}), which leads to a heat of atomization of 398.0 kcal mol^{-1} (1665 kJ mol^{-1}) or a value of E for the C—H bond at 25 °C of 99.5 kcal mol^{-1} (416 kJ mol^{-1}). This method is fine for molecules like methane in which all the

[95] Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* ***2003***, *36*, 255. For reviews including methods of determination, see Wayner, D.D.M.; Griller, D. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 159; Kerr, J.A. *Chem. Rev.* ***1966***, *66*, 465; Wiberg, K.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 207–245.

[96] Cohen, N.; Benson, S.W. *Chem. Rev.* ***1993***, *93*, 2419; Korth, H.-G.; Sicking, W. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 715.

[97] Matsunaga, N.; Rogers, D.W.; Zavitsas, A.A. *J. Org. Chem*, ***2003***, *68*, 3158.

[98] For the four steps, D values are 101–102, 88, 124, and 80 kcal mol^{-1} (423–427, 368, 519, and 335 kJ mol^{-1}), respectively, though the middle values are much less reliable than the other two: Knox, B.E.; Palmer, H.B. *Chem. Rev.* ***1961***, *61*, 247; Brewer, R.G.; Kester, F.L. *J. Chem. Phys.* ***1964***, *40*, 812; Linevsky, M.J. *J. Chem. Phys.* ***1967***, *47*, 3485.

[99] See Cox, J.D.; Pilcher, G., *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***; Domalski, E.S. *J. Phys. Chem. Ref. Data* ***1972***, *1*, 221–277; Stull, D.R.; Westrum Jr., E.F.; Sinke, G.C. *The Chemical Thermodynamics of Organic Compounds*, Wiley, NY, ***1969***.

				kcal	kJ
$C_2H_{6\,(gas)}$	$+ 3.5\ O_2$	$= 2\ CO_{2\,(gas)}$	$+ 3\ H_2O_{(liq)}$	+372.9	+1560
	$2\ CO_{2\,(gas)}$	$= 2\ C_{(graphite)}$	$+ 2\ O_{2\,(gas)}$	−188.2	−787
	$3\ H_2O_{(liq)}$	$= 3\ H_{2\,(gas)}$	$+ 1.5\ O_{2\,(gas)}$	−204.9	−857
	$3\ H_{2\,(gas)}$	$= 6\ H_{(gas)}$		−312/5	−1308
	$2\ C_{(graphite)}$	$= 2\ C_{(gas)}$		−343.4	−1437
	$C_2H_{6\,(gas)}$	$= 6\ H_{(gas)}$	$+ 2\ C_{(gas)}$	−676.1 kcal	−2829 kJ

FIG. 1.12. Calculation of the heat of atomization of ethane at 25 °C.

bonds are equivalent, but for more complicated molecules, assumptions must be made. Thus for ethane, the heat of atomization at 25 °C is 676.1 kcal mol^{-1} or 2829 kJ mol^{-1} (Fig. 1.12), and it must be decided how much of this energy is due to the C—C bond and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If the assumption is made that E for each of the C—H bonds is the same as E for the C—H bond in methane (99.5 kcal mol^{-1} or 416 kJ mol^{-1}), then 6×99.5 (or $416) = 597.0$ (or 2498), leaving 79.1 kcal mol^{-1} (331 kJ mol^{-1}) for the C—C bond. However, a similar calculation for propane gives a value of 80.3 (or 336) for the C—C bond, and for isobutane, the value is 81.6 (or 341). A consideration of heats of atomization of isomers also illustrates the difficulty. The E values for the C—C bonds in pentane, isopentane, and neopentane, similarly calculated from heats of atomization, are (at 25 °C) 81.1, 81.8, and 82.4 kcal mol^{-1} (339, 342, 345 kJ mol^{-1}), respectively, even though all of them have twelve C—H bonds and four C—C bonds.

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane has a tertiary carbon whose C—H bond does not have exactly the same amount of *s* character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that D values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 5.2). There is also the steric factor (see Sec. 4.Q). Hence it is certainly incorrect to use the value of 99.5 kcal mol^{-1} (416 kJ mol^{-1}) from methane as the E value for all C—H bonds. Several empirical equations have been devised that account for these factors; the total energy can be computed[100] if the proper set of parameters (one for each structural feature) is inserted. Of course, these parameters are originally calculated from the known total energies of some molecules that contain the structural feature.

Table 1.7 gives E values for various bonds.[101–104] The values given are averaged over a large series of compounds. The literature contains charts that take hybridization into account (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).[105] Bond dissociation

[100] For a review, see Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597. See also, Gasteiger, J.; Jacob, P.; Strauss, U. *Tetrahedron* ***1979***, *35*, 139.

[101] These values, except where noted, are from Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* ***1960***, *38*, 2367; Levi, G.I.; Balandin, A.A. *Bull. Acad. Sci. USSR*, *Div. Chem. Sci.* ***1960***, 149.

[102] Grelbig, T.; Pötter, B.; Seppelt, K. *Chem. Ber.* ***1987***, *120*, 815.

[103] Bedford, A.F.; Edmondson, P.B.; Mortimer, C.T. *J. Chem. Soc.* ***1962***, 2927.

[104] The average of the values obtained was DH^o(O—O). dos Santos, R.M.B.; Muralha, V.S.F.; Correia, C.F.; Simões, J.A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 12670.

[105] Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597; Cox, J.D. *Tetrahedron* ***1962***, *18*, 1337.

TABLE 1.7 Bond Energy (E) Values at 25 °C for Some Important Bond Types[a,b]

Bond	kcal mol^{-1}	kJ mol^{-1}	Bond	kcal mol^{-1}	kJ mol^{-1}
O—H	110–111	460–464	C—S [102]	61	255
C—H	96–99	400–415	C—I	52	220
N—H	93	390			
S—H	82	340	C≡C	199–200	835
			C=C	146–151	610–630
C—F			C—C	83–85	345–355
C—H	96–99	400–415			
C—O	85–91	355–380	C≡N	204	854
C—C	83–85	345–355	C=O	173–81	724–757
C—Cl	79	330			
C—N [103]	69–75	290–315	C=N[103]	143	598
C—Br	66	275	O—O [104]	42.9	179.6 ± 4.5

[a]The E values are arranged within each group in order of decreasing strength. The values are averaged over a large series of compounds.

[b]See Ref. 101.

[Reprinted with permission from Lovering E.G.; Laidler, K.J. *Can. J. Chem.* ***1960***, *38*, 2259. Copyright © 1960 with permission from Canadian Science Publishing or its Licensors.]

energies, both calculated and experientially determined, are constantly being refined. Improved values are available for the O—O bond of peroxides,[106] the C—H bond in alkyl amines,[107] the N—H bond in aniline derivatives,[108] the N—H bond in protonated amines,[109] the O—H bond in phenols,[110] the C—H bond in alkenes,[111] amides and ketones,[112] and in CH_2X_2 and CH_3X derivatives (X = COOR, C=O, SR, NO_2, etc.),[113] the O—H and S—H bonds of alcohols and thiols,[114] and the C—Si bond of aromatic silanes.[115] Solvent plays a role in the E values. When phenols bearing electron-releasing groups are in aqueous media, calculations show that the bond dissociation energies decrease due to hydrogen-bonding interactions with water molecules, while electron-withdrawing substituents on the phenol increase the bond dissociation energies.[116]

Certain generalizations can be derived from the data in Table 1.7.

1. There is a correlation of bond strengths with bond distances. A comparison of Tables 1.5 and 1.7 shows that, in general, *shorter bonds are stronger bonds*. Since it is

[106] Bach, R.D.; Ayala, P.Y.; Schlegel, H.B. *J. Am. Chem. Soc.* ***1996***, *118*, 12758.
[107] Wayner, D.D.M.; Clark, K.B.; Rauk, A.; Yu, D.; Armstrong, D.A. *J. Am. Chem. Soc.* ***1997***, *119*, 8925. For the α C—H bond of tertiary amines, see Dombrowski, G.W.; Dinnocenzo, J.P.; Farid, S.; Goodman, J.L. Gould, I.R. *J. Org. Chem.* ***1999***, *64*, 427.
[108] Bordwell, F.G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* ***1993***, *58*, 6410. See also, Li, Z.; Cheng, J.-P. *J. Org. Chem.* ***2003***, *68*, 7350.
[109] Liu, W.-Z.; Bordwell, F.G. *J. Org. Chem.* ***1996***, *61*, 4778.
[110] Lucarini, M.; Pedrielli, P.; Pedulli, G.F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* ***1996***, *61*, 9259. For the O—H, E of polymethylphenols, see de Heer, M.I.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* ***1999***, *64*, 6969.
[111] Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.
[112] Bordwell, F.G.; Zhang, X.-M.; Filler, R. *J. Org. Chem.* ***1993***, *58*, 6067.
[113] Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.
[114] Hadad, C.M.; Rablen, P.R.; Wiberg, K.B. *J. Org. Chem.* ***1998***, *63*, 8668.
[115] Cheng, Y.-H.; Zhao, X.; Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* ***2002***, *67*, 6638.
[116] Guerra, M.; Amorati, R.; Pedulli, G.F. *J. Org. Chem.* ***2004***, *69*, 5460.

known that increasing *s* character shortens bonds (Sec. 1.J), it follows that bond strengths increase with increasing *s* character. Calculations show that ring strain has a significant effect on bond dissociation energy, particularly the C—H bond of hydrocarbons, because it forces the compound to adopt an undesirable hybridization.[117]

2. Bonds become weaker moving down the periodic table. Compare C—O and C—S, or the carbon–halogen bonds C—F, C—Cl, C—Br, C—I. This is a consequence of the first generalization, since bond distances must increase going down the periodic table because the number of inner electrons increases. However, note that "high-level *ab initio* molecular orbital calculations confirm that the effect of alkyl substituents on R—X bond dissociation energies varies according to the nature of X (the stabilizing influence of the ionic configurations to increase in the order Me < Et < *i*-Pr < *t*-Bu), accounting for the *increase* (rather than expected decrease) in the R—X bond dissociation energies with increasing alkylation in the R—OCH_3, R—OH, and R—F molecules. This effect of X has been explained in terms of the increasing contribution of the ionic R^+X^- configuration for electronegative X substituents."[118]
3. Double bonds are both shorter and stronger than the corresponding single bonds, but not twice as strong, because π overlap is $< \sigma$ overlap. This means that a σ bond is stronger than a π bond. The difference in energy between a single bond, say C—C, and the corresponding double bond is the amount of energy necessary to cause rotation around the double bond.[119]

Calculations suggest that covalent bond strength and also equilibrium bond length are not determined by maximum overlap of the σ valence orbitals, as described in previous sections.[120] Rather, orbital interactions, Pauli repulsion, and quasiclassical electrostatic attraction determine both.

Solvents are thought to play a role in bond dissociation energy of molecules, as noted for phenol above, and also for intermediates (see Chap 5). It has been assumed that the solvation enthalpies were small and they have been largely ignored in calculations involving various reactions. Solvent effects on the bond dissociation energy of a molecule may arise from the difference in solvation enthalpies between the molecule and the key intermediate. For radical reactions that involve polar molecules, the radical–solvent interaction may be larger.[121]

[117] Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.X. *J. Org. Chem.* ***2004***, *69*, 3129; Song, K.-S.; Liu, L.; Guo, Q.X. *Tetrahedron* ***2004***, *60*, 9909.
[118] Coote, M.L.; Pross, A.; Radom, L. *Org. Lett.* ***2003***, *5*, 4689.
[119] See Miller, S.I. *J. Chem. Educ.* ***1978***, *55*, 778.
[120] Krapp, A.; Bickelhaupt, F.M.; Frenking, G. *Chem.: Eur. J.* ***2006***, *12*, 9196.
[121] Borges dos Santos, R.M.; Costa Cabral, B.J.; Martinho Simões, J.A. *Pure Appl. Chem.* ***2007***, *79*, 1369.

CHAPTER 2

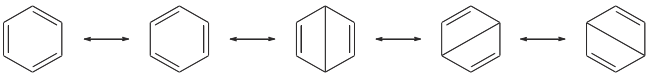
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (Sec. 1.F), this is insufficient for many other compounds. Such compounds contain one or more bonding orbitals that are not restricted to two atoms, but rather they are spread out over three or more atoms. Such bonding is said to be *delocalized*.[1] In other words, the bonding electrons are dispersed over several atoms rather than localized on one atom. This Chapter 2 will discuss those compounds that must be represented in this way.

The two chief general methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.[2] In the valence bond method, several possible Lewis structures (called *canonical forms*) are drawn, and the molecule is taken to be a weighted average of them. Each Ψ in Eq. (1–3), represents one of these structures. Therefore,

$$\Psi = c_1\psi_1 + c_1\psi_1 + \cdots$$

is the representation of a real structure as a weighted average of two or more canonical forms, which is called *resonance*. For benzene the canonical forms are drawn as **1** and **2**. Double-headed arrows (↔) are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by equal participation of **1** and **2** is lower than that for **1** or **2** alone. If **3**–**5** (called *Dewar structures*) are also considered, the value is lower still. According to this method, **1** and **2** contribute 39% each to the actual molecule and the others 7.3% each.[3] The carbon–carbon bond order is 1.463 (not 1.5, which would be the case if only **1** and **2** contributed).



1 **2** **3** **4** **5**

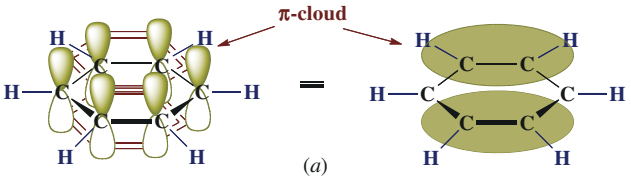
In the valence bond method, the *bond order* of a particular bond is the sum of the weights of those canonical forms in which the bond is double plus 1 for the single bond that

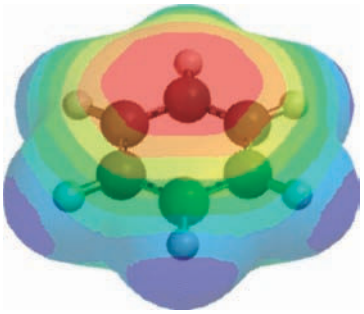
[1] See Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***.

[2] There are other methods. See Streitwieser, Jr., A. *Molecular Orbital Theory for Organic Chemists*, Wiley, NY, ***1961***, pp. 27–29; Hirst, D.M.; Linnett, J.W. *J. Chem. Soc.* ***1962***, 1035; Firestone, R.A. *J. Org. Chem.* ***1969****, 34*, 2621.

[3] Pullman, A. *Prog. Org. Chem.* ***1958****, 4*, 31, p. 33.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.





(b)

FIG. 2.1. (*a*) Traditional drawing of the overlapping *p* orbitals that comprise the π-cloud in benzene. (*b*) The electrostatic potential map of benzene, indicating the high concentration of electron density above and below the plane of the atoms, but in the center of the six-membered ring, consistent with the aromatic cloud.

is present in all of them.[4] Thus, according to this picture, each C—C bond is not halfway between a single and a double bond but is somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy is called the *resonance energy*. Of course, the Lewis structures are not real, and their energies can only be estimated. Resonance in benzene is possible by overlap of the *p* orbitals, orthogonal to the plane of carbon and hydrogen atoms. This resonance is associated with the aromatic π-cloud. Figure 2.1 shows the planar σ-bond framework of benzene, with the overlapping *p*-orbitals forming the aromatic π-cloud. Figure 2.1 also shows the electron potential map of benzene. Note the darker area above the middle of the ring that corresponds to high electron density, consistent with the high electron density of the aromatic π-cloud.

2.A. MOLECULAR ORBITALS

While the resonance picture is often used to describe the structure of molecules, as structures become more complicated (e.g., naphthalene and pyridine), quantitative valence bond calculations become much more difficult. Therefore, the MO method is used much more often for the solution of wave equations.[5] Examination of benzene by this method (qualitatively) shows that each carbon atom, being connected to three other atoms, uses sp^2

[4] See Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963****, 19*, 2153. See also, Herndon, W.C.; Párkányi, C. *J. Chem. Educ.* ***1976****, 53*, 689.
[5] See Dewar, M.J.S. *Mol. Struct. Energ.* ***1988****, 5*, 1.

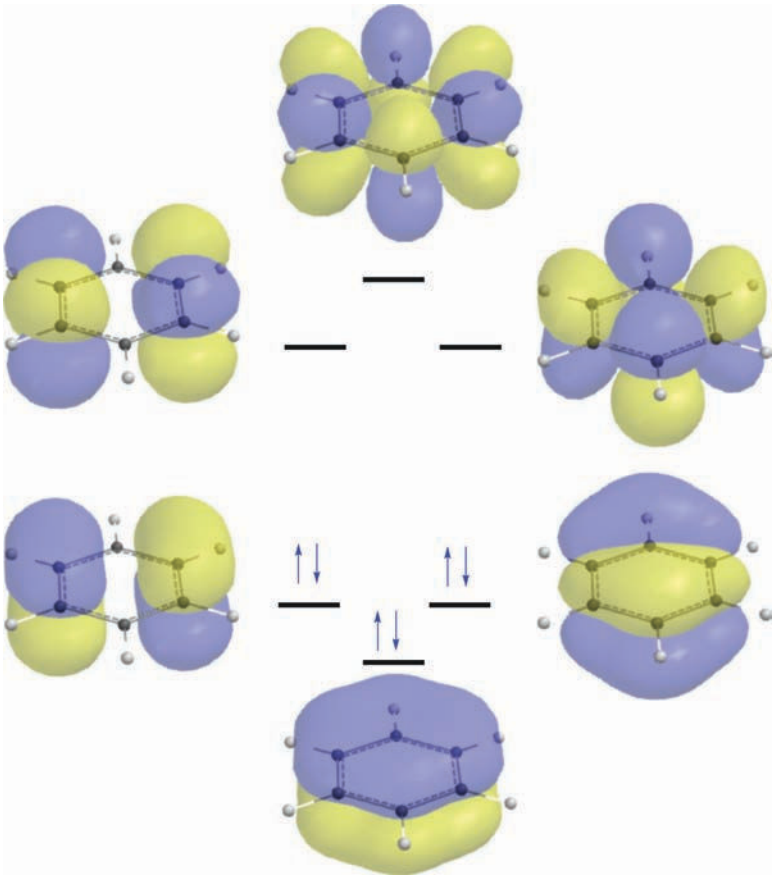


FIG. 2.2. The molecular orbitals of benzene, showing the three bonding orbitals, as generated by Spartan.10, v.1.0.1.

orbitals to form σ bonds, so that all 12 atoms are in one plane. This method shows that each carbon has a remaining *p* orbital that contains one electron, and each orbital can overlap equally with the two adjacent *p* orbitals. This overlap of six orbitals (see Fig. 2.2) produces six new orbitals, and the three lower energy orbitals are bonding. These three (called π orbitals) all occupy approximately the same space.[6] One of the three is of lower energy than the other two, which are degenerate. They each have the plane of the ring as a node and so are in two parts, one above and one below the plane. The two orbitals of higher energy also have another node. The six electrons that occupy this torus-shaped cloud are called the *aromatic sextet*. A torus-shaped object is essentially a doughnut-shaped object. According to this explanation, the symmetrical hexagonal structure of benzene is caused by both the σ bonds and the (orbitals. Based on MO calculations, this symmetry is probably caused by the σ framework alone, and that the (π system would favor three localized double

[6] Shaik, S.S.; Hiberty, P.C.; Lefour, J.; Ohanessian, G. *J. Am. Chem. Soc.* ***1987****, 109*, 363; Stanger, A.; Vollhardt, K.P.C. *J. Org. Chem.* ***1988****, 53*, 4889. See also, Jug, K.; Köster, A.M. *J. Am. Chem. Soc.* ***1990****, 112*, 6772; Aihara, J. *Bull. Chem. Soc. Jpn.* ***1990****, 63*, 1956.

bonds.[6] The carbon–carbon bond order for benzene, calculated by the MO method, is 1.667.[7]

For planar unsaturated molecules that are aromatic, many *MO calculations* have been made by treating the σ and π electrons separately. It is assumed that the σ orbitals can be treated as localized bonds and the calculations involve only the π electrons. The first such calculations were made by Hückel, and such calculations are often called *Hückel molecular orbital* (*HMO*) *calculations*.[8] Because electron–electron repulsions are either neglected or averaged out in the HMO method, another approach, the *self-consistent field* (*SCF*), or *Hartree–Fock*, method, was devised.[9] Although these methods give many useful results for planar unsaturated and aromatic molecules, they are often unsuccessful for other molecules. It would obviously be better if all electrons, both σ and π, could be included in the calculations. The development of modern computers has now made this possible.[10] Many such calculations have been made[11] using a number of methods, among them an extension of the Hückel method [12] and the application of the SCF method to all valence electrons.[13]

One type of MO calculation that includes all electrons is called *ab initio*.[14] Despite the name (which means "from first principles") this type does involve some assumptions. Treatments that use certain simplifying assumptions (but still include all electrons) are called *semiempirical* methods.[15] One of the first of these was called CNDO (Complete Neglect of Differential Overlap),[16] but as computers have become more powerful, this has been superseded by more modern methods, including MINDO/3 (Modified Intermediate Neglect of Differential Overlap),[17] MNDO (Modified Neglect of Diatomic Overlap),[17] and AM1 (Austin Model 1), all of which were introduced by M.J. Dewar et al.[18] There is also the PM3, or Parameterized Model number 3, which the same formalism and equations as the AM1 method, but AM1 takes some of the parameter values from spectroscopic

[7] See Pullman, A. *Prog. Org. Chem.* ***1958****, 4*, 31, p. 36; Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963****, 19*, 2153. For a MO picture of aromaticity, see Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2007****, 13,* 6321.

[8] See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***; Coulson, C.A.; O'Leary, B.; Mallion, R.B. *Hückel Theory for Organic Chemists*, Academic Press, NY, ***1978***; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 100–121.

[9] Pople, J.A. *Trans. Faraday Soc.* ***1953****, 49,* 1375*, J. Phys. Chem.* ***1975****, 61*, 6; Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, NY, ***1969***; Dewar, M.J.S., in *Aromaticity*, Pub. no. 21, ***1967***, pp. 177–215. See Merino, G.; Vela, A.; Heine, T. *Chem. Rev.* ***2005****, 105,* 3812; Poater, J.; Duran, M.; Solà, M.; Silvi, B. *Chem. Rev.* ***2005****, 105,* 3911.

[10] See Ramsden, C.A. *Chem. Ber.* ***1978****, 14*, 396; Hall, G.G. *Chem. Soc. Rev.* ***1973****, 2*, 21.

[11] See Herndon, W.C. *Prog. Phys. Org. Chem.* ***1972****, 9*, 99.

[12] Hoffmann, R. *J. Chem. Phys.* ***1963****, 39*, 1397. See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 190–201.

[13] Dewar, M.J.S. *The Molecular Orbital Theory of Chemistry*, McGraw-Hill, NY, ***1969***; Jaffé, H.H. *Acc. Chem. Res.* ***1969****, 2*, 136; Kutzelnigg, W.; Del Re, G.; Berthier, G. *Fortschr. Chem. Forsch.* ***1971****, 22*, 1.

[14] Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, Wiley, NY, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 233–317; Richards, W.G.; Cooper, D.L. *Ab Initio Molecular Orbital Calculations for Chemists,* 2nd ed., Oxford University Press, Oxford, ***1983***.

[15] For a review, see Thiel, W. *Tetrahedron* ***1988****, 44*, 7393.

[16] Pople, J.A.; Segal, G.A. *J. Chem. Phys.* ***1965****, 43,* S136; ***1966****, 44*, 3289; Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory*, McGraw-Hill, NY, ***1970***.

[17] For a discussion of MNDO and MINDO/3, and a list of systems for which these methods have been used, with references, see Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 93–232. For a review of MINDO/3, see Lewis, D.F.V. *Chem. Rev.* ***1986****, 86*, 1111.

[18] See Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1985****, 107*, 3902.

measurements, whereas PM3 treats them as optimizable values.[19] Semiempirical calculations are generally regarded as less accurate than *ab initio* methods,[20] but are much faster and cheaper.[21] Note that modern computers are capable of completing >3 billion calculations per second, which makes MO calculations practical in modern organic chemistry.

Molecular orbital calculations, whether by *ab initio* or semiempirical methods, can be used to obtain structures (bond distances and angles), energies (e.g., heats of formation), dipole moments, ionization energies, and other properties of molecules, ions, and radicals: not only of stable ones, but also of those so unstable that these properties cannot be obtained from experimental measurements.[22] Many of these calculations have been performed on transition states (Sec. 6.D). This is the only way to get this information, since transition states are not directly observable. Of course, it is not possible to check data obtained for unstable molecules and transition states against any experimental values, so that the reliability of the various MO methods for these cases is always a question. However, confidence in them increases when (1) different MO methods give similar results, and (2) a particular MO method works well for cases that can be checked against experimental methods.[23]

Both the valence bond and MO methods show that there is delocalization in benzene. For example, each predicts that the six carbon–carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, one or the other will be used as appropriate. Recent *ab initio,* SCF calculations confirm that the delocalization effect acts to strongly stabilize symmetric benzene, consistent with the concepts of classical resonance theory.[24] It is known that substituents influence the extent of resonance.[25]

2.B. BOND ENERGIES AND DISTANCES IN COMPOUNDS CONTAINING DELOCALIZED BONDS

If the energies of all the bonds in benzene are added, taking the values from a source like Table 1.7, the value for the heat of atomization is less than the experimentally determined value (Fig. 2.3) of 1323 kcal mol^{-1} (5535 kJ mol^{-1}). If E values for a C=C double bond obtained from cyclohexene (148.8 kcal mol^{-1}; 622.6 kJ mol^{-1}) are used, a C—C single bond from cyclohexane (81.8 kcal mol^{-1}, 342 kJ mol^{-1}), and C—H bonds from methane (99.5 kcal mol^{-1}, 416 kJ mol^{-1}), a value of 1289 kcal mol^{-1} (5390 kJ mol^{-1}) is obtained for structure **1** or **2**. By this calculation, the resonance energy is 34 kcal mol^{-1} (145 kJ mol^{-1}). Of course, this is an arbitrary calculation since, in addition to the fact that a heat of atomization is calculated for a nonexistent structure (**1**), E values must be used that do not have a firm basis in reality. The actual C—H bond energy for benzene has been measured to be 113.5 ± 0.5 kcal mol^{-1} at 300 K and estimated to be 112.0 ± 0.6 kcal mol^{-1} (469 kJ mol^{-1}) at 0 K.[26] The heat of atomization of a real molecule can be measured, but resonance

[19] Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209, 221.
[20] See Dewar, M.J.S.; Storch, D.M. *J. Am. Chem. Soc.* ***1985****, 107*, 3898.
[21] Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, p. 141.
[22] Another method of calculating such properies is molecular mechanics (Sec. 4.O).
[23] Dias, J.R. *Molecular Orbital Calculations Using Chemical Graph Theory,* Spring-Verlag, Berlin, ***1993***.
[24] Glendening, E.D.; Faust, R.; Streitwieser, A.; Vollhardt, K.P.C.; Weinhold, F. *J. Am. Chem.Soc.* ***1993****, 115*, 10952.
[25] For an electrostatic scale of substituent resonance effects, see Sayyed, F.B.; Suresh, C.H. *Tetrahedron Lett.* ***2009****, 50*, 7351.
[26] Davico, G.E.; Bierbaum, V.M.; DePuy, C.H.; Ellison, G.B.; Squires, R.R. *J. Am. Chem. Soc.* ***1995****, 117*, 2590. See also, Pratt, D.A.; DiLabio, G.A.; Mulder, P.; Ingold, K.U. *Acc. Chem. Res.* ***2004****, 37*, 334.

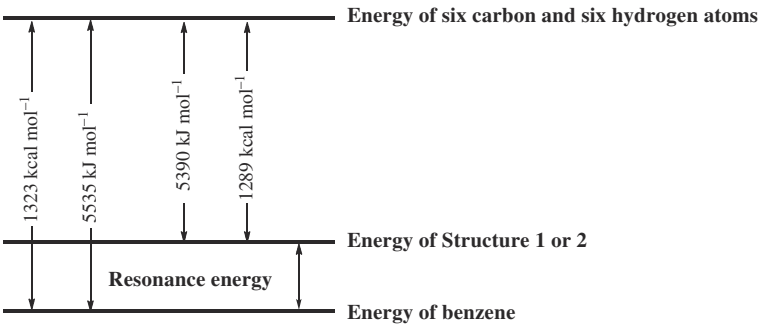


FIG. 2.3. Resonance energy in benzene.

energy can never be measured, only estimated, because only an intelligent guess can be made at that of the Lewis structure of lowest energy.

Another method frequently used for estimation of resonance energy involves measurements of heats of hydrogenation.[27] The heat of hydrogenation of cyclohexene is 28.6 kcal mol^{-1} (120 kJ mol^{-1}), so a hypothetical **1** or **2** with three double bonds is expected to have a heat of hydrogenation of $\sim$ 85.8 kcal mol^{-1} (360 kJ mol^{-1}). Benzene has a measured heat of hydrogenation of 49.8 kcal mol^{-1} (208 kJ mol^{-1}), and the difference between the measured and expected value is the *resonance energy*, 36 kcal mol^{-1} (152 kJ mol^{-1}). By any calculation, the real molecule is more stable than a hypothetical **1** or **2**.

The energies of the six benzene orbitals can be calculated from HMO theory in terms of two quantities that are labeled α and β. Here α is the amount of energy possessed by an isolated 2*p* orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree of stabilization resulting from π-orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (lowest to highest): $\alpha + 2\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha - \beta$, $\alpha - \beta$, and $\alpha - 2\beta$.[28] The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** has an energy of $6\alpha + 6\beta$ and the resonance energy of benzene is 2β. Unfortunately, there is no convenient way to calculate the value of β from MO theory. Benzene is often given a value of β of $\sim$ 18 kcal mol^{-1} (76 kJ mol^{-1}); this number is one-half of the resonance energy calculated from heats of combustion or hydrogenation. Using *ab initio* calculations, bond resonance energies for many aromatic hydrocarbons other than benzene have been reported.[29]

Isodesmic and homodesmotic reactions are frequently used for the study of aromaticity from the energetic point of view.[30] However, the energy of the reactions used experimentally, or in calculations, may reflect only the relative aromaticity of benzene and not its absolute

[27] See Jensen, J.L. *Prog. Phys. Org. Chem.* ***1976****, 12*, 189.

[28] For the method for calculating these and similar results given in this chapter, see Higasi, K.; Baba, H.; Rembaum, A. *Quantum Organic Chemistry*, Interscience, NY, ***1965***. For values of calculated orbital energies and bond orders for many conjugated molecules, see Coulson, C.A.; Streitwieser, Jr., A. *Dictionary of* π *Electron Calculations*, W.H. Freeman, San Francisco, ***1965***.

[29] Aihara, J-i. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 2185.

[30] George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1222; George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *Tetrahedron* ***1976****, 32,* 317; George, P.; Trachtman, M.; Brett, A.M.; Bock, C.W. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1036.

aromaticity. New homodesmotic reactions based on radical systems predict an absolute aromaticity of 29.13 kcal mol^{-1} (121.9 kJ mol^{-1}) for benzene and an absolute antiaromaticity (Sec. 2.K.ii) of 40.28 kcal mol^{-1} (168,5 kJ mol^{-1}) for cyclobutadiene at the MP4 (SDQ)/6-31G-(d,p) level.[31]

Compounds that exhibit delocalization are expected to have bond distances that lie between the values given in Table 1.5. This is certainly the case for benzene, since the carbon–carbon bond distance is 1.40 Å,[32] which is between the 1.48 Å for an sp^2–sp^2 C—C single bond and the 1.32 Å of the sp^2–sp^2 C=C double bond.[33]

2.C. MOLECULES THAT HAVE DELOCALIZED BONDS

There are four main types of structure that exhibit delocalization:

1. *Double (or Triple) Bonds in Conjugation*.[34] The double bonds in benzene are conjugated, of course, but the conjugation exists in acyclic molecules (e.g., butadiene, **6**). In the MO picture (Fig. 2.4), the overlap of four orbitals gives

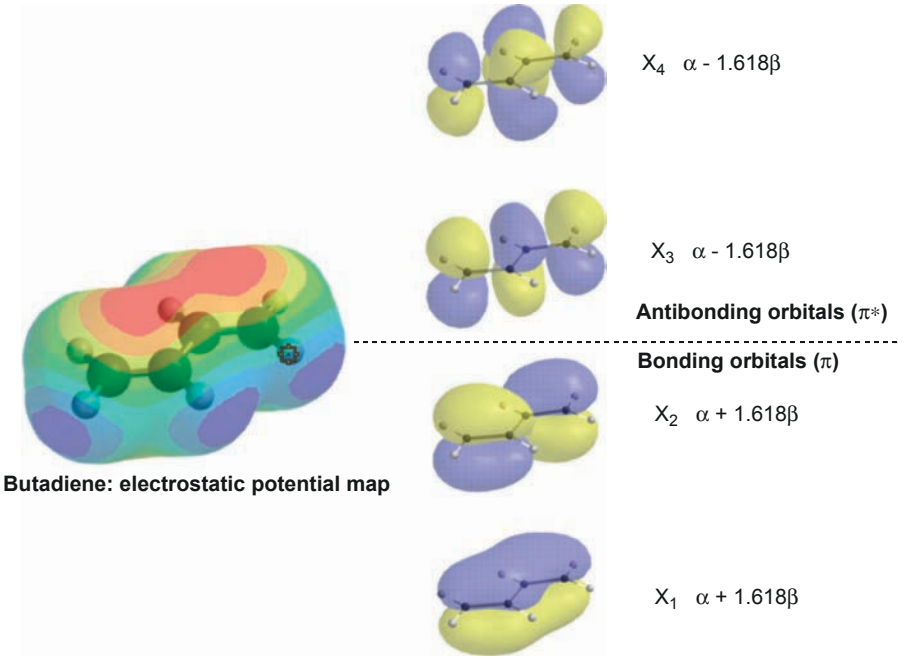


FIG. 2.4. The four π orbitals of butadiene, formed by overlap of four *p* orbitals.

[31] Suresh, C.H.; Koga, N. *J. Org. Chem.* ***2002****, 67*, 1965. The heat of hydrogenation of phenylcyclobutadiene is reported to be 57.4 ± 4.9 kcal mol^{-1}(240.3 kJ mol^{-1}): Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* ***2005****, 127,* 3065.

[32] Tamagawa, K.; Iijima, T.; Kimura, M. *J. Mol. Struct.* ***1976****, 30*, 243.

[33] The average C–C bond distance in aromatic rings is 1.38 Å: Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, p. S8.

[34] See Simmons, H.E. *Prog. Phys. Org. Chem. 1970, 7*, 1; Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev. 1968, 37*, 119.

two bonding orbitals that contain four electrons and two vacant antibonding orbitals. It can be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (lowest to highest): $\alpha + 1.618\beta$, $\alpha + 0.618\beta$, $\alpha - 0.618\beta$, and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β.

In the resonance picture, structures **7** and **8** are considered to contribute.

$$\underset{\mathbf{6}}{CH_2{=}CH{-}CH{=}CH_2} \leftrightarrow \underset{\mathbf{7}}{\overset{+}{C}H_2{-}CH{=}CH{-}\overset{-}{C}H_2} \leftrightarrow \underset{\mathbf{8}}{\overset{-}{C}H_2{-}CH{=}CH{-}\overset{+}{C}H_2}$$

Despite the invocation of structures **7** and **8** in the resonance picture, butadiene and similar conjugated systems are *not* considered to be resonance stabilized in the ground state. The bond order of the central bond should be > 1 and that of the other carbon–carbon bonds < 2, although neither predicts that the three bonds have equal electron density. Molecular orbital bond orders of 1.894 and 1.447 have been calculated.[35]

The existence of delocalization in butadiene and similar molecules has been questioned. The bond lengths in butadiene are 1.34 Å for the double bonds and 1.48 Å for the single bond.[36] Since the typical single-bond distance of a bond that is not adjacent to an unsaturated group is 1.53 Å (Sec. 1.K), it has been argued that the shorter single bond in butadiene provides evidence for resonance. However, this shortening can also be explained by hybridization changes (See Sec. 1.K); and other explanations have also been offered.[37] Resonance energies for butadienes, calculated from heats of combustion or hydrogenation, are only $\sim 4\,\text{kcal mol}^{-1}$ ($17\,\text{kJ mol}^{-1}$), and these values may not be entirely attributable to resonance.[38] Thus, a calculation from heat of atomization data gives a resonance energy of $4.6\,\text{kcal mol}^{-1}$ ($19\,\text{kJ mol}^{-1}$) for *cis*-1,3-pentadiene, and $-0.2\,\text{kcal mol}^{-1}$ ($-0.8\,\text{kJ mol}^{-1}$), for 1,4-pentadiene. These two compounds, each of which possesses two double bonds, two C—C single bonds, and eight C—H bonds, would seem to offer a direct comparison of a conjugated with a nonconjugated compound, but they are nevertheless not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds of the 1,4-diene are both sp^2–sp^3 bonds, while in the 1,3-diene, one is sp^2–sp^3 and the other is sp^2–sp^2. Therefore, it may be that some of the already small value of $4\,\text{kcal mol}^{-1}$ ($17\,\text{kJ mol}^{-1}$) is not resonance energy, but arises from differing energies of bonds of different hybridization.[39] As noted above, butadiene and related molecules are generally considered not to be resonance stabilized in the ground state.

[35] Coulson, C.A. *Proc. R. Soc. London, Ser. A* ***1939****, 169*, 413.

[36] Marais, D.J.; Sheppard, N.; Stoicheff, B.P. *Tetrahedron* ***1962****, 17,* 163.

[37] Politzer, P.; Harris, D.O. *Tetrahedron* ***1971****, 27*, 1567.

[38] For a discussion of so-called Y-aromaticity, and the relative stability of the butadienyl dication in relation to other dications, see Dworkin, A.; Naumann, R.; Seigfred, C.; Karty. J.M.; Mo, Y. *J. Org. Chem.* ***2005****, 70,* 7605.

[39] For negative views on delocalization in butadiene and similar molecules, see Dewar, M.J.S.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1965****, 87*, 692; Mikhailov, B.M. *J. Gen. Chem. USSR* ***1966****, 36*, 379. For positive views, see Miyazaki, T.; Shigetani, T.; Shinoda, H. *Bull. Chem. Soc. Jpn.* ***1971****, 44*, 1491; Altmann, J.A.; Reynolds, W.F. *J. Mol. Struct,* ***1977****, 36*, 149. In general, the negative argument is that resonance involving excited structures, (e.g., **7** and **8**) is unimportant. (see rule 6 in Sec.2.E). See Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* ***1968****, 37*, 119, pp. 119–124.

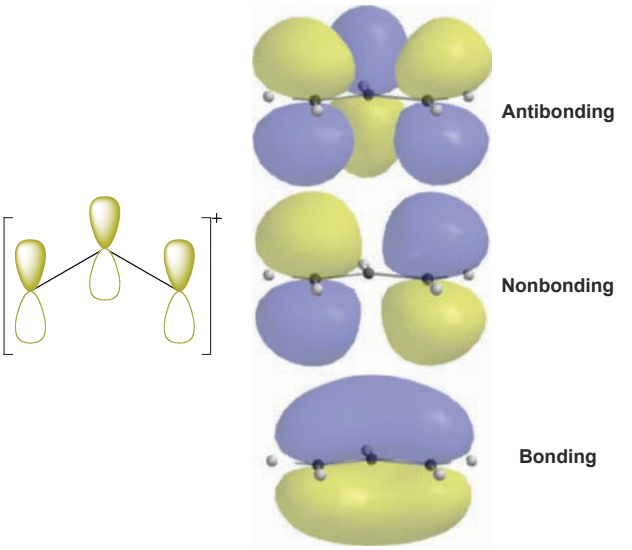


FIG. 2.5. Three orbitals of an allylic carbon, formed by overlap of three *p* orbitals.

Although bond distances fail to show it and the resonance energy is low, butadiene is planar.[40] This has been taken as an indication that there is some delocalization. Similar effects are found in other conjugated systems (e.g., C=C—C=O[41] and C=C—C=N), in longer systems with three or more multiple bonds in conjugation, and where double or triple bonds are conjugated with aromatic rings. Diynes (e.g., 1,3-butadiyne, **9**) are also conjugated molecules. Based on calculations, Rogers et al.[42] reported that the conjugation stabilization of 1,3-butadiyne is zero. Later calculations concluded that consideration of hyperconjugative interactions (Sec. 2.M) provides a more refined measure of conjugative stabilization.[43] When this measure is used, the conjugation energies of the isomerization and hydrogenation reactions considered agree with a conjugative stabilization of 9.3 (0.5 kcal mol^{-1} for diynes and 8.2 0.1 kcal mol^{-1} for dienes).

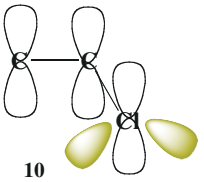
$$\mathrm{H-C{\equiv}C-C{\equiv}C-H}$$

9

2. *Double (or Triple) Bonds in Conjugation with a p Orbital on an Adjacent Atom.* When a *p* orbital is on an atom adjacent to a double bond, there are three parallel *p* orbitals that overlap. As previously noted, it is a general rule that the overlap of *n* atomic orbitals creates *n* molecular orbitals, so overlap of a *p* orbital with an adjacent double bond gives rise to three new orbitals, as shown in Fig. 2.5. The middle orbital is a *nonbonding orbital* of zero-bonding energy. The central carbon atom does not participate in the nonbonding orbital.

[40] Wiberg, K.B.; Rosenberg, R.E.; Rablen, P.R. *J. Am. Chem. Soc.* ***1991****, 113*, 2890.
[41] See Patai, S.; Rappoport, Z. *The Chemistry of Enones*, two parts; Wiley, NY, ***1989***.
[42] Rogers, D.W.; Matsunaga, N.; McLafferty, F.J.; Zavitsas, A.A.; Liebman, J.F. *J. Org. Chem.* ***2004****, 69,* 7143.
[43] Jarowski, P.D.; Wodrich, M.D.; Wannere, C.S.; Schleyer, P.v.R.; Houk, K.N. *J. Am. Chem. Soc.* ***2004****, 126,* 15036.

There are three cases: the original *p* orbital may have contained two, one, or no electrons. Since the original double bond contributes two electrons, the total number of electrons accommodated by the new orbitals is four, three, or two, respectively. A typical example of the first situation is vinyl chloride, (CH_2=CH—Cl). Although the *p* orbital of the chlorine atom is filled, it still overlaps with the double bond (See **10**). The four electrons occupy the two molecular orbitals of lowest energies, which is an example of resonance involving overlap between unfilled orbitals and a *filled* orbital. Canonical forms for vinyl chloride are shown in **11** (see Sec. 2.M).

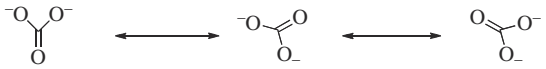


10

CH_2=CH–Cl ⟷ $^-CH_2$–CH=Cl^+

11

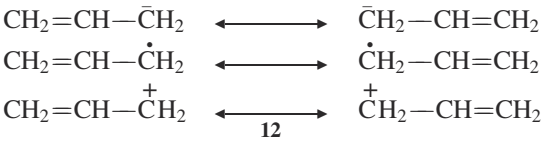
Any system that contains an atom that has an unshared pair and is directly attached to a multiple-bond atom can show this type of delocalization. Resonance delocalization is more important with charged species (e.g., the carbonate ion) and true resonance contributors can be drawn:



The resonance delocalization in allylic carbanions, (e.g., CH_2=CH—CH_2^-), is another example.

The other two cases have a *p* orbital that contains only one electron (radicals) or no electrons (cations). Allylic free radicals have one electron in the nonbonding orbital. In allylic cations, this orbital is vacant and only the bonding orbital is occupied. The orbital structures of the allylic carbanion, free radical, and cation differ from each other, only in that the nonbonding orbital is filled, half-filled, or empty. Since this is an orbital of zero bonding energy, it follows that the bonding π energies of the three species relative to electrons in the 2*p* orbitals of free atoms are the same. The electrons in the nonbonding orbital do not contribute to the bonding energy, positively or negatively.[44]

The resonance picture best describes three species that are charged or contain an unshared electron with double bonds in conjugation with, respectively, an unshared pair, an unpaired electron, and an empty orbital as in the allyl cation **12** (also see Chap 5).

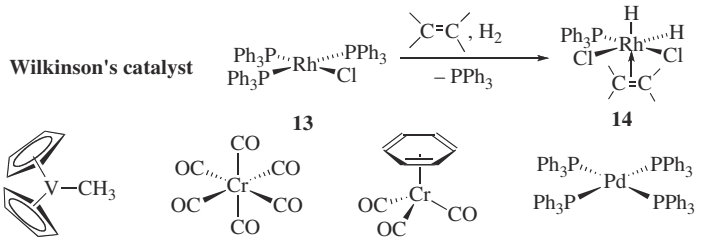


12

[44] It has been argued that the geometry is forced upon allylic systems by the σ framework, and not the π system: Shaik, S.S.; Hiberty, P.C.; Ohanessian, G.; Lefour, J. *Nouv. J. Chim.*, ***1985***, *9,* 385. *ab initio* calculations suggest that the allyl cation has significant resonance stabilization, but the allyl anion has little stabilization: Wiberg, K.B.; Breneman, C.M.; LePage, T.J. *J. Am. Chem. Soc.* ***1990***, *112*, 61.

3. *π-Allyl and Other η-Complexes*. In the presence of transition metals, delocalized electrons in allylic cations may be donated to the metal, resulting in stabilization.[45] In a carbon–metal bond (e.g., H_3C—Fe), the carbon donates (shares) one electron with the metal, and is considered to be a one-electron donor. With a π bond (e.g., that found in ethylene), both electrons can be donated to the metal to form a complex (e. g., **14**) by reaction of Wilkinson's catalyst (**13**) with an alkene and hydrogen gas,[46] in addition, π bond is considered to be a two-electron donor. In these two cases, the electron donating ability of the group coordinated to the metal (the ligand) is indicated by terminology η^1, η^2, η^3, and so on, for a one-, two-, and three-electron donor, respectively.

Ligands are categorized as η-ligands according to the ability to donate electrons to the metal. A hydrogen atom (as in **14**) or a halogen ligand (as in **13**) are η^1 ligands. An amine (NR_3), a phosphine (PR_3, as in **13**, **14**, and **18**), CO (as in **16** or **17**), an ether (OR_2) or a thioether (SR_2) are η^2 ligands. Hydrocarbon ligands include alkyl (as the methyl in **15**) or aryl with a carbon-metal bond (η^1), alkenes or carbenes (η^2, see Sec. 3.C.i), π-allyl (η^3), conjugated dienes (e.g., 1,3-butadiene) (η^4), cyclopentadienyl (η^5, as in **15** and see Sec. 2.I.ii), and arenes or benzene (η^6).[47] Note that in the formation of **14** from **13**, the two-electron donor alkene displaces a two-electron donor phosphine. Other typical complexes include chromium hexacarbonyl ($Cr(CO)_6$, **16**), with six η^2 CO ligands; η^6-$C_6H_6Cr(CO)_3$ (**18**), and *tetrakis*-triphenylphosphinopalladium (0), (**17**), with four η^2 phosphine ligands.



In the context of this section, the electron-delocalized ligand π-allyl (**12**) is an η^3 donor and it is well known that allylic halides react with $PdCl_2$ to form a bis-η^3-complex **19** (see **20**).[48] Complexes (e.g., **19**) react with nucleophiles to give the corresponding coupling product (**10–60**).[49] The reaction of allylic acetates or carbons and a catalytic amount of Pd(0) compounds also lead to an η^3-complex that can react with nucleophiles.[50]

[45] Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley-Interscience, NY, ***2005***; Hill, A.F. *Organotransition Metal Chemistry*, Wiley Interscience, Canberra, ***2002***.

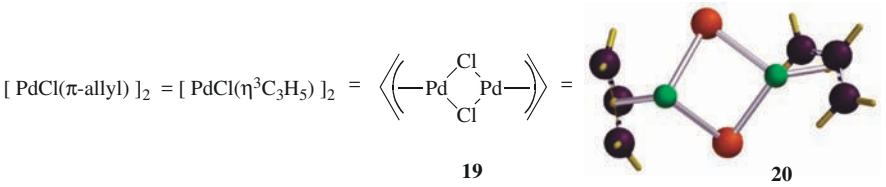
[46] Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. *Chem. Ind. (London)* ***1965***, 560; Imperial Chem. Ind. Ltd., *Neth. Appl. 6,602,062* [*Chem. Abstr., 66*: 10556y ***1967***]; Bennett, M.A.; Longstaff, P.A. *Chem. Ind.* ***1965***, 846.

[47] Davies, S.G. *Organotransition Metal Chemistry*, Pergamon, Oxford, ***1982***, p. 4.

[48] Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3407.

[49] Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3416.

[50] Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* ***1976***, *41*, 265; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.,* ***1978***, *100*, 3435; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* ***1980***, *102*, 4730.



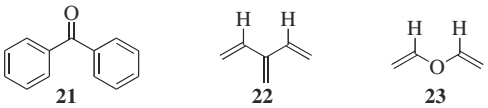
19 **20**

4. *Hyperconjugation*. The type of delocalization called *hyperconjugation* is discussed in Section 2.M.

Note that there are examples of delocalization that cannot be strictly classified as any of these types.

2.D. CROSS-CONJUGATION[51]

In a cross-conjugated compound, three groups are present, two of which are not conjugated with each other, although each is conjugated with the third. Some examples are benzophenone (**21**), triene (**22**),[52] and divinyl ether (**23**). The MO method shows that the overlap of six *p* orbitals in **22** (a member of a family of compounds known as dendralenes)[52] gives six molecular orbitals, and the three bonding orbitals are shown in Fig. 2.6, along with their energies. Note that two of the carbon atoms do not participate in the $\alpha + \beta$ orbital.



21 **22** **23**

The total energy of the three occupied orbitals is $6\alpha + 6.900\beta$, so the resonance energy is 0.900β. Molecular orbital bond orders are 1.930 for the C-1–C-2 bond, 1.859 for the C-3–C-6 bond, and 1.363 for the C-2–C-3 bond.[51] Comparing these values with those for butadiene (Sec. 2.C), the C-1–C-2 bond contains more and the C-3–C-6 bond less double-bond character than the double bonds in butadiene. The resonance picture supports

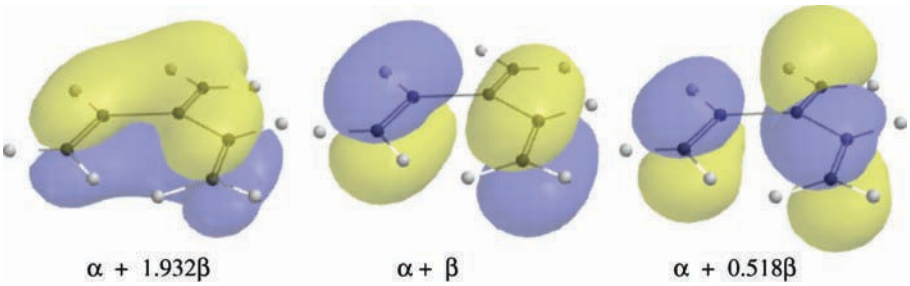


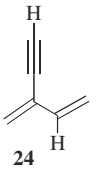
FIG. 2.6. The three bonding orbitals of the dendralene, 3-methylene-1,4-pentadiene (**22**).

[51] See Phelan, N.F.; Orchin, M. *J. Chem. Educ.* ***1968****, 45*, 633.
[52] For a review of such compounds, see Hopf, H. *Angew. Chem. Int. Ed.* ***1984****, 23*, 948.

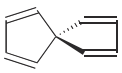
this conclusion, since each C-1–C-2 bond is double in three of the five canonical forms, while the C-3–C-6 bond is double in only one. In most cases, it is easier to treat cross-conjugated molecules by the MO method than by the valence bond method.

One consequence of this phenomenon is that the bond length of a cross-conjugated C=C unit is slightly longer than that of a non-cross-conjugated bond. In **24**, for example, the cross–conjugated bond is ~ 0.01 Å longer.[53] The conjugative effect of a C=C or C≡C unit can be measured for a conjugated enone: 4.2 kcal mol^{-1} (17.6 kj mol^{-1}) for an ethenyl substituent, but ~ 2.3 kcal mol^{-1} (9.6 kj mol−1) for an ethynyl substituent, which is more variable.[54]

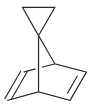
The phenomenon of homoconjugation is related to cross-conjugation in that there are C=C units in close proximity, but not conjugated one to the other. Homoconjugation arises when the termini of two orthogonal π-systems are held in close proximity, as in compounds with a spiro-tetrahedral carbon atom.[55] Spiro[4.4]nonatetraene (**25**)[56] is an example and it is known that the HOMO (see Sec. **15.60**) of **25** is raised relative to cyclopentadiene, whereas the LUMO is unaffected.[57] Another example is **26**, where there are bond length distortions caused by electronic interactions between the unsaturated bicyclic moiety and the cyclopropyl moiety.[58] It is assumed that cyclopropyl homoconjugation is responsible for this effect.



24



25



26

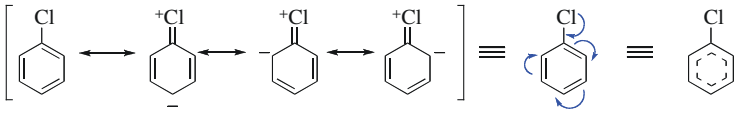
2.E. THE RULES OF RESONANCE

One way to express the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of them. These structures are called canonical forms, but they are not real structures. In other words, the molecule does *not* rapidly shift between them and a given compound has a single actual structure. That structure is always the same all the time and is taken to be a weighted average of all the canonical forms. Drawing canonical forms and deriving the true structures from them is guided by certain rules, including the following:

1. All the canonical forms must be *bona fide* Lewis structures (Sec. 1.F). For example, none of them may have a carbon with five bonds.
2. The positions of the nuclei must be the same in all the structures. This means that when drawing the various canonical forms, the *electrons* are simply arranged in different ways. For this reason, shorthand ways of representing resonance are easy

[53] Trætteberg, M.; Hopf, H. *Acta Chem. Scand. B* ***1994****, 48*, 989.
[54] Trætteberg, M.; Liebman, J.F.; Hulce, M.; Bohn, A.A.; Rogers, D.W. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 1925.
[55] See Durr, H.; Gleiter, R. *Angew. Chem. Int. Ed.* ***1978****, 17*, 559.
[56] For the synthesis of **25**, see Semmelhack, M.F.; Foos, J.S.; Katz, S. *J. Am. Chem. Soc.* ***1973****, 95*, 7325.
[57] Raman, J.V.; Nielsen, K.E.; Randall, L.H.; Burke, L.A.; Dmitrienko, G.I. *Tetrahedron Lett.* ***1994****, 35*, 5973.
[58] Haumann, T.; Benet-Buchholz, J.; Klärner, F.-G.; Boese, R. *Liebigs Ann. Chem.* ***1997***, 1429.

to devise:



27 **28**

Invoking hyperconjugation (Sec. 2.M), resonance interaction of chlorine with the benzene ring can be represented as shown in **27** or **28** and both representations have been used in the literature to save space. However, the curved-arrow method of **27** will not be used since arrows in this book are used to express the actual movement of electrons in reactions. Representations like **28** will be used occasionally, but more often one or more of the canonical forms will be used. The convention used in dashed-line formulas like **28** is that bonds that are present in all canonical forms are drawn as solid lines, while bonds that are not present in all forms are drawn as dashed lines. A downside of this model is that electron transfer in reactions associated with benzene rings is difficult to track. For this reason, one of the canonical forms is most often used, as mentioned. In most resonance, σ bonds are not involved, and only the π or unshared electrons are utilized. This finding means that writing one canonical form for a molecule, allowed the others to be written by merely moving π and unshared electrons.

3. All atoms taking part in the resonance, (i.e., covered by delocalized electrons), must lie in a plane or nearly so (see Sec. 2.G). This, of course, does not apply to atoms that have the same bonding in all the canonical forms. Maximum overlap of the *p* orbitals leads to the planarity.
4. All canonical forms must have the same number of unpaired electrons. Thus the diradical structure $\bullet CH_2CH{=}CH{-}CH_2\bullet$ is not a valid canonical form for butadiene.
5. The energy of the actual molecule is lower than that of any form, so delocalization is a stabilizing phenomenon.[59]
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethylene, the form $^{+}CH_2{-}CH_2{}^{-}$ has such a high energy compared to $CH_2{=}CH_2$ that it essentially does not contribute at all. This argument was applied to butadiene.[39] Equivalent canonical forms, (e.g., **1** and **2**) contribute equally. The greater the number of significant structures that can be written and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures; the chemist is often guided by intuition.[60] However, the following rules may be helpful:

(a) Structures with more covalent bonds are ordinarily more stable than those with fewer (cf. **6** and **7**).

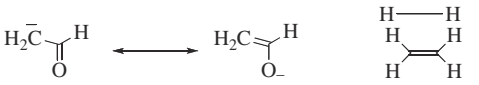
(b) Stability is decreased by an increase in charge separation. Structures with formal charges are less stable than uncharged structures. Structures with more than two

[59] It has been argued that resonance is not a stabilizing phenomenon in all systems, especially in acyclic ions: Wiberg, K.B. *Chemtracts. Org. Chem.* ***1989****, 2*, 85. See also, Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812.

[60] A quantitative method for weighting canonical forms was proposed by Gasteiger, J.; Saller, H. *Angew. Chem. Int. Ed.* ***1985****, 24,* 687.

formal charges usually contribute very little. An especially unfavorable type of structure is one with two like charges on adjacent atoms.

(c) Structures that carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, enolate anion **30** is more stable than canonical form **29**. Similarly, positive charges are best carried on atoms of low electronegativity.

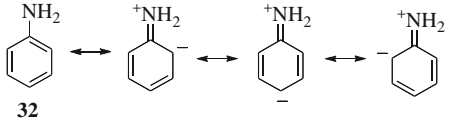


29 **30** **31**

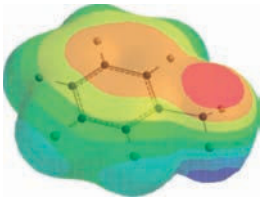
(d) Structures with distorted bond angles or lengths are unstable, (e.g., contributor **31** for ethane).

2.F. THE RESONANCE EFFECT

Resonance always results in a different distribution of electron density than would be the case if there were no resonance (i.e., the electrons are dispersed over several atoms rather than concentrated on one atom). For example, if **32** were the actual structure of aniline, the two unshared electrons of the nitrogen would reside entirely on that atom. The structure of **32** can be represented as a hybrid that includes contributions from the canonical forms shown, indicating that the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. However, as shown by the accompanying electron potential map for aniline, the charge distribution is such that most of the electron density resides on nitrogen. The decrease in electron density at one position (and corresponding increase elsewhere) means that the NH_2 contributes or donates electrons to the ring by a resonance effect ("electron releasing," although no actual contribution takes place), and is called the *resonance* or *mesomeric effect*. To emphasize this point, the canonical forms associated with **32** indicate electron release from the nitrogen to the benzene ring (the mesomeric effect), and do not necessarily indicate that there are four canonical forms. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the field effect (Sec. 1.I), a certain molecule (in this case ammonia) maybe thought of as a substrate and effects of substitution on the electron density may be studied. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring (to make aniline, **32**), the electrons are "withdrawn" from the ring by the resonance effect, just as when a methyl group replaces a hydrogen atom of benzene, electrons are "donated" by the field effect of the methyl. Note the increassed electron density on the nitrogen in the model, as indicated by the darker area that is above the middle of the model as well and on the nitrogen (on the right side of the model) when compared to benzene in Fig. 2.1*b*. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one or a real compound with a canonical form.



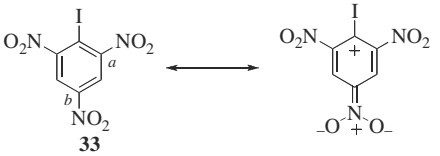
32



2.G. STERIC INHIBITION OF RESONANCE AND THE INFLUENCES OF STRAIN

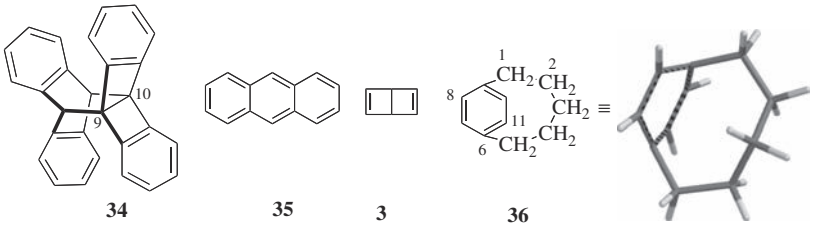
Rule 3 above states that all the atoms covered by delocalized electrons must lie in a plane or nearly so. Many examples are known where resonance is diminished or prevented because the atoms are sterically forced out of planarity. It is known that if para substituents are able to interact via the through-resonance mechanism, π-electron delocalization due to the substituent effects leads to an increase of stability.[61] If the substituents are both electron donating, there is a significant decrease in stability.

Bond lengths for the *o*- and *p*-nitro groups in picryl iodide (**33**) are quite different.[62] Distance *a* in **33** is 1.45 Å, whereas *b* is 1.35 Å. This phenomenon can be explained if the oxygen atoms of the *p*-nitro group are in the plane of the ring and thus in resonance with it, so that *b* has partial double-bond character, while the oxygen atoms of the *o*-nitro groups are forced out of the plane by the large iodine atom. As discussed in Section 2.M, the difference in bond length is associated with hyperconjugative effects, represented by the canonical form.



33

Compound **34** is recognized as a Dewar-form of anthracene.[63] Dewar benzene forms (e.g., benzvalene) (**3**) are recognized as possible valence isomers of benzene.[64] Since **35** is the actual structure of anthracene, it is reasonable to ask if **34** is a canonical structure? The answer is no, because the 9,10 substituents prevent the system from being planar, so **34** is the actual structure of the molecule and it is not in resonance with forms like **35**. This finding is a consequence of rule 2 (Sec. 2.E). In order for a **35**-like structure to contribute to resonance in **34**, the nuclei would have to be in the same positions in both forms. In anthracene itself (**35**), Dewar structures are thought to contribute to the structure, however.



34 **35** **3** **36**

Even the benzene ring can be forced out of planarity.[65] In [5]-paracyclophane[66] (**36**) the presence of a short bridge (this is the shortest para bridge known for a benzene ring) forces

[61] Krygowski, T.M.; Stepień, B.T. *Chem. Rev.* ***2005****, 105*, 3482.

[62] Wepster, B.M. *Prog. Stereochem.* ***1958****, 2*, 99, p. 125. Also see Exner, O.; Folli, U.; Marcaccioli, S.; Vivarelli, P. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 757.

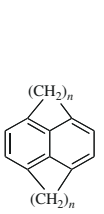
[63] Applequist, D.E.; Searle, R. *J. Am. Chem. Soc.* ***1964****, 86,* 1389.

[64] Cardillo, M.J.; Bauer, S.H. *J. Am. Chem. Soc.* ***1970****, 92*, 2399. See Hiickel, E. *Elektrochem.* ***1937***, *43,* 752; van Tamelen, E. *Angew. Chem. Int. Ed.* ***1965****, 4*, 738; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1965***, *4,* 746.

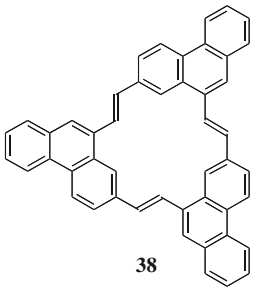
[65] See Ferguson, G.; Robertson, J.M. *Adv. Phys. Org. Chem.* ***1963****, 1*, 203.

[66] For a monograph, see Keehn, P.M.; Rosenfeld, S.M. *Cyclophanes*, 2 Vols., Academic Press, NY, ***1983***. For reviews, see Bickelhaupt, F. *Pure Appl. Chem.* ***1990****, 62,* 373; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* ***1971****, 4,* 204; Vögtle, F.; Neumann, P. Reviews in *Top. Curr. Chem.* ***1985****, 115,* 1.

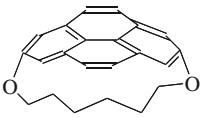
the benzene ring to become boat shaped. The distortion in the benzene ring is apparent in the molecular model of **36** that is provided. The parent **36** has so far not proven stable enough for isolation, but a UV spectrum was obtained and showed that the benzene ring was aromatic, despite the distortion.[67] The 8,11-dichloro analogue of **36** is a stable solid, and X-ray diffraction showed that benzene ring to be boat-shaped, with one end of the boat bending ∼27° out of the plane, and the other ∼12°.[68] This compound too is aromatic, as shown by UV and NMR spectra. [6]-Paracyclophanes are also bent,[69] but in [7]-paracyclophanes the bridge is long enough so that the ring is only moderately distorted. Similarly, [*n,m*]paracyclophanes (**37**), where *n* and *m* are both 3 or less (the smallest yet prepared is [2.2]-paracyclophane),[70] have bent (boat-shaped) benzene rings. All these compounds have properties that depart significantly from those of ordinary benzene compounds. Strained paracyclophanes exhibit both π- and σ-strain, and the effect of the two types of strain on the geometry is approximately additive.[71] In "belt" cyclophane (**38**),[72] the molecule has a pyramidal structure with C_3 symmetry rather than the planar structure found in [18]annulene. 1,8-Dioxa[8](2,70-pyrenophane (**39**)[73] is another severely distorted aromatic hydrocarbon (see **39A**), in which the bridge undergoes rapid pseudorotation (Sec. 4.O.iv). A recent study showed that despite substantial changes in the hybridization of carbon atoms involving changes in the σ-electron structure of pyrenephane (e.g., **39**), the aromaticity of the system decreases slightly and regularly upon increasing the bend angle θ from 0° to 109.2°.[74] Heterocyclic paracyclophane analogues have been prepared, (e.g., the [2.*n*](2,5)pyridinophanes).[75]



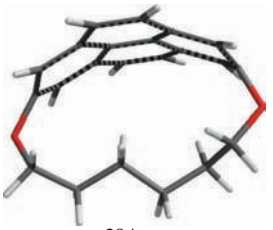
37



38



39



39A

[67] Kostermans, G.B.M.; de Wolf, W.E.; Bickelhaupt, F. *Tetrahedron Lett.* ***1986****, 27*, 1095; van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.E.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1986****, 108,* 1415; Rice, J.E.; Lee, T.J.; Remington, R.B.; Allen, W.D.; Clabo, Jr., D.A.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1987****, 109,* 2902.

[68] Jenneskens, L.W.; Klamer, J.C.; de Boer, H.J.R.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H. *Angew. Chem. Int. Ed.* ***1984****, 23*, 238.

[69] See Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* ***1986****, 42*, 1851.

[70] For a computational study of [2.2]cyclophanes, see Caramori, G.F.; Galembeck, S.E.; Laali, K.K. *J. Org. Chem.* ***2005****, 70,* 3242.

[71] Stanger, A.; Ben-Mergui, N.; Perl, S. *Eur. J. Org. Chem.* ***2003***, 2709.

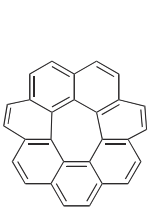
[72] Meier, H.; Müller, K. *Angew. Chem. Int. Ed.,* ***1995****, 34*, 1437.

[73] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed.,* ***1996****, 35*, 1320.

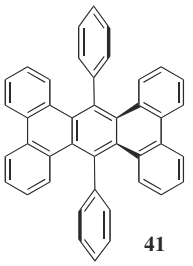
[74] Bodwell, G.J.; Bridson, J.N.; Cyrański, M.K.; Kennedy, J.W.J.; Krygowski, T.M.; Mannion, M.R.; Miller, D.O. *J. Org. Chem.* ***2003****, 68,* 2089; Bodwell, G.J.; Miller, D.O.; Vermeij, R.J. *Org. Lett.* ***2001****, 3,* 2093

[75] Funaki, T.; Inokuma, S.; Ida, H.; Yonekura, T.; Nakamura, Y.; Nishimura, J. *Tetrahedron Lett.* ***2004****, 45*, 2393.

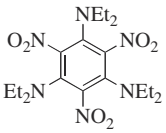
There are many examples of molecules in which benzene rings are forced out of planarity, including 7-circulene (**40**),[76] 9,8-diphenyltetrabenz[*a,c,h,j*]anthracene (**41**),[77] and **42**[78] (see also, Sec. 4.Q.iv). These have been called tormented aromatic systems.[79] The "record" for twisting an aromatic π-electron system appears to be 9,10,11,12,13,14,15,16-octaphenyldibenzo[*a,c*]naphthacene (**43**),[80] which has an end-to-end twist of 105°. This was 1.5 times greater than that observed in any previous polyaromatic hydrocarbon. Perchlorotriphenylene has been reported in the literature and said to show severe molecular twisting, however, recent work suggests this molecule was not actually isolated, with perchlorofluorene-9-spirocyclohexa-2',5'-diene being formed instead.[81] The X-ray structure of the linear [3]phenylene (benzo[3,4]cyclobuta[1,2-*b*]biphenylene, **44**) has been obtained, and it shows a relatively large degree of bond alternation while the center distorts to a cyclic bis-(allyl) frame.[82]



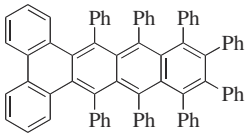
40



41

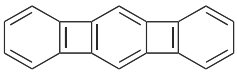


42

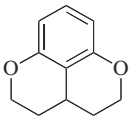


43

It is also possible to fuse strained rings on benzene, which induces great strain on the benzene ring. In **45**, the benzene ring is compressed by the saturated environment of the tetrahydropyran units and the strain leads to distortion of the benzene ring into a *boat* conformation.[83]



44



45



46



47

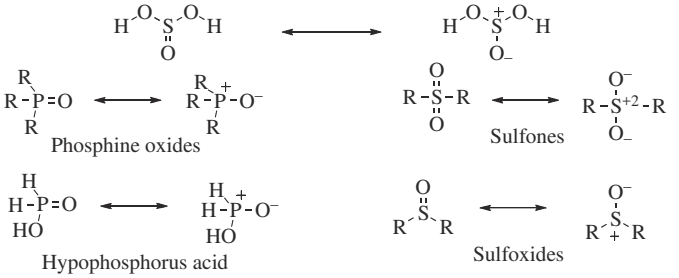
The term strain-induced bond localization was introduced in 1930 by Mills and Nixon[84] and is commonly referred to as the *Mills–Nixon effect* (see Sec. 11.B.v). Ortho-fused aromatic compounds, (e.g., benzocyclopropene, **46**), are known as cyclopropararenes[85] and are highly strained. Cyclopropabenzene (**46**) is a stable molecule with a strain energy of 68 kcal mol^{-1} (284.5 kJ mol^{-1}),[86] and the annellated bond is always the shortest, although

[76] Yamamoto, K.; Harada, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M.; Kai, Y.; Nakao, T.; Tanaka, M.; Harada, S.; Kasai, N. *J. Am. Chem. Soc.* ***1988****, 110*, 3578.
[77] Pascal Jr., R.A.; McMillan, W.D.; Van Engen, D.; Eason, R.G. *J. Am. Chem. Soc.* ***1987****, 109,* 4660.
[78] Chance, J.M.; Kahr, B.; Buda, A.B.; Siegel, J.S. *J. Am. Chem. Soc.* ***1989****, 111,* 5940.
[79] Pascal Jr., R.A. *Pure Appl. Chem.* ***1993****, 65*, 105.
[80] Qiao, X.; Ho, D.M.; Pascal Jr., R.A. *Angew. Chem. Int. Ed.,* ***1997****, 36*, 1531.
[81] Campbell, M.S.; Humphries, R.E.; Munn, N.M. *J. Org. Chem.* ***1992****, 57*, 641.
[82] Schleifenbaum, A.; Feeder, N.; Vollhardt, K.P.C. *Tetrahedron Lett.* ***2001****, 42,* 7329.
[83] Hall, G.G *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1491.
[84] Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* ***1930***, 2510.
[85] See Halton, B. *Chem. Rev.* ***2003****, 103,* 1327 and reviews cited therein.
[86] Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1986****, 108,* 3241.

in benzocyclobutene (**47**) the adjacent bond is the shortest.[87] The bonds of annellation and those adjacent are strained. In cycloproparenes, there is the expectation of partial aromatic bond localization, with bond length alternation in the aromatic ring.[88] When the bridging units are saturated, the benzene ring current is essentially unchanged, but annelation with one or more cyclobutadieno units disrupts the benzene ring current.[89] The chemistry of the cycloproparenes is dominated by the influence of the high strain energy. When fused to a benzene ring, the bicyclo[1.1.0]butane unit also leads to strain-induced localization of aromatic π bonds.[90]

2.H. $p\pi$–$d\pi$ BONDING. YLIDS

In Section 1.D, it was stated that, in general, atoms of the second row of the periodic table do not form stable double bonds of the type discussed in Chapter 1 (π bonds formed by overlap of parallel *p* orbitals). However, there is another type of double bond that is particularly common for the second-row atoms sulfur and phosphorus. Such a double bond is found in sulfurous acid, (H_2SO_3). While the S=O double bond contains one *s* orbital, the second orbital is not a π orbital formed by overlap of half-filled *p* orbitals. Instead it is formed by overlap of a filled *p* orbital from the oxygen with an empty *d* orbital from the sulfur. It is called a *$p\pi$–$d\pi$ orbital*.[91] Note that this molecule may be represented by two canonical forms, but the bond is nevertheless localized, despite the resonance that is inherent to this structure. Some other examples of $p\pi$–$d\pi$ bonding are the phosphine oxides, sulfones, hypophosphorus acid, and sulfoxides. Nitrogen analogues are known, but they are less stable than the phosphorus compounds because the resonance is lacking. For example, amine oxides, analogues of phosphine oxides, can only be written $R_3N^+—O^-$. The $p\pi$–$d\pi$ canonical form is impossible since nitrogen is limited to eight outer-shell electrons.



In all the examples given above, an oxygen atom donates the electron pair and, indeed, oxygen is the most common such atom. In another important class of compounds, called

[87] Boese, R.; Bläser, D.; Billups, W.E.; Haley, M.M.; Maulitz, A.H.; Mohler, D.L.; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.,* ***1994****, 33*, 313.

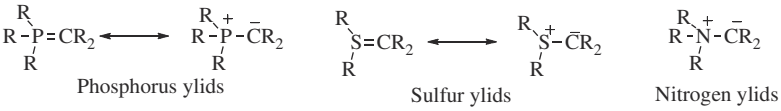
[88] Stanger, A. *J. Am. Chem. Soc.* ***1998****, 120,* 12034; Yáñez, O.M.O.; Eckert- Maksić, M.; Maksić, Z.B. *J.Org. Chem.* ***1995****, 60,* 1638; Eckert- Maksić, M.; Glasovac, Z.; Maksić, Z.B.; Zrinski, I. *J. Mol. Struct. (THEOCHEM)* ***1996****, 366,* 173; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***1992****, 114,* 9583.

[89] Soncini, A.; Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W.; Steiner, E. *J. Org. Chem.* ***2002****, 67,* 4753

[90] Cohrs, C.; Reuchlein, H.; Musch, P.W.; Selinka, C.; Walfort, B.; Stalke, D.; Christl, M. *Eur. J. Org. Chem.* ***2003***, 901.

[91] For a monograph, see Kwart, H.; King, K. *d-Orbitals in the Chemistry of Silicon, Phosphorus, and Sulfur*, Springer, NY, ***1977***.

ylids, this atom is carbon.[92] There are three common types of ylids: P,[93] S,[94] and N ylids,[95] although As,[96] Se, and so on, ylids are also known. Ylids may be defined as compounds in which a positively charged atom from group 15 or 16 of the periodic table is connected to a carbon atom carrying an unshared pair of electrons (+ and – charges on adjacent atoms). Because of $p\pi$–$d\pi$ bonding, two canonical forms can be written for P and S, but there is only one for N ylids. Phosphorus ylids are much more stable than N ylids (see also **12–22**) which is one reason why N ylids tend to react more like carbanions (see **13–31** and **18–21**). While S ylids are generally less stable than P ylids, they are rather common.



In almost all compounds that have $p\pi$-$d\pi$ bonds, the central atom is connected to four or three atoms and an unshared pair, and the bonding is approximately tetrahedral. The $p\pi$–$d\pi$ bond, therefore, does not greatly change the geometry of the molecule in contrast to the normal π bond, which changes an atom from tetrahedral to trigonal. Calculations show that nonstabilized phosphonium ylids have nonplanar ylid carbon geometries whereas stabilized ylids have planar ylid carbons.[97]

2.I. AROMATICITY[98]

In the 19th century, it was recognized that aromatic compounds[99] differ greatly from unsaturated aliphatic compounds,[100] but for many years chemists were hard pressed to

[92] See Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***; Morris, D.G., *Surv. Prog. Chem.* ***1983****, 10,* 189; Lowe, P.A. *Chem. Ind. (London)* ***1970***, 1070. See Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* ***1991****, 91*, 263.

[93] Although the phosphorus ylid shown has three R groups on the phosphorus atom, other phosphorus ylids are known where other atoms, (e.g, oxygen), replace one or more of these R groups. When the three groups are all alkyl or aryl, the phosphorus ylid is also called a phosphorane.

[94] See Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***; Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981****, 50,* 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, p. 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, ***1978***, pp. 91–127.

[95] For a review of nitrogen ylids, see Musker, W.K. *Fortschr. Chem. Forsch.* ***1970****, 14,* 295.

[96] For reviews of arsenic ylids, see Lloyd, D.; Gosney, I.; Ormiston, R.A. *Chem. Soc. Rev.* ***1987****, 16,* 45; Yaozeng, H.; Yanchang, S. *Adv. Organomet. Chem.* ***1982****, 20,* 115.

[97] Bachrach, S.M. *J. Org. Chem.* ***1992****, 57*, 4367.

[98] Krygowski, T.M.; Cyrański, M.K. *Chem. Rev.* ***2001****, 101*, 1385; Katritzky, A.R.; Jug, K.; Oniciu, D.C. *Chem. Rev.* ***2001***, 1421; Fowler, P.W.; Lillington, M.; Olson, L.P. *Pure Appl. Chem.* ***2007****, 79*, 969. See also, Cyrański, M. K.; Krygowski, T.M.; Katritzky, A.R.; Schleyer, Pv. R. *J. Org. Chem.* ***2002****, 67,* 1333.

[99] See Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*, Wiley, NY, ***1989***; *Non-Benzenoid Conjugated Carbocyclic Compounds*, Elsevier, NY, ***1984***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo-Derivatives and their Valence Isomers*, 3 Vols., CRC Press, Boca Raton, FL, ***1987***; Badger, G.M. *Aromatic Character and Aromaticity*, Cambridge University Press, Cambridge, ***1969***; Snyder, J.P. *Nonbenzenoid Aromatics*, 2 Vols., Academic Press, NY, ***1969–1971***; Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***. See Gorelik, M.V. *Russ. Chem. Rev*. ***1990***, 59, 116; Stevenson, G.R. *Mol. Struct. Energ*., ***1986***, 3, 57; Figeys, H.P. *Top. Carbocyclic Chem*. ***1969***, 1, 269; Garratt, P.J.; Sargent, M.V. Papers in *Top. Curr. Chem*. ***1990***, 153 and *Pure Appl. Chem.* ***1980***, 52, 1397.

[100] See Snyder, J.P., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, NY, ***1971***, pp. 1–31. See also, Balaban, A.T. *Pure Appl. Chem.* ***1980****, 52*, 1409.

arrive at a mutually satisfactory definition of aromatic character.[101] Qualitatively, there has never been real disagreement. Definitions include statements that aromatic compounds are characterized by a special stability and that they undergo substitution reactions more easily than addition reactions. These definitions are vague, however, and not easily applied to borderline cases. Definitions of aromaticity[102] must encompass molecules ranging from polycyclic conjugated hydrocarbons,[103] to heterocyclic compounds[104] of various ring sizes, to reactive intermediates. In 1925, Armit and Robinson[105] recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the aromatic sextet (aromatic compounds are thus the archetypal examples of delocalized bonding), but determining whether rings other than the benzene ring possessed such a loop remained difficult. With the advent of magnetic techniques, most notably NMR, it is possible to determine experimentally whether or not a compound has a closed ring of electrons. Aromaticity can now be defined as the ability to sustain an induced ring current. A compound with this ability is called ***diatropic***. Although this definition also has its flaws,[106] it is the one most commonly accepted today. There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on NMR chemical shifts.[107] Water-soluble calix[4]resorcarenes (see Sec. 3.C.ii) have been developed as an enantioselective NMR shift reagents for aromatic compounds.[108] In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in an NMR spectrum depends on the electron density of its bond; the greater the density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ). However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in an NMR instrument), the closed loop of aromatic electrons circulates in a diamagnetic ring current, which generates a field of its own (ring current; known as magnetic anisotropy). As seen in Fig. 2.7, this induced field curves around and in the area of the proton is parallel to the external field, so the field "seen" by the aromatic protons is greater than it would have been in the absence of the diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron density were the only factor. Thus ordinary alkene hydrogen atoms are found at ∼ 5–6 δ, while the hydrogen atoms of benzene rings are located at 7–8 δ. However, if there were protons located above or within the ring, they would be subjected to a *decreased* field and should appear at lower δ values than normal CH_2 groups (normal δ for CH_2 is ∼ 1–2). The NMR spectrum of [10]paracyclophane (**48A**)

[101] See Jones, A.J. *Pure Appl. Chem.* ***1968****, 18*, 253. For methods of assigning Aromaticity, see Jug, K.; Köster, A. M. *J. Phys. Org. Chem.* ***1991****, 4,* 163; Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989****, 111,* 7371; Katritzky, A.R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* ***1989****, 111*, 7. See also, Bird, C.W. *Tetrahedron* ***1985****, 41*, 1409; ***1986****, 42,* 89; ***1987****, 43,* 4725.

[102] For a critique of the concept of aromaticity, see Stanger, A. *Chem. Commun.* ***2009***, 1939.

[103] Randic, M. *Chem. Rev.* ***2003****, 103*, 3449.

[104] Balaban, A.T.; Oniciu, D.C.; Katritzky, A.R. *Chem. Rev.* ***2004****, 104*, 2777.

[105] Armit, J.W.; Robinson; R. *J. Chem. Soc.* ***1925****, 127*, 1604.

[106] Jones, A.J. *Pure Appl. Chem.* ***1968****, 18*, 253, pp. 266–274; Mallion, R.B. *Pure Appl. Chem.* ***1980***, 52, 1541. Also see, Schleyer, P.v.R.; Jiao, H. *Pure Appl. Chem.* ***1996****, 68*, 209. For a discussion of the relationship between Pauing resonance energy and ring current, see Havenith, R.W.A. *J. Org. Chem.* ***2006****, 71,* 3559.

[107] Geuenich, D.; Hess, K.; Felix Köhler, F.; Herges, R. *Chem. Rev.* **2005***, 105*, 3758; Haddon, R.C.; Haddon, V.R.; Jackman, L.M. *Fortschr. Chem. Forsch.* ***1971****, 16,* 103; Dauben, Jr., H.J.; Wilson, J.D.; Laity, J.L. in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, ***1971***, pp. 167–206.

[108] Dignam, C.F.; Zopf, J.J.; Richards, C.J.; Wenzel, T.J. *J. Org. Chem.* ***2005****, 70,* 8071.

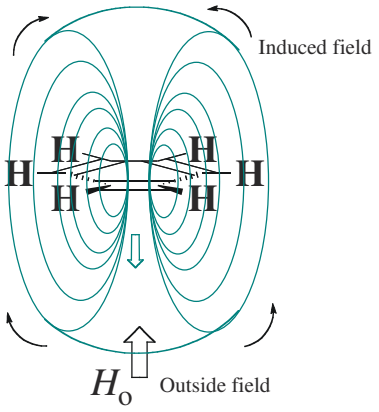
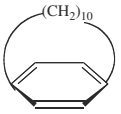
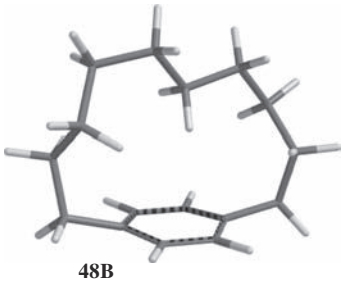


FIG. 2.7. Ring current in benzene.

showed that this was indeed the case,[109] and the CH_2 peaks were shifted to lower δ the closer they were to the middle of the chain. This fact that a portion of the methylene chain is positioned directly over the benzene ring is easier to see in the molecular model **48B**, and those protons are subject to the anisotropy shift.



48A



48B

It follows from this analysis that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, it can be concluded that the molecule is diatropic and hence aromatic. In addition, if the compound has protons above or within the ring (see an example of the latter in Sec. 2.K.vi), then these will be shifted upfield if the compound is diatropic. However, local framework effects are important to aromaticity, and it has been argued that downfield chemical shifts of arene hydrogen atoms are not reliable indicators of aromaticity.[110] One drawback to this method is that it cannot be applied to compounds that have no protons in either category (e.g, the dianion of squaric acid see Sec. 2.L). Unfortunately, ^{13}C NMR is of no help here, since these spectra do not show ring currents.[111]

[109] Waugh, J.S.; Fessenden, R.W. *J. Am. Chem. Soc.* ***1957****, 79*, 846. See also, Pascal, Jr., R.A.; Winans, C.G.; Van Engen, D. *J. Am. Chem. Soc.* ***1989****, 111,* 3007.
[110] Wannere, C.S.; Corminboeuf, C.; Allen, W.D.; Schaefer, III, H.F.; v. R. Schleyer, P. *Org. Lett.* ***2005****, 7,* 1457.
[111] See Günther, H.; Schmickler, H. *Pure Appl. Chem.* ***1975****, 44,* 807. See Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2007****, 13*, 6321; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A* ***2008****, 112*, 12816.

Bickelhaupt has argued that "double-bond delocalization" actually refers to bond-length equalization. The major effect is argued to be optimal sigma overlap, where the π electrons force the bonds to a somewhat shorter distance. For antiaromatic systems, the π electrons are said to have a stronger localizing drive.[111]

It has been shown that when the nucleus independent chemical shifts for a set of aromatic and antiaromatic hydrocarbons are summed, there is a linear relationship with the magnetic susceptibility exaltation (the difference between the measured magnetic susceptibility of a compound and a calculated value based on group additivity tables) for neutral, cationic, and monoanionic species.[112] Aromatic and antiaromatic dianions show a similar relationship, but with a different slope.[112]

It appears that there are both energetic and magnetic criteria for aromaticity. The so-called *circuit resonance energy*[113] is an important quantity that connects energetic and magnetic criteria of aromaticity. It is defined as a contribution of each cyclic path in a polycyclic π-system to the aromatic stabilization energy. The individual circuit contributions to aromaticity from the magnetic response of a polycyclic system have been determined, and named circuit resonance energies, with the same sign and essentially the same magnitude as the corresponding cyclic conjugation energy defined by Bosanac and by Gutman.[114] Ring-current diamagnetism was taken as the tendency of a cyclic π system to retain aromatic stabilization energy of the individual circuits.

Antiaromatic systems exhibit a *paramagnetic* ring current,[115] which causes protons on the outside of the ring to be shifted *upfield* while any inner protons are shifted *downfield*, in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions (see above). Compounds that sustain a paramagnetic ring current are called *paratropic* and are prevalent in four and eight-electron systems. As with aromaticity, antiaromaticity should be at a maximum when the molecule is planar and when bond distances are equal. The diamagnetic and paramagnetic effects of the ring currents associated with aromatic and antiaromatic compounds (i.e., shielding and deshielding of nuclei) can be measured by a simple and efficient criterion known as nucleus independent chemical shift (NICS).[116] The aromatic–antiaromatic ring currents reflect the extra π-effects that the molecules experience. The unique near zero value of NICS at the cyclobutadiene ring center is due to cancellation by large and opposite anisotropic components.[117]

Apart from the experimental NMR techniques, there are at least four theoretical models for aromaticity that have been compared and evaluated for predictive ability.[118] The *Hess–Schaad model*[119] is good for predicting aromatic stability of benzenoid hydrocarbons, but does not predict reactivity. The *Herndon model*[120] is also good for predicting aromatic stability, but is unreliable for benzenoidicity and does not predict reactivity. The *conjugated-circuit model*[121]

[112] Mills, N.S.; Llagostera, K.B. *J. Org. Chem.* ***2007****, 72,* 9163.
[113] Aihara, J. J. *Am. Chem. Soc.* ***2006****, 128*, 2873.
[114] Gutman, I. *Monatsh. Chem*. **2005**, *136*, 1055.; Bosanac, S.; Gutman, I. *Z. Naturforsch*. ***1977****, 32a*, 10; Gutman, I.; Bosanac, S. *Tetrahedron* **1977**, *33*, 1809.
[115] Pople, J.A.; Untch, K.G. *J. Am. Chem. Soc.* ***1966****, 88,* 4811; Longuet-Higgins, H.C. in Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 109–111.
[116] Schleyer, P.v.R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N.J.R.v.E. *J. Am. Chem. Soc.* ***1996****, 118*, 6317.
[117] Schleyer, P.v.R.; Manoharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; Hommes, N.J.R.v.E. *Org. Lett.* ***2001****, 3,* 2465
[118] Plavšić, D.; Babić, D.; Nikolić, S.; Trinajstic, N. *Gazz. Chim. Ital.,* ***1993****, 123*, 243.
[119] Hess, Jr., B.A.; Schaad, L.J. *J. Am. Chem. Soc.* ***1971****, 93*, 305.
[120] Herndon, W.C. *Isr. J. Chem.* ***1980****, 20*, 270.
[121] Randić, *M.Chem.Phys.Lett*. ***1976***, *38*, 68.

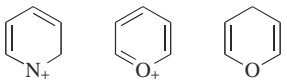
is very good for predicting aromatic stability but not reactivity, and the *hardness model*[122] is best for predicting kinetic stability. Delocalization energy of π electrons has been used as an index for aromaticity in polycyclic aromatic hydrocarbons.[123] The claims for linear relationships between aromaticity and energetics, geometries, and magnetic criteria were said to be *invalid* for any representative set of heteroaromatics in which the number of heteroatoms varies.[124]

It should be emphasized that the old and new definitions of aromaticity are not necessarily parallel. If a compound is diatropic, and therefore aromatic under the new definition, it is more stable than the canonical form of lowest energy, but this does not mean that it will be stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy, but by the difference in free energy between the molecule and the transition states for the reactions involved. These differences may be quite small, even if the resonance energy is large. A unified theory has been developed that relates ring currents, resonance energies, and aromatic character.[125] Note that aromaticity varies in magnitude relatively and sometimes absolutely with the molecular environment, which includes the polarity of the medium.[126]

The vast majority of aromatic compounds have a closed loop of six electrons in a ring (the aromatic sextet), and those compounds will be considered first.[127] Note that a "formula periodic table" for the benzenoid polyaromatic hydrocarbons has been developed.[128]

2.I.i. Six-Membered Rings

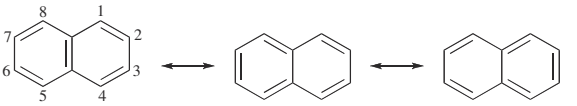
Not only is the benzene ring aromatic, but so are many heterocyclic analogues in which one or more heteroatoms replace carbon in the ring.[129] When nitrogen is the heteroatom, there is a sextet and there is an unshared pair on the nitrogen that does not participate in the aromaticity. Therefore, derivatives (e.g., *N*-oxides or pyridinium ions) are still aromatic. There are more significant canonical forms (e.g., **49**) for nitrogen heterocycles than for benzene. Where oxygen or sulfur is the heteroatom, it must be present in its ionic form (**50**) in order to possess the valence of 3 demanded for participation in such a system. Thus, pyran (**51**) is not aromatic, but the pyrylium ion (**50**) is.[130]



49 **50** **51**

[122] Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989****, 111*, 7371; Zhou, Z.; Navangul, H.V. *J. Phys. Org. Chem.* ***1990****, 3,* 784.
[123] See Cyrański, M.K. *Chem. Rev.* ***2005****, 105*, 3773.
[124] Katritzky, A.R.; Karelson, M.; Sild, S.; Krygowski, T.M.; Jug, K. *J. Org. Chem.* ***1998****, 63*, 5228.
[125] Haddon, R.C. *J. Am. Chem. Soc.* ***1979****, 101,* 1722; Haddon, R.C.; Fukunaga, T. *Tetrahedron Lett.* ***1980****, 21*, 1191.
[126] Katritzky, A.R.; Karelson, M.; Wells, A.P. *J. Org. Chem.* ***1996****, 61*, 1619.
[127] Values of MO energies for many aromatic systems, calculated by the HMO method, are given in Coulson, C.A.; Streitwieser, Jr., A. *A Dictonary of π Electron Calculations*, W.H. Freeman, San Francisco, ***1965***. Values calculated by a variation of the SCF method are given by Dewar, M.J.S.; Trinajstic, N. *Collect. Czech. Chem. Commun.* ***1970****, 35,* 3136, 3484.
[128] Dias, J.R. *Chem. in Br.* ***1994***, 384.
[129] See Katritzky, A.R.; Karelson, M.; Malhotra, N. *Heterocycles* ***1991****, 32*, 127.
[130] See Balaban, A.T.; Schroth, W.; Fischer, G. *Adv. Heterocycl. Chem.* ***1969****, 10*, 241.

In systems of fused six-membered aromatic rings,[131] the principal canonical forms are usually not all equivalent. Naphthalene, (**52**) has a central double bond and is thus different from the other two canonical forms, which are equivalent to each other.[132] For naphthalene, these are the only forms that can be drawn



52

without consideration of Dewar forms or those with charge separation.[133] If it is assumed that the three forms contribute equally, the 1,2-bond has more double-bond character than the 2,3-bond. Molecular orbital calculations show bond orders of 1.724 and 1.603, respectively (cf. benzene, 1.667). In agreement with these predictions, the 1,2 and 2,3 bond distances are 1.36 and 1.415 Å, respectively,[134] and ozone (**19–09** and **15–58**) preferentially attacks the 1,2-bond.[135] This nonequivalency of bonds, called *partial bond fixation*,[136] is found in nearly all fused aromatic systems. Note that a strained naphthalene derivative has been prepared in which one benzene ring is fused to two bicyclic systems. In this new naphthalene derivative, one six-membered ring has equalized bond lengths, but the other ring has alternating bond lengths.[137] The aromaticity of cation, anion, and ion–radical derivatives of naphthalene and other arenes has also been calculated.[138] A six-membered ring with a circle is often used to indicate an aromatic system, but Kekulé structures having the C=C units rather than a circle are used most often in this book. This statement is made here because one circle can be used for benzene, but it would be misleading to use two circles for naphthalene, for example, because that would imply 12 aromatic electrons, when naphthalene has only 10.[139]

In phenanthrene, where the 9,10-bond is a single bond in only one of five canonical forms (**53**), bond fixation is significant and this bond is readily attacked by many reagents:[140] It has been observed that increased steric crowding leads to an increase in Dewar-benzene-type structures.[141] In general, there is a good correlation between bond distances in fused aromatic compounds and bond orders. Another experimental quantity that correlates well with the bond order of a given bond in an aromatic system is the NMR

[131] See Gutman, I.; Cyvin, S.J. *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer, NY, ***1989***; Dias, J.R. *Handbook of Polycyclic Hydrocarbons, Part A: Benzenoid Hydrocarbons*, Elsevier, NY, ***1987***; Clar, E. *Polycyclic Hydrocarbons*, 2 Vols., Academic Press, NY, ***1964***. For a "periodic table" that systematizes fused aromatic hydrocarbons, see Dias, J.R. *Acc. Chem. Res.* ***1985***, 18, 241; *Top. Curr. Chem.* ***1990***, *253*, 123; *J. Phys. Org. Chem.* **1990**, *3*, 765.

[132] See Fuji, Z.; Xiaofeng, G.; Rongsi, C. *Top. Curr. Chem.* ***1990***, *153,* 181; Wenchen, H.; Wenjie, H. *Top. Curr. Chem.* ***1990***, *153,* 195; Sheng, R. *Top. Curr. Chem.* ***1990***, *153,* 211; Rongsi, C.; Cyvin, S.J.; Cyvin, B.N.; Brunvoll, J.; Klein, D.J. *Top. Curr. Chem.* ***1990***, *153*, 227, and references cited in these papers. For a monograph, see Cyvin, S.J.; Gutman, I. *Kekulé Structures in Benzenoid Hydrocarbons*, Springer, NY, ***1988***.

[133] See Sironi, M.; Cooper, D.L.; Gerratt, J.; Raimondi, M. *J. Chem. Soc. Chem. Commun.* ***1989***, 675.

[134] Cruickshank, D.W.J. *Tetrahedron* ***1962***, *17*, 155.

[135] Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas,* ***1947***, *66,* 201.

[136] For a review, see Efros, L.S. *Russ. Chem. Rev.* ***1960***, *29,* 66.

[137] Uto, T.; Nishinaga, T.; Matsuura, A.; Inoue, R.; Komatsu, K. *J. Am. Chem. Soc.* ***2005***, *127,* 10162.

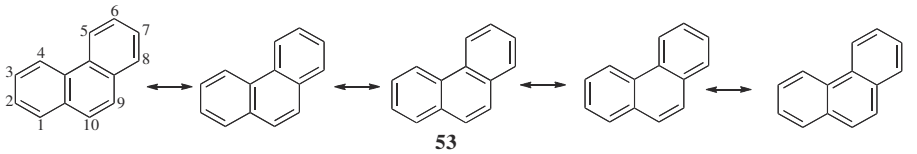
[138] Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2006***, *71,* 9357.

[139] See Belloli, R. *J. Chem. Educ.* ***1983***, *60,* 190.

[140] See also, Lai, Y. *J. Am. Chem. Soc.* ***1985***, *107,* 6678.

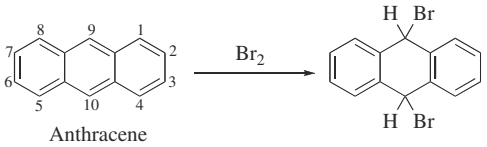
[141] Zhang, J.; Ho, D.M.; Pascal, Jr., R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 10919.

coupling constant for coupling between the hydrogen atoms on the two carbons of the bond.[142]



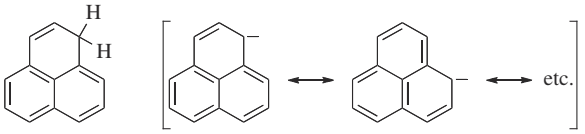
53

The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (Sec. 2.E).[143] Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which can be drawn, respectively, two, three, four, and five principal canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal mol^{-1} (152, 255, 351, and 385 kJ mol^{-1}), calculated from heat of combustion data.[144] Note that when phenanthrene, which has a total resonance energy of 92 kcal mol^{-1} (385 kJ mol^{-1}), loses the 9,10-bond by attack of a reagent (e.g., ozone or bromine), two complete benzene rings remain, each with 36 kcal mol^{-1} (152 kJ mol^{-1}) that would be lost if those rings were similarly attacked. The fact that anthracene undergoes many reactions across the 9,10-positions can be explained in a similar manner. Resonance energies for fused systems can be estimated by counting canonical forms.[145] Calculations offer complementary evidence for the repulsive character of the H-H interactions in phenanthrene's bay region.[146]



Anthracene

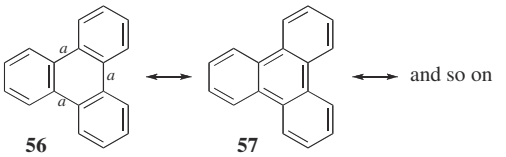
Not all fused systems can be fully aromatic. Thus for phenalene (**54**) there is no way to distribute double bonds so that each carbon has one single and one double bond.[147] However, phenalene is acidic and reacts with potassium methoxide to give the corresponding anion (**55**), which is completely aromatic. So are the corresponding radical and cation, in which the resonance energies are the same (see Sec. 2.I.iii).[148]



54 **55**

[142] Cooper, M.A.; Manatt, S.L. *J. Am. Chem. Soc.* ***1969****, 91,* 6325.
[143] See Herndon, W.C.; Ellzey, Jr., M.L. *J. Am. Chem. Soc.* ***1974****, 96*, 6631.
[144] Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***, p. 98.
[145] Swinborne-Sheldrake, R.; Herndon, W.C. *Tetrahedron Lett.* ***1975***, 755.
[146] Poater, J.; Visser, R.; Solà, M.; Bickelhaupt, F.M. *J. Org. Chem.* ***2007****, 72*, 1134.
[147] For reviews of phenalenes, see Murata, I. *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1,* 159; Reid, D.H. *Q. Rev. Chem. Soc.* ***1965****, 19*, 274.
[148] Pettit, R. *J. Am. Chem. Soc.* ***1960****, 82,* 1972.

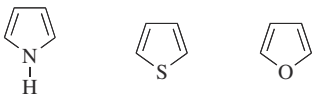
Molecules that contain fused rings (e.g., phenanthrene or anthracene) are generally referred to as linear or angular polyacenes. ***Acenes*** are a class of organic compounds and polycyclic aromatic hydrocarbons made up of linearly fused benzene rings. In a fused system, with a focus on each individual ring, there are not six electrons for each ring.[149] In naphthalene, for example, if one ring is to have six, the other must have only four. The greater reactivity of the ring system of naphthalene compared with benzene has been explained by regarding one of the naphthalene rings as aromatic and the other as a butadiene system.[150] This effect can become extreme, as in the case of triphenylene.[151] For this compound, there are eight canonical forms like **56**, in which none of the three bonds marked *a* is a double bond and only one form (**57**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is "empty". Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene. Triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.[152] This phenomenon, whereby some rings in fused systems give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by UV spectra,[131] as well as chemical reactivity. In general, an increase of size of both linear and angular polyacenes is associated with a substantial decrease in their aromaticity, with a greater decrease for the linear polyacenes.[153] Note that molecular loops and belts can be made that involve acenes.[154]



56 **57**

2.I.ii. Five, Seven, and Eight-Membered Rings

Aromatic sextets can also be present in five- and seven-membered rings. If a five-membered ring has two double bonds, and the fifth atom possesses an unshared pair of electrons, as in pyrrole, the ring has five *p* orbitals that can overlap to create five new orbitals: three bonding and two antibonding. There are six electrons for these orbitals: the four *p* orbitals of the double bonds each contribute one and the filled orbital contributes



Pyrrole Thiophene Furan

the other two. The six electrons occupy the bonding orbitals and constitute an aromatic sextet, illustrated in Fig. 2.8 . The electron potential map of pyrrole in Fig. 2.8 shows the aromatic cloud (dark area near the top of the model), indicative of significant electron

[149] See Glidewell, C.; Lloyd, D. *Tetrahedron* ***1984****, 40,* 4455, *J. Chem. Educ.* ***1986****, 63*, 306; Hosoya, H. *Top. Curr. Chem.* ***1990****, 153*, 255.
[150] Meredith, C.C.; Wright, G.F. *Can. J. Chem.* ***1960****, 38,* 1177.
[151] For a review of triphenylenes, see Buess, C.M.; Lawson, D.D. *Chem. Rev.* ***1960****, 60,* 313.
[152] Clar, E.; Zander, M. *J. Chem. Soc.* ***1958***, 1861.
[153] Cyrański, M.K.; Stçepień, B.T.; Krygowski, T.M. *Tetrahedron* ***2000****, 56*, 9663.
[154] Tahara, K.; Tobe, Y. *Chem. Rev.* ***2006****, 106,* 5274

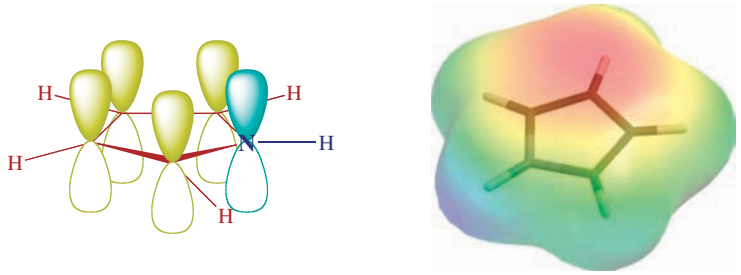
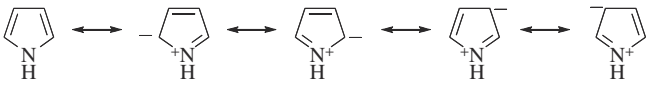


FIG. 2.8. Overlap of five *p* orbitals in pyrrole and the electron potential map of pyrrole.

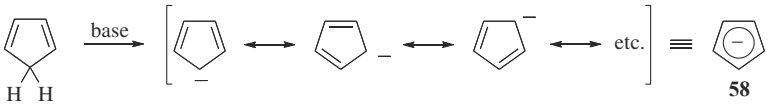
density. The heterocyclic compounds pyrrole, thiophene, and furan are the most important examples of this kind of aromaticity, although furan has a lower degree of aromaticity when compared to the other two.[155] Resonance energies for these three compounds are, respectively, 21, 29, and 16 kcal mol^{-1} (88, 121, and 67 kJ mol^{-1}).[156] The aromaticity can also be shown by canonical forms, (e.g., for pyrrole):



A

In contrast to pyridine, the unshared pair in canonical structure **A** in pyrrole is needed for the aromatic sextet. Since the electron pair is not available for donation, pyrrole is a much weaker base than pyridine.

The fifth atom may be carbon rather than a heteroatom, if carbon has an unshared pair (as in an anion). Cyclopentadiene is known to react with a suitable base, and loss of a proton to give a carbanion that is aromatic and therefore quite stable, although it is reactive to alkylating agents and electrophilic reagents. Due to formation of the stable cyclopentadienyl anion, cyclopentadiene (p$K_a \sim 16$) is approximately as strong an acid as water. The cyclopentadienide ion is sometimes represented as in **58**, although more commonly one of the canonical forms is used. Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five



58

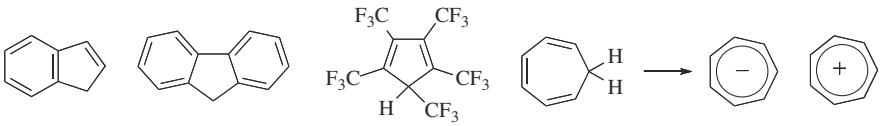
forms are equivalent, and the resonance energy for **58** has been estimated to be 24-27 kcal mol^{-1} (100–113 kJ mol^{-1}).[157] All five carbons are equivalent, as demonstrated by labeling the starting compound with ^{14}C and finding all positions equally labeled when

[155] The order of aromaticity of these compounds is benzene > thiophene > pyrrole > furan, as calculated by an aromaticity index based on bond distance measurements. This index has been calculated for five- and six-membered monocyclic and bicyclic heterocycles: Bird, C.W. *Tetrahedron* ***1985****, 41*, 1409; ***1986****, 42,* 89; ***1987****, 43,* 4725.

[156] Wheland, G.W. *Resonance in Organic Chemistry,* Wiley, NY, ***1955***, p. 99. See also, Calderbank, K.E.; Calvert, R.L.; Lukins, P.B.; Ritchie, G.L.D. *Aust. J. Chem.* ***1981****, 34,* 1835.

[157] Bordwell, F.G.; Drucker, G.E.; Fried, H.E. *J. Org. Chem.* ***1981****, 46,* 632.

cyclopentadiene was regenerated.[158] As expected for an aromatic system, **58** is diatropic[159] and aromatic substitutions (see Chapters 11 and 13) on it have been successfully carried out.[160] Average bond order has been proposed as a parameter to evaluate the aromaticity of such rings, but there is poor correlation with nonaromatic and antiaromatic systems.[161] A model that relies on calculating relative aromaticity from appropriate molecular fragments has also been developed.[162] Bird[163] devised the aromatic index (I_A, or aromaticity index), which is a statistical evaluation of the extent of ring bond order, and has been used as a criterion of aromaticity. Another bond-order index was proposed by Pozharskii,[164] which builds on the work of Fringuelli et al.[165] Absolute hardness (see Sec. 8.E), calculated from molecular refractions for a range of aromatic and heteroaromatic compounds, shows good linear correlation with aromaticity.[166] Indene and fluorene are also acidic ($pK_a \sim 20$ and 23, respectively), but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring. On the other hand, the acidity of 1,2,3,4,5-pentakis(trifluoromethyl)cyclopentadiene (**59**) is greater than that of nitric acid,[167] because of the electron-withdrawing effects of the trifluoromethyl groups (see Sec. 8.F). Modifications of the Bird[163] and Pozharskii[164] systems have been introduced that are particularly useful for five-membered ring heterocycles.[168] Recent work introduced a new local aromaticity measure, defined as the mean of Bader's electron delocalization index (DI)[169] of para-related carbon atoms in six-membered rings.[170] Bond resonance energy has been used as an indicator of local aromaticity.[171] The relative merits of several aromaticity indices has been discussed.[172]

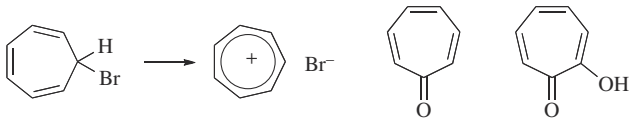


Indene Fluorene **59** **60** **61** **62**

As seen above, relative acidity can be used to study the aromatic character of the resulting conjugate base of a given compound. In sharp contrast to cyclopentadiene (see Sec. 2.I.ii) is cycloheptatriene (**60**), which has no unusual acidity. This would be hard to explain without the aromatic sextet theory, since, on the basis of resonance forms or a simple consideration of orbital overlaps, **61** should be as stable as the cyclopentadienyl anion (**58**). This eight electron system is antiaromatic, however. While **61** has been

[158] Tkachuk, R.; Lee, C.C. *Can. J. Chem.* ***1959****, 37,* 1644.
[159] Bradamante, S.; Marchesini, A.; Pagani, G. *Tetrahedron Lett.* ***1971***, 4621.
[160] Webster, O.W. *J. Org. Chem.* ***1967****, 32*, 39; Rybinskaya, M.I.; Korneva, L.M. *Russ. Chem. Rev.* ***1971****, 40*, 247.
[161] Jursic, B.S. *J. Heterocyclic Chem.* ***1997****, 34*, 1387.
[162] Hosmane, R.S.; Liebman, J.F. *Tetrahedron Lett.* ***1992****, 33*, 2303.
[163] Bird, C.W. *Tetrahedron* ***1996****, 52,* 9945; Hosoya, H. *Monat. Chemie* ***2005****, 136*, 1037.
[164] Pozharskii, A.F. *Khimiya Geterotsikl Soedin* ***1985***, 867.
[165] Fringuelli, F. Marino, G.; Taticchi, A.; Grandolini, G. J. *Chem. Soc. Perkin Trans. 2* ***1974***, 332.
[166] Bird, C.W. *Tetrahedron* ***1997****, 53*, 3319; *Tetrahedron* ***1998****, 54,* 4641.
[167] Laganis, E.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1980****, 102*, 6633.
[168] Kotelevskii, S.I.; Prezhdo, O.V. *Tetahedron* ***2001****, 57*, 5715.
[169] See Bader, R.F.W. *Atoms in Molecules: A Quantum Theory*, Clarendon, Oxford, ***1990***; Bader, R.F.W. *Acc. Chem. Res.* ***1985****, 18,* 9; Bader, R.F.W. *Chem. Rev.* ***1991****, 91*, 893.
[170] Poater, J.; Fradera, X.; Duran, M.; Solà, M. *Chem. Eur. J.* ***2003****, 9*, 400; 1113.
[171] Aihara, J.; Ishida, T.; Kanno, H. *Bull. Chem. Soc. Jpn.* ***2007****, 80*, 1518.
[172] Fallah-Bagher-Shaidaei, H.; Wannere, C.S.; Corminboeuf, C.; Puchta, R.; v.R. Schleyer, P. *Org. Lett.* ***2006****, 8*, 863.

prepared in solution,[173] it is less stable than **58** and far less stable than **62**, in which **60** has lost not a proton but the equivalent of a hydride ion. The six double-bond electrons of **62** overlap with the empty orbital on the seventh carbon and there is a sextet of electrons covering seven carbon atoms. The cycloheptatrienyl cation (known as the *tropylium ion*, **62**) is quite stable,[174] but are generally formed from the corresponding halide rather than by loss of a hydride. Tropylium bromide (**63**), which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually better viewed as an ionic compound.[175] Many substituted tropylium ions have been prepared to probe the aromaticity, structure, and reactivity of such systems.[176] As with **58**, the equivalence of the carbon atoms in **62** has been demonstrated by isotopic labeling.[177] The aromatic cycloheptatrienyl cations $C_7Me_7^+$ and $C_7Ph_7^+$ are known,[178] although their coordination complexes with transition metals have been problematic, possibly because they assume a boat-like rather than a planar conformation[179]



63 **64** **65**

Tropone (**64**) is another seven-membered ring that shows some aromatic character. This molecule would have an aromatic sextet if the two C=O electrons stayed away from the ring and resided near the electronegative oxygen atom. In fact, tropones are stable compounds, and tropolones (**65**) are found in nature.[180] However, analyses of dipole moments, NMR spectra, and X-ray diffraction measurements show that tropones and tropolones display appreciable bond alternations.[181] These molecules must be regarded as essentially non-aromatic, although some have aromatic character. Tropolones readily undergo aromatic substitution, emphasizing that the old and the new definitions of aromaticity are not always parallel. It is known that **65** is acidic ($pK_a \sim 6.7$),[182] in large part because the resulting anion has aromatic character. Indeed, **65** is considered to be a vinylogous carboxylic acid. In sharp contrast to **64**, cyclopentadienone (**66**) has been isolated only in an Ar matrix < 38 K.[183] Above this temperature it dimerizes. Many earlier

[173] Dauben Jr., H.J.; Rifi, M.R. *J. Am. Chem. Soc.* ***1963****, 85,* 3041; also see, Breslow, R.; Chang, H.W. *J. Am. Chem. Soc.* ***1965****, 87*, 2200.

[174] See Pietra, F. *Chem. Rev.* ***1973****, 73,* 293; Bertelli, D.J. *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1*, 29; Kolomnikova, G.D.; Parnes, Z.N. *Russ. Chem. Rev.* ***1967****, 36,* 735; Harmon, K.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4; Wiley, NY, 1973, pp. 1579–1641.

[175] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1954****, 76,* 3203.

[176] Pischel, U.; Abraham, W.; Schnabel, W.; Müller, U. *Chem. Commun.* ***1997***, 1383. See Komatsu, K.; Nishinaga, T.; Maekawa, N.; Kagayama, A.; Takeuchi, K. *J. Org. Chem.* ***1994****, 59*, 7316 for a tropylium dication.

[177] Vol'pin, M.E.; Kursanov, D.N.; Shemyakin, M.M.; Maimind, V.I.; Neiman, L.A. *J. Gen. Chem. USSR* ***1959****, 29,* 3667.

[178] Takeuchi, K.; Yokomichi, Y.; Okamoto, K. *Chem. Lett.* ***1977***,1177; Battiste, M. A. *J. Am. Chem. Soc.* ***1961****, 83*, 4101.

[179] Tamm, M.; Dreßel, B.; Fröhlich, R. *J. Org. Chem.* ***2000****, 65,* 6795.

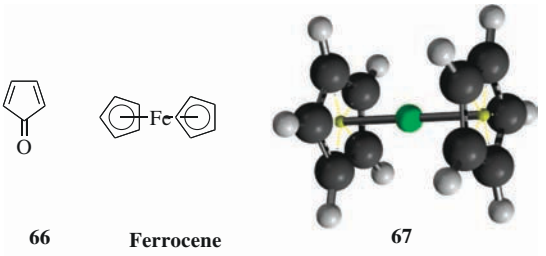
[180] Pietra, F. *Acc. Chem. Res.* ***1979****, 12*, 132; Nozoe, T. *Pure Appl. Chem.* ***1971****, 28,* 239.

[181] Schaefer, J.P.; Reed, L.L. *J. Am. Chem. Soc.* ***1971****, 93,* 3902; Watkin, D.J.; Hamor, T.A. *J. Chem. Soc. B* ***1971***, 2167; Barrow, M.J.; Mills, O.S.; Filippini, G. *J. Chem. Soc. Chem. Commun.* ***1973***, 66.

[182] von E. Doering, W.; Knox, L.H. *J. Am. Chem. Soc.* **1951**, *73*, 828.

[183] Maier, G.; Franz, L.H.; Hartan, H.; Lanz, K.; Reisenauer, H.P. *Chem. Ber.* ***1985****, 118,* 3196.

attempts to prepare it were unsuccessful.[184] As in **64**, the electronegative oxygen atom draws electron density to itself, but in this case it leaves only four electrons and the molecule is unstable. Some derivatives of **66** have been prepared.[145]



66 **Ferrocene** **67**

The *metallocenes* (also called *sandwich compounds*) constitute another type of five-membered aromatic compound in which two cyclopentadienide rings form a sandwich around a metal. The best known of these is ferrocene, where the η^5-coordination of the two cyclopentadienyl rings to iron is apparent in the 3D model **67**. Other metallocenes have been prepared with Co, Ni, Cr, Ti, V, and many other metals.[185] As a reminder (see Sec. 2.C), the η terminology refers to π-donation of electrons to the metal (η^3 for π-allyl systems, η^6 for coordination to a benzene ring, etc.), and η^5 refers to donation of five π-electrons to the iron. Ferrocene is quite stable, subliming $>100°C$ and unchanged at 400°C. The two rings rotate freely.[186] Many aromatic substitutions (Chapter 11) have been carried out on metallocenes.[187] Metallocenes containing two metal atoms and three cyclopentadienyl rings have also been prepared and are known as *triple-decker sandwiches*.[188] Even tetradecker, pentadecker, and hexadecker sandwiches have been reported.[189]

The bonding in ferrocene may be looked upon in simplified MO terms as follows.[190] Each of the cyclopentadienide rings has five molecular orbitals:three filled bonding and two empty antibonding orbitals (Sec. 2.I.ii). The outer shell of the Fe atom possesses nine atomic orbitals, that is, one 4*s*, three 4*p*, and five 3*d* orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the *s*, three *p*, and two of the *d* orbitals of the Fe to form 12 new orbitals, six of which are bonding. These six orbitals make up two ring–metal triple bonds. In addition, further bonding results from the overlap of the empty antibonding orbitals of the rings with additional filled *d* orbitals of the iron. All told, there are 18 electrons (10 of which may be considered to come from the rings and 8 from iron in the

[184] See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965****, 65,* 261.

[185] See Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, ***1965***; Lukehart, C.M. *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole, Monterey, CA, ***1985***, pp. 85–118; Sikora, D.J.; Macomber, D.W.; Rausch, M.D. *Adv. Organomet. Chem.* ***1986****, 25*, 317; Pauson, P.L. *Pure Appl. Chem.* ***1977****, 49*, 839; Perevalova, E.G.; Nikitina, T.V. *Organomet. React.* ***1972****, 4,* 163; Bublitz, D.E.; Rinehart, Jr., K.L. *Org. React.*, ***1969****, 17*, 1; Rausch, M.D. *Pure Appl. Chem.* ***1972****, 30,* 523; Bruce, M.I. *Adv. Organomet. Chem.* ***1972****, 10*, 273, 322–325.

[186] For a discussion of the molecular structure, see Haaland, A. *Acc. Chem. Res.* ***1979****, 12,* 415.

[187] See Plesske, K. *Angew. Chem. Int. Ed.* ***1962****, 1,* 312, 394.

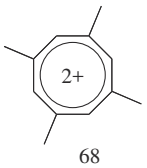
[188] For a review, see Werner, H. *Angew. Chem. Int. Ed.* ***1977****, 16,* 1.

[189] See, for example, Siebert, W. *Angew. Chem. Int. Ed.* ***1985****, 24,* 943.

[190] Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, ***1965***, pp. 13–28; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 2, Methuen, London, ***1968***, pp. 97–104; Grebenik, P.; Grinter, R.; Perutz, R.N. *Chem. Soc. Rev.* ***1988****, 17*, 453, 460.

zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.

The tropylium ion has an aromatic sextet spread over seven carbon atoms. An analogous ion, with the sextet spread over eight carbon atoms, is the 1,3,5,7-tetramethylcyclooctatetraene dictation (**68**). This ion, which is stable in solution at −50°C, is diatropic and approximately planar. The dication **68** is not stable above about −30°C.[191]



68

2.I.iii. Other Systems Containing Aromatic Sextets

Simple resonance theory predicts that pentalene (**69**), azulene (**70**), and heptalene (**71**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular orbital calculations show that azulene should be stable but not the other two. This finding is borne out by experiment. Heptalene has been prepared,[192] but reacts readily with oxygen, acids, and bromine, is easily hydrogenated, and polymerizes on standing. Analysis of its NMR spectrum shows that it is not planar.[193] The 3,8-dibromo and 3,8-dicarbomethoxy derivatives of **71** are stable in air at room temperature, but are not diatropic.[194] A number of methylated heptalenes and dimethyl 1,2-heptalenedicarboxylates have also been prepared and are stable non-aromatic compounds.[195] Pentalene has not been prepared,[196] but the hexaphenyl[197] and 1,3,5-tri-*tert*-butyl derivatives[198] are known. The former is air sensitive in solution. The latter is stable, but X-ray diffraction and photoelectron spectral data show bond alternation.[199] Pentalene and its methyl and dimethyl derivatives have been formed in solution, but they dimerize before they can be isolated.[200] Many other attempts to prepare these two systems have failed.

[191] Olah, G.A.; Staral, J.S.; Liang, G.; Paquette, L.A.; Melega, W.P.; Carmody, M.J. *J. Am. Chem. Soc.* ***1977****, 99,* 3349. See also, Radom, L.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1977****, 99,* 7522; Olah, G.A.; Liang, G. *J. Am. Chem. Soc.* ***1976****, 98,* 3033; Willner, I.; Rabinovitz, M. *Nouv. J. Chim.,* ***1982****, 6*, 129.

[192] Paquette, L.A.; Browne, A.R.; Chamot, E. *Angew. Chem. Int. Ed.* ***1979****, 18,* 546. For a review of heptalenes, see Paquette, L.A. *Isr. J. Chem.* ***1980****, 20*, 233.

[193] Bertelli, D.J., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, p. 326. See also, Stegemann, J.; Lindner, H.J. *Tetrahedron Lett.* ***1977***, 2515.

[194] Vogel, E.; Ippen, J. *Angew. Chem. Int. Ed.* ***1974****, 13*, 734; Vogel, E.; Hogrefe, F. *Angew. Chem. Int. Ed.* ***1974****, 13,* 735.

[195] Hafner, K.; Knaup, G.L.; Lindner, H.J. *Bull. Soc. Chem. Jpn.* ***1988****, 61,* 155.

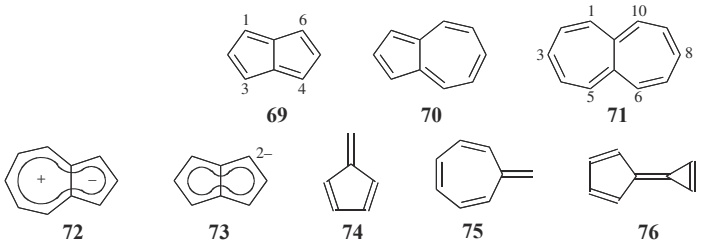
[196] See Knox, S.A.R.; Stone, F.G.A. *Acc. Chem. Res.* ***1974****, 7*, 321.

[197] LeGoff, E. *J. Am. Chem. Soc.* ***1962****, 84,* 3975. See also, Hartke, K.; Matusch, R. *Angew. Chem. Int. Ed.* ***1972****, 11,* 50.

[198] Hafner, K.; Süss, H.U. *Angew. Chem. Int. Ed.* ***1973****, 12,* 575. See also, Hafner, K.; Suda, M. *Angew. Chem. Int. Ed.* ***1976****, 15*, 314.

[199] Bischof, P.; Gleiter, R.; Hafner, K.; Knauer, K.H.; Spanget-Larsen, J.; Süss, H.U. *Chem. Ber.* ***1978****, 111*, 932.

[200] Hafner, K.; Dönges, R.; Goedecke, E.; Kaiser, R. *Angew. Chem. Int. Ed.* ***1973****, 12*, 337.



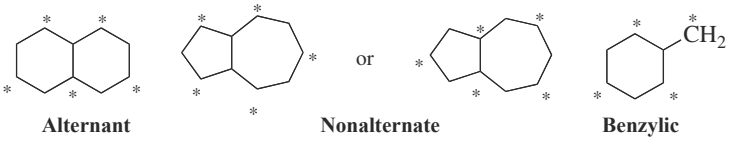
69 **70** **71**

72 **73** **74** **75** **76**

In sharp contrast to **69** and **71**, azulene (**70**) is a blue solid, is quite stable, and many of its derivatives are known.[201] Azulene readily undergoes aromatic substitution. Azulene may be regarded as a combination of **58** and **62** and, indeed, possesses a dipole moment of 0.8 *D* (see **72**).[202] Interestingly, if two electrons are added to pentalene, a stable dianion (**73**) results.[203] It can be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons (not 8 or 12) are available for aromaticity. [*n*,*m*]-Fulvalenes ($n \neq m$, where fulvalene is **74**), as well as azulene are known to shift their π-electrons due to the influence of dipolar aromatic resonance structures.[204] However, calculations showed that dipolar resonance structures contribute only 5% to the electronic structure of heptafulvalene (**75**), although 22–31% to calicene (**76**).[205] Based on Baird's theory,[206] these molecules are influenced by aromaticity in both the ground and excited states, therefore acting as aromatic "chameleons." This premise was confirmed in work by Ottosson and co-workers.[204] Aromaticity indexes for various substituted fulvalene compounds has been reported.[207]

2.J. ALTERNANT AND NONALTERNANT HYDROCARBONS[208]

Aromatic hydrocarbons can be divided into alternant and nonalternant hydrocarbons. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets such that no two atoms of the same set are directly linked. For convenience, one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon:



Alternant **Nonalternate** **Benzylic odd alternant**

In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; that is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$

[201] For a review on azulene, see Mochalin, V.B.; Porshnev, Yu.N. *Russ. Chem. Rev.* ***1977****, 46*, 530.
[202] Tobler, H.J.; Bauder, A.; Günthard, H.H. *J. Mol. Spectrosc.,* ***1965****, 18,* 239.
[203] Katz, T.J.; Rosenberger, M.; O'Hara, R.K. *J. Am. Chem. Soc.* ***1964****, 86,* 249. See also, Willner, I.; Becker, J.Y.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1979****, 101*, 395.
[204] Möllerstedt, H.; Piqueras, M.C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* ***2004****, 126*, 13938.
[205] Scott, A.P.; Agranat, A.; Biedermann, P.U.; Riggs, N.V.; Radom, L. *J. Org. Chem.* ***1997****, 62,* 2026.
[206] Baird, N.C. *J. Am. Chem. Soc.* ***1972****, 94,* 4941.
[207] Stepien, B.T.; Krygowski, T.M.; Cyrański, M.K. *J. Org. Chem.* ***2002****, 67,* 5987.
[208] See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 122–129; Dewar, M.J.S. *Prog. Org. Chem.* ***1953****, 2*, 1.

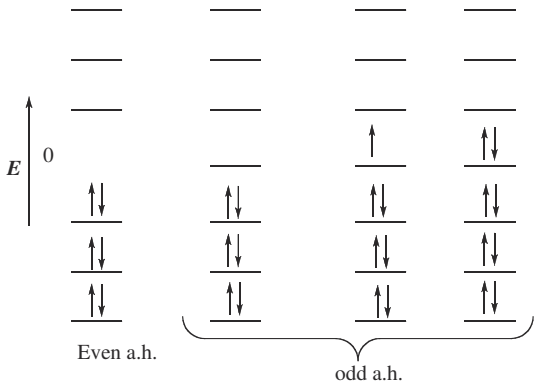


FIG. 2.9. Energy levels in odd- and even-alternant hydrocarbons.[209] The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

(Fig. 2.9[209]). Even-alternant hydrocarbons are those with an even number of conjugated atoms, that is, an equal number of starred and unstarred atoms. For these hydrocarbons all the bonding orbitals are filled and the (electrons are uniformly spread over the unsaturated atoms.

As with the allylic system, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero-bonding energy. For example, in the benzylic system the cation has an unoccupied nonbonding orbital, the free radical has one electron there and the carbanion has two (Fig. 2.10). As with the allylic system, all three species have the same bonding energy. The charge distribution (or unpaired-electron

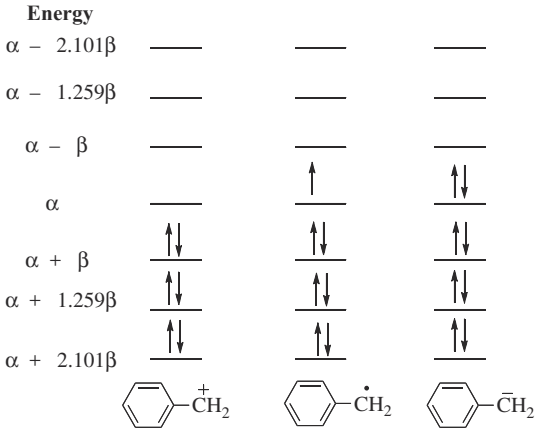


FIG. 2.10. Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a *p* orbital (Sec. 2.B), the nonbonding orbital has no bonding energy.

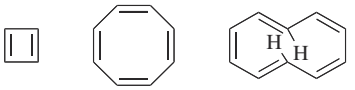
[209] Taken from Dewar, M.J.S *Prog. Org. Chem.* ***1953****, 2*, 1, p. 8.

distribution) over the entire molecule is also the same for the three species and can be calculated by a relatively simple process.[208]

For nonalternant hydrocarbons, the energies of the bonding and antibonding orbitals are not equal and opposite and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult, but have been carried out.[210] Theoretical approaches to calculate topological polarization and reactivity of these hydrocarbons have been reported.[211]

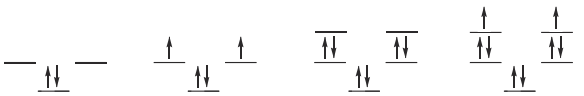
2.K. AROMATIC SYSTEMS WITH ELECTRON NUMBERS OTHER THAN SIX

The special stability of benzene is well recognized, and this stability is also associated with rings that are similar, but of different sizes, (e.g., cyclobutadiene (**77**), cyclooctatetraene (**78**), cyclodecapentaene (**79**)[212],



77 **78** **79**

and so on. The general name *annulene* is given to these compounds,[213] benzene being [6] annulene, and **77**–**79** being called, respectively, [4], [8], and [10]annulene.[214] By a naïve consideration of resonance forms, these annulenes and higher ones should be as aromatic as benzene. Yet they proved remarkably elusive. The ubiquitous benzene ring is found in thousands of natural products, in coal and petroleum, and is formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature and, except for cyclooctatetraene, their synthesis is not simple. Obviously, there is something special about the number six in a cyclic system of electrons.



Duet (aromatic) Quartet (diradical) Sextet (aromatic) Octet (diradical)

Hückel's rule, based on MO calculations,[215] predicts that electron rings will constitute an aromatic system only if the number of electrons in the ring is of the form $4n + 2$, where n is zero or any position integer. Systems that contain $4n$ electrons are predicted to be nonaromatic.

[210] Brown, R.D.; Burden, F.R.; Williams, G.R. *Aust. J. Chem.* ***1968****, 21*, 1939. For reviews, see Zahradnik, R., in Snyder, J.P. *Nonbenzenoid Aromatics* Vol. 2, Academic Press, NY, ***1971***, pp. 1–80; Zahradnik, R. *Angew. Chem. Int. Ed.* ***1965****, 4,* 1039.

[211] Langler, R.F. *Aust. J. Chem.* ***2000****, 53,* 471; Fredereiksen, M.U.; Langler, R.F.; Staples, M.A.; Verma, S.D. *Aust. J. Chem.* ***2000****, 53*, 481.

[212] For other stereoisomers, see Section 2.K.iv.

[213] Spitler, E.L.; Johnson, II, C.A.; Haley, M.M. *Chem. Rev.* ***2006****, 106*, 5344; for a discussion of annulenylenes, annulynes, and annulenes, see Stevenson, C.D. *Acc. Chem. Res.* ***2007***, *40*, 703.

[214] For a discussion of bond shifting and automerization in [10]annulene, see Castro, C.; Karney, W.L.; McShane, C.M.; Pemberton, R.P. *J. Org. Chem.* ***2006****, 71*, 3001.

[215] See Nakajima, T. *Pure Appl. Chem.* ***1971****, 28,* 219; *Fortschr. Chem. Forsch.* ***1972****, 32*, 1.

The rule predicts that rings of 2, 6, 10, 14, and so on, electrons will be aromatic, while rings of 4, 8, 12, and so on, will not be. This is actually a consequence of *Hund's rule*. The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate and occur in pairs of equal energy. When there is a total of four electrons, Hund's rule predicts that two will be in the lowest orbital, but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. The degeneracy can be removed if the molecule is distorted from maximum molecular symmetry to a structure of lesser symmetry. For example, if **77** assumes a rectangular rather than a square shape, one of the previously degenerate orbitals has a lower energy than the other and will be occupied by two electrons. In this case, of course, the double bonds are essentially separate and the molecule is still not aromatic. Distortions of symmetry can also occur when one or more carbons are replaced by heteroatoms or in other ways.[216] The enthalpy of formation of cyclobutadiene was reported by Kass and co-workers.[217] There is a brief discussion of the importance of cyclobutadiene with respect to antiaromaticity.[218] A word of caution is in order for MO calculations in these systems. It is known that *ab initio* computations on benzene at electron-correlated MP2, MP3, CISD, and CCSD levels using a number of popular basis sets[219] give anomalous, nonplanar equilibrium structures. [220] The origin of these anomalies has been addressed.[220]

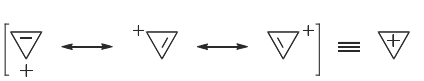
In the following sections, systems with various numbers of electrons are discussed. Any probe of aromaticity must include (1) the presence of a diamagnetic ring current; (2) equal or approximately equal bond distances, except when the symmetry of the system is disturbed by a heteroatom or in some other way; (3) planarity; (4) chemical stability; (5) the ability to undergo aromatic substitution.

2.K.i Systems of Two Electrons[221]

Obviously, there can be no ring of two carbon atoms (a double bond may be regarded as a degenerate case). However, by analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) is a $4n + 2$ system and expected to show aromaticity. Unsubstituted **80** has been prepared,[222] as well as several derivatives, (e.g., the trichloro, diphenyl, and dipropyl derivatives), and they are stable despite bond angles of only 60°. Tripropylcyclopropenyl,[223] tricyclopropylcyclopropenyl,[224] chlorodipropylcyclopropenyl,[225] and chloro-bis-dialkylaminocyclopropenyl[226] cations are among the most stable carbocations known, being stable even in

[216] See Hoffmann, R. *Chem. Commun.* ***1969***, 240.
[217] Fattahi, A.; Liz, L.; Tian, Z.; Kass, S.R. *Angew. Chem.* ***2006****, 118*, 5106.
[218] Bally, *T. Angew. Chem. Int. Ed.* **2006**, 45*, 6616–6619*
[219] Hehre, W. J.; Radom, L.; Pople, J. A.; Schleyer, P. v. R. *Ab Initio Molecular Orbital Theory*, John Wiley & Sons: New York, ***1986***; v.R. Schleyer, P.; Allinger, N.L.; Clark, T.; Gasteiger, J.; Kollman, P.A.; Schaefer, III, H.F.; Schreiner, P.R. (Eds.) *The Encyclopedia of Computational Chemistry*, John Wiley & Sons, Ltd., Chichester, ***1998***.
[220] Moran, D.; Simmonett, A.C.; Leach, III, F.E.; Allen, W.D.; v. R. Schleyer, P.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***2006****, 128,* 9342.
[221] See Billups, W.E.; Moorehead, A.W., in Rappoport *The Chemistry of the Cyclopropyl Group,* pt. 2, Wiley, NY, ***1987***, pp. 1533–1574; Potts, K.T.; Baum, J.S. *Chem. Rev.* ***1974****, 74*, 189; Closs, G.L. *Adv. Alicyclic Chem.* ***1966****, 1,* 53, 102–126; Krebs, A.W. *Angew. Chem. Int. Ed.* ***1965****, 4,* 10.
[222] Breslow, R.; Groves, J.T. *J. Am. Chem. Soc.* ***1970****, 92,* 984.
[223] Breslow, R.; Höver, H.; Chang, H.W. *J. Am. Chem. Soc.* ***1962****, 84*, 3168.
[224] Moss, R.A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J.A.; Schugar, H.J.; Munjal, R.C. *J. Am. Chem. Soc.* ***1986****, 108*, 134.
[225] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992****, 33*, 3773.
[226] Taylor, M.J.; Surman, P.W.J.; Clark, G.R. *J. Chem. Soc. Chem. Commun.* ***1994***, 2517.

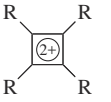
water solution. The tri-*tert*-butylcyclopropenyl cation is also very stable.[227] In addition, cyclopropenone and several of its derivatives are stable compounds,[228] in accord with the corresponding stability of the tropones.[229] The ring system **80** is nonalternant and the corresponding radical and anion, which do not have an aromatic duet, have electrons in antibonding orbitals, so that their energies are much higher. As with **58** and **62**, the equivalence of the three carbon atoms in the triphenylcyclopropenyl cation has been demonstrated by ^{14}C labeling experiments.[230] The interesting dications **81** (R = Me or Ph) have been prepared,[231] and they too should represent aromatic systems of two electrons.[232]



80



Cyclopropenone



81

2.K.ii. Systems of Four Electrons: Antiaromaticity

The most obvious compound in which to look for a closed loop of four electrons is cyclobutadiene (**77**).[233] *Hückel's rule* predicts no aromatic character since 4 is not a number generated from $4n + 2$. There is a long history of attempts to prepare this compound and its simple derivatives, and those experiments fully bear out *Hückel's* prediction. Cyclobutadienes display none of the characteristics that would lead us to call them aromatic, and there is evidence that a closed loop of four electrons is actually *antiaromatic*.[234] If such compounds simply lacked aromaticity, we would expect them to be about as stable as similar nonaromatic compounds, but both theory and experiment show that they are *much less stable*.[235] An antiaromatic compound may be defined as a compound that is destabilized by a closed loop of electrons.

Cyclobutadiene was first prepared by Pettit and co-workers.[236] It is now clear that **77** and its simple derivatives are extremely unstable compounds with very short lifetimes (they dimerize by a *Diels–Alder reaction*; see **15–60**) unless they are stabilized in some fashion,

[227] Ciabattoni, J.; Nathan, III, E.C. *J. Am. Chem. Soc.* ***1968****, 90,* 4495.

[228] See Breslow, R.; Oda, M. *J. Am. Chem. Soc.* ***1972****, 94*, 4787; Yoshida, Z.; Konishi, H.; Tawara, Y.; Ogoshi, H. *J. Am. Chem. Soc.* ***1973****, 95,* 3043.

[229] See Eicher, T.; Weber, J.L. *Top. Curr. Chem. Soc.* ***1975****, 57,* 1; Tobey, S.W., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, pp. 351–362; Greenberg, A.; Tomkins, R.P.T.; Dobrovolny, M.; Liebman, J.F. *J. Am. Chem. Soc.* ***1983****, 105*, 6855.

[230] D'yakonov, I.A.; Kostikov, R.R.; Molchanov, A.P. *J. Org. Chem. USSR* ***1969****, 5,* 171; ***1970****, 6,* 304.

[231] Olah, G.A.; Staral, J.S. *J. Am. Chem. Soc.* ***1976****, 98,* 6290. See also, Lambert, J.B.; Holcomb, A.G. *J. Am. Chem. Soc.* ***1971****, 93*, 2994; Seitz, G.; Schmiedel, R.; Mann, K. *Synthesis,* ***1974***, 578.

[232] See Pittman Jr., C.U.; Kress, A.; Kispert, L.D. *J. Org. Chem.* ***1974****, 39,* 378. See, however, Krogh-Jespersen, K.; Schleyer, P.v.R.; Pople, J.A.; Cremer, D. *J. Am. Chem. Soc.* ***1978****, 100,* 4301.

[233] For a monograph, see Cava, M.P.; Mitchell, M.J. *Cyclobutadiene and Related Compounds*, Academic Press, NY, ***1967***. For reviews, see Maier, G. *Angew. Chem. Int. Ed.* ***1988****, 27,* 309; ***1974****, 13,* 425–438; Bally, T.; Masamune, S. *Tetrahedron* ***1980****, 36*, 343; Vollhardt, K.P.C. *Top. Curr. Chem.* ***1975****, 59,* 113.

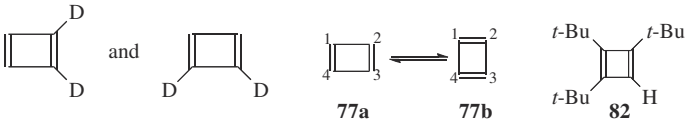
[234] See Glukhovtsev, M.N.; Simkin, B.Ya.; Minkin, V.I. *Russ. Chem. Rev.* ***1985****, 54,* 54; Breslow, R. *Pure Appl. Chem.* ***1971****, 28,* 111; *Acc. Chem. Res.* ***1973****, 6,* 393.

[235] See Bauld, N.L.; Welsher, T.L.; Cessac, J.; Holloway, R.L. *J. Am. Chem. Soc.* ***1978****, 100,* 6920.

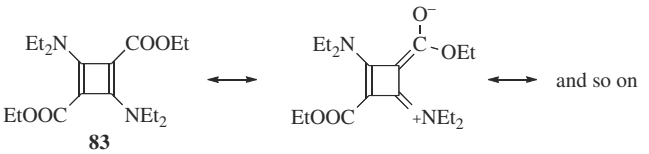
[236] Watts, L.; Fitzpatrick, J.D.; Pettit, R. *J. Am. Chem. Soc.* ***1965****, 87*, 3253, ***1966****, 88,* 623. See also, Cookson, R. C.; Jones, D.W. *J. Chem. Soc.* ***1965***, 1881.

either at ordinary temperatures embedded in the cavity of a hemicarcerand[237] (see the structure of a carcerand in Sec. 3.C.iii), or in matrices at very low temperatures (generally < 35 K). In either of these cases, the cyclobutadiene molecules are forced to remain apart from each other, and other molecules cannot get in. The structures of **77** and some of its derivatives have been studied a number of times using the low-temperature matrix technique.[238] The ground-state structure of **77** is a rectangular diene (not a diradical), as shown by the (Ir) spectra of **77** and deuterated **77** trapped in matrices,[239] as well as by a photoelectron spectrum.[240] Molecular orbital calculations agree.[241] The same conclusion was also reached in an elegant experiment in which 1,2-dideuterocyclobutadiene was generated. If **77** is a rectangular diene, the dideutero compound should exist as two isomers, as shown.

The compound was generated (as an intermediate that was not isolated) and two isomers were indeed found.[242] The cyclobutadiene molecule is not static, even in the matrices. There are two forms (**77a** and **77b**) that rapidly interconvert.[243] Note that there is experimental evidence that the aromatic and antiaromatic characters of neutral and dianionic systems are measurably increased via deuteration.[244]



There are some simple cyclobutadienes that are stable at room temperature for varying periods of time. These either have bulky substituents or carry certain other stabilizing substituents, such as seen in tri-*tert*-butylcyclobutadiene (**83**).[245] Such compounds are relatively stable because dimerization is sterically hindered. Examination of the NMR spectrum of **82** showed that the ring proton ($\delta = 5.38$) was shifted *upfield*, compared with the position expected for a nonaromatic proton, (e.g., cyclopentadiene). As will be seen in Section. 2.K.vi, this indicates that the compound is antiaromatic.



[237] Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem. Int. Ed.* ***1991****, 30,* 1024.

[238] See Chapman, O.L.; McIntosh, C.L.; Pacansky, J. *J. Am. Chem. Soc.* ***1973****, 95,* 614; Maier, G.; Mende, U. *Tetrahedron Lett*. ***1969***, 3155. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987****, 8,* 159; pp. 167–181.

[239] Masamune, S.; Souto-Bachiller, F.A.; Machiguchi, T.; Bertie, J.E. *J. Am. Chem. Soc.* ***1978****, 100*, 4889.

[240] Kreile, J.; Münzel, N.; Schweig, A.; Specht, H. *Chem. Phys. Lett.* ***1986****, 124,* 140.

[241] See Ermer, O.; Heilbronner, E. *Angew. Chem. Int. Ed.* ***1983****, 22*, 402; Voter, A.F.; Goddard, III, W.A. *J. Am. Chem. Soc.* ***1986****, 108,* 2830.

[242] Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1980****, 102,* 4272. See also, Whitman, D.W.; Carpenter, B. K. *J. Am. Chem. Soc.* ***1982****, 104*, 6473.

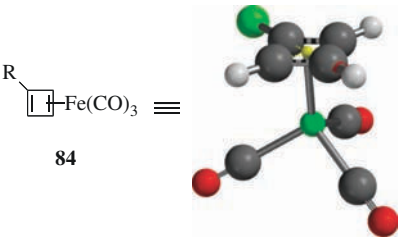
[243] Orendt, A.M.; Arnold, B.R.; Radziszewski, J.G.; Facelli, J.C.; Malsch, K.D.; Strub, H.; Grant, D.M.; Michl, J. *J. Am. Chem. Soc.* ***1988****, 110*, 2648. See, however, Arnold, B.R.; Radziszewski, J.G.; Campion, A.; Perry, S.S.; Michl, J. *J. Am. Chem. Soc.* ***1991****, 113*, 692.

[244] For experiments with [16]annulene (see Sec. 2.K.v), see Stevenson, C. D.; Kurth, T. L. *J. Am. Chem. Soc.* ***1999****, 121*, 1623

[245] Masamune, S.; Nakamura, N.; Suda, M.; Ona, H. *J. Am. Chem. Soc.* ***1973****, 95*, 8481; Maier, G.; Alzérreca, A. *Angew. Chem. Int. Ed.* ***1973****, 12,* 1015; Masamune, S. *Pure Appl. Chem.* ***1975****, 44*, 861.

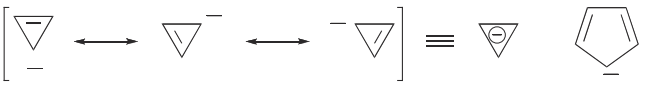
The other type of stable cyclobutadiene has two electron-donating and two electron-withdrawing groups,[246] and is stable in the absence of water.[247] An example is **83**. The stability of these compounds is generally attributed to the resonance shown, a type of resonance stabilization called the *push–pull or captodative effect*,[248] although it has been concluded from a PES that second-order bond fixation is more important.[249] An X-ray crystallographic study of **83** has shown[250] the ring to be a distorted square with bond lengths of 1.46 Å and angles of 87° and 93°.

It is clear that simple cyclobutadienes, which could easily adopt a square planar shape if that would result in aromatic stabilization, do not in fact do so and are not aromatic. The high reactivity of these compounds is not caused merely by steric strain, since the strain should be no greater than that of simple cyclopropenes, which are known compounds. It is probably caused by antiaromaticity.[251]



84

The cyclobutadiene system can be stabilized as a η^4-complex with metals,[252] as with the iron complex **84** (see Chap 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene–metal complexes can be looked upon as systems containing an aromatic duet. The ring is square planar,[253] the compounds undergo aromatic substitution,[254] and NMR spectra of mono-substituted derivatives show that the C-2 and C-4 protons are equivalent.[229]

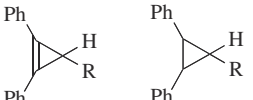


85 **86** **87**

Other systems that have been studied as possible aromatic or antiaromatic four-electron systems include the cyclopropenyl anion (**86**) and the cyclopentadienyl cation (**87**).[255] With respect to **86**, HMO theory predicts that an unconjugated **85** (i.e., a single canonical

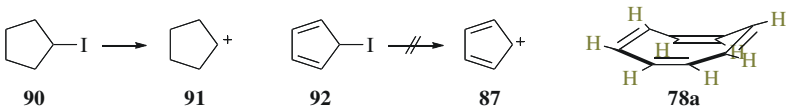
[246] See Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1988****, 27,* 1437.
[247] Gompper, R.; Kroner, J.; Seybold, G.; Wagner, H. *Tetrahedron* ***1976****, 32*, 629.
[248] Hess, Jr., B.A.; Schaad, L.J. *J. Org. Chem.* ***1976****, 41*, 3058.
[249] Gompper, R.; Holsboer, F.; Schmidt, W.; Seybold, G. *J. Am. Chem. Soc.* ***1973****, 95,* 8479.
[250] Lindner, H.J.; von Ross, B. *Chem. Ber.* ***1974****, 107*, 598.
[251] For evidence, see Breslow, R.; Murayama, D.R.; Murahashi, S.; Grubbs, R. *J. Am. Chem. Soc.* ***1973****, 95,* 6688; Herr, M.L. *Tetrahedron* ***1976****, 32*, 2835.
[252] Efraty, A. *Chem. Rev.* ***1977****, 77,* 691; Pettit, R. *Pure Appl. Chem.* ***1968****, 17,* 253; Maitlis, P.M. *Adv. Organomet. Chem.* ***1966****, 4*, 95; Maitlis, P.M.; Eberius, K.W., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, ***1971***, pp. 359–409.
[253] See Yannoni, C.S.; Ceasar, G.P.; Dailey, B.P. *J. Am. Chem. Soc.* ***1967****, 89,* 2833.
[254] Fitzpatrick, J.D.; Watts, L.; Emerson, G.F.; Pettit, R. *J. Am. Chem. Soc.* ***1965****, 87*, 3255. For a discussion, see Pettit, R. *J. Organomet. Chem.* ***1975****, 100,* 205.
[255] See Breslow, R. *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1,* 81.

form) is more stable than a conjugated **86**,[256] so that **85** would actually lose stability by forming a closed loop of four electrons. The HMO theory is supported by experiment. Among other evidence, it has been shown that **88** (R = COPh) loses its proton in hydrogen-exchange reactions ~ 6000 times more slowly than **89** (R = COPh).[257] Where R = CN, the ratio is ~ 10,000.[258] This indicates that **88** are much more reluctant to form carbanions (which would have to be cyclopropenyl carbanions) than **89**, which form ordinary carbanions. Thus the carbanions of **88** are less stable than corresponding ordinary carbanions. Although derivatives of cyclopropenyl anion have been prepared as fleeting intermediates (as in the exchange reactions mentioned above), all attempts to prepare the ion or any of its derivatives as relatively stable species have so far met with failure.[259]



88 **89**

In the case of **87**, the ion has been prepared and shown to be a diradical in the ground state,[260] as predicted by the discussion in Section 2.K.ii.[261] Evidence that **87** is not only nonaromatic, but is antiaromatic comes from studies on **90** and **92**.[262] When **90** is treated with silver perchlorate in propionic acid, the molecule is rapidly solvolyzed (a reaction in which the intermediate **91** is formed; see Chapters 5 and 10). Under the same conditions, **92** undergoes no solvolysis at all; that is, **87** does not form. If **87** were merely nonaromatic, it should be about as stable as **91** (which of course has no resonance stabilization at all). The fact that it is so much more reluctant to form indicates that **87** is much less stable than **91**. Note that under certain conditions, **91** can be generated solvolytically.[263]



90 **91** **92** **87** **78a**

The fact that **86** and **87** are not aromatic while the cyclopropenyl cation (**80**) and the cyclopentadienyl anion (**58**) is strong evidence for *Hückel's rule* since simple resonance theory predicts no difference between **86** and **80** or **87** and **58** (the same number of equivalent canonical forms can be drawn for **86** as for **80** and for **87** as for **58**).

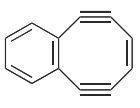
[256] Breslow, R. *Pure Appl. Chem.* ***1971****, 28,* 111; *Acc. Chem. Res.* ***1973****, 6,* 393.
[257] Breslow, R.; Brown, J.; Gajewski, J.J. *J. Am. Chem. Soc.* ***1967****, 89,* 4383.
[258] Breslow, R.; Douek, M. *J. Am. Chem. Soc.* ***1968****, 90,* 2698.
[259] See Breslow, R.; Cortés, D.A.; Juan, B.; Mitchell, R.D. *Tetrahedron Lett.* ***1982****, 23,* 795. See Bartmess, J.E.; Kester, J.; Borden, W.T.; Köser, H.G. *Tetrahedron Lett.* ***1986****, 27,* 5931.
[260] Saunders, M.; Berger, R.; Jaffe, A.; McBride, J.M.; O'Neill, J.; Breslow, R.; Hoffman, Jr., J.M.; Perchonock, C.; Wasserman, E.; Hutton, R.S.; Kuck, V.J. *J. Am. Chem. Soc.* ***1973****, 95,* 3017.
[261] See Breslow, R.; Chang, H.W.; Hill, R.; Wasserman, E. *J. Am. Chem. Soc.* ***1967****, 89*, 1112; Gompper, R.; Glöckner, H. *Angew. Chem. Int. Ed.* ***1984****, 23*, 53.
[262] Breslow, R.; Mazur, S. *J. Am. Chem. Soc.* ***1973****, 95,* 584. See Lossing, F.P.; Treager, J.C. *J. Am. Chem. Soc.* ***1975****, 97*, 1579. See also, Breslow, R.; Canary, J.W. *J. Am. Chem. Soc.* ***1991****, 113,* 3950.
[263] Allen, A.D.; Sumonja, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1997****, 119*, 2371.

2.K.iii. Systems of Eight Electrons

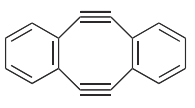
Cyclooctatetraene[264] ([8]annulene, **78a**) is not planar, but tub shaped,[265] so it is neither aromatic nor antiaromatic, since both these conditions require overlap of parallel *p* orbitals. The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp^2 angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished.[266] Single- and double-bond distances in **78** are, respectively, 1.46 and 1.33 Å, which is expected for a compound made up of four individual double bonds.[265] The *Jahn–Teller effect* has been invoked to explain the instability of such antiaromatic compounds.[267] The Jahn-Teller effect arises from molecular distortions due to an electronically degenerate *ground* state.[268]

The reactivity is also what would be expected for a linear polyene. Reactive intermediates can be formed in solution. Dehydrohalogenation of bromocyclooctatetraene at −100 °C has been reported, for example, and trapping by immediate electron transfer gave a stable solution of the [8]annulyne anion radical.[269]

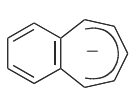
The cyclooctadiendiynes **93** and **94** are planar conjugated eight-electron systems (the four extra triple-bond electrons do not participate), which NMR evidence show to be antiaromatic.[270] There is evidence that part of the reason for the lack of planarity in **78** itself is that a planar molecule would have to be antiaromatic.[271] The cycloheptatrienyl anion (**61**) also has eight electrons, but does not behave like an aromatic system.[167] The bond lengths for a series of molecules containing the cycloheptatrienide anion have recently been published.[272] The NMR spectrum of the benzocycloheptatrienyl anion (**95**) shows that, like **82**, **93**, and **94**, this compound is antiaromatic.[273] A new antiaromatic compound 1,4-biphenylene quinone (**96**) was prepared, but it rapidly dimerizes due to instability.[274]



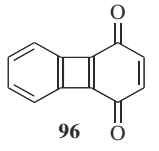
93



94



95



96

[264] See Fray, G.I.; Saxton, R.G. *The Chemistry of Cyclooctatetraene and its Derivatives*, Cambridge University Press, Cambridge, ***1978***; Paquette, L.A. *Tetrahedron* ***1975***, *31,* 2855. For reviews of heterocyclic 8π systems, see Kaim, W. *Rev. Chem. Intermed.* ***1987***, *8,* 247; Schmidt, R.R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 581.

[265] Bastiansen, O.; Hedberg, K.; Hedberg, L. *J. Chem. Phys.* ***1957***, *27*, 1311. See Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W. *Org. Lett.* ***2006***, *8,* 1255.

[266] See Einstein, F.W.B.; Willis, A.C.; Cullen, W.R.; Soulen, R.L. *J. Chem. Soc. Chem. Commun.* ***1981***, 526. See also, Paquette, L.A.; Wang, T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1987***, *109,* 3730.

[267] Frank-Gerrit Klärner, F-G. *Angew. Chem. Int. Ed.* ***2001*** . *40,* 3977.

[268] *The Jahn–Teller Effect* Bersuker, I.B. Cambridge University Press, ***2006***; Ceulemans, A.; Lijnen, E. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 1229.

[269] Peters, S.J.; Turk, M.R.; Kiesewetter, M.K.; Stevenson, C.D. *J. Am. Chem. Soc.* ***2003***, *125,* 11264.

[270] Huang, N.Z.; Sondheimer, F. *Acc. Chem. Res.* ***1982***, *15,* 96. See also, Chan, T.; Mak, T.C.W.; Poon, C.; Wong, H.N.C.; Jia, J.H.; Wang, L.L. *Tetrahedron* ***1986***, *42,* 655.

[271] Figeys, H.P.; Dralants, A. *Tetrahedron Lett.* ***1971***, 3901; Buchanan, G.W. *Tetrahedron Lett.* ***1972***, 665.

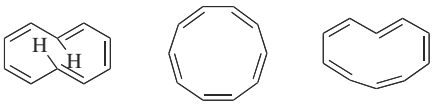
[272] Dietz, F.; Rabinowitz, M.; Tadjer, A.; Tyutyulkov, N. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 735.

[273] Staley, S.W.; Orvedal, A.W. *J. Am. Chem. Soc.* ***1973***, *95,* 3382.

[274] Kiliç, H.; Balci, M. *J. Org. Chem.* ***1997***, *62*, 3434.

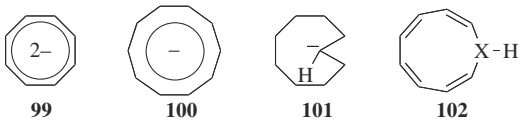
2.K.iv. Systems of Ten Electrons[275]

There are three possible geometrical isomers of [10]annulene: the all-*cis* (**97**), the mono-*trans* (**98**), and the *cis-trans-cis-cis-trans* (**79**). If Hückel's rule applies, they should be planar. But it is far from obvious that the



79 **97** **98**

molecules would adopt a planar shape, since they must overcome considerable strain to do so. For a regular decagon (**97**) the angles would have to be 144°, considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **98**, but this kind of strain is eliminated in **79** since all the angles are 120°. However, it was pointed out by Mislow[276] that the hydrogen atoms in the 1 and 6 positions should interfere with each other and force the molecule out of planarity. Such configurational changes are not necessarily without cost energetically. It has been determined that configurational changes in [14]annulene, for example. requires Möbius antiaromatic bond shifting.[277]

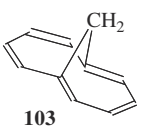


99 **100** **101** **102**

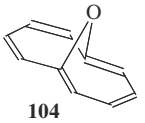
Compounds **97** and **98** have been prepared[278] as crystalline solids at −80 °C. The NMR spectra show that all the hydrogen atoms lie in the alkene region, and it was concluded that neither compound is aromatic. Calculations on **98** suggest that it may indeed be aromatic, although the other isomers are not.[279] It is known that the Hartree–Fock (HF) method incorrectly favors bond-length-alternating structures for [10]annulene, and aromatic structures are incorrectly favored by density functional theory. Improved calculations predict that the twist conformation is lowest in energy, and the naphthalene-like and heart-shaped conformations lie higher than the twist by 1.40 and 4.24 kcal mol^{-1}(5.86 and 17.75 kJ mol^{-1}), respectively.[280] Analysis of ^{13}C and ^{1}H NMR spectra suggest that neither is planar. However, the preparation of several compounds that have large angles, but that are definitely planar 10-electron aromatic systems, clearly demonstrate that the angle strain is not insurmountable. Among these are the dianion **99**, the anions **100** and **101**, and the

[275] See Kemp-Jones, A.V.; Masamune, S. *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1,* 121; Masamune, S.; Darby, N. *Acc. Chem. Res.* ***1972****, 5,* 272; Burkoth, T.L.; van Tamelen, E.E. in Snyder, J.P. *Nonbenzenoid Aromaticty*, Vol. 1, Academic Press, NY, ***1969***, pp. 63–116; Vogel, E., in Garratt, P.J. Aromaticity, Wiley, NY, ***1986***, pp. 113–147.
[276] Mislow, K. *J. Chem. Phys.* ***1952****, 20*, 1489.
[277] Moll, J.F.; Pemberton, R.P.; Gertrude Gutierrez, M.; Castro, C.; Karney, W.L. *J. Am. Chem. Soc.* ***2007****, 129,* 274.
[278] Masamune, S.; Hojo, K.; Bigam, G.; Rabenstein, D.L. *J. Am. Chem. Soc.* ***1971****, 93*, 4966; van Tamelen, E.E.; Burkoth, T.L.; Greeley, R.H. *J. Am. Chem. Soc.* ***1971****, 93*, 6120.
[279] Sulzbach, H.M.; Schleyer, P.v.R.; Jiao, H.; Xie, Y.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1995****, 117*, 1369; Sulzbach, H.M.; Schaefer, III, H.F.; Klopper, W.; Lüthi, H.P. *J. Am. Chem. Soc.* ***1996****, 118*, 3519.
[280] King, R.A.; Crawford, T.D.; Stanton, J.F.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1999****, 121,* 10788.

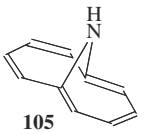
azonine **102**.[281] Compound **99**[282] has angles of $\sim -135°$, while **100**[283] and **101**[284] have angles of $\sim 140°$, which are not very far from 144°. The inner proton in **101**[285] which is the mono-trans isomer of the all-*cis* **100** is found far upfield in the NMR ($-3.5\,\delta$). For **97** and **98**, the cost in strain energy to achieve planarity apparently outweighs the extra stability that would come from an aromatic ring. Further emphasizing the delicate balance between these factors, it is known that the oxygen analogue of **102** (X = O, oxonin) and the *N*-carbethoxy derivative of **102** (X = CH) are nonaromatic and nonplanar, while **102** (X = N) is aromatic and planar.[286] Other azaannulenes are known, including Vogel's 2,7-methanoazaannulene,[287] as well as 3,8-methanoaza[10]annulene,[288] and the alkoxy derivative of both.[289] Calculations for aza[10]annulene concluded that the best olefinic twist isomer is 2.1 kcal mol^{-1} (8.8 kJ mol^{-1}) more stable than the aromatic form,[290] and is probably the more stable form.



103



104



105

So far, **79** from above has not been prepared despite many attempts. However, there are various ways of avoiding the interference between the two inner protons. The approach that has been most successful involves bridging the 1 and 6 positions.[291] Thus, 1,6-methano[10] annulene (**103**)[292] and its oxygen and nitrogen analoges **104**[293] and **105**[294] have been prepared, and they are stable compounds, are diatropic, and undergo aromatic substitution.[295] For example, the perimeter protons of **103** are found at 6.9–7.3 δ, while the bridge protons are at $-0.5\,\delta$. The crystal structure of **103** shows that the perimeter is nonplanar,

[281] See Anastassiou, A.G. *Acc. Chem. Res.* ***1972****, 5*, 281, *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1*, 1, *Pure Appl. Chem.* ***1975****, 44,* 691. For a review of heteroannulenes in general, see Anastassiou, A.G.; Kasmai, H.S. *Adv. Heterocycl. Chem.* ***1978****, 23*, 55.

[282] Evans, W.J.; Wink, D.J.; Wayda, A.L.; Little, D.A. *J. Org. Chem.* ***1981****, 46*, 3925; Heinz, W.; Langensee, P.; Müllen, K. *J. Chem. Soc. Chem. Commun.* ***1986***, 947.

[283] Paquette, L.A.; Ley, S.V.; Meisinger, R.H.; Russell, R.K.; Oku, M. *J. Am. Chem. Soc.* ***1974****, 96*, 5806; Radlick, P.; Rosen, W. *J. Am. Chem. Soc.* ***1966****, 88,* 3461.

[284] Anastassiou, A.G.; Gebrian, J.H. *Tetrahedron Lett.* ***1970***, 825.

[285] Boche, G.; Weber, H.; Martens, D.; Bieberbach, A. *Chem. Ber.* ***1978****, 111,* 2480. See also, Anastassiou, A.G.; Reichmanis, E. *Angew. Chem. Int. Ed.* ***1974****, 13,* 728.

[286] Chiang, C.C.; Paul, I.C.; Anastassiou, A.G.; Eachus, S.W. *J. Am. Chem. Soc.* ***1974****, 96,* 1636.

[287] Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967****, 89*, 6310; Bailey, N.A.; Mason, R. *J. Chem. Soc. Chem. Commun.* ***1967***,1039.

[288] Destro, R.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1981****, 103,* 2863.

[289] Schleyer, P.v.R.; Jiao, H.; Sulzbach, H.M.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1996****, 118,* 2093.

[290] Bettinger, H.F.; Sulzbach, H.M.; Schleyer, P.v.R.; Schaefer, III, H.F. *J. Org. Chem.* ***1999***, *64,* 3278.

[291] See Vogel, E. *Pure Appl. Chem.* ***1982****, 54,* 1015; *Isr. J. Chem.* ***1980****, 20*, 215; *Chimia,* ***1968****, 22,* 21; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967****, 6*, 385.

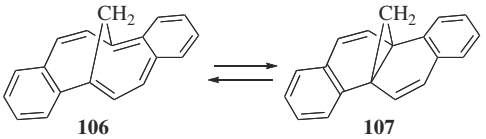
[292] Vogel, E.; Roth, H.D. *Angew. Chem. Int. Ed.* ***1964****, 3*, 228; Vogel, E.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964****, 3,* 642; Vogel, E.; Böll, W.A.; Biskup, M. *Tetrahedron Lett.* ***1966***, 1569.

[293] Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964****, 3,* 642; Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967****, 89,* 6310; Bailey, N.A.; Mason, R. *Chem. Commun.* ***1967***, 1039.

[294] Vogel, E.; Pretzer, W.; Böll, W.A. *Tetrahedron Lett.* ***1965***, 3613. See also, Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964****, 3,* 642.

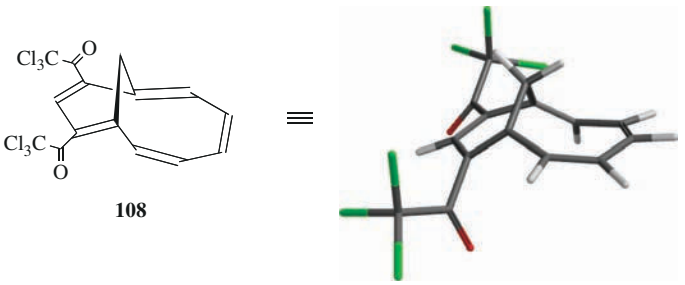
[295] Also see McCague, R.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 165, 175; Gibbard, H.C.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 731, 735.

but the bond distances are in the range 1.37–1.42 Å.[296] It has therefore been amply demonstrated that a closed loop of 10 electrons is an aromatic system, although some molecules that could conceivably have such a system are too distorted from planarity to be aromatic. A small distortion from planarity (as in **103**) does not prevent aromaticity, at least in part because the σ orbitals so distort themselves as to maximize the favorable (parallel) overlap of p orbitals to form the aromatic 10-electron loop.[297]



106 **107**

In **106**, where **103** is fused to two benzene rings in such a way that no canonical form can be written in which both benzene rings have six electrons, the aromaticity is diminished by annellation, as shown by the fact that the molecule rapidly converts to the more stable **107**, in which both benzene rings can be fully aromatic[298] (this is similar to the cycloheptatriene–norcaradiene conversions discussed in **18–32**).



108

Molecules can sustain significant distortion from planarity and retain their aromatic character. 1,3-Bis(trichloroacetyl)homoazulene (**108**) qualifies as aromatic using the geometric criterion that there is only a small average deviation from the C—C bond length in the [10]annulene perimeter.[299] The X-ray crystal structure shows that the 1,5-bridge distorts the [10]annulene π-system away from planarity (see the 3D model) with torsion angles as large as 42.2° at the bridgehead position, but **108** does not lose its aromaticity.

2.K.v. Systems of More Than Ten Electrons: $4n + 2$ Electrons[300]

Extrapolating from the discussion of [10]annulene, larger $4n + 2$ systems are expected to be aromatic if they are planar. Mislow[276] predicted that [14]annulene (**109**) would possess

[296] Bianchi, R.; Pilati, T.; Simonetta, M. *Acta Crystallogr. Sect. B, **1980**, 36*, 3146. See also, Dobler, M.; Dunitz, J. D. *Helv. Chim. Acta **1965**, 48*, 1429.

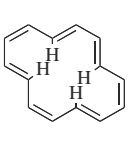
[297] For a discussion, see Haddon, R.C. *Acc. Chem. Res. **1988**, 21*, 243.

[298] Hill, R.K.; Giberson, C.B.; Silverton, J.V. *J. Am. Chem. Soc. **1988**, 110*, 497. See also, McCague, R.; Moody, C.J.; Rees, C.W.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1 **1984***, 909.

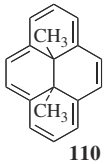
[299] Scott, L.T.; Sumpter, C.A.; Gantzel, P.K.; Maverick, E.; Trueblood, K.N. *Tetrahedron **2001**, 57,* 3795.

[300] See Sondheimer, F. *Acc. Chem. Res. **1972**, 5*, 81-91, *Pure Appl. Chem. **1971**, 28*, 331, *Proc. R. Soc. London. Ser. A, **1967**, 297*, 173; Sondheimer, F.; Calder, I.C.; Elix, J.A.; Gaoni, Y; Garratt, P.J.; Grohmann, K.; di Maio, G.; Mayer, J.; Sargent, M.V.; Wolovsky, R. in Garratt, P.G. *Aromaticity*, Wiley, NY, ***1986***, pp. 75–107; Nakagawa, M. *Angew. Chem. Int. Ed. **1979**, 18,* 202; Müllen, K. *Chem. Rev. **1984**, 84,* 603; Rabinovitz, M. *Top. Curr. Chem. **1988**, 146,* 99. Also see, Cyvin, S.J.; Brunvoll, J.; Chen, R.S.; Cyvin, B.N.; Zhang, F.J. *Theory of Coronoid Hydrocarbons II*, Springer-Verlag, Berlin, ***1994***.

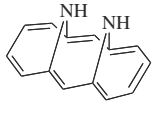
the same type of interference as **79**, although to a lesser degree. This is borne out by experiment. Compound **109** is aromatic (it is diatropic; inner protons at 0.00 δ, outer protons at 7.6 δ),[301] but is highly reactive and is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds (the molecule is not planar).[302] A number of stable bridged [14]annulenes have been prepared[303] [e.g., *trans*-15,16-dimethyldihydropyrene (**110**),[304] *syn*-1,6:8,13-diimino[14]annulene (**111**),[305] and *syn*- and *anti*-1,6:8,13-bismethano[14]annulene (**112** and **113**)].[306] The dihydropyrene (**110**, and its diethyl and dipropyl homologues) is undoubtedly aromatic: The π perimeter is approximately planar,[307] the bond distances are all 1.39–1.40 Å, and the molecule undergoes aromatic substitution[304] as well as being diatropic.[308] The outer protons are found at 8.14–8.67 δ, while the CH_3 protons are at −4.25 δ. Other nonplanar aromatic dihydropyrenes are known.[309] Annulenes **111** and **112** are also diatropic,[310] although X-ray crystallography indicates that the π periphery in **111** is not quite planar.[311] In **113**, the geometry of the molecule greatly reduces the overlap of the *p* orbitals at the bridgehead positions with adjacent *p* orbitals, and it is definitely not aromatic,[312] as shown by NMR spectra[306] and X-ray crystallography, from which bond distances of 1.33–1.36 Å for the double bonds and 1.44–1.49 Å for the single bonds have been obtained.[313] In contrast, all the bond distances in **111** are ∼ 1.38–1.40 Å.[311]



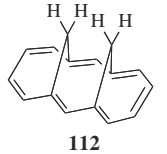
109



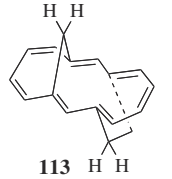
110



111



112



113

Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene

[301] Gaoni, Y.; Melera, A.; Sondheimer, F.; Wolovsky, R. *Proc. Chem. Soc.* ***1964***, 397.

[302] Chiang, C.C.; Paul, I.C. *J. Am. Chem. Soc.* ***1972****, 94*, 4741; Oth, J.F.M.; Schröder, G. *J. Chem. Soc. B,* ***1971***, 904. See also, Oth, J.F.M.; Müllen, K.; Königshofen, H.; Mann, M.; Sakata, Y.; Vogel, E. *Angew. Chem. Int. Ed.* ***1974****, 13*, 284; Wife, R.L.; Sondheimer, F. *J. Am. Chem. Soc.* ***1975****, 97*, 640; Willner, I.; Gutman, A.L.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1977****, 99,* 4167; Röttele, H.; Schröder, G. *Chem. Ber.* ***1982****, 115*, 248.

[303] For a review, see Vogel, E. *Pure Appl. Chem.* ***1971****, 28,* 355.

[304] Boekelheide, V.; Phillips, J.B. *J. Am. Chem. Soc.* ***1967****, 89*, 1695; Boekelheide, V.; Miyasaka, T. *J. Am. Chem. Soc.* ***1967****, 89,* 1709. For reviews of dihydropyrenes, see Mitchell, R.H. *Adv. Theor. Interesting Mol.* ***1989****, 1*, 135; Boekelheide, V. *Top. Nonbenzoid Arom. Chem.* ***1973****, 1*, 47; *Pure Appl. Chem.* ***1975****, 44*, 807.

[305] Destro, R.; Pilati, T.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1985****, 107,* 3185, 3192. For the di -*O*-analogue of **102**, see Vogel, A.; Biskup, M.; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1966****, 5,* 734.

[306] Vogel, E.; Sombroek, J.; Wagemann, W. *Angew. Chem. Int. Ed.* ***1975****, 14*, 564.

[307] Hanson, A.W. *Acta Crystallogr.* ***1965****, 18,* 599, 1967, 23, 476.

[308] See Mitchell, R.H.; Williams, R.V.; Mahadevan, R.; Lai, Y.H.; Dingle, T.W. *J. Am. Chem. Soc.* ***1982****, 104*, 2571 and other papers in this series.

[309] Bodwell, G. J.; Bridson, J. N.; Chen, S.-L.; Poirier, R. A. *J. Am. Chem. Soc.* ***2001****, 123,* 4704; Bodwell, G.J.; Fleming, J.J.; Miller, D.O. *Tetrahedron* ***2001****, 57,* 3577.

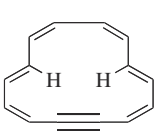
[310] See Vogel, E.; Wieland, H.; Schmalstieg, L.; Lex, J. *Angew. Chem. Int. Ed.* ***1984****, 23*, 717; Neumann, G.; Müllen, K. *J. Am. Chem. Soc.* ***1986****, 108,* 4105.

[311] Ganis, P.; Dunitz, J.D. *Helv. Chim. Acta,* ***1967****, 50*, 2369.

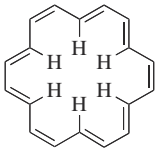
[312] See Vogel, E.; Nitsche, R.; Krieg, H. *Angew. Chem. Int. Ed.* ***1981****, 20*, 811. See also, Vogel, E.; Schieb, T.; Schulz, W.H.; Schmidt, K.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1986****, 25,* 723.

[313] Gramaccioli, C.M.; Mimun, A.; Mugnoli, A.; Simonetta, M. *Chem. Commun.* ***1971***, 796. See also, Destro, R.; Simonetta, M. *Tetrahedron* ***1982****, 38,* 1443.

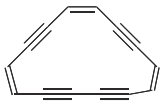
(**114**).[314] All five known dehydro[14]annulenes are diatropic, and **87** can be nitrated or sulfonated.[315] The extra electrons of the triple bond do not form part of the



114



115



116

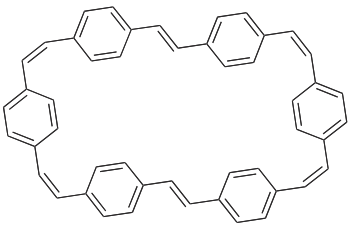
aromatic system, but it simply exists as a localized bond. There has been a debate concerning the extent of delocalization in dehydrobenzoannulenes,[316] but there is evidence for a weak, but discernible ring current.[317] 3,4,7,8,9,10,13,14-Octahydro[14]annulene (**116**) has been prepared, for example, and the evidence supported its aromaticity.[318] This study suggested that increasing benzoannelation of the parent **116** led to a step-down in aromaticity, a result of competing ring currents in the annulenic system. Note that [12]annulyne has been prepared.[319]

[18]Annulene (**115**) is diatropic:[320] the 12 outer protons are found at $\sim\delta = 9$ and the 6 inner protons at $\sim\delta = -3$. X-ray crystallography[321] shows that it is nearly planar, so that interference of the inner hydrogen atoms is not important in annulenes this large. Compound **115** is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions[322] (Chapter 11). The C—C bond distances are not equal, but they do not alternate. There are 12 inner bonds of ~1.38 Å and 6 outer bonds of ~1.42 Å.[321] Compound **115** has been estimated to have a resonance energy of ~37 kcal mol^{-1} (155 kJ mol^{-1}), similar to that of benzene.[323]

The known bridged [18]annulenes are also diatropic,[324] as are most of the known dehydro[18]annulenes.[325] The dianions of open and bridged [16]annulenes[326] are also 18-electron aromatic systems,[327] and there are dibenzo[18]annulenes.[328]

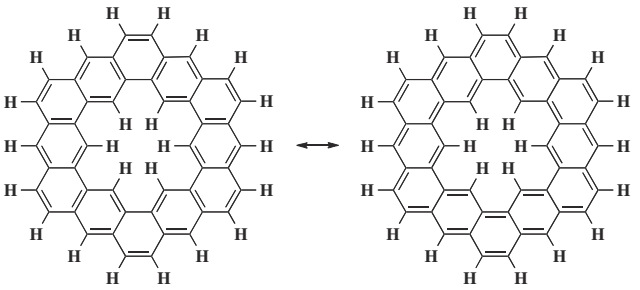
[314] For a review of dehydroannulenes, see, Nakagawa, M. *Top. Nonbenzenoid Aromat. Chem.* ***1973****, 1*, 191.
[315] Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1964****, 86,* 521.
[316] Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo- Derivatives and their Valence Isomers,* Vols. 1–3, CRC Press, Boca Raton, FL, ***1987***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Minkin, V.I.; Glukhovtsev, M.N.; Simkin, B.Ya. *Aromaticity and Antiaromaticity,* Wiley, NY, ***1994***.
[317] Bell, M.L.; Chiechi, R.C.; Johnson, C.A.; Kimball, D.B.; Matzger, A.J.; Wan, W.B.; Weakley, T.J.R.; Haley, M.M. *Tetahedron* ***2001****, 57,* 3507; Wan, W.B.; Chiechi, R.C.; Weakley, T.J.R.; Haley, M.M. *Eur. J. Org. Chem.* ***2001***, 3485.
[318] Boydston, A.J.; Haley, M.M.; Williams, R.V.; Armantrout, J.R. *J. Org. Chem.* ***2002****, 67,* 8812.
[319] Gard, M.N.; Kiesewetter, M.K.; Reiter, R.C.; Stevenson, C.D. *J. Am. Chem. Soc.* ***2005****, 127,* 16143.
[320] Gilles, J.; Oth, J.F.M.; Sondheimer, F.; Woo, E.P. *J. Chem. Soc. B,* ***1971***, 2177. For a thorough discussion, see Baumann, H.; Oth, J.F.M. *Helv. Chim. Acta,* ***1982****, 65,* 1885.
[321] Bregman, J.; Hirshfeld, F.L.; Rabinovich, D.; Schmidt, G.M.J. *Acta Crystallogr.* ***1965****, 19*, 227; Hirshfeld, F. L.; Rabinovich, D. *Acta Crystallogr.* ***1965****, 19,* 235.
[322] Sondheimer, F. *Tetrahedron* ***1970****, 26,* 3933.
[323] Oth, J.F.M.; Bünzli, J.; de Julien de Zélicourt, Y. *Helv. Chim. Acta,* ***1974****, 57,* 2276.
[324] Ogawa, H.; Sadakari, N.; Imoto, T.; Miyamoto, I.; Kato, H.; Taniguchi, Y. *Angew. Chem. Int. Ed.* ***1983****, 22,* 417; Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed.* ***1988****, 27,* 411.
[325] Sondheimer, F. *Acc. Chem. Res.* ***1972****, 5*, 81. For two that are not, see Endo, K.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 2465.
[326] See Rabinovitz, M.; Willner, I.; Minsky, A. *Acc. Chem. Res.* ***1983****, 16*, 298.
[327] Oth, J.F.M.; Baumann, H.; Gilles, J.; Schröder, G. *J. Am. Chem. Soc.* ***1972****, 94,* 3948. See also, Brown, J.M.; Sondheimer, F. *Angew. Chem. Int. Ed.* ***1974****, 13*, 337; Rabinovitz, M.; Minsky, A. *Pure Appl. Chem.* ***1982****, 54,* 1005.
[328] Michels, H.P.; Nieger, M.; Vögtle, F. *Chem. Ber.* ***1994****, 127*, 1167.

[22]Annulene[329] and dehydro[22]annulene[330] are also diatropic. A dehydrobenzo[22] annulene has been prepared that has eight C≡C units, is planar, and possesses a weak induced ring current.[331] In the latter compound, there are 13 outer protons at 6.25–8.45 δ and 7 inner protons at 0.70–3.45 δ. Some aromatic bridged [22]annulenes are known.[332] [26]Annulene has not yet been prepared, but several dehydro[26]annulenes are aromatic.[333] Furthermore, the dianion of 1,3,7,9,13,15,19,21-octadehydro[24]annulene is another 26-electron system that is aromatic.[334] Ojima and et al.[335] prepared bridged dehydro derivatives of [26], [30], and [34]annulenes. All are diatropic. The same workers prepared a bridged tetradehydro[38] annulene,[335] which showed no ring current. On the other hand, the dianion of the cyclophane, (**117**) also has 38 perimeter electrons, and this species is diatropic.[336]



117

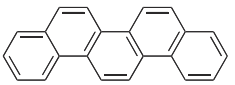
There is now no doubt that $4n + 2$ systems are aromatic if they can be planar, although **97** and **113** among others, demonstrate that not all such systems are in fact planar enough for aromaticity. Both **109** and **111** prove that absolute planarity is not required for aromaticity, but that aromaticity decreases with decreasing planarity.



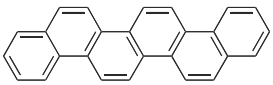
118a **118b**

[329] McQuilkin, R.M.; Metcalf, B.W.; Sondheimer, F. *Chem. Commun.* ***1971***, 338.
[330] Iyoda, M.; Nakagawa, M. *J. Chem. Soc. Chem. Commun.* ***1972***, 1003. See also, Akiyama, S.; Nomoto, T.; Iyoda, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* ***1976****, 49,* 2579.
[331] Wan, W.B.; Kimball, D.B.; Haley, M.M. *Tetrahedron Lett.* ***1998****, 39*, 6795.
[332] See Ojima, J.; Ejiri, E.; Kato, T.; Nakamura, M.; Kuroda, S.; Hirooka, S.; Shibutani, M. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 831; Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 395.
[333] Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 385.
[334] McQuilkin, R.M.; Garratt, P.J.; Sondheimer, F. *J. Am. Chem. Soc.* ***1970****, 92*, 6682. See also, Huber, W.; Müllen, K.; Wennerström, O. *Angew. Chem. Int. Ed.* ***1980****, 19*, 624.
[335] Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 385.
[336] Müllen, K.; Unterberg, H.; Huber, W.; Wennerström, O.; Norinder, U.; Tanner, D.; Thulin, B. *J. Am. Chem. Soc.* ***1984****, 106*, 7514.

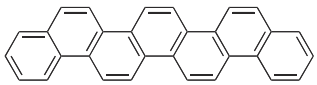
The ^{1}H NMR spectrum of **118** (called kekulene) showed that in a case where electrons can form either aromatic sextets or larger systems, the sextets are preferred.[337] There was initial speculation that kekulene might be *superaromatic*, that is, it would show enhanced aromatic stabilization. Calculations suggest that there is no enhanced stabilization.[338] The 48 π electrons of **118** might, in theory, prefer structure **118a**, where each ring is a fused benzene ring, or **118b**, which has a [30]annulene on the outside and an [18]annulene on the inside. The ^{1}H NMR spectrum of this compound shows three peaks at δ = 7.94, 8.37, and 10.45 in a ratio of 2:1:1. Examination of the structure shows that **118** contains three groups of protons. The peak at 7.94 δ is attributed to the 12 ortho protons and the peak at 8.37 δ to the six external para protons. The remaining peak comes from the six inner protons. If the molecule preferred **118b**, this peak should be upfield, probably with a negative δ, as in the case of **115**. The fact that this peak is far downfield indicates that the electrons prefer to be in benzenoid rings. Note that in the case of the dianion of **117**, the opposite situation prevails. In this ion, the 38-electron system is preferred even though 24 of these must come from the six benzene rings, which therefore cannot have aromatic sextets.



119



120



121

Phenacenes are a family of "graphite ribbons," where benzene rings are fused together in an alternating pattern. Phenanthrene is the simplest member of this family and other members include the 22 electron system picene (**119**), the 26 electron system fulminene (**120**) and the larger member of this family, the 30 electron [7]phenancene, with seven rings (**121**).[339] In the series benzene to heptacene, reactivity increases although acene resonance energies per π electron are nearly constant. The inner rings of the "acenes" are more reactive, and calculations showed that those rings are more aromatic than the outer rings, and are even more aromatic than benzene itself.[340] *N*-Heteroacenes are also known.[341]

A super-ring molecule is formed by rolling a polyacene molecule into one ring with one edge benzene ring folding into the other. These are called cyclopolyacenes or cyclacenes.[342] Although the *zigzag* cyclohexacenes (**122**) are highly aromatic (this example is a 22 electron system), the linear cyclohexacenes (e.g., the 24 electron **123**) are much less aromatic.[343] It is possible to deform an acene by attaching bulky substituents to its periphery by single covalent bonds. The presence of these substituents, which often leads to twisting of torsion angles, is usually easier than distortion of bond angles or C-C bond lengths. Such compounds are called twisted acenes.[344]

[337] Staab, H.A.; Diederich, F. *Chem. Ber.* ***1983****, 116*, 3487; Staab, H.A.; Diederich, F.; Krieger, C.; Schweitzer, D. *Chem. Ber.* ***1983****, 116*, 3504; Funhoff, D.J.H.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986****, 25*, 742.

[338] Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.,* ***1996****, 35*, 2383.

[339] Mallory, F.B.; Butler, K.E.; Evans, A.C.; Mallory, C.W. *Tetrahedron Lett.* ***1996****, 37*, 7173.

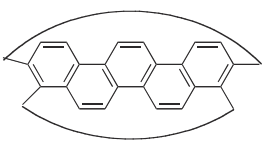
[340] Schleyer, P.v.R.; Manoharan, M.; Jiao, H.; Stahl, F. *Org. Lett.* ***2001****, 3*, 3643. For a discussion of local aromaticity, see Portella, G.; Poater, J.; Bofill, J.M.; Alemany, P.; Solà, M. *J. Org. Chem.* ***2005****, 70*, 2509.

[341] Bunz, U.H.F. *Chemistry: Eur. J.* ***2009****, 15,* 6780.

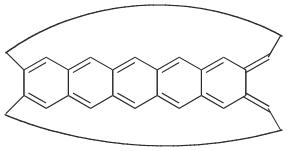
[342] Ashton, P.R.; Girreser, U.; Giuffrida, D.; Kohnke, F.H.; Mathias, J.P.; Raymo, F.M.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* ***1993****, 115*, 5422.

[343] Aihara, J-i. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 971. For a discussion of hexacene stability, see Mondal, R.; Adhikari, R.M.; Shah, B.K.; Neckers, D.C. *Org. Lett.* ***2007****, 9,* 2505.

[344] Pascal, Jr., R.A. *Chem. Rev.* ***2006****, 106,* 4809. See also, Chauvin, R.; Lepetit, C.; Maraval, V.; Leroyer, L. *Pure Appl. Chem.* ***2010****, 82*, 769.



122



123

2.K.vi. Systems of More Than 10 Electrons: 4*n* Electrons[249]

As seen in Section 2.K.ii, these systems are expected to be not only nonaromatic, but also antiaromatic. The [12]annulene (**124**) has been prepared.[345] In solution, **124** exhibits rapid conformational mobility (as do many other annulenes),[346] and above $-150°C$ in this particular case, all protons are magnetically equivalent. However, at $-170°C$ the mobility is greatly slowed and the three inner protons are found at $\sim 8\,\delta$ while the nine



124 **125**

outer protons are at $\sim 6\,\delta$. Interaction of the 'internal' hydrogen atoms in annulene (**124**) leads to nonplanarity. Above $-50°C$, **124** is unstable and rearranges to **125**. Several bridged and dehydro[12]annulenes are known, for example, 5-bromo-1,9-didehydro[12]annulene (**126**),[347] cycl[3.3.3]azine (**127**),[348] *s*-indacene (**128**),[349] and 1,7-methano[12]annulene (**129**).[350] *s*-Indacene is a planar, conjugated system perturbed by two cross links, and studies showed that the low-energy structure has *localized* double bonds. In these compounds, both hydrogen interference and conformational mobility are prevented. In **127**–**129**, the bridge prevents conformational changes, while in **126** the bromine atom is too large to be found inside the ring. The NMR spectra show that all four compounds are paratropic, the inner proton of **126** being found at 16.4 δ. The dication of **112**[351] and the dianion of **103**[352] are also 12-electron paratropic species. An interesting 12-electron [13] annulenone has recently been reported, 5,10-dimethyl[13]annulenone (**130**). This annulenone is the first monocyclic annulene larger than tropane,[353] and a linearly–fused benzodehydro[12]annulene system has been reported.[354]

[345] Oth, J.F.M.; Röttele, H.; Schröder, G. *Tetrahedron Lett.* ***1970***, 61; Oth, J.F.M.; Gilles, J.; Schröder, G. *Tetrahedron Lett.* ***1970***, 67. See Braten, M.N.; Castro, C.; Herges, R.; Köhler, F.; Karney, W.L. *J. Org. Chem.* ***2008****, 73,* 1532.

[346] For a review of conformational mobility in annulenes, see Oth, J.F.M. *Pure Appl. Chem.* ***1971****, 25,* 573.

[347] Untch, K.G.; Wysocki, D.C. *J. Am. Chem. Soc.* ***1967****, 89*, 6386.

[348] Farquhar, D.; Leaver, D. *Chem. Commun.* ***1969***, 24. For a review, see Matsuda, Y.; Gotou, H. *Heterocycles* ***1987****, 26*, 2757.

[349] Hertwig, R.H.; Holthausen, M.C.; Koch, W.; Maksić, Z.B. *Angew. Chem. Int. Ed.* ***1994****, 33*, 1192.

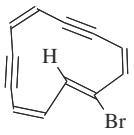
[350] Scott, L.T.; Kirms, M.A.; Günther, H.; von Puttkamer, H. *J. Am. Chem. Soc.* ***1983****, 105*, 1372; Destro, R.; Ortoleva, E.; Simonetta, M.; Todeschini, R. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1227.

[351] Müllen, K.; Meul, T.; Schade, P.; Schmickler, H.; Vogel, E. *J. Am. Chem. Soc.* ***1987****, 109,* 4992. See also, Hafner, K.; Thiele, G.F. *Tetrahedron Lett.* ***1984****, 25*, 1445.

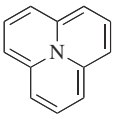
[352] Schmalz, D.; Günther, H. *Angew. Chem. Int. Ed.* ***1988****, 27*, 1692.

[353] Higuchi, H.; Hiraiwa, N.; Kondo, S.; Ojima, J.; Yamamoto, G. *Tetrahedron Lett.* ***1996****, 37*, 2601.

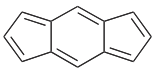
[354] Gallagher, M.E.; Anthony, J.E. *Tetrahedron Lett.* ***2001****, 42*, 7533.



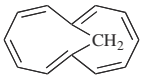
126



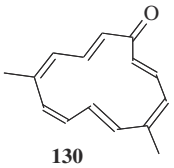
127



128

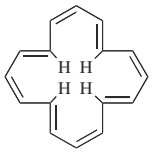


129

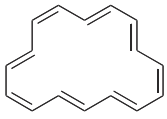


130

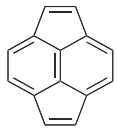
The results for [16]annulene are similar. The compound was synthesized in two different ways,[355] both of which gave **131**, which in solution is in equilibrium with **132**. Above −50 °C there is conformational mobility, resulting in the magnetic equivalence of all protons, but at −130 °C the compound is clearly paratropic: There are 4 protons at 10.56 δ and 12 at 5.35 δ. In the solid state, where the compound exists entirely as **131**, X-ray crystallography[356] shows that the molecules are nonplanar with almost complete bond alternation: The single bonds are 1.44–1.47 Å and the double bonds are 1.31–1.35 Å. A number of dehydro and bridged [16] annulenes are also paratropic,[357] as are [20]annulene,[358] and [24]annulene.[359] However, a bridged tetradehydro[32]annulene was atropic.[333]



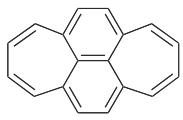
131



132



133



134

Both pyracyclene (**133**),[360] which because of strain is stable only in solution, and dipleiadiene (**134**)[361] are paratropic, as shown by NMR spectra. These molecules might have been expected to behave like naphthalenes with outer bridges, but the outer π frameworks (12 and 16 electrons, respectively) constitute antiaromatic systems with an extra central double bond. With respect to **133**, the $4n + 2$ rule predicts pyracylene to be "aromatic" if it is regarded as a 10-π-electron naphthalene unit connected to two 2-π-electron etheno systems, but "antiaromatic" if it is viewed as a 12-π-electron cyclododecahexaene periphery perturbed by an internal cross-linked etheno unit.[362] Recent studies have concluded on energetic grounds that **133** is a "borderline" case, in terms of aromaticity–antiaromaticity character.[360] Dipleiadiene appears to be antiaromatic.[361]

The fact that many $4n$ systems are paratropic even though they may be nonplanar and have unequal bond distances indicates that if planarity were enforced, the ring currents

[355] Gilles, J. *Tetrahedron Lett.* ***1968***, 6259; Calder, I.C.; Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1968****, 90*, 4946. See Schröder, G.; Kirsch, G.; Oth, J.F.M. *Chem. Ber.* ***1974****, 107*, 460.

[356] Johnson, S.M.; Paul, I.C.; King, G.S.D. *J. Chem. Soc. B* ***1970***, 643.

[357] See Ogawa, H.; Kubo, M.; Tabushi, I. *Tetrahedron Lett.* ***1973***, 361; Nakatsuji, S.; Morigaki, M.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* ***1975***, 1233; Vogel, E.; Kürshner, U.; Schmickler, H.; Lex, J.; Wennerström, O.; Tanner, D.; Norinder, U.; Krüger, C. *Tetrahedron Lett.* ***1985****, 26,* 3087.

[358] Metcalf, B.W.; Sondheimer, F. *J. Am. Chem. Soc.* ***1971****, 93*, 6675. See also, Wilcox, Jr., C.F.; Farley, E.N. *J. Am. Chem. Soc.* ***1984****, 106*, 7195.

[359] Calder, I.C.; Sondheimer, F. *Chem. Commun.* ***1966***, 904. See also, Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 395.

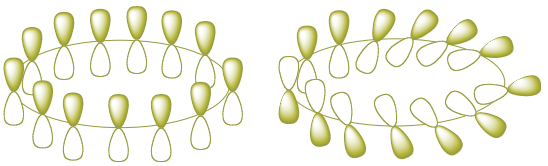
[360] Trost, B.M.; Herdle, W.B. *J. Am. Chem. Soc.* ***1976****, 98,* 4080.

[361] Vogel, E.; Neumann, B.; Klug, W.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1985****, 24*, 1046.

[362] Diogo, H. P.; Kiyobayashi, T.; Minas da Piedade, M. E.; Burlak, N.; Rogers, D. W.; McMasters, D.; Persy, G.; Wirz, J.; Liebman, J. F. *J. Am. Chem. Soc.* ***2002****, 124*, 2065.

might be even greater. The NMR spectrum of the dianion of **110**[363] (and its diethyl and dipropyl homologues)[364] effectively illustrate this point. Recall that in **110**, the outer protons were found at 8.14–8.67 δ with the methyl protons at −4.25 δ. For the dianion, however, which is forced to have approximately the same planar geometry, but now has 16 electrons, the outer protons are shifted to about −3 δ while the methyl protons are found at ∼ 21 δ, a shift of ∼ 25 δ! A converse shift was made when [16]annulenes that were antiaromatic were converted to 18-electron dianions that were aromatic.[282] In these cases, the changes in NMR chemical shifts were almost as dramatic. Heat-of-combustion measures also show that [16]annulene is much less stable than its dianion.[365] It has also been reported that the fluorenyl cation shows substantial destabilization, suggesting that it is an antiaromatic species.[366]

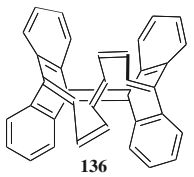
It seems clear that 4*n* systems will be at a maximum where a molecule is constrained to be planar (as in **86** or the dianion of **110**) but, where possible, the molecule will distort itself from planarity and avoid equal bond distances in order to reduce. In some cases (e.g., cyclooctatraene), the distortion and bond alternation are great enough to be completely avoided. In other cases, (e.g., **124** or **131**), it is apparently not possible for the molecules to avoid at least some p orbital overlap. Such molecules show evidence of paramagnetic ring currents, although the degree of is not as great as in molecules (e.g., **86** or the dianion of **110**).



Hückel **Möbius**



135



136

The concept of "Möbius aromaticity" was conceived by Helbronner in 1964,[367] when he suggested that large cyclic [4*n*]annulenes might be stabilized if the π orbitals were twisted gradually around a Möbius strip. This concept is illustrated by the diagrams labeled Hückel, which is a destabilized [4*n*] system, in contrast to the Möbius model, which is a stabilized [4*n*] system.[368] Zimmerman generalized this idea and applied the "Hückel–Möbius concept" to the analysis of ground-state systems [e.g., barrelene (**135**)].[369] In 1998, a computational reinterpretation of existing experimental evidence for $(CH)_9^+$ as a Möbius aromatic cyclic annulene with 4*n* π-electrons was reported.[370] This reversal of

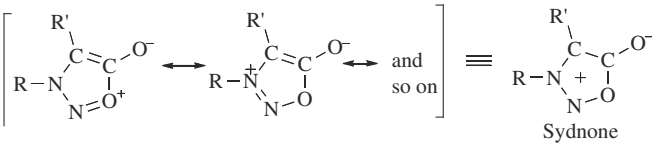
[363] For a review of polycyclic dianions, see Rabinovitz, M.; Cohen, Y. *Tetrahedron* ***1988****, 44,* 6957.
[364] Mitchell, R.H.; Klopfenstein, C.E.; Boekelheide, V. *J. Am. Chem. Soc.* ***1969****, 91*, 4931. For another example, see Deger, H.M.; Müllen, K.; Vogel, E. *Angew. Chem. Int. Ed.* ***1978****, 17*, 957.
[365] Stevenson, G.R.; Forch, B.E. *J. Am. Chem. Soc.* ***1980****, 102,* 5985.
[366] Herndon, W.C.; Mills, N.S. *J. Org. Chem.* ***2005****, 70,* 8492.
[367] Heilbronner, E. *Tetrahedron Lett.* ***1964***, 1923.
[368] Kawase, T; Oda, M. *Angew. Chem. Int. Ed.,* ***2004****, 43,* 4396.
[369] Zimmerman, H. E. *J. Am. Chem. Soc.* ***1966****, 88*, 1564; Zimmerman, H. E. *Acc. Chem. Res.* ***1972****, 4,* 272.
[370] Mauksch, M.; Gogonea, V.; Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1998****, 37*, 2395.

[4*n*]annulene antiaromaticity has been demonstrated by stacking rings into a superphane.[371] A superphane is a sixfold bridged cyclophane with all arene positions in the corresponding dimer taken up by ethylene spacers.[372] A recent computational study predicted several Möbius local minima for [12], [16], and [20]annulenes.[373] A twisted [16]annulene has been prepared and calculations suggested it should show Möbius aromaticity.[374] High-performance liquid chromatography (HPLC) separation of isomers gave **136**, and the authors concluded it is Möbius aromatic. The synthesis and study of molecules that demonstrate Möbius aromaticity continues to be an area of interest.[375]

2.L. OTHER AROMATIC COMPOUNDS

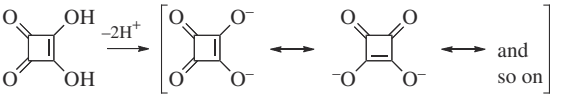
Three additional types of aromatic compounds must be noted.

1. *Mesoionic Compounds*:[376] These compounds cannot be satisfactorily represented by Lewis structures not involving charge separation. Most of them contain five-membered rings. The most common are the *sydnones*, stable aromatic compounds that undergo aromatic substitution when R' is hydrogen.

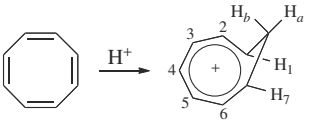


2. *The Dianion of Squaric Acid*.[377] The stability of this system is illustrated by the fact that the pK_1 of squaric acid[378] is $\sim$ 1.5 and the pK_2 is $\sim$ 3.5,[379] which means that even the second proton is given up much more readily than the proton of acetic acid.[380] The analogous three-,[381] five-, and six-membered ring compounds are also known.[382]

[371] Bean, D.E.; Fowler, P.W. *Org. Lett.* ***2008****, 10,* 5573.
[372] For a discussion of superphanes and beltenes, see Gleiter, R.; Hellbach, B.; Gath, S.; Schaller, R.J. *Pure Appl. Chem.* ***2006****, 78*, 699.
[373] Castro, C.; Isborn, C. M.; Karney, W. L.; Mauksch, M.; Schleyer, P.v.R. *Org. Lett.* ***2002****, 4,* 3431.
[374] Ajami, D.; Oeckler, O.; Simon, A.; Herges, R. *Nature*(*London*) ***2003****, 426*, 819; Rappaport, S.M.; Rzepa, H.S. *J. Am. Chem. Soc.* ***2008****, 130,* 7613.
[375] Rzepa, H.S. *Chem. Rev.* ***2005****, 105,* 3697; Herges, R. *Chem. Rev.* ***2006****, 106,* 4820. For monocyclic [11] annulenium cations see Warner, P.M. *J. Org. Chem.* ***2006****, 71,* 9271. For lemniscular hexaphyrins see Rzepa, H.S. *Org. Lett.* ***2008****, 10,* 949.
[376] For reviews, see Newton, C.G.; Ramsden, C.A. *Tetrahedron* ***1982****, 38*, 2965; Ollis, W.D.; Ramsden, C.A. *Adv. Heterocycl. Chem.* ***1976***, *19*, 1; Yashunskii, V.G.; Kholodov, L.E. *Russ. Chem. Rev*. ***1980****, 49*, 28; Ohta, M.; Kato, H., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 117–248.
[377] West, R.; Powell, D.L. *J. Am. Chem. Soc*. ***1963***, 85, 2577; Ito, M.; West, R. *J. Am. Chem. Soc*. ***1963***, 85, 2580.
[378] See Wong, H.N.C.; Chan, T.; Luh, T. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1501–1563.
[379] MacDonald, D.J. *J. Org. Chem.* ***1968****, 33,* 4559.
[380] There has been a controversy as to whether this dianion is in fact aromatic. See Aihara, J. *J. Am. Chem. Soc.* ***1981****, 103,* 1633.
[381] Eggerding, D.; West, R. *J. Am. Chem. Soc.* ***1976****, 98*, 3641; Pericás, M.A.; Serratosa, F. *Tetrahedron Lett.* ***1977***, 4437; Semmingsen, D.; Groth, P. *J. Am. Chem. Soc.* ***1987****, 109*, 7238.
[382] See West, R. *Oxocarbons*, Academic Press, NY, ***1980***; Serratosa, F. *Acc. Chem. Res.* ***1983****, 16,* 170; Schmidt, A.H. *Synthesis* ***1980***, 961; West, R. *Isr. J. Chem.* ***1980****, 20*, 300; West, R.; Niu, J., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 311–345; Maahs, G.; Hegenberg, P. *Angew. Chem. Int. Ed.* ***1966****, 5*, 888.



3. *Homoaromatic Compounds*. When cyclooctatetraene is dissolved in concentrated H_2SO_4, a proton adds to one of the double bonds to form the homotropylium ion (**137**).[383] In this species, an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. The NMR spectra show the presence of a diatropic ring current: H_b is found at $\delta = -0.3$; H_a at 5.1 δ; H_1 and H_7 at 6.4 δ; H_2–H_6 at 8.5 δ. This ion is an example of a *homoaromatic* compound, generally defined as a compound that contains one or more[384] sp^3-hybridized carbon atoms in an otherwise conjugated cycle.[385]



137

In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the aromatic atoms.[386] In **137**, H_b is directly above the aromatic sextet, and so is shifted far upfield in the NMR. Virtually all homoaromatic compounds so far discovered are ions, and the existence of homoaromatic character in uncharged systems[387] has been questioned.[388] However, neutral homoaromaticity in some heterocyclic compounds has been observed by replacing CH_2 at C-2 in bicyclo[3.2.1]octa-3,6-diene with X = BH, AlH, Be, Mg, O, S, PH, NH (antihomoaromatic for X = BH, AlH, and Be; nonhomoaromatic for X = O, S, NH, PH); replacement of CH at C-3 in bicyclo [3.2.1]octa-3,6-dien-2-yl anion with PH, S, NH, O (homoaromatic for X = S, PH, NH, O); and replacement at C-2 and C-3 with N and O (homoaromatic).[389] Homoaromatic ions of 2 and 10 electrons are also known.

[383] Haddon, R.C. *J. Am. Chem. Soc.* ***1988****, 110,* 1108. See also, Childs, R.F.; Mulholland, D.L.; Varadarajan, A.; Yeroushalmi, S. *J. Org. Chem.* ***1983****, 48,* 1431. See also, Alkorta, I.; Elguero, J.; Eckert- Maksić, M.; Maksić, Z.B. *Tetrahedron* ***2004****, 60,* 2259.

[384] If a compound contains two such atoms it is bishomoaromatic; if three, trishomoaromatic, and so on. For examples see Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978****, 17*, 106.

[385] See Childs, R.F. *Acc. Chem. Res.* ***1984****, 17,* 347; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978****, 17*, 106; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 5–45; and in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Wiley, NY, Vol. 3, ***1972***, the reviews by Story, P.R.; Clark Jr., B.C. 1007-1098, pp. 1073–1093.

[386] Calculations show that only ∼ 60% of the chemical shift difference between H_a and H_b is the result of the aromatic ring current, and that even H_a is shielded; it would appear at $\delta \sim 5.5$ without the ring current: Childs, R.F.; McGlinchey, M.J.; Varadarajan, A. *J. Am. Chem. Soc.* ***1984****, 106*, 5974.

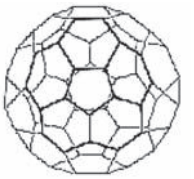
[387] Examples of uncharged homoantiaromatic compounds have been claimed: See Scott, L.T.; Cooney, M.J.; Rogers, D.W.; Dejroongruang, K. *J. Am. Chem. Soc.* ***1988****, 110,* 7244.

[388] Houk, K.N.; Gandour, R.W.; Strozier, R.W.; Rondan, N.G.; Paquette, L.A. *J. Am. Chem. Soc.* ***1979****, 101,* 6797; Paquette, L.A.; Snow, R.A.; Muthard, J.L.; Cynkowski, T. *J. Am. Chem. Soc.* ***1979****, 101*, 6991. See, however, Liebman, J.F.; Paquette, L.A.; Peterson, J.R.; Rogers, D.W. *J. Am. Chem. Soc.* ***1986****, 108*, 8267.

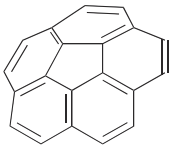
[389] Freeman, P.K. *J. Org. Chem.* ***2005****, 70,* 1998. See the discussion for methano[10]annulenes, Caramori, G.F.; de Oliveira,K.T.; Galembeck, S.E.; Bultinck, P.; Constantino, M.G. *J. Org. Chem.* ***2007****, 72,* 76.

New conceptual applications to 3D homoaromatic systems with cubane, dodecahedrane, and adamantane frameworks have been presented.[390] This concept includes families of spherical homoaromatics with both two and eight mobile electrons. Each set has complete *spherical homoaromaticity*, that is, all the sp^2 carbon atoms in a highly symmetrical framework are separated by one or two sp^3-hybridized atoms.

4. *Fullerenes*. Fullerenes are a family of aromatic hydrocarbons[391] based on the parent buckminsterfullerene (**138**; C_{60})[392] that have a variety of very interesting properties.[393] Derivatives of **138** are sometimes called buckyballs. Molecular orbital calculations show that "fullerene aromaticity lies within 2 kcal mol^{-1} (8.4 kJ mol^{-1}) per carbon of a hypothetical ball of rolled up graphite.[394] Fullerenes may exhibit what is known as spherical aromaticity (3D aromaticity),[395] and the *Hückel rule* cannot be used for spherical systems (e.g., fullerenes). The $2(n + 1)^2$ rule was proposed by Hirsch et al,[396] as the 3D analogue of the $4n + 2$ rule for planar systems proposed by Hückel.[397] Heterofullerenes are also known.[398]



138



139

Buckybowls constitute another class of polynuclear aromatic hydrocarbons, and they are essentially fragments of **138**. Corannulene (**139**)[399] (also called 5-circulene), for example, is the simplest curved-surface hydrocarbon possessing a carbon framework that be identified with the buckminsterfullerene surface. It has been synthesized by Scott, et al.[399] and several other groups.[400] Corannulene is a flexible molecule, with a bowl–bowl inversion barrier of $\sim$ 10–11 kcal mol^{-1}

[390] Chen, Z.; Jiao, H.; Hirsch, A.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.,* ***2002****, 41,* 4309

[391] Thilgen, C.; François Diederich, F. *Chem. Rev.* ***2006****, 106*, 5049.

[392] Billups, W. E.; Ciufolini, M.A. *Buckminsterfullerenes*, VCH, NY, ***1993***; Taylor, R. *The Chemistry of Fullerenes*, World Scientific, River Edge, NJ, Singapore, ***1995***; Aldersey-Williams, H. *The Most Beautiful Molecule: The Discovery of the Buckyball,* Wiley, NY, ***1995***; Baggott, J.E. *Perfect Symmetry: the Accidental Discovery of Buckminsterfullerene*, Oxford University Press, Oxford, NY, ***1994***. Also see, Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature (London)* ***1985****, 318*, 162.

[393] Smalley, R.E. *Acc. Chem. Res.* ***1992****, 25,* 98; Diederich, F.; Whetten, R.L. *Acc. Chem. Res.* ***1992****, 25,* 119; Hawkins, J. M. *Acc. Chem. Res.* ***1992****, 25,* 150; Wudl, F. *Acc. Chem. Res.* ***1992****, 25,* 157; McElvany, S.W.; Ross, M.M.; Callahan, J.H. *Acc. Chem. Res.* ***1992****, 25,* 162; Johnson, R.D.; Bethune, D.S.; Yannoni, C.S. *Acc. Chem. Res.* ***1992****, 25,* 169.

[394] Warner, P.M. *Tetrahedron Lett.* ***1994****, 35,* 7173.

[395] Chen, Z.; King, R.B. *Chem. Rev* **. *2005***, *105*, 3613; Bühl, M.; Hirsch, A. *Chem. Rev*. ***2001***, *101*, 1153.

[396] Hirsch, A.; Chen, Z.; Jiao, H. *Angew. Chem., Int. Ed.* ***2000****, 39*, 3915.

[397] Hückel, E. *Z. Phys.* ***1931****, 70*, 204; Hückel, E. *Z. Phys.* ***1931****, 72*, 310; Hückel, E. *Z. Phys.* ***1932****, 76*, 628.

[398] Vostrowsky, O.; Hirsch, A. *Chem. Rev.* ***2006****, 106,* 5191

[399] Scott, L.T.; Hashemi, M.M.; Meyer, D.T.; Warren, H.B. *J. Am. Chem. Soc.* ***1991****, 113,* 7082.

[400] Liu, C.Z.; Rabideau, P.W. *Tetrahedron Lett.* ***1996****, 37*, 3437.

(41.8–46.0 kJ mol^{-1}).[401] Benzocorannulenes are known,[402] and other bowl-shaped hydrocarbons include acenaphtho[3,2,1,8-*ijklm*]diindeno[4,3,2,1-*cdef*-1',2',3',4'*pqra*]triphenylene.[403] The inversion barrier to buckybowl inversion has been lowered by such benzannelation of the rim.[404] Other semibuckminsterfullerenes include C_{2v}-$C_{30}H_{12}$ and C_3-$C_{30}H_{12}$.[399] Larger fullerenes include C_{60},C_{80}, $C_{84,}$ and fullerenes are known that contain an endohedral metal (e.g., scandium or even Sc_3N).[405] Synthetic methods often generate mixtures of fullerenes that must be separated, as in the report of new methods for separating C_{84}-fullerenes.[406] A homofullerene has been prepared,[407] and the azaacepentalenide anion, which is a bowl-shaped hetereocycle, has been prepared.[408]

2.M. HYPERCONJUGATION

Conjugation in molecules (e.g., 1,3-butadiene and benzene) was well known to organic chemists in the 19th century. For example, it became understood that one could view 1,3-butadiene as two ethylene units. The overlap of the end *p* orbitals of the two ethylenes that are to be attached leads to conjugation, which in turn leads to a lowering of the energy of the system, a change in geometry in several respects, and most obviously, to changes in chemical and physical properties of the molecule. In this case, two *p* orbitals overlap. Mulliken suggested that if one has a sigma orbital overlapping with a *p* orbital, then one has "hyperconjugation." Qualitatively hyperconjugation is similar to conjugation, but smaller. When a methyl group is attached to ethylene, for example, there is a shift of the UV absorption spectrum to longer wavelength, an increase in the reactivity of the molecule, and a lowering of energy, similar to the changes that occur in the ethylene to butadiene case, but to a lesser extent. Hyperconjugation shows the same effects, but to a lesser amount, because the sigma orbital lies at a lower energy than the π orbital. Hence the electrons delocalize out of the sigma orbital in hyperconjugation to a lesser extent than from a π orbital in conjugation. The term hyperconjugation therefore arises from the hyperconjugative forms that make small but definite contributions to the ground state of a molecule.[409]

[401] Biedermann, P.U.; Pogodin, S.; Agranat, I. *J. Org. Chem.* ***1999****, 64*, 3655; Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* ***1996****, 29*, 235; Hagan, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew. Chem. Int. Ed.* ***1997****, 36,* 406. See also, Dinadayalane, T.C.; Sastry, G.N. *Tetrahedron* ***2003****, 59*, 8347.

[402] Dinadayalane, T.C.; Sastry, G.N. *J. Org. Chem.* ***2002****, 67,* 4605.

[403] Marcinow, Z.; Grove, D.I.; Rabideau, P.W. *J. Org. Chem.* ***2002****, 67*, 3537. Multiethynyl corannulenes have been prepared: Wu, Y.-T.; Bandera, D.; Maag, R.; Linden, A.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***2008****, 130,* 10729.

[404] Marcinow, Z.; Sygula, A.; Ellern, D.A.; Rabideau, P.W. *Org. Lett.* ***2001****, 3*, 3527.

[405] Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M.R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M.M.; Maitra, K.; Fisher, A.J.; Balch, A.L.; Dorn, H.C. *Nature (London)* ***1999****, 401*, 55.

[406] Wang, G.-W.; Saunders, M.; Khong, A.; Cross, R.J. *J. Am. Chem. Soc.* ***2000****, 122*, 3216.

[407] Kiely, A.F.; Haddon, R.C.; Meier, M.S.; Selegue, J.P.; Brock, C.P.; Patrick, B.O.; Wang, G.-W.; Chen, Y. *J. Am. Chem. Soc.* ***1999****, 121,* 7971.

[408] Mascal, M.; Bertran, J.C. *J. Am. Chem. Soc.* ***2005****, 127,* 1352.

[409] Pauling, L.; Springall, H. D.; Palmer, K. J. *J. Am. Chem. Soc.* ***1939,*** *61,* 927; Wheland, G.W. *J. Chem. Phys.* ***1934****, 2,* 474.

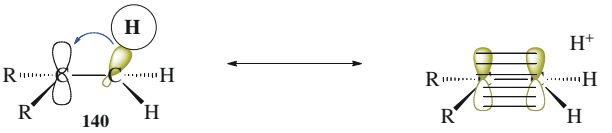
Another delocalization phenomenon has been discussed that involves σ electrons.[410] Baker and Nathan[411] observed that the rates of reaction of p-substituted benzyl bromides with pyridine (see Reaction **10-31**) were opposite from the results expected from electron release. That is, the methyl-substituted compound reacted fastest and the tert-butyl substituted compounded reacted slowest. This appeared to be an anomalous electron-release pattern for alkyl groups because the field effect predicted the order of electron release for simple alkyl groups connected to an unsaturated system should be tert-butyl > isopropyl > ethyl > methyl. At least one hydrogen atom should be attached to the α-carbon that is connected to the sp^2 carbon for the Baker–Nathan effect. The Baker–Nathan effect has clouded the issue because some interpreted that it indicates hyperconjugation occurs with hydrogen and a double bond, but either did not occur or occurred to a very small amount with carbon. In the 1930s, Baker and Nathan did not have the tools to experimentally or theoretically understand hyperconjugation to any great extent. Those chemists looked for lowering of energy that could be detected, but these experiments do not necessarily help to explain hyperconjugation. Indeed, it is now known that the Baker–Nathan effect is a result of changes in solvation energy[412] and has very little to do with hyperconjugation. It was recently reported that hyperconjugation is an important factor determining alkane C—H bond dissociation energies.[413] In certain instances where the *Baker–Nathan effect* was found to apply in solution, the order was completely reversed in the gas phase.[414] Since the molecular structures are unchanged in going from the gas phase into solution, it appears that each alkyl group is solvated to a different extent.[415] However, this only demonstrates that the Baker–Nathan effect is not the same as hyperconjugation. The structural changes that occur upon hyperconjugation can be determined from quantum mechanics and from experiment. Such changes can be qualitatively predicted by looking at the resonance structures involved.

Hyperconjugation is probably important for carbocations, as well as for free radicals[416] and for excited states of molecules.[417] In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*.

Apart from contributions to aromaticity, hyperconjugation has been used to explain the stability of intermediates (e.g., carbocations, see Chapter 5 for an introduction to carbocations). It was stated that C—C hyperconjugation is most important in stabilizing carbocations when the C—C bond(s) involved have more than 75% *p* character.[418] This effect can be illustrated by a typical case (e.g., carbocation **140**), where hyperconjugation is invoked to explain the relative stability of the ion as attached groups are varied. If the

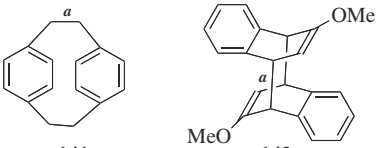
[410] For monographs, see Baker, J.W. *Hyperconjugation*, Oxford University Press, Oxford, ***1952***; Dewar, M.J.S. *Hyperconjugation*, Ronald Press, NY, ***1962***. For a review, see de la Mare, P.B.D. *Pure Appl. Chem.* ***1984****, 56*, 1755.
[411] Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840, 1844.
[412] This idea was first suggested by Schubert, W.M.; Sweeney, W.A. *J. Org. Chem.* ***1956****, 21*, 119.
[413] Ingold, K.U.; DiLabio, G.A. *Org. Lett.* ***2006****, 8,* 5923.
[414] Hehre, W.J.; McIver, Jr., R.T.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1974****, 96*, 7162; Arnett, E.M.; Abboud, J.M. *J. Am. Chem. Soc.* ***1975****, 97,* 3865; Glyde, E.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 678. See also, Taylor, R. *J. Chem. Res. (S),* ***1985***, 318.
[415] For an opposing view, see Cooney, B.T.; Happer, D.A.R. *Aust. J. Chem.* ***1987****, 40,* 1537.
[416] Symons, M.C.R. *Tetrahedron* ***1962****, 18*, 333.
[417] Rao, C.N.R.; Goldman, G.K.; Balasubramanian, A. *Can. J. Chem.* ***1960****, 38,* 2508.
[418] Jensen, F.R.; Smart, B.E. *J. Am. Chem. Soc.* **1969**, *91*, 5686.

orbitals of an adjacent C—H bond align with the empty orbital of the positive center; a canonical form can be



140

drawn by electron donation to C^+ to form a canonical form that is formally an alkene and H^+. Note that the H in **140** could be any atom and C could be any sp^2-hybridized atom and hyperconjugation would still occur. The key part is that a σ-bond overlaps a π-bond. For **140**, an alkene and a closely bound proton constitute a canonical form that helps stabilize the carbocation. Each of the three methyl hydrogen atoms in **140** can contribute to the hyperconjugative stabilization. In other words, resonance contributors involving the C—H bonds represent the bond elongation due to hyperconjugation, and provide stabilization of a carbocation.[419] To determine whether hyperconjugation is important in a given situation using molecular modeling, one must ask if the localized model is adequate for that situation at the particular level of precision, or whether the model must be corrected by including some delocalization.[420] To a first approximation, delocalization can be neglected, but it is needed for better approximations. The effect of the alkene canonical form on **140** is that the electrons in the C—H bond are closer to the carbon than if hyperconjugation did not contribute at all.



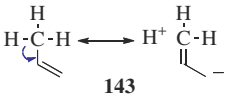
141 **142**

In neutral molecules, the structural elements noted above should be present for hyperconjugation. There is usually at least one sp^2-hybridized atom, usually carbon, but for hyperconjugation in general, all that is needed is a σ-bond. Resonating structures due to hyperconjugation may be written involving "no bonds" between the alpha carbon and hydrogen atoms, as shown below for propene.

Contributions of this type are seen by a comparison of the X-ray data for **141** and **142** with the calculated data (MM40). The bond length for bond *a* in **141** is 1.571 Å by analysis of the X-ray data, but analysis by MM40 calculations gave a value of 1.565 A.[421] Similar analysis of bond *a* in **142** gave an experimental value of 1.627 Å, but MM40 calculations gave a value of 1.589 Å. The calculated values are shorter than the actual values. When hyperconjugation was included in the MM4 calculations, the calculated values were 1.574 Å for **141** and 1.623 Å for **142**.[421] The hyperconjugative stretching effect was calculated to be 0.009 Å for **141** and 0.034 Å for **142**. This work suggests that hyperconjugation is actually a bond stretching effect,[421] and it has been represented as resonance contributors several times in this

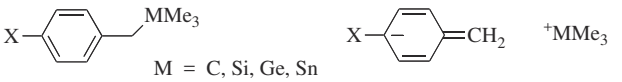
[419] See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5; Wiley, NY, ***1976***, pp. 2303–2426.
[420] Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry,* 3rd Ed., Harper Collins, NY, ***1987***, p. 68.
[421] Allinger, N.L. *J. Comput. Aided Mol. Des.* ***2011****, 25,* 295.

chapter. If the bond elongation found in propene, due to hyperconjugation, is represented as the canonical forms shown for **143**, the charge separation illustrates bond elongation. In a different example using toluene, there is evidence that the main interaction between methyl groups and the ring system in the positive ions of aromatic hydrocarbons is due to hyperconjugation rather than an inductive effect.[422]



143

There is evidence that bond length effects were the result of the *s* character of the saturated carbon rather than of neutral hyperconjugation.[423] These experimental results seem to follow from hyperconjugation in the ground states of neutral molecules, and there is evidence in favor of hyperconjugation.[424] Indeed, hyperconjugation appears to operate for both carbon and hydrogen in various systems (supported by quantum mechanics).[425] These works tie together experimental and computational results into a unified picture that supports hyperconjugation.[424,425] A study of the one-bond coupling constants for the aromatic system **144**



M = C, Si, Ge, Sn
X = NO_2, CN, H, Me, OMe

144

appears to provide structural evidence for hyperconjugation in a neutral ground state.[426] Hyperconjugation in the ground state of neutral molecules has been called *sacrificial hyperconjugation* by Muller and Mulliken.[427]

Another way to view this phenomenon is to say that electron release is permitted by a mechanism that is essentially a type of tautomeric effect (Sec. 2.N). Dewar suggested that the delocalization of electrons of single bonds (hyperconjugation) and of p or π electrons (conjugation) should be included as part of the electronic description only if the localized bond picture fails.[428] This result is a good first approximation, but modern molecular mechanics allows a much better analysis.

Hyperconjugation has been invoked to explain various aspects of aromaticity, as utilized early in this chapter. It is known that 5,5-disubstituted cyclopentadienes, where the substituents are electropositive groups, show enhanced cyclic conjugation in comparison with cyclopentadiene itself.[429] 5,5-Distannylcyclopentadiene, for example, was found to be nearly as aromatic as furan. This is explained by hyperconjugative electron donation by the substituents, resulting in a partially anionic ring.[424] Another effect is the so-called C^*-aromaticity, which is a

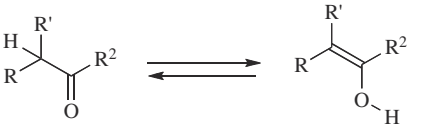
[422] Bolton, J.R.; Carrington, A.; McLachlan, A.D. *Mol. Phys.* ***1962****, 5*, 31
[423] Dewar, M.J.S.; Schmeising, H.N. Tetrahedron **1959**, 5, 166; Dewar, M.J.S. *Hyperconjugation,* Ronald Press, New York, ***1962***; Alden, R. A.; Kraut, J.; Traylor, T. G. *J. Am. Chem. Soc.* ***1968****, 90,* 74. Also see Lambert, J.B.; Shawl, C.E.; Basso, E. *Can. J. Chem.* **2000**, 78, 1441.
[424] See Laube, T.; Ha, T. *J. Am. Chem. Soc.* ***1988****, 110*, 5511.
[425] Allinger, N.L. *Molecular Structure: Understanding Steric and Electronic Effect from Molecular Mechanics* Wiley, Hoboken, NJ, ***2010***.
[426] Lambert, J.B.; Singer, R.A. *J. Am. Chem. Soc.* ***1992****, 114*, 10246.
[427] Muller, N.; Mulliken, R.S. *J. Am. Chem. Soc.* ***1958****, 80,* 3489.
[428] Dewar, M.J.S. *Hyperconjugation* Ronald Press Co., New York, ***1962***.
[429] Nyulászi, L.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999****, 121*, 6872.

hyperconjugative effect found in small disubstituted rings that leads to lowering of ring-strain energies for the unsaturated rings, particularly when electronegative substituents are attached.[430]

2.N. TAUTOMERISM[431]

There is another topic that is important for an understanding of chemical bonding in organic compounds. For most compounds, all the molecules are represented by a single structure. But for many compounds, there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[432] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another. Mass spectrometry was used to study tautomerism,[433] which takes several forms.

2.N.i Keto–Enol Tautomerism[434–444]



Keto form **Enol form**

A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:[445] Such equilibria are pH dependent, as in the case of 2-acetylcyclohexanone.[446] In simple cases (R^2 = H, alkyl, OR, etc.), the equilibrium lies well to the left (Table 2.1). Examining the bond energies in Table 1.7 leads to an explanation for this fact. The keto form differs from the enol form by the presence of a C—H, a C—C, and a

[430] Goller, A.; Clark, T.J. *J. Mol. Model.* ***2000****, 6*, 133.
[431] Baker, J.W. *Tautomerism*, D. Van Nostrand Company, Inc., New York, ***1934***; Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Y.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co.: Dordrecht, Holland, ***1988***.
[432] Toullec, J. *Adv. Phys. Org. Chem.* ***1982****, 18*, 1; Kolsov, A.I.; Kheifets, G.M. *Russ. Chem. Rev.* ***1971****, 40*, 773; ***1972****, 41*, 452–467; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 157–240.
[433] Furlong, J.J.P.; Schiavoni, M.M.; Castro, E.A.; Allegretti, P.E. *Russ. J. Org. Chem.* ***2008****, 44*, 1725.
[434] The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (Reaction **12-3**).
[435] Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984*** *, 106,* 460. See also, Dubois, J.E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* ***1981*** *, 103,* 5393; Toullec, J. *Tetrahedron Lett.* ***1984*** *, 25*, 4401; Chiang, Y.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* ***1989*** *, 111*, 3977.
[436] Keeffe, J.R.; Kresge, A.R.; Toullec, J. *Can. J. Chem.* ***1986*** *, 64,* 1224.
[437] Keeffe, J.R.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* ***1990*** *, 112*, 4862; Iglesias, E. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 431. See these papers for values for other simple compounds.
[438] Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1987*** *, 109,* 4000.
[439] Bohne, C.; MacDonald, I.D.; Dunford, H.B. *J. Am. Chem. Soc.* ***1986*** *, 108*, 7867.
[440] Chiang, Y.; Kresge, A.J.; Walsh, P.A. *J. Am. Chem. Soc.* ***1986*** *, 108,* 6314.
[441] Chiang, Y.; Kresge, A.J.; Krogh, E.T. *J. Am. Chem. Soc.* ***1988*** *, 110,* 2600.
[442] Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 515. For enolization of β-ketoamides, see Hynes, M.J.; Clarke, E.M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 901.
[443] Jefferson, E.A.; Keeffe, J.R.; Kresge, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 2041.
[444] Williams, D.L.H.; Xia, L. *J. Chem. Soc. Chem. Commun.* ***1992***, 985.
[445] Capponi, M.; Gut, I.G.; Hellrung, B.; Persy, G.; Wirz, J. *Can. J. Chem.* ***1999****, 77*, 605. For a treatise, see Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***.
[446] Iglesias, E. *J. Org. Chem.* ***2003****, 68*, 2680.

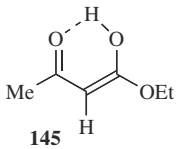
TABLE 2.1 The Enol Content of Some Carbonyl Compounds

Compound	Enol Content (%)	Reference
Acetone	6×10^{-7}	435
$PhCOCH_3$	1.1×10^{-6}	436
Cyclopentanone	1×10^{-6}	437
CH_3CHO	6×10^{-5}	438
Cyclohexanone	4×10^{-5}	437
Butanal	5.5×10^{-4}	439
$(CH_3)_2CHCHO$	1.4×10^{-2}	439,440
Ph_2CHCHO	9.1	441
CH_3COOEt	No enol found[a]	437
CH_3COCH_2COOEt	8.4	442
$CH_3COCH_2COCH_3$	80	353
$PhCOCH_2COCH_3$	89.2	437
$EtOOCCH_2COOEt$	7.7×10^{-3}	437
$N{\equiv}CCH_2COOEt$	2.5×10^{-1}	437
Indane-1-one	3.3×10^{-8}	443
Malonamide	No enol found	444

[a]Less than 1 part in 10 million.

C=O bond, whereas the enol has a C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal mol^{-1} (1500 kJ mol^{-1}) and of the second three is 347 kcal mol^{-1} (1452 kJ mol^{-1}). The keto form is thermodynamically more stable by ~12 kcal mol^{-1} (48 kJ mol^{-1}), and in most cases the enol forms cannot normally be isolated.[447] In certain cases, however, a larger amount of the enol form is present, and it can even be the predominant form.[448] There are three main types of the more stable enols:[449]

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. Carboxylic esters have a much smaller enol content than ketones, for example. In molecules like acetoacetic ester (**145**), the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



145

Analysis of acetoacetamide by gas electron diffraction shows that it exists as a mixture of 63% enol tautomer and 37% diketo form at 74°C.[450] There is a discussion of electron delocalization with respect to amides.[451]

[447] For reviews on the generation of unstable enols, see Kresge, A.J. *Pure Appl. Chem.* ***1991****, 63,* 213; Capon, B. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 307–322.

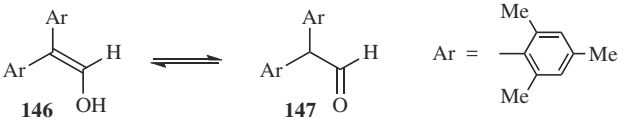
[448] For reviews of stable enols, see Kresge, A.J. *Acc. Chem. Res.* ***1990****, 23*, 43; Hart, H.; Rappoport, Z.; Biali, S.E. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 481–589; Hart, H. *Chem. Rev,* ***1979****, 79,* 515; Hart, H.; Sasaoka, M. *J. Chem. Educ.* ***1980****, 57*, 685.

[449] For some examples of other types, see Pratt, D.V.; Hopkins, P.B. *J. Am. Chem. Soc.* ***1987****, 109*, 5553; Nadler, E. B.; Rappoport, Z.; Arad, D.; Apeloig, Y. *J. Am. Chem. Soc.* ***1987****, 109,* 7873.

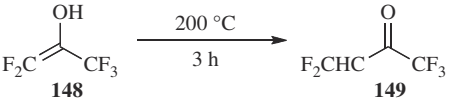
[450] Belova,, N.V.; Girichev, G.V.; Shlykov, S.A.; Oberhammer, H. *J. Org. Chem.* ***2006****, 71*, 5298.

[451] Mujika, J.I.; Matxain, J.M.; Eriksson, L.A.; Lopez, X. *Chem. Eur. J.* ***2006****, 12,* 7215; Kemnitz, C.R.; Loewen, M.J. *J. Am. Chem. Soc.* ***2007****, 129,* 2521.

2. Molecules that contain two or three bulky aryl groups.[452] An example is 2,2-dimesitylethenol (**146**), where the keto content at equilibrium is only 5%.[453] In cases such as this, steric hindrance (Sec. 4.Q.iv) destabilizes the keto form. In **146**, the two aryl groups are ~ 120° apart, but in **147** they must move closer together (~ 109.5°). Such compounds are often called *Fuson-type enols*.[454] There is one example of an amide with a bulky aryl group [*N*-methyl bis(2,4,6-triisopropylphenyl)acetamide] that has a measurable enol content, in sharp contrast to most amides.[455]



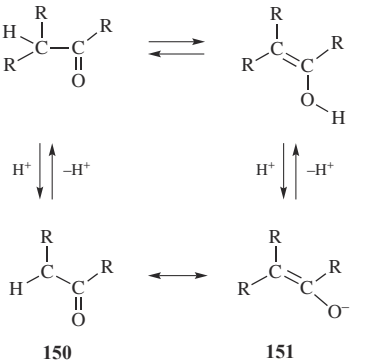
3. Highly fluorinated enols (e.g., **148**).[456]



In this case, the enol form is not more stable than the keto form (**149**). The enol form is less stable, and converts to the keto form upon prolonged heating. It can, however, be kept at room temperature for long periods of time because the tautomerization Reaction (**12-3**) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39 °C, while the enol is a liquid even at −78 °C. Each can be kept at room temperature for days if catalysts, (e.g., acids or bases) are rigorously excluded.[457] Even the simplest enol, vinyl alcohol (CH_2=CHOH), has been prepared in the gas phase at room temperature, where it has a half-life of ~ 30 min.[458] The enol Me_2C=CCHOH is indefinitely stable in the solid state at −78 °C and has a half-life of ~ 24 h in the liquid state at 25 °C.[459] When both forms cannot be isolated, the extent of enolization is often measured by NMR.[460]

[452] For a review, see Rappoport, Z.; Biali, S.E. *Acc. Chem. Res.* ***1988****, 21*, 442. For a discussion of their structures, see Kaftory, M.; Nugiel, D.A.; Biali, D.A.; Rappoport, Z. *J. Am. Chem. Soc.* ***1989****, 111*, 8181.
[453] Nugiel, D.A.; Nadler, E.B.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987****, 109,* 2112; O'Neill, P.; Hegarty, A.F. *J. Chem. Soc. Chem. Commun.* ***1987***, 744; Becker, H.; Andersson, K. *Tetrahedron Lett.* ***1987****, 28*, 1323.
[454] See Fuson, R.C.; Southwick, P.L.; Rowland, S.P. *J. Am. Chem. Soc.* ***1944****, 66*, 1109.
[455] Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* ***1996****, 118*, 3994.
[456] For a review, see Bekker, R.A.; Knunyants, I.L. *Sov. Sci. Rev. Sect. B* ***1984****, 5,* 145.
[457] For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg, J.W. *J. Am. Chem. Soc.* ***1968****, 90*, 7008.
[458] Saito, S. *Chem. Phys. Lett.* ***1976****, 42,* 399. See also, Rodler, M.; Blom, C.E.; Bauder, A. *J. Am. Chem. Soc.* ***1984****, 106,* 4029; Capon, B.; Guo, B.; Kwok, F.C.; Siddhanta, A.K.; Zucco, C. *Acc. Chem. Res.* ***1988****, 21,* 135.
[459] Chin, C.S.; Lee, S.Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* ***1988****, 110,* 8244.
[460] Cravero, R.M.; González-Sierra, M.; Olivieri, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1067.



150 **151**

The extent of enolization[461] is greatly affected by solvent,[462] concentration, and temperature. Lactone enols, for example, have been shown to be stable in the gas phase, but unstable in solution.[463] Another example is acetoacetic ester, which has an enol content of 0.4% in water and 19.8% in toluene.[464] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. The effect of temperature is clear from the enol content of pentan-2,4-dione (CH_3COCH_2-$COCH_3$), which was found to be 95, 68, and 44%, respectively, at 22, 180, and 275 °C.[465] When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **150** and **151** differ only in placement of electrons, *they are not tautomers, but canonical forms*. The true structure of the enolate ion is a hybrid of **150** and **151** although **151** contributes more, since in this form the negative charge is on the more electronegative atom.

2.N.ii Other Proton-Shift Tautomerism

The valence tautomerism is discussed of a proton from either tautomer is the same because of resonance. Some examples follows:[466]

[461] See Toullec, J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 323–398.

[462] For an extensive study, see Mills, S.G.; Beak, P. *J. Org. Chem.* ***1985****, 50*, 1216. for keto–enol tautomerism in aqueous alcohol solutions, see Blokzijl, W.; Engberts, J.B.F.N.; Blandamer, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 455; For theoretical calculations of keto-enol tautomerism in aqueous solutions, see Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* ***1996****, 52*, 11325.

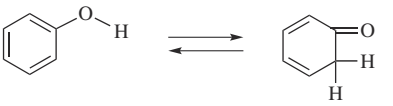
[463] Tureček, F.; Vivekananda, S.; Sadílek, M.; Polášek, M. *J. Am. Chem. Soc,.* ***2002****, 124*, 13282.

[464] Meyer, K.H. *Leibigs Ann. Chem.* ***1911****, 380,* 212. See also, Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 515.

[465] Hush, N.S.; Livett, M.K.; Peel, J.B.; Willett, G.D. *Aust. J. Chem.* ***1987****, 40,* 599.

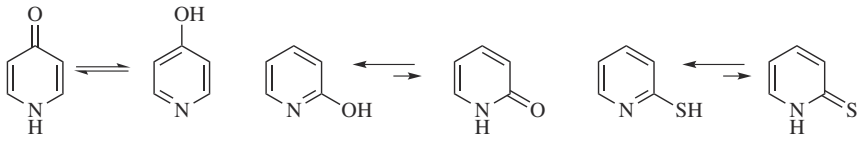
[466] For a review of the use of X-ray crystallography to determine tautomeric forms, see Furmanova, N.G. *Russ. Chem. Rev.* ***1981****, 50*, 775.

1. Phenol–Keto Tautomerism.[467]



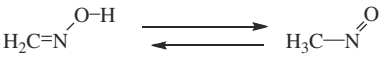
Phenol Cyclohexadienone

For most simple phenols, this equilibrium lies well to the side of the phenol, which is aromatic. For phenol itself, there is no evidence for the existence of the keto form.[468] However, the keto form becomes important and may predominate: (1) where certain groups, (e.g., a second OH group or an N=O group), are present;[469] (2) in systems of fused aromatic rings[470]; (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[471] although in the vapor phase the positions of many of these equilibria are reversed.[472] For example, **152** is the only form detectable in ethanolic solution in the equilibrium between 4-pyridone (**152**) and 4-hydroxypyridine (**153**), while **153** predominates in the vapor phase.[472] In other heterocycles, the hydroxy-form predominates. 2-Hydroxypyridone (**154**) and pyridone-2-thiol (**156**)[473] are in equilibrium with their tautomers, 2-pyridone (**155**) and pyridine-2-thione (**157**), respectively. In both cases, the most stable form is the hydroxy or thiol tautomer, **154** and **156**.[474]



152 **153** **154** **155** **156** **157**

2. Nitroso–Oxime Tautomerism.



The equilibrium shown for formaldehyde oxime and nitrosomethane illustrates this process.[475] In molecules where the products are stable, the equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is not a hydrogen.

[467] For reviews, see Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966****, 35*, 817; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group,* Vol. 2, Wiley, NY, ***1970***, pp. 168–198.

[468] See Lasne, M.; Ripoll, J.; Denis, J. *Tetrahedron Lett.* ***1980****, 21*, 463. See also, Capponi, M.; Gut, I.; Wirz, J. *Angew. Chem. Int. Ed.* ***1986****, 25*, 344.

[469] Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966****, 35*, 817. See also, Highet, R.J.; Chou, F.E. *J. Am. Chem. Soc.* ***1977****, 99,* 3538.

[470] See, for example, Majerski, Z.; Trinajstic, N. *Bull. Chem. Soc. Jpn.* ***1970****, 43*, 2648.

[471] See Elguero, J.; Marzin, C.; Katritzky, A.R.; Linda, P. *The Tautomerism of Heterocycles*, Academic Press, NY, ***1976***. For reviews, see Katritzky, A.R.; Karelson, M.; Harris, P.A. *Heterocycles* ***1991****, 32,* 329; Beak, P. *Acc. Chem. Res.* ***1977****, 10,* 186; Katritzky, A.R. *Chimia,* ***1970****, 24*, 134.

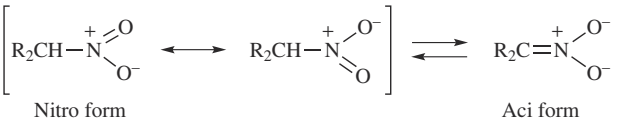
[472] Beak, P.; Fry, Jr., F.S.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* ***1976****, 98*, 171.

[473] Moran, D.; Sukcharoenphon, K.; Puchta, R.; Schaefer, III, H.F.; Schleyer, P.v.R.; Hoff, C.D. *J. Org. Chem.* ***2002****, 67,* 9061.

[474] Parchment, O.G.; Burton, N.A.; Hillier, I.H.; Vincent, M.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 861.

[475] Long, J.A.; Harris, N.J.; Lammertsma, K. *J. Org. Chem.* ***2001****, 66*, 6762.

3. Aliphatic Nitro Compounds Are in Equilibrium with Aci Forms.



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine–Enamine Tautomerism.[476]



Enamine

Enamines are normally stable only when no hydrogen is attached to the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[477] The energy of various imine–enamine tautomers has been calculated.[478] In the case of 6-amino-fulvene-1-aldimines, tautomerism was observed in the solid state, as well as in solution.[479] Porphyrins and porphycenes also undergo this type of tautomerism, and the two tautomers may be imaged using single-molecule spectroscopy.[480]

5. Ring–Chain Tautomerism. Ring–chain tautomerism[481] occurs in sugars (aldehyde vs the pyranose or furanose structures), and in γ-oxocarboxylic acids.[482] In benzamide carbaldehyde, (**159**), whose ring-chain tautomer is **158**, the equilibrium favors the cyclic form (**159**).[483] Similarly, benzoic acid 2-carbaldehyde (**160**) exists largely as the cyclic form (**161**).[484] In these latter cases, and in many others, this tautomerism influences chemical reactivity. Conversion of **160** to an ester, for example, is difficult since most standard methods lead to the OR derivative of **161** rather than the ester of **160**. Ring–chain tautomerism also occurs in sprioxathianes,[485] in decahydroquinazolines (e.g. **162** and **163**),[486] in other 1,3-heterocycles,[487] and in 2-ferrocenyl-2,4-dihydro-1H-3,1-benzoxazine derivatives.[488]

[476] See Shainyan, B.A.; Mirskova, A.N. *Russ. Chem. Rev.* ***1979****, 48*, 107; Mamaev, V.P.; Lapachev, V.V. *Sov. Sci. Rev. Sect. B.* ***1985****, 7*, 1.

[477] For examples of the isolation of primary and secondary enamines, see Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 1657; de Jeso, B.; Pommier, J. *J. Chem. Soc. Chem. Commun.* ***1977***, 565.

[478] Lammertsma, K.; Prasad, B.V. *J. Am. Chem. Soc.* ***1994****, 116*, 642.

[479] Sanz, D.; Perez-Torralba, M.; Alarcon, S.H.; Claramunt, R.M.; Foces-Foces, C.; Elguero, J. *J. Org. Chem.* ***2002****, 67,* 1462.

[480] Piwoński, H.; Stupperich, C.; Hartschuh, A.; Sepioł, J.; Meixner, A.; Waluk, J. *J. Am. Chem. Soc.* ***2005****, 127,* 5302.

[481] Valters, R.E.; Flitsch, W. *Ring-Chain Tautomerism*, Plenum, NY, ***1985***. For reviews, see Valters, R.E. *Russ. Chem. Rev.* ***1973****, 42*, 464; ***1974****, 43*, 665; Escale, R.; Verducci, J. *Bull. Soc. Chim. Fr.,* ***1974***, 1203.

[482] Fabian, W.M.F.; Bowden, K. *Eur. J. Org. Chem.* ***2001***, 303.

[483] Bowden, K.; Hiscocks, S.P.; Perjéssy, A. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 291.

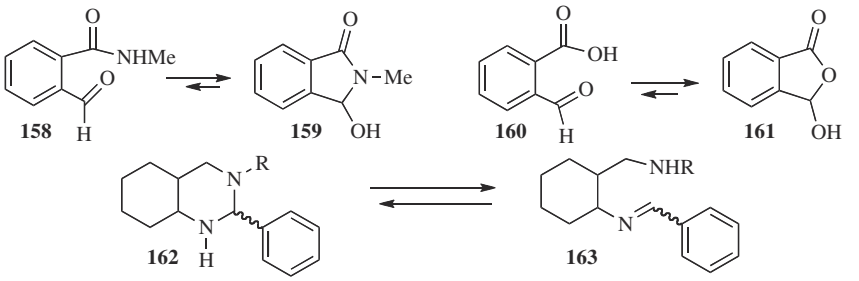
[484] Ring chain tautomer of benzoic acid 2-carboxaldehyde.

[485] Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* ***2001****, 57,* 8751; Muntean, L.; Grosu, I.; Mager, S.; Plé, G.; Balog, M. *Tetrahedron Lett.* ***2000****, 41*, 1967.

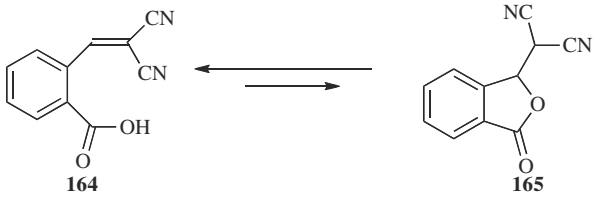
[486] Lazar, L.; Goblyos, A.; Martinek, T. A.; Fulop, F. *J. Org. Chem.* ***2002****, 67,* 4734.

[487] Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* ***2003***, 3025.

[488] Pérez, S.; López, C.; Caubet, A.; Roig, A.; Molins, E. *J. Org. Chem.* ***2005****, 70,* 4857.



There are many other highly specialized cases of proton-shift tautomerism, including an internal *Michael reaction* (see **15-24**) in which 2-(2,2-dicyano-1-methylethenyl)benzoic acid (**164**) exists largely in the open-chain form rather than its tautomer (**162**) in the solid state, but in solution there is an increasing amount of **165** as the solvent becomes more polar.[489]



[489] Kolsaker, P.; Arukwe, J.; Barcóczy, J.; Wiberg, A.; Fagerli, A.K. *Acta Chem. Scand. B* ***1998****, 52,* 490.

CHAPTER 3

Bonding Weaker Than Covalent

The discussions in Chapters 1 and 2 focused on the structure of molecules as an aggregate of atoms in a distinct 3D arrangement, held together by bonds with energies on the order of 50–100 kcal mol^{-1} (200–400 kJ mol^{-1}). There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, called *van der Waals forces*,[1] are caused by electrostatic attractions, such as those between dipole and dipole, or induced dipole and induced dipole, and are responsible for liquefaction of gases at sufficiently low temperatures. The bonding discussed in this chapter has energies on the order of 2–10 kcal mol^{-1} (9–40 kJ/mol^{-1}), which is intermediate between the bond orders given above, and produces clusters of molecules. Compounds will also be discussed in which portions of molecules are held together without any attractive forces at all.

3.A. HYDROGEN BONDING[2]

A *hydrogen bond* is less than a covalent bond, but it is an attractive force between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[3] With exceptions to be noted later, hydrogen bonds are *assumed to form only when A is oxygen, nitrogen, or fluorine and when B is oxygen, nitrogen, or fluorine*.[4] The ability of functional groups to act as hydrogen-bond acids and bases can be obtained from either equilibrium constants for 1:1 hydrogen bonding or overall hydrogen-bond constants.[4] There are so-called unconventional hydrogen bonds, particularly with organometallic complexes

[1] For a theoretical treatment, see Becke, A.A.A.; Kannemann, F.O. *Can. J. Chem.* ***2010****, 88,* 1057.

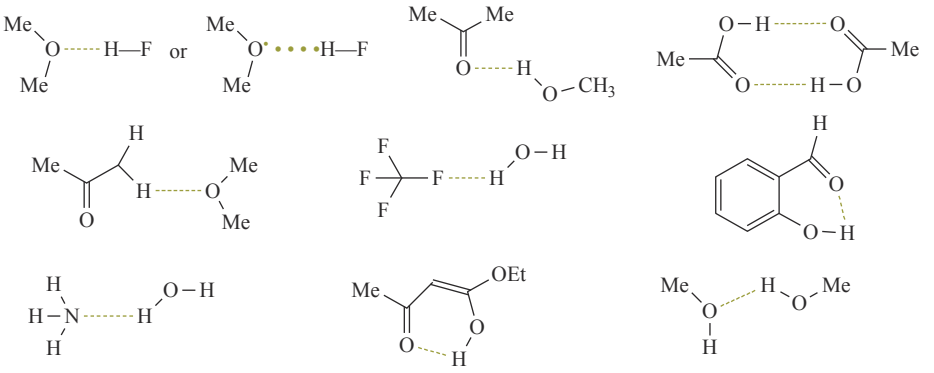
[2] For a discussion of hydrogen bonding in organic synthesis, *Hydrogen Bonding in Organic Synthesis*, see Pihko, M. (Ed.), Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim, ***2009***.

[3] See Schuster, P.; Zundel, G.; Sandorfy, C. *The Hydrogen Bond,* 3 Vols., North Holland Publishing Co., Amsterdam, The Netherlands, ***1976***. For a monograph, see Joesten, M.D.; Schaad, L.J. *Hydrogen Bonding*, Marcel Dekker, NY, ***1974***. For reviews, see Meot-Ner, M. *Mol. Struct. Energ.* ***1987****, 4,* 71; Joesten, M.D. *J. Chem. Educ.* ***1982****, 59,* 362; Gur'yanova, E.N.; Gol'dshtein, I.P.; Perepelkova, T.I. *Russ. Chem. Rev.* ***1976****, 45,* 792; Kollman, P.A.; Allen, L.C. *Chem. Rev.* ***1972****, 72*, 283; Huggins, M.L. *Angew. Chem. Int. Ed.* ***1971****, 10,* 147; Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group,* pt. 1, Wiley, NY, ***1971***, pp. 327–392. See also, Hamilton, W.C.; Ibers, J.A. *Hydrogen Bonding in Solids*, W.A. Benjamin, NY, ***1968***. Also see, Chen, J.; McAllister, M.A.; Lee, J. K.; Houk, K.N. *J. Org. Chem.* ***1998****, 63*, 4611.

[4] See Abraham, M.H.; Platts, J.A. *J. Org. Chem.* ***2001****, 66*, 3484.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

and transition metal or main group hydrides.[5] This chapter will largely ignore such compounds. In normal hydrogen bonds, to oxygen or nitrogen, oxygen may be singly or doubly bonded and the nitrogen singly, doubly, or triply bonded. In structures, hydrogen bonds are usually represented by dotted or dashed lines, as shown in the following examples:



Hydrogen bonds can exist in solid[6] and liquid phases, and in solution.[7] The efficacy of many organic reactions that will be discussed in later chapters is due to the use of an aqueous media,[8] which is due in part, to the hydrogen-bonding nature of such media.[9] Even in the gas phase, compounds that form particularly strong hydrogen bonds may remain associated.[10] Acetic acid, for example, exists in the gas phase as a dimer, except at very low pressures.[11] In the liquid phase and in solution, hydrogen bonds rapidly form and break. The mean lifetime of the $NH_3 \cdots H_2O$ bond is 2×10^{-12} s, for example.[12] Except for a few very strong hydrogen bonds[13] (e.g., the $FH \cdots F^-$ bond) which has an energy of $\sim$50 kcal mol^{-1} or 210 kJ mol^{-1}, the strongest hydrogen bonds are those connecting one carboxylic acid with another. The energies of these bonds are in the range of 6–8 kcal mol^{-1} or 25–30 kJ mol^{-1} (for carboxylic acids, this refers to the energy of each bond). In general, short contact hydrogen bonds between fluorine and HO or NH are rare.[14] Other $OH \cdots O$ and $NH \cdots N$ bonds[15] have energies of 3–6 kcal mol^{-1} (12–25 kJ mol^{-1}). The intramolecular O—H$\cdots$N hydrogen bond in hydroxy-amines is also rather strong.[16]

[5] Belkova, N.V.; Shubina, E.S.; Epstein, L.M. *Acc. Chem. Res.* ***2005****, 38*, 624. For a review of hydrogen bonding in cluster ions, see Meot-Ner (Mautner), M. *Chem. Rev.* ***2005****, 105*, 213.

[6] Steiner, T. *Angew. Chem. Int. Ed.* ***2002****, 41*, 48. See also, Damodharan, L.; Pattabhi, V. *Tetrahedron Lett.* ***2004****, 45*, 9427.

[7] See Nakahara, M.; Wakai, C. *Chem. Lett.* ***1992***, 809.

[8] Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*, Wiley, NY, ***1997***.

[9] Li, C.-J. *Chem. Rev.* ***1993****, 93*, 2023.

[10] See Curtiss, L.A.; Blander, M. *Chem. Rev.* ***1988****, 88,* 827.

[11] For a review of hydrogen bonding in carboxylic acids and acid derivatives, see Hadž i, D.; Detoni, S. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 213–266.

[12] Emerson, M.T.; Grunwald, E.; Kaplan, M.L.; Kromhout, R.A. *J. Am. Chem. Soc.* ***1960****, 82*, 6307.

[13] For a review of very strong hydrogen bonding, see Emsley, J. *Chem. Soc. Rev.* ***1980****, 9,* 91.

[14] Howard, J.A.K.; Hoy, V.J.; O'Hagan, D.; Smith, G.T. *Tetrahedron* ***1996****, 52*, 12613. For a discussion of the strength of such hydrogen bonds, see Perrin, C.L. *Acc. Chem. Res.* ***2010****, 43*, 1550.

[15] See Sorensen, J.B.; Lewin, A.H.; Bowen, J.P. *J. Org. Chem.* ***2001****, 66*, 4105. Also see Ohshima, Y.; Sato, K.; Sumiyoshi, Y.; Endo, Y. *J. Am. Chem. Soc.* ***2005****, 127,* 1108.

[16] Grech, E.; Nowicka-Scheibe, J.; Olejnik, Z.; Lis, T.; Pawêka, Z.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 343. See Steiner, T. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 1315.

To a first approximation, the strength of a hydrogen bond will increase with increasing acidity of A—H[17] and basicity of B, but the parallel is far from exact.[18] A quantitative measure of the strengths of hydrogen bonds has been established, involving the use of an α scale to represent hydrogen-bond donor acidities and a β scale for hydrogen-bond acceptor basicities.[19] The use of the β scale, along with another parameter (ξ), allows hydrogen-bond basicities to be related to proton-transfer basicities (p*K* values).[20] A database has been developed to locate all possible occurrences of bimolecular cyclic hydrogen-bond motifs in the Cambridge Structural Database,[21] and donor–acceptor, as well as polarity parameters, have been calculated for hydrogen-bonding solvents.[22] Bickelhaupt and co-workers[22] has stated that hydrogen bonds (X—H···Y) have significant covalent interactions that stem from donor–acceptor orbital interactions between the lone-pair electrons of Y and the empty σ^* acceptor orbital of X—H, so they are not predominantly electrostatic phenomena.

When two compounds whose molecules form hydrogen bonds with each other are both dissolved in water, the hydrogen bond between the two molecules is usually greatly weakened or completely removed.[23] This finding means that the molecules generally form hydrogen bonds with the water molecules (intermolecular) rather than with each other (intramolecular), presumably because the water molecules are present in such great numbers. In amides, the oxygen atom is the preferred site of protonation or complexation with water.[24] In the case of dicarboxylic acids, arguments have been presented that there is little or no evidence for strong hydrogen bonding in aqueous solution,[25] although other studies concluded that strong, intramolecular hydrogen bonding can exist in aqueous acetone solutions (0.31 mole-fraction water) of hydrogen maleate and hydrogen *cis*-cyclohexane-1,2-dicarboxylate.[26]

Many studies have been made of the geometry of hydrogen bonds,[27] and in most (though not all) cases the evidence shows that the hydrogen is on or near the straight line

[17] For a comparison of the relative strengths of OH···Cl versus OH···F hydrogen bonds, see Caminati, W.; Melandri, S.; Maris, A.; Paolo Ottaviani, P. *Angew. Chem. Int. Ed.* ***2006****, 45,* 2438.

[18] For reviews of the relationship between hydrogen bond strength and acid-base properties, see Pogorelyi, V.K.; Vishnyakova, T.B. *Russ. Chem. Rev.* ***1984****, 53,* 1154; Epshtein, L.M. *Russ. Chem. Rev.* ***1979****, 48,* 854.

[19] See Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Taft, R.W. *Chem. Br.* ***1986***, 551; Kamlet, M.J.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *J. Org. Chem.* ***1983****, 48,* 2877. For a criticism of the β scale, see Laurence, C.; Nicolet, P.; Helbert, M. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1081. See also, Roussel, C.; Gentric, E.; Sraidi, K.; Lauransan, J.; Guihéneuf, G.; Kamlet, M.J.; Taft, R.W. *J. Org. Chem.* ***1988****, 53,* 1545; Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 521. Deuterium exchange has been used as an indicator of hydrogen-bond donors and acceptors: see Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* ***2007****, 129,* 9544.

[20] Kamlet, M.J.; Gal, J.; Maria, P.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1583.

[21] Allen, F.H.; Raithby, P.R.; Shields, G.P.; Taylor, R. *Chem. Commun.* ***1998***, 1043.

[22] Joerg, S.; Drago, R.S.; Adams, J. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 2431. See Guerra, C.F.; van der Wijst, T.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2006****, 12*, 3032; Guerra, C.F.; Zijlstra, H.; Paragi, G.T.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2011****, 17*, 12612.

[23] Stahl, N.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986****, 108,* 4196.

[24] Scheiner, S.; Wang, L. *J. Am. Chem. Soc.* ***1993****, 115*, 1958.

[25] Perrin, C. L. *Annu. Rev. Phys. Org. Chem.* ***1997****, 48*, 511.

[26] Lin, J.; Frey, P. A. *J. Am. Chem. Soc.* ***2000****, 122,* 11258.

[27] Etter, M.C. *Acc. Chem. Res.* ***1990****, 23,* 120; Taylor, R.; Kennard, O. *Acc. Chem. Res.* ***1984****, 17,* 320.

formed by A and B.[28] This is true both in the solid state (where X-ray crystallography and neutron diffraction have been used to determine structures),[29] and in solution.[30] It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable. Intramolecular hydrogen bonding is much rarer in five-membered rings, where linearity is usually not favored (although it is known). A novel nine-membered intramolecular hydrogen bond has been reported.[31]

In certain cases X-ray crystallography has shown that a single H—A can form simultaneous hydrogen bonds with two B atoms (*bifurcated* or *three-center hydrogen bonds*). An example is an adduct (**1**) formed from pentane-2,4-dione in its enol form (Sec. 2.N.i) and diethylamine. In **1**, the O—H hydrogen simultaneously bonds[32] to an O and an N, where the N—H hydrogen forms a hydrogen bond with the O of another pentane-2,4-dione molecule.[33] On the other hand, the B atom (in this case oxygen) forms simultaneous hydrogen bonds with two A···H hydrogens in the adduct (**2**) formed from 1,8-biphenylenediol and hexamethylphosphoramide (HMPA),[34] Another such case is found in methyl hydrazine carboxylate (**3**).[35] Except for the special case of FH···F^- bonds (see above), the hydrogen is not equidistant between A and B. For example, the O—H distance in ice is 0.97 Å, while the H···O distance is 1.79 Å.[36] A theoretical study of the vinyl alcohol–vinyl alcoholate system (i.e., an enol–enolate anion system) concluded the hydrogen bonding is strong but asymmetric.[37] The hydrogen bond in the enol of malonaldehyde, in organic solvents, is asymmetric with the hydrogen atom closer to the basic oxygen atom.[38] There is evidence, however, that symmetrical hydrogen bonds to carboxylates should be regarded as two-center rather than three-center hydrogen bonds since the criteria traditionally used to infer three-center hydrogen bonding are inadequate for carboxylates.[39] There is also an example of cooperative hydrogen bonding [O—H···C≡C—H···Ph] in crystalline 2-ethynyl-6,8-diphenyl-7*H*-benzocyclohepten-7-ol (**4**).[40] Related to this discussion is the work that showed the hydrogen bond radii for OH, NH, and acidic CH groups to be 0.60 ± 0.15, 0.76 ± 0.15, and 1.10 ± 0.20 Å, respectively.[41]

[28] Stewart, R. *The Proton: Applications to Organic Chemistry,* Academic Press, NY, ***1985***, pp. 148–153.

[29] A statisical analysis of X-ray crystallographic data has shown that most hydrogen bonds in crystals are nonlinear by ∼10–15°: Kroon, J.; Kanters, J.A.; van Duijneveldt-van de Rijdt, J.G.C.M.; van Duijneveldt, F.B.; Vliegenthart, J.A. *J. Mol. Struct.* ***1975****, 24,* 109. See also, Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1983****, 105,* 5761; ***1984****, 106,* 244.

[30] For a discussion of the symmetry of hydrogen bonds in solution, see Perrin, C.L. *Pure Appl. Chem.* ***2009****, 81*, 571. For reviews of a different aspect of hydrogen bond geometry, see Legon, A.C.; Millen, D.J. *Chem. Soc. Rev.* ***1987****, 16,* 467, *Acc. Chem. Res.* ***1987****, 20,* 39.

[31] Yoshimi, Y.; Maeda, H.; Sugimoto, A.; Mizuno, K. *Tetrahedron Lett.* ***2001****, 42,* 2341.

[32] Emsley, J.; Freeman, N.J.; Parker, R.J.; Dawes, H.M.; Hursthouse, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 471.

[33] For some other three-center hydrogen bonds, see Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1984****, 106,* 244; Jeffrey, G.A.; Mitra, J. *J. Am. Chem. Soc.* ***1984****, 106,* 5546; Staab, H.A.; Elbl, K.; Krieger, C. *Tetrahedron Lett.* ***1986****, 27,* 5719.

[34] Hine, J.; Hahn, S.; Miles, D.E. *J. Org. Chem.* ***1986****, 51,* 577.

[35] Caminati, W.; Fantoni, A.C.; Schäfer, L.; Siam, K.; Van Alsenoy, C. *J. Am. Chem. Soc.* ***1986****, 108,* 4364.

[36] Pimentel, G.C.; McClellan, A.L. *The Hydrogen Bond*, W.H. Freeman, San Francisco, ***1960***, p. 260.

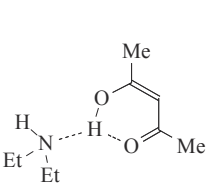
[37] Chandra, A.K.; Zeegers-Huyskens, T. *J. Org. Chem.* ***2003****, 68,* 3618.

[38] Perrin, C.L.; Kim, Y.-J. *J. Am. Chem. Soc.* ***1998****, 120*, 12641.

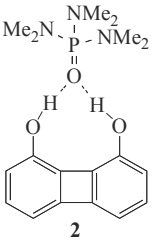
[39] Görbitz, C.H.; Etter, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 131.

[40] Steiner, T.; Tamm, M.; Lutz, B.; van der Maas, J. *Chem. Commun.* ***1996***, 1127.

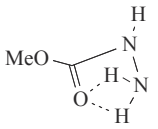
[41] Lakshmi, B.; Samuelson, A.G.; Jovan Jose, K.V.; Gadre, S.R.; Arunan, E. *New J. Chem.* ***2005****, 29,* 371.



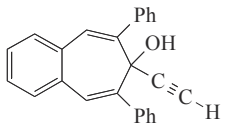
1



2



3



4

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but one important way is by the effect of the hydrogen bond on IR spectroscopy.[42] The IR frequencies of functional groups (e.g., O—H or C=O) are shifted when the group is hydrogen bonded. Hydrogen bonding always moves the peak toward lower frequencies, for both the A—H and the B groups, though the shift is greater for the former. For example, a free OH group of an alcohol or phenol absorbs at $\sim$ 3590–3650 cm^{-1}, and a hydrogen-bonded OH group is found $\sim$ 50–100 cm^{-1} lower.[43] In many cases, in dilute solution, there is partial hydrogen bonding, that is, some OH groups are free and some are hydrogen bonded. In such cases, two peaks appear.

Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra that have been used for the detection of hydrogen bonding include Raman, electronic,[44] and NMR.[45] Since hydrogen bonding involves a rapid movement of protons from one atom to another, NMR records an average value that is often broadened. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. For example, carboxylic acid–carboxylate systems arising from either mono- or diacids generally exhibit a downfield resonance (16–22 ppm), which indicates "strong" hydrogen bonding in anhydrous, aprotic solvents.[46] Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with IR spectra, intramolecular hydrogen bonding in the NMR can be distinguished from intermolecular by its constancy when the concentration is varied. The spin–spin coupling constant across a hydrogen bond, obtained by NMR studies, has been shown to provide a "fingerprint" for hydrogen-bond type.[47] Indeed, the determination of $^1J_{CH}$ correlates with the strength of the hydrogen bonds formed by an alcohol.[48]

[42] See Symons, M.C.R. *Chem. Soc. Rev.* ***1983****, 12,* 1; Egorochkin, A.N.; Skobeleva, S.E. *Russ. Chem. Rev.* ***1979****, 48,* 1198; Aaron, H.S. *Top. Stereochem.* ***1979****, 11,* 1. For a review of the use of rotational spectra to study hydrogen bonding, see Legon, A.C. *Chem. Soc. Rev.* ***1990****, 19,* 197.

[43] Tichy, M. *Adv. Org. Chem.* ***1965****, 5,* 115 contains a lengthy table of free and intramolecularly hydrogen-bonding peaks. For a discussion of the role of methyl groups in the formation of hydrogen bonds in dimithyl sulfide(DMS)–methanol mixtures, see Li, Q.; Wu, G.; Yu, Z. *J. Am. Chem. Soc.* ***2006****, 128,* 1438.

[44] See Lees, W.A.; Burawoy, A. *Tetrahedron* ***1963****, 19,* 419.

[45] See Davis, Jr., J.C.; Deb, K.K. *Adv. Magn. Reson.* ***1970****, 4,* 201. Also see, Kumar, G.A.; McAllister, M.A. *J. Org. Chem.* ***1998****, 63*, 6968.

[46] Bruck, A.; McCoy, L.L.; Kilway, K.V. *Org. Lett.* ***2000****, 2,* 2007. For a discussion of the effect of solvents on hydrogen bonding, see Cook, J.L.; Hunter, C.A.; Low, C.M.R.; Perez-Velasco, A.; Vinter, J.G. *Angew. Chem. Int. Ed.* ***2007****, 46,* 3706.

[47] Del Bene, J.E.; Perera, S.A.; Bartlett, R.J. *J. Am. Chem. Soc.* ***2000****, 122*, 3560.

[48] Maiti, N.C.; Zhu, Y.; Carmichael, I.; Serianni, A.S.; Anderson, V.E. *J. Org. Chem.* ***2006****, 71,* 2878.

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.
2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected.
3. Hydrogen bonding causes lack of ideality in gas and solution laws.
4. As previously mentioned, hydrogen bonding changes spectral absorption positions.
5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see Sec. 2.N). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.[49] Hydrogen bonding is also important in maintaining the 3D structures of protein and nucleic acid molecules.

Besides oxygen, nitrogen, and fluorine, there is evidence that weaker hydrogen bonding exists in other systems.[50] Although many searches have been made for hydrogen bonding where A is carbon,[51] only three types of C—H bonds have been found that are acidic enough to form weak hydrogen bonds.[52] These are found in terminal alkynes (RC≡CH),[53] chloroform and some other halogenated alkanes, and HCN. Sterically unhindered C—H groups ($CHCl_3$, CH_2Cl_2, RC≡CH) form short contact hydrogen bonds with carbonyl acceptors, where there is a significant preference for coordination with the conventional carbonyl lone-pair direction.[54] Weak hydrogen bonds are formed by compounds containing S—H bonds.[55] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds,[56] but Br and I form very weak bonds if at all.[57] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds that are much stronger than those of the covalently bonded atoms.[58] As noted above, the $FH\cdots F^-$ bond is especially strong. In this case, the

[49] For reviews of the effect of hydrogen bonding on reactivity, see Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* ***1990****, 26,* 255; Sadekov, I.D.; Minkin, V.I.; Lutskii, A.E. *Russ. Chem. Rev.* ***1970****, 39,* 179.

[50] For a review, see Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977****, 46,* 316.

[51] See Green, R.D. *Hydrogen Bonding by C—H Groups*, Wiley, NY, ***1974***. See also, Nakai, Y.; Inoue, K.; Yamamoto, G.; Öki, M. *Bull. Chem. Soc. Jpn.* ***1989****, 62,* 2923; Seiler, P.; Dunitz, J.D. *Helv. Chim. Acta* ***1989****, 72,* 1125.

[52] For a theoretical study of weak hydrogen-bonds, see Calhorda, M.J. *Chem. Commun.* ***2000***, 801.

[53] For a review, see Hopkinson, A.C., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 75–136. See also, DeLaat, A.M.; Ault, B.S. *J. Am. Chem. Soc.* ***1987****, 109,* 4232.

[54] Streiner, T.; Kanters, J.A.; Kroon, J. *Chem. Commun.* ***1996***, 1277.

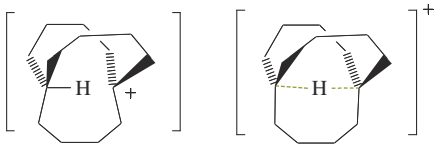
[55] See Zuika, I.V.; Bankovskii, Yu.A. *Russ. Chem. Rev.* ***1973****, 42*, 22; Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, 1974, pp. 379–396; Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977****, 46,* 316.

[56] See Smith, J.W. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley, NY, ***1973***, pp. 265–300. See also, Bastiansen, O.; Fernholt, L.; Hedberg, K.; Seip, R. *J. Am. Chem. Soc.* ***1985****, 107,* 7836.

[57] Fujimoto, E.; Takeoka, Y.; Kozima, K. *Bull. Chem. Soc. Jpn.* ***1970****, 43,* 991; Azrak, R.G.; Wilson, E.B. *J. Chem. Phys.* ***1970****, 52*, 5299.

[58] Fujiwara, F.Y.; Martin, J.S. *J. Am. Chem. Soc.* ***1974****, 96*, 7625; French, M.A.; Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1982****, 60,* 1907.

hydrogen is equidistant from the fluorine atoms.[59] Similarly, a sulfur atom[55] can be the B component (A···B) in weak hydrogen bonds,[60] but the $^{-}$SH ion forms much stronger bonds.[61] There are theoretical studies of weak hydrogen bonding.[62] Hydrogen bonding has been directly observed (by NMR and IR) between a negatively charged carbon (see carbanions in Chapter 5) and an OH group in the same molecule.[63] Isocyanides ($R—^{+}N{\equiv}C^{-}$) constitute another type of molecule in which carbon is the B component that forms a rather strong hydrogen bond.[64] There is evidence that double and triple bonds, aromatic rings,[65] and even cyclopropane rings[66] may be the B component of hydrogen bonds, but these bonds are very weak. An interesting case is that of the *in*-bicyclo[4.4.4]-1-tetradecyl cation **5** (see out–in isomerism, Sec. 4.L The NMR and IR spectra show that the actual structure of this ion is **6**, in which both the A and the B component of the hydrogen bond is a carbon.[67] These are sometimes called 3-center-2-electron C—H—C bonds.[68] A technique called generalized population analysis has been developed to study this type of multicenter bonding.[69]



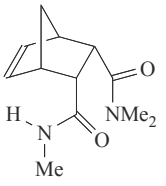
5 **6**

A weak (~1.5 kcal mol^{-1}, 6.3 kJ mol^{-1}) and rare C—H···O=C hydrogen bond has been reported in a class of compounds known as a [6]semirubin (a dipyrrinone).[70] There is also evidence for a C—H···N/CH···OH bond in the crystal structures of α,β-unsaturated ketones carrying a terminal pyridine subunit,[71] and for R_3N^{+}—C—H···O=C hydrogen bonding.[72]

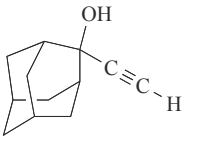
Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[73] Weak hydrogen bonds can be formed between a π bond (from both alkenes and aromatic compounds) and an appropriate hydrogen. For example, IR data in dilute dichloromethane suggests that the predominant

[59] In a few cases, the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams, J.M.; Schneemeyer, L.F. *J. Am. Chem. Soc.* ***1973****, 95*, 5780.
[60] Schaefer, T.; McKinnon, D.M.; Sebastian, R.; Peeling, J.; Penner, G.H.; Veregin, R.P. *Can. J. Chem.* ***1987****, 65*, 908; Marstokk, K.; Møllendal, H.; Uggerud, E. *Acta Chem. Scand.* ***1989****, 43,* 26.
[61] McDaniel, D.H.; Evans, W.G. *Inorg. Chem,* ***1966****, 5,* 2180; Sabin, J.R. *J. Chem. Phys.* ***1971****, 54,* 4675.
[62] Calhorda, M.J. *Chem. Commun.* ***2000***, 801.
[63] Ahlberg, P.; Davidsson, O.; Johnsson, B.; McEwen, I.; Rönnqvist, M. *Bull. Soc. Chim. Fr.* ***1988***, 177.
[64] Allerhand, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963****, 85,* 866.
[65] For example, see Bakke, J.M.; Chadwick, D.J. *Acta Chem. Scand. Ser. B* ***1988****, 42,* 223: Atwood, J.L.; Hamada, F.; Robinson, K.D.; Orr, G.W.; Vincent, R.L. *Nature* ***1991****, 349,* 683.
[66] Yoshida, Z.; Ishibe, N.; Kusumoto, H. *J. Am. Chem. Soc.* ***1969****, 91,* 2279.
[67] McMurry, J.E.; Lectka, T.; Hodge, C.N. *J. Am. Chem. Soc.* ***1989****, 111,* 8867. See also, Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1990****, 112,* 8135.
[68] McMurry, J.E.; Lectka, T. *Accts. Chem. Res.* ***1992****, 25*, 47.
[69] Ponec, R.; Yuzhakov, G.; Tantillo, D. J. *J. Org. Chem.* ***2004****, 69,* 2992.
[70] Huggins, M.T.; Lightner, D.A. *J. Org. Chem.* ***2001****, 66,* 8402.
[71] Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron* ***2001****, 57*, 5791.
[72] Cannizzaro, C.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2002****, 124*, 7163.
[73] Cummings, D.L.; Wood, J.L. *J. Mol. Struct.* ***1974****, 23,* 103.

conformation for bis-(amide) (**7**) contains an N—H···π hydrogen bond involving the C=C unit.[74] The strength of an intramolecular π-facial hydrogen bond between an NH group and an aromatic ring in chloroform has been estimated to have a lower limit of -4.5 ± 0.5 kcal mol^{-1} (-18.8 kJ mol^{-1}).[75] A neutron diffraction study of crystalline 2-ethynyladamantan-2-ol (**8**) shows the presence of an unusual O—H···π hydrogen bond, which is short and linear, as well as the more common O—H···O and C—H···O hydrogen bonds.[76]



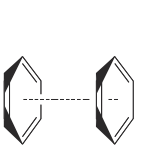
7



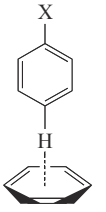
8

3.B. π–π INTERACTIONS

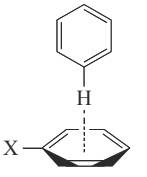
Many theoretical and experimental studies clearly show the importance of π–π interactions,[77] which are fundamental to many supramolecular organization and recognition processes.[78] Perhaps the simplest prototype of aromatic π–π interactions is the benzene dimer.[79] Within dimeric aryl systems such as this, possible π–π interactions are the sandwich and T-shaped interactions shown. It has been shown that all substituted sandwich dimers bind more strongly than a benzene dimer, whereas the T-shaped configurations bind more or less favorably depending on the substituent.[80] Electrostatic, dispersion, induction, and exchange-repulsion contributions are all significant to the overall binding energies.[80]



Sandwich



T-shaped (1)



T-shaped (2)

[74] Gallo, E.A.; Gelman, S.H. *Tetrahedron Lett.* ***1992****, 33*, 7485.
[75] Adams, H.; Harris, K.D.M.; Hembury, G.A.; Hunter, C.A.; Livingstone, D.; McCabe, J.F. *Chem. Commun.* ***1996***, 2531. See Steiner, T.; Starikov, E.B.; Tamm, M. *J. Chem. Soc., Perkin Trans. 2* ***1996***.
[76] Allen, F.H.; Howard, J.A.K.; Hoy, V.J.; Desiraju, G.R.; Reddy, D.S.; Wilson, C.C. *J. Am. Chem. Soc.* ***1996****, 118*, 4081.
[77] Tsuzuki, S.; Lüthi, H.P. *J. Chem. Phys.* ***2001****, 114*, 3949; Arunan, E.; Gutowsky, H S. *J. Chem. Phys.* ***1993****, 98,* 4294; Felker, P.M.; Maxton, P.M.; Schaeffer, M.W. *Chem. Rev.* ***1994****, 94,* 1787; Venturo, V.A.; Felker, P.M. *J. Chem. Phys.* ***1993****, 99,* 748; Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* ***2002****, 124,* 104; Hobza, P.; Jurecčka, P. *J. Am. Chem. Soc.* ***2003****, 125*, 15608.
[78] Meyer, E.A.; Castellano, R.K.; Diederich, F. *Angew. Chem. Int. Ed.* ***2003****, 42,* 1210.
[79] Sinnokrot, M.O.; Valeev, E.F.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2002****, 124,* 10887.
[80] Sinnokrot, M.O.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2004****, 126,* 7690.

The π electrons of aromatic rings can interact with charged species, yielding strong cation–π interactions that are dominated by electrostatic and polarization effects.[81] An interaction with CH units is also possible. For CH–π interactions in both alkyl- and aryl-based model systems, dispersion effects dominate the interaction, but the electrostatics term is also relevant for aryl CH–π interactions.[82]

Detection of π–π interactions has largely relied on NMR based techniques (e.g., chemical shifts variations),[83] and Nuclear Overhauser Effect Spectroscopy (NOESY) or Rotating-Frame NOE Spectroscopy (ROESY).[84] Diffusion-ordered NMR spectroscopy (DOSY) has also been used to detect π–π stacked complexes.[85]

3.C. ADDITION COMPOUNDS

When the reaction of two compounds results in a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. The remainder of this chapter will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. There are four broad classes: electron donor–acceptor complexes, complexes formed by crown ethers and similar compounds, inclusion compounds, and catenanes.

3.C.i. Electron Donor–Acceptor Complexes[86]

In *electron donor–acceptor* (*EDA*) *complexes*,[87] there is always a donor and an acceptor molecule. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). The electronic spectrum constitutes a good test for the presence of an EDA complex. These complexes generally exhibit a spectrum (called a *charge-transfer spectrum*) that is not the same as the sum of the spectra of the two individual molecules.[88] Because the first excited state of the

[81] Lindeman, S.V.; Kosynkin, D.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998****, 120,* 13268; Ma, J.C.; Dougherty, D.A. *Chem. Rev.* ***1997****, 97,* 1303; Dougherty, D.A. *Science* ***1996****, 271*, 163; Cubero, E.; Luque, F.J.; Orozco, M. *Proc. Natl. Acad. Sci. USA* ***1998****, 95,* 5976.

[82] Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* ***2002****, 67,* 7057.

[83] Petersen, S.B.; Led, J.J.; Johnston, E.R.; Grant, D.M. *J. Am. Chem. Soc.* ***1982****, 104,* 5007.

[84] Wakita, M.; Kuroda, Y.; Fujiwara, Y.; Nakagawa, T. *Chem. Phys. Lipids* ***1992****, 62,* 45.

[85] Viel, S.; Mannina, L.; Segre, A. *Tetrahedron Lett.* ***2002****, 43,* 2515. See also, Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* ***2002****, 67*, 7057. For a discussion of substituent effects on aromatic stacking interactions, see Cockroft, S.L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S.E.; Low, C.M.R.; Vinter, J.G.; Lawson, K.R.; Urch, C.J.; Hunter, C.A. *Org. Biomol. Chem.* **2007**, 5, 1062.

[86] Foster, R. *Organic Charge-Transfer Complexes*, Academic Press, NY, ***1969***; Mulliken, R.S.; Person, W.B. *Molecular Complexes*, Wiley, NY, ***1969***; Rose, J. *Molecular Complexes*, Pergamon, Elmsford, NY, ***1967***; Poleshchuk, O.Kh.; Maksyutin, Yu.K. *Russ. Chem. Rev.* ***1976****, 45,* 1077; Banthorpe, D.V. *Chem. Rev.* ***1970****, 70*, 295; Kosower, E.M. *Prog. Phys. Org. Chem.* ***1965****, 3,* 81; Foster, R. *Chem. Br.* ***1976****, 12,* 18.

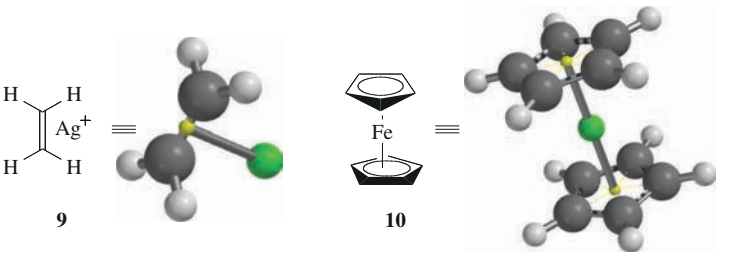
[87] These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969****, 91,* 3409.

[88] Also see Bentley, M.D.; Dewar, M.J.S. *Tetrahedron Lett.* ***1967***, 5043.

complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-UV region, and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes, the donor and acceptor molecules are present in an integral ratio, most often 1:1, but complexes with nonintegral ratios are also known. There are several types of acceptor molecules; complexes formed by two of them will be discussed.

1. *Complexes in which the Acceptor is a Metal Ion and the Donor is an Alkene or an Aromatic Ring.*

   The *n* donors do not give EDA complexes with metal ions, but form covalent bonds instead).[89] Many metal ions form complexes with alkenes, dienes (usually conjugated, but not always), alkynes, and aromatic rings that are often stable solids. The donor (or ligand) molecules in these complexes are classified by the prefix *hapto*[90] and/or the descriptor η^n (the Greek letter *eta*), where *n* indicates how many atoms the ligand uses to bond with the metal.[91]



9 **10**

   The generally accepted picture of the bonding in these complexes,[92] first proposed by Dewar,[93] can be illustrated by the ethylene complex with silver (**9**), in which the alkene unit forms an η^2-complex with the silver ion (the alkene functions as a 2-electron donating ligand to the metal). There is evidence of π-complexation of Na^+ by C=C.[94] In the case of the silver complex, the bond is not from one atom of the C=C unit to the silver ion, but from the π center (two electrons are transferred from the alkene to the metal ion). Ethene has two π-electrons and is a dihapto or η^2 ligand, as are other simple alkenes. Similarly, benzene has six π electrons and is a hexahapto or η^6 ligand. Ferrocene (**10**) is an

[89] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed, University Science Books, Mill Valley, CA, ***1987***; Alper, H. *Transition Metal Organometallics in Organic Synthesis,* 2 Vols., Academic Press, NY, ***1976***, ***1978***. For general reviews, see Churchill, M.R.; Mason, R. *Adv. Organomet. Chem.* ***1967****, 5,* 93; Cais, M. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 335–385; Nakamura, A. *J. Organomet. Chem.* ***1990****, 400*, 35; Bennett, M.A.; Schwemlein, H.P. *Angew. Chem. Int. Ed.* ***1989****, 28,* 1296; metals-pentadienyl ions, Powell, P. *Adv. Organomet. Chem.* ***1986****, 26*, 125; complexes of main group metals. For a list of review articles on this subject, see Bruce, M.I. *Adv. Organomet. Chem.* ***1972****, 10*, 273, pp. 317–321.

[90] For a discussion of how this system originated, see Cotton, F.A. *J. Organomet. Chem.* ***1975****, 100,* 29.

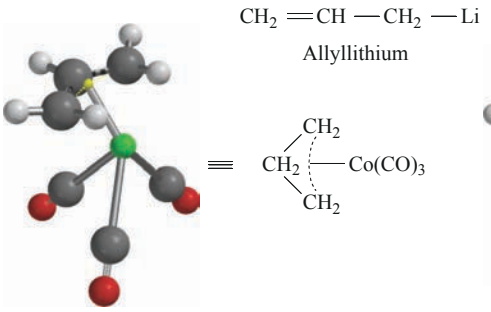
[91] Another prefix used for complexes is μ (mu), which indicates that the ligand bridges two metal atoms.

[92] See Pearson, A.J. *Metallo-organic Chemistry* Wiley, NY, ***1985***; Ittel, S.D.; Ibers, J.A. *Adv. Organomet. Chem.* ***1976****, 14,* 33; Hartley, F.R. *Chem. Rev.* ***1973****, 73*, 163; *Angew. Chem. Int. Ed.* ***1972****, 11*, 596.

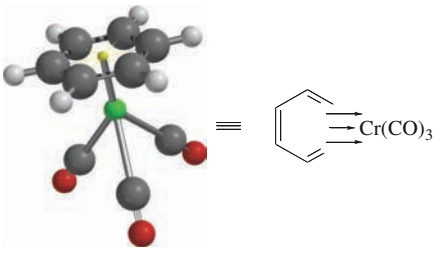
[93] Dewar, M.J.S. *Bull. Soc. Chim. Fr.* ***1951****, 18*, C79.

[94] Hu, J.; Gokel, G.W.; Barbour, L.J. *Chem. Commun.* ***2001***, 1858.

example of a *metallocene*, with two cyclopentadienyl ligands (each is a five-electron donor or an η^5 ligand), and ferrocene is properly called bis(η^5-cyclopentadienyl)iron(II). This system can be extended to compounds in which only a single σ bond connects the organic group to the metal, (e.g., C_6H_5—Li a monohapto or η^1 ligand), and to complexes in which the organic group is an ion, (π-allyl complexes, e.g., **11**), in which the allyl ligand is trihapto or η^3. Note that in a compound such as allyllithium, where a σ bond connects the carbon to the metal, the allyl group is referred to as monohapto or η^1.

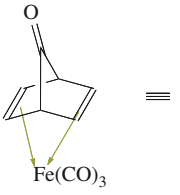


11

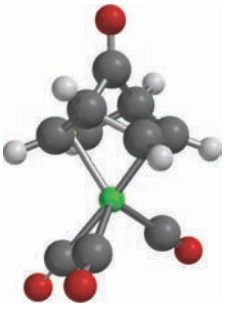


12

As mentioned, benzene is an η^6 ligand that forms complexes with silver and other metals.[95] When the metal involved has a coordination number > 1, more than one donor molecule (ligand) participates. The CO group is a common ligand (a two-electron donating or η^2 ligand), and in metal complexes the CO group is classified as a metal carbonyl. Benzenechromium tricarbonyl (**12**) is a stable compound[96] that illustrates both benzene and carbonyl ligands. Three arrows are shown to represent the six-electron donation (an η^6 ligand), but the accompanying model gives a clearer picture of the bonding. Cyclooctatetraene is an eight-electron donating or η^8 ligand that also forms complexes with metals. Metallocenes (e.g., **10**) may be considered a special case of this type of complex, although the bonding in metallocenes is much stronger.



13



[95] See Zeiss, H.; Wheatley, P.J.; Winkler, H.J.S. *BenzenoidMetal Complexes*, Ronald Press, NY, ***1966***.
[96] Nicholls, B.; Whiting, M.C. *J. Chem. Soc.* ***1959***, 551. For reviews of arene–transition metal complexes, see Uemura, M. *Adv. Met.-Org. Chem.* ***1991***, *2,* 195; Silverthorn, W.E. *Adv. Organomet. Chem.* ***1975***, *13*, 47.

In a number of cases, alkenes that are too unstable to be isolated as discreet molecules have been isolated in the form of their metal complexes. An example is norbornadienone, which was isolated as its iron–tricarbonyl complex (**13**),[97] where the norbornadiene unit is an η^4 ligand, and each of the carbonyl units are η^2 ligands. The free dienone spontaneously decomposes to carbon monoxide and benzene (see Reaction **17**–**28**).

2. *Complexes in Which the Acceptor Is an Organic Molecule*.

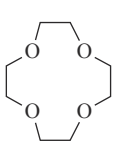
Picric acid (2,4,6-trinitrophenol) and similar polynitro compounds are the most important of these.[98] Picric acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, alkenes, and other compounds. These addition compounds are usually solids that have definite melting points and have been used as derivatives of the compounds in question. They are called picrates, and are addition compounds and not salts of picric acids. Unfortunately, the actual salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinhydrones).[99] Alkenes that contain electron-withdrawing substituents also act as acceptor molecules, as do carbon tetrahalides[100] and certain anhydrides.[101] A particularly strong alkene acceptor is tetracyanoethylene.[102]

The bonding in these cases is more difficult to explain than in the previous case, and indeed no truly satisfactory explanation is available.[103] The difficulty is that the donor has a pair of electrons to contribute (both *n* donors and π donors are found here), but the acceptor does not have a vacant orbital. Simple attraction of the dipole–induced-dipole type accounts for some of the bonding,[104] but is too weak to explain the bonding in all cases.[105] Nitromethane, with about the same dipole moment as nitrobenzene, is an example of a molecule that forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor–acceptor interaction.

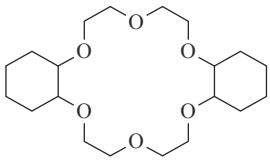
[97] Landesberg, J.M.; Sieczkowski, J. *J. Am. Chem. Soc.* ***1971****, 93,* 972.
[98] See Parini, V.P. *Russ. Chem. Rev.* ***1962****, 31,* 408; for a review of complexes in which the acceptor is an organic cation, see Kampar, V.E. *Russ. Chem. Rev.* ***1982****, 51,* 107; also see, Ref. 86.
[99] For a review of quinone complexes, see Foster, R.; Foreman, M.I. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 1, Wiley, NY, ***1974***, pp. 257–333.
[100] See Blackstock, S.C.; Lorand, J.P.; Kochi, J.K. *J. Org. Chem.* ***1987****, 52,* 1451.
[101] See Foster, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 175–212.
[102] See Melby, L.R. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 639–669. See also, Fatiadi, A.J. *Synthesis* ***1987***, 959.
[103] For reviews, see Bender, C.J. *Chem. Soc. Rev.* ***1986****, 15,* 475; Kampar, E.; Neilands, O. *Russ. Chem. Rev.* ***1986****, 55,* 334; Bent, H.A. *Chem. Rev.* ***1968****, 68,* 587.
[104] See, for example, Le Fevre, R.J.W.; Radford, D.V.; Stiles, P.J. *J. Chem. Soc. B* ***1968***, 1297.
[105] Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969****, 91,* 3409.

3.C.ii Crown Ether Complexes and Cryptates[106]

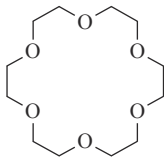
Crown ethers are large-ring compounds that contain several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**14**; where 12 is the size of the ring and 4 represents the number of coordinating atoms, here oxygen),[107] dicyclohexano-18-crown-6 (**15**), and 15-crown-5 (**16**). These compounds have the property[108] of forming complexes with positive ions, generally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.[109] The crown ether is called the *host* and the ion is the *guest*. In most cases, the ions are held tightly in the center of the cavity.[110] Each crown ether binds different ions, depending on the size of the cavity. For example, **14** binds Li^{+}[111], but not K^{+},[112] while **15** binds K^{+} but not Li^{+}.[113] Similarly, **15** binds Hg^{2+}, but not Cd^{2+} or Zn^{2+}, and Sr^{2+} but not Ca^{2+}.[114] 18-Crown-5 binds alkali and ammonium cations >1000 times weaker than 18-crown-6, presumably because the larger 18-crown-6 cavity involves more hydrogen bonds.[115] The complexes can frequently be prepared as well-defined sharp-melting solids.



14



15



16

[106] See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, 3 Vols., Academic Press, NY, ***1984***; Vögtle, F. *Host Guest Complex Chemistry I, II, and III (Top. Curr. Chem.* **1998**, *101*, 121), Springer, Berlin, ***1981***, ***1982***, ***1984***; Vögtle, F.; Weber, E. *Host Guest Complex Chemistry/Macrocycles*, Springer, Berlin, ***1985***; Izatt, R. M.; Christensen, J.J. *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, NY, ***1978***. For reviews, see McDaniel, C.W.; Bradshaw, J.S.; Izatt, R.M. *Heterocycles, **1990**, 30*, 665; Sutherland, I.O. *Chem. Soc. Rev. **1986**, 15,* 63; Franke, J.; Vögtle, F. *Top. Curr. Chem. **1986**, 132*, 135; Cram, D.J. *Angew. Chem. Int. Ed. **1986**, 25*, 1039; Gutsche, C.D. *Acc. Chem. Res. **1983**, 16,* 161; Tabushi, I.; Yamamura, K. *Top. Curr. Chem. **1983**, 113,* 145; Stoddart, J.F. *Prog. Macrocyclic Chem. **1981**, 2,* 173; Cram, D.J.; Cram, J.M. *Acc. Chem. Res. **1978**, 11*, 8; *Science, **1974**, 183,* 803; Gokel, G.W.; Durst, H.D. *Synthesis **1976***, 168; *Aldrichim. Acta **1976**, 9,* 3; Lehn, J.M. *Struct. Bonding (Berlin) **1973**, 16,* 1; Christensen, J.J.; Eatough, D.J.; Izatt, R.M. *Chem. Rev. **1974**, 74,* 351; Pedersen, C.J.; Frensdorff, H.K. *Angew. Chem. Int. Ed. **1972**, 11,* 16. For reviews of acyclic molecules with similar properties, see Vögtle, E. *Chimia **1979**, 33*, 239; Vögtle, E.; Weber, E. *Angew. Chem. Int. Ed. **1979**, 18,* 753. See *Angew. Chem. Int. Ed. **1988**, 27,* pp. 1021, 1009, 89; and *Chem. Scr., **1988**, 28*, pp. 229, 263, 237. See also, the series *Advances in Supramolecular Chemistry*.

[107] Cook, F.L.; Caruso, T.C.; Byrne, M.P.; Bowers, C.W.; Speck, D.H.; Liotta, C. *Tetrahedron Lett. **1974***, 4029.

[108] Discovered by Pedersen, C.J. *J. Am. Chem. Soc. **1967**, 89,* 2495, 7017. For an account of the discovery, see Schroeder, H.E.; Petersen, C.J. *Pure Appl. Chem. **1988**, 60,* 445.

[109] See Inoue, Y.; Gokel, G.W. *Cation Binding by Macrocycles*, Marcel Dekker, NY, ***1990***.

[110] See Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev. **1985**, 85,* 271; Parsonage, N.G.; Staveley, L.A.K. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–36.

[111] Anet, F.A.L.; Krane, J.; Dale, J.; Daasvatn, K.; Kristiansen, P.O. *Acta Chem. Scand. **1973**, 27,* 3395.

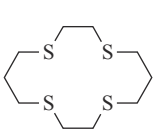
[112] See Dale, J.; Eggestad, J.; Fredriksen, S.B.; Groth, P. *J. Chem. Soc., Chem. Commun. **1987***, 1391; Dale, J.; Fredriksen, S.B. *Pure Appl. Chem. **1989**, 61,* 1587.

[113] Izatt, R.M.; Nelson, D.P.; Rytting, J.H.; Haymore, B.L.; Christensen, J.J. *J. Am. Chem. Soc. **1971**, 93,* 1619.

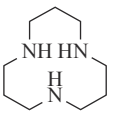
[114] Kimura, Y.; Iwashima, K.; Ishimori, T.; Hamaguchi, H. *Chem. Lett. **1977***, 563.

[115] Raevsky, O.A.; Solov'ev, V.P.; Solotnov, A.F.; Schneider, H.-J.; Rüdiger, V. *J. Org. Chem. **1996**, 61*, 8113.

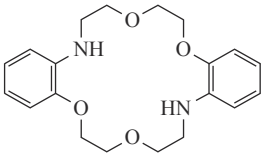
Apart from their obvious utility in separating mixtures of cations,[116] crown ethers are widely used in organic synthesis (see the discussion on Sec. 10.G.v). Chiral crown ethers have been used for the resolution of racemic mixtures (Sec. 4.A). Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed[117] (see Sec. 4.L for the complexing of anions).[118] Macrocycles containing nitrogen (azacrown ethers) or sulfur atoms (thiacrown ethers)[119] (e.g., **17** and **18**),[120] have complexing properties similar to other crown ethers, as do mixed-heteroatom crown ethers (e.g., **19**,[121] **20**,[122] or **21**[123]).



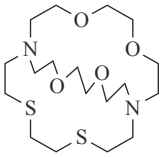
17



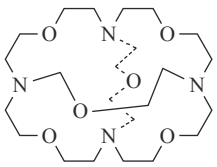
18



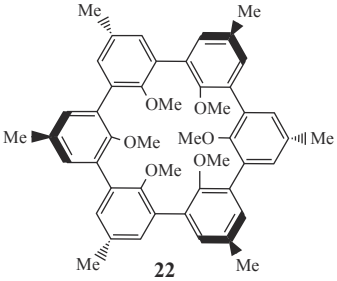
19



20



21



22

Bicyclic molecules (e.g., **20**) can surround the enclosed ion in 3D, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order[124] are called *cryptands* and the complexes formed are called *cryptates* (monocyclic compounds are sometimes called cryptands). When the molecule contains a cavity that can accommodate a guest molecule, usually through hydrogen-bonding interactions,

[116] Crown ethers have been used to separate isotopes of cations, (e.g., ^{44}Ca from ^{40}Ca). For a review, see Heumann, K.G. *Top. Curr. Chem.* ***1985****, 127,* 77.

[117] For reviews, see Vögtle, F.; Müller, W.M.; Watson, W.H. *Top. Curr. Chem.* ***1984****, 125,* 131; Weber, E. *Prog. Macrocycl. Chem.* ***1987****, 3,* 337; Diederich, F. *Angew. Chem. Int. Ed.* ***1988****, 27,* 362.

[118] See van Staveren, C.J.; van Eerden, J.; van Veggel, F.C.J.M.; Harkema, S.; Reinhoudt, D.N. *J. Am. Chem. Soc.* ***1988****, 110,* 4994. See also, Rodrigue, A.; Bovenkamp, J.W.; Murchie, M.P.; Buchanan, G.W.; Fortier, S. *Can. J. Chem.* ***1987****, 65,* 2551; Fraser, M.E.; Fortier, S.; Markiewicz, M.K.; Rodrigue, A.; Bovenkamp, J.W. *Can. J. Chem.* ***1987****, 65*, 2558.

[119] Voronkov, M.G.; Knutov, V.I. *Sulfur Rep.* ***1986****, 6,* 137, *Russ. Chem. Rev.* ***1982****, 51,* 856; Reid, G.; Schröder, M. *Chem. Soc. Rev.* ***1990****, 19,* 239.

[120] For a review of **17** and its derivatives, see Chaudhuri, P.; Wieghardt, K. *Prog. Inorg. Chem.* ***1987****, 35,* 329. *N*-Aryl-azacrown ethers are known, see Zhang, X.-X.; Buchwald, S.L. *J. Org. Chem.* ***2000****, 65,* 8027.

[121] Gersch, B.; Lehn, J.-M.; Grell, E. *Tetrahedron Lett.* ***1996****, 37*, 2213.

[122] Newcomb, M.; Gokel, G.W.; Cram, D.J. *J. Am. Chem. Soc.* ***1974****, 96,* 6810.

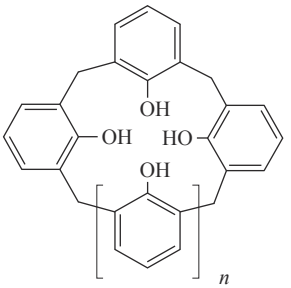
[123] Ragunathan, K.G.; Shukla, R.; Mishra, S.; Bharadwaj, P.K. *Tetrahedron Lett.* ***1993****, 34*, 5631.

[124] See Potvin, P.G.; Lehn, J.M. *Prog. Macrocycl. Chem.* ***1987****, 3,* 167; Kiggen, W.; Vögtle, F. *Prog. Macrocycl. Chem.* ***1987****, 3,* 309; Dietrich, B. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 337–405; Parker, D. *Adv. Inorg. Radichem.* ***1983****, 27,* 1; Lehn, J.M. *Acc. Chem. Res.* ***1978****, 11,* 49, *Pure Appl. Chem.* ***1977****, 49,* 857.

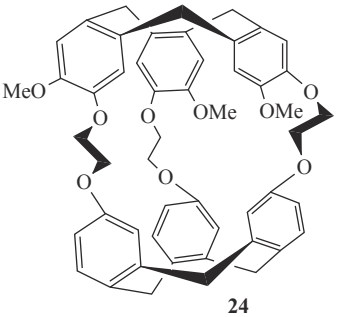
it is sometimes called a *cavitand*.[125] The tricyclic cryptand **21** has 10 binding sites and a spherical cavity.[98] Another molecule with a spherical cavity (though not a cryptand) is **22**, which complexes Li^+ and Na^+ (preferentially Na^+), but not K^+, Mg^{2+}, or Ca^{2+}.[126] Molecules such as these, whose cavities can be occupied only by spherical entities, have been called *spherands*.[83] Other types are *calixarenes*[127] (e.g., **23**).[128] Spherand-type calixarenes are known.[129] There is significant hydrogen bonding involving the phenolic OH units in [4]calixarenes, but this diminishes as the size of the cavity increases in larger ring calixarenes.[130] There are also calix[6]arenes[131] that have been shown to have conformational isomers (Sec. 4.O) in equilibrium (cone vs alternate) that can sometimes be isolated:[132] calix[8]arenes,[133] azacalixarenes,[134] homooxacalixarenes,[135] and calix[9–20]arenes.[136] Note that substitution of the unoccupied "meta" positions immobilizes calix[4]arenes and the conformational mobility (Sec. 4.O.iv) in calix[8] arenes is substantially diminished.[137] Amide-bridged calix[4]arenes[138] calix[4]azulene,[139] and quinone-bridged calix[6]arenes.[140] are known, and diammoniumcalix[4] arene has been prepared.[141] Enantiopure calix[4]resorcinarene derivatives are known,[142] and water-soluble calix[4]arenes have been prepared.[143] There are also a variety of calix [*n*]crown ethers,[144] some of which are cryptands[145] and there is evidence for formation of a calix[4]arene-proton complex.[146]

[125] Shivanyuk, A.; Spaniol, T.P.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Angew. Chem. Int. Ed.* ***2000****, 39*, 3497.
[126] Bryany, J.A.; Ho, S.P.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1990****, 112,* 5837.
[127] Shinkai, S. *Tetrahedron* ***1993****, 49*, 8933.
[128] See Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluver: Dordrecht, ***1991***; Gutsche, C.D. *Calixarenes*; Royal Society of Chemistry, Cambridge, ***1989***; Gutsche, C.D. *Prog. Macrocycl. Chem.* ***1987****, 3*, 93. Also see, Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1995****, 36*, 5429; Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron Lett.* ***1995****, 36*, 6735; No, K.; Kim, J.E.; Kwon, K.M. *Tetrahedron Lett.* ***1995,*** *36*, 8453.
[129] Agbaria, K.; Aleksiuk, O.; Biali, S.E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* ***2001****, 66,* 2891. See Agbaria, K.; Biali, S.E.; Böhmer, V.; Brenn, J.; Cohen, S.; Frings, M.; Grynszpan, F.; Harrowfield, J.Mc B.; Sobolev, A.N.; Thondorf, I. *J. Org. Chem.* ***2001****, 66,* 2900.
[130] Cerioni, G.; Biali, S.E.; Rappoport, Z. *Tetrahedron Lett.* ***1996****, 37*, 5797; Molard, Y.; Bureau, C.; Parrot-Lopez, H.; Lamartine, R.; Regnourf-de-Vains, J.-B. *Tetrahedron Lett.* ***1999****, 40*, 6383.
[131] Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* ***1995****, 60*, 4862.
[132] Kanamathareddy, S.; Gutsche, C.D. *J. Org. Chem.* ***1994****, 59*, 3871.
[133] Cunsolo, F.; Consoli, G.M.L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996****, 37*, 715.
[134] Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* ***2002****, 43*, 7945; Khan, I.U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* ***1993****, 58*, 3158.
[135] Masci, B. *J. Org. Chem.* ***2001****, 66*, 1497; Seri, N.; Thondorf, I.; Biali, S.E. *J. Org. Chem.* ***2004****, 69*, 4774; Tsubaki, K.; Morimoto, T.; Otsubo, T.; Kinoshita, T.; Fuji, K. *J. Org. Chem.* ***2001****, 66*, 4083.
[136] Stewart, D.R.; Gutsche, C.D. *J. Am. Chem. Soc.* ***1999****, 121*, 4136.
[137] Mascal, M.; Naven, R.T.; Warmuth, R. *Tetrahedron Lett.* ***1995****, 36*, 9361.
[138] Wu, Y.; Shen, X.-P.; Duan, C.-y.; Liu, Y.-i.; Xu, Z. *Tetrahedron Lett.* ***1999****, 40*, 5749.
[139] Colby, D.A.; Lash, T.D. *J. Org. Chem.* **2002**, 67, 1031.
[140] Akine, S.; Goto, K.; Kawashima, T. *Tetrahedron Lett.* ***2000****, 41*, 897.
[141] Aeungmaitrepirom, W.; Hagège, A.; Asfari, Z.; Bennouna, L.; Vicens, J.; Leroy, M. *Tetrahedron Lett.* ***1999****, 40*, 6389.
[142] Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* ***2008***, 5957.
[143] Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem. Int. Ed.* ***2000****, 39,* 1256.
[144] Stephan, H.; Gloe, K.; Paulus, E.F.; Saadioui, M.; Böhmer, V. *Org. Lett.* ***2000****, 2*, 839; Asfari, Z.; Thuéry, P.; Nierlich, M.; Vicens, J. *Tetrahedron Lett.* ***1999****, 40,* 499; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996****, 37*, 3899; Pappalardo, S.; Petringa, A.; Parisi, M.F.; Ferguson, G. *Tetrahedron Lett.* ***1996****, 37*, 3907.
[145] Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* ***1996****, 37*, 6315.
[146] Makrlík, E.; Vaňura, P. *Monat. Chemie* ***2006****, 137*, 1185-.

calix[4]arene, $n = 1$
calix[6]arene, $n = 3$
calix[8]arene, $n = 5$

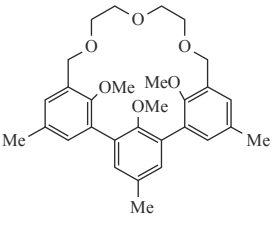


23

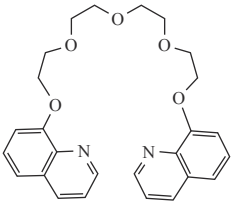


24

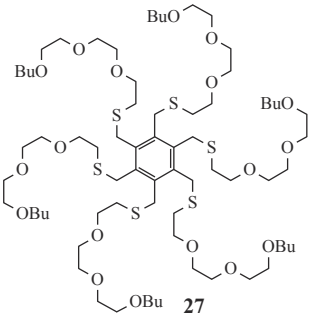
Other molecules include *cryptophanes* (e.g., **24**),[147] *hemispherands* (an example is **25**[148]), and *podands*.[149] The last-named are host compounds in which two or more arms come out of a central structure. Examples are **26**[150] and **27**[151] and the latter molecule binds simple cations (e.g., Na^+, K^+, and Ca^{2+}. *Lariat ethers*[152] are compounds containing a crown ether ring with one or more side chains that can also serve as ligands, (e.g., **28**).[153] There is also a class of ortho cyclophanes that are crown ethers (see **29**) and have been given the name *starands*.[154]



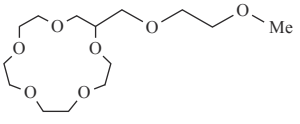
25



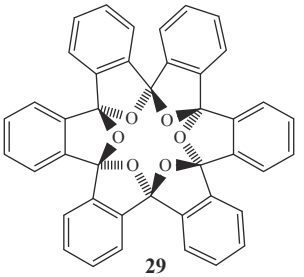
26



27



28



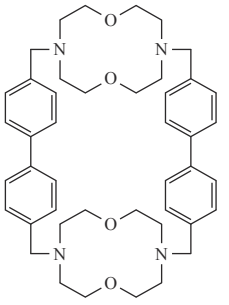
29

[147] See Collet, A. *Tetrahedron* ***1987****, 43,* 5725, in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 97–121.
[148] Lein, G.M.; Cram, D.J. *J. Am. Chem. Soc.* ***1985****, 107,* 448.
[149] Fo Kron, T.E.; Tsvetkov, E.N. *Russ. Chem. Rev.* ***1990****, 59,* 283; Menger, F.M. *Top. Curr. Chem.* ***1986****, 136,* 1.
[150] Tümmler, B.; Maass, G.; Weber, E.; Wehner, W.; Vögtle, F. *J. Am. Chem. Soc.* ***1977****, 99,* 4683.
[151] Vögtle, F.; Weber, E. *Angew. Chem. Int. Ed.* ***1974****, 13,* 814.
[152] For the synthesis of *N*-pivot lariat ethers, see Elwahy, A.H.M.; Abbas, A.A. *J. Het. Chem.* ***2008****, 45,* 1.
[153] Gatto, V.J.; Gokel, G.W. *J. Am. Chem. Soc.* ***1984****, 106,* 8240; Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* ***1988****, 110,* 531.
[154] Lee, W.Y.; Park, C.H. *J. Org. Chem.* ***1993****, 58*, 7149.

The bonding in these complexes is the result of ion-dipole attractions between the heteroatoms and the positive ions. The parameters of the host–guest interactions can sometimes be measured by NMR.[155]

It has been implied that the ability of these host molecules to bind guests is often very specific, often linked to the hydrogen-bonding ability of the host,[156] enabling the host to pull just one molecule or ion out of a mixture. This is called *molecular recognition*.[157] In general, cryptands, with their well-defined 3D cavities, are better for this than monocyclic crown ethers or ether derivatives. An example is the host (**30**), which selectively binds the dication **31** ($n = 5$) rather than **31** ($n = 4$), and **31** ($n = 6$) rather than **31** ($n = 7$).[158] The host **32**, which is water-soluble, forms 1:1 complexes with neutral aromatic hydrocarbons (e.g., pyrene and fluoranthene), and even (though more weakly) with biphenyl and naphthalene, I is also capable of transporting them through an aqueous phase.[159]

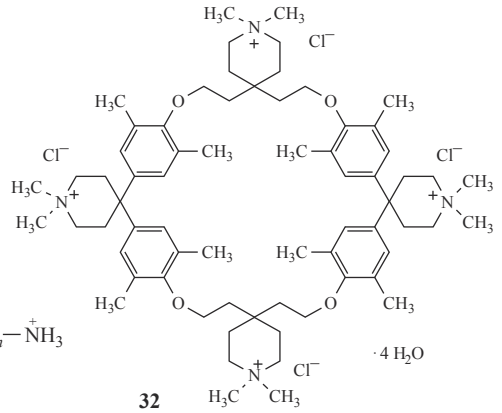
Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is extremely specific because these molecules also have host cavities that are able to recognize only one or a few particular types of guest molecules. Now, organic chemists can synthesize non-natural hosts that can also perform crude (compared to biological molecules) molecular recognition. The macrocycle **33** has been used as a catalyst, for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.[160]



30



31



32

No matter what type of host, the strongest attractions occur when combination with the guest causes the smallest amount of distortion of the host.[161] That is, a fully preorganized

[155] Wang, T.; Bradshaw, J.S.; Izatt, R.M. *J. Heterocylic Chem.* ***1994****, 31*, 1097.

[156] Fujimoto, T.; Yanagihara, R.; Koboyashi, K.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* ***1995****, 68*, 2113.

[157] For reviews, see Rebek, Jr., *J. Angew. Chem. Int. Ed.* ***1990***, *29*, 245; *Acc. Chem. Res.* ***1990***, *23*, 399; *Top. Curr. Chem.* ***1988***, *149*, 189; Diederich, *F. J. Chem. Educ.* ***1990***, *67*, 813; Hamilton, A.D. *J. Chem. Educ.* ***1990***, *67*, 821; Raevskii, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 219.

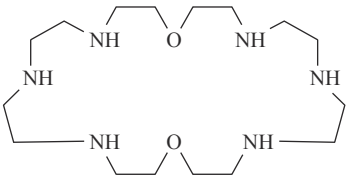
[158] Mageswaran, R.; Mageswaran, S.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* ***1979***, 722.

[159] Diederich, F.; Dick, K. *J. Am. Chem. Soc.* ***1984****, 106,* 8024; Diederich, F.; Griebe, D. *J. Am. Chem. Soc.* ***1984****, 106,* 8037. See also, Vögtle, F.; Müller, W.M.; Werner, U.; Losensky, H. *Angew. Chem. Int. Ed.* ***1987****, 26,* 901.

[160] Hosseini, M.W.; Lehn, J.M. *J. Am. Chem. Soc.* ***1987****, 109,* 7047. For a discussion, see Mertes, M.P.; Mertes, K. B. *Acc. Chem. Res.* ***1990****, 23,* 413.

[161] See Cram, D.J. *Angew. Chem. Int. Ed.* ***1986****, 25,* 1039.

host will bind better than a host whose molecular shape must change in order to accommodate the guest.



33

3.C.iii Inclusion Compounds

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. Here, the host forms a crystal lattice that has spaces large enough for the guest to fit into. *van der Waals forces* constitute the only bonding between the host and the guest. There are two main types, depending on the shape of the space.[162] The spaces in *inclusion compounds,* are in the shape of long tunnels or channels, while the other type, often called *clathrate*,[163] or *cage compounds*, have spaces that are completely enclosed. In both types, the guest molecule must fit into the space and potential guests that are too large or too small will not go into the lattice, so that the addition compound will not form. Such structures need not be restricted to large molecules. Indeed, the structure and stability of the hydrogen clathrate hydrate with cyclohexanone is known.[164]

Several important host molecules are known, and inclusion compounds include small molecules (e.g., urea).[165] Hydrogen sulfide forms hexagonal clathrate hydrate cages, and a guest molecule (e.g., pinacolone), may be present, as shown in Fig. 3.1.[166] Commonly, *van der Waals forces* between the host and the guest, while small, are essential to the stability of the structure. Which molecules can be a guest is usually dependent on their shapes and sizes and not necessarily on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also, both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate nor diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[167] In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane/urea ratio is 1:6.73.[168] A deuterium quadrupole echo spectroscopy study of a urea complex showed that the urea molecules do not remain rigid, but undergo 180° flips about the C=O axis at the rate of $>10^6\ s^{-1}$ at 30 °C.[169]

[162] See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vols. 1–3, Academic Press, NY, ***1984***; Weber, E. *Top. Curr. Chem.* ***1987****, 140,* 1; Gerdil, R. *Top. Curr. Chem.* ***1987****, 140,* 71; Mak, T.C.W.; Wong, H.N.C. *Top. Curr. Chem.* ***1987****, 140,* 141; Bishop, R.; Dance, I.G. *Top. Curr. Chem.* ***1988****, 149,* 137.

[163] For reviews, see Goldberg, I. *Top. Curr. Chem.* ***1988****, 149,* 1; Weber, E.; Czugler, M. *Top. Curr. Chem.* ***1988****, 149,* 45; MacNicol, D.D.; McKendrick, J.J.; Wilson, D.R. *Chem. Soc. Rev.* ***1978****, 7,* 65.

[164] Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* ***2007****, 129,* 9544.

[165] For a review of urea and thiourea inclusion compounds, see Takemoto, K.; Sonoda, N. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 47–67.

[166] Taken from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* ***2010****, 16*, 1017.

[167] Radell, J.; Connolly, J.W.; Cosgrove, Jr., W.R. *J. Org. Chem.* ***1961****, 26,* 2960.

[168] Redlich, O.; Gable, C.M.; Dunlop, A.K.; Millar, R.W. *J. Am. Chem. Soc.* ***1950****, 72,* 4153.

[169] Heaton, N.J.; Vold, R.L.; Vold, R.R. *J. Am. Chem. Soc.* ***1989****, 111*, 3211.

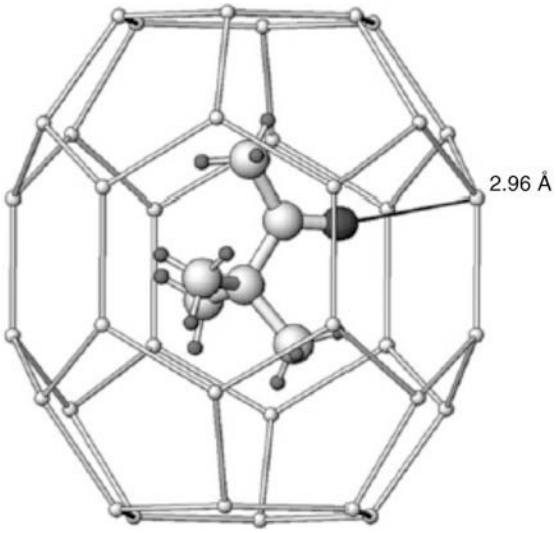


FIG. 3.1. X-ray strucutre of pinacolone in a H_2S hexagonal clathrate hydrate cage molecule at 100 K.[166] [Reprinted with permission from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* ***2010****, 16*, 1017, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © *2010* by Wiley–VCH Verlag.]

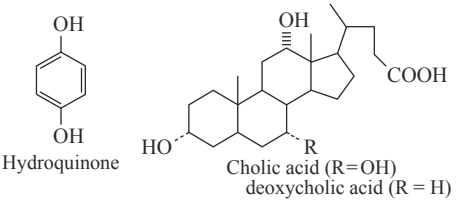
The complexes are solids, but are not useful as derivatives, since they melt, with decomposition of the complex at the melting point of urea. They are useful, however, in separating isomers that would be quite difficult to separate otherwise. Thiourea also forms inclusion compounds though with channels of larger diameter, so that *n*-alkanes cannot be guests but, (e.g., 2-bromooctane, cyclohexane, and chloroform readily fit).

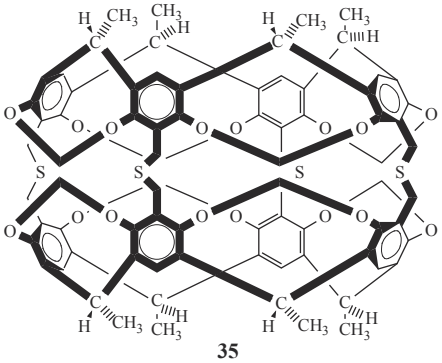
Hydroquinone is a useful host for clathrates.[170] Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), sulfur dioxide, carbon dioxide, and argon (but not neon). One important use is the isolation of anhydrous hydrazine as complex.[171] Anhydrous hydrazine is highly explosive, so preparation by distillation of aq hydrazine solutions is both difficult and dangerous. The inclusion complex can be readily isolated and reactions done in the solid state (e.g., the reaction with esters to give hydrazides, Reaction **16**–**75**).[172] In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage and many guest molecules, among them Cl_2, propane, and methyl iodide, can fit. The water clathrates (see Fig. 3.1), which are solids, can normally be kept only at low temperatures; at room temperature, they decompose.[171] Methane hydrate, which is a promising energy source that exists is vast quantities at in the seabed of various oceans,[173] is an example of this type of

[170] For a review, see MacNicol, D.D. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 1–45.
[171] Toda, F.; Hyoda, S.; Okada, K.; Hirotsu, K. *J. Chem. Soc., Chem. Commun.* ***1995***, 1531.
[172] For a monograph on water clathrates, see Berecz, E.; Balla-Achs, M. *Gas Hydrates*; Elsevier, NY, ***1983***. For reviews, see Jeffrey, G.A. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 135–190; Cady, G.H. *J. Chem. Educ.* ***1983****, 60*, 915.
[173] Sloan, E.D. *Clathrate Hydrate of Natural Gases*, Marcel Dekker, Inc., ***1998***.

clathrate. Another inorganic host is sodium chloride (and some other alkali halides), which can encapsulate organic molecules (e.g., benzene, naphthalene, and diphenylmethane).[174]

Among other hosts[175] for inclusion and/or clathrate compounds are deoxycholic acid,[176] cholic acid,[177] anthracene compounds, (e.g., **34**),[178] dibenzo-24-crown-8,[179] and the compound **35**, which has been called a *carcerand*.[180] When carcerand-type molecules trap ions or other molecules (called guests), the resulting complex is called a carciplex.[181] It has been shown that in some cases, the motion of the guest within the carciplex is restricted.[182]





[174] Kirkor, E.; Gebicki, J.; Phillips, D.R.; Michl, J. *J. Am. Chem. Soc.* ***1986****, 108,* 7106.

[175] See also, Toda, F. *Pure App. Chem.* ***1990****, 62*, 417, *Top. Curr. Chem.* ***1988****, 149,* 211; ***1987****, 140,* 43; Davies, J. E.; Finocchiaro, P.; Herbstein, F.H. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 407–453.

[176] For a review, see Giglio, E. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 207–229.

[177] See Miki, K.; Masui, A.; Kasei, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* ***1988****, 110,* 6594.

[178] Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 2321. Also see, Barbour, L. J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1413.

[179] Lämsä, M.; Suorsa, T.; Pursiainen, J.; Huuskonen, J.; Rissanen, K. *Chem. Commun.* ***1996***, 1443.

[180] Sherman, J.C.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1991****, 113,* 2194.

[181] van Wageningen, A.M.A.; Timmerman, P.; van Duynhoven, J.P.M.; Verboom, W.; van Veggel, F.C.J.M.; Reinhoudt, D.N. *Chem. Eur.J.* ***1997****, 3*, 639; Fraser, J.R.; Borecka, B.; Trotter, J.; Sherman, J.C. *J. Org. Chem.* ***1995****, 60*, 1207; Place, D.; Brown, J.; Deshayes, K. *Tetrahedron Lett.* ***1998****, 39,* 5915. See also: Jasat, A.; Sherman, J.C. *Chem. Rev.* ***1999****, 99,* 931.

[182] Chapman, R.G.; Sherman, J.C. *J. Org. Chem.* ***2000****, 65,* 513.

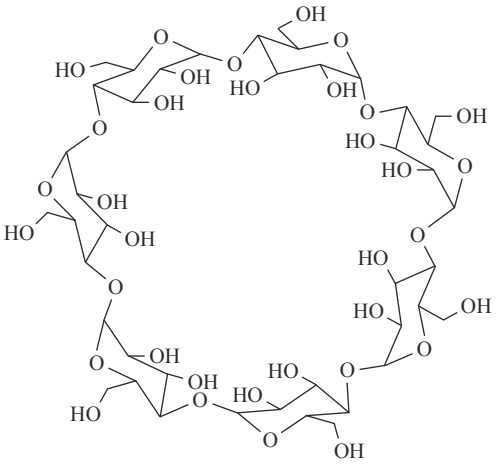


FIG. 3.2. β-Cyclodextrin.

3.C.iv Cyclodextrins

There is one type of host that can form both channel and cage complexes. This type is called *cyclodextrins* or *cycloamyloses*.[183] The host molecules are made up of six, seven, or eight glucose units connected in a large ring, called, respectively, α-, β-, or γ-cyclodextrin (Fig. 3.2 shows the β or seven-membered ring compound). The three molecules are in the shape of hollow truncated cones (Fig. 3.3) with primary OH groups projecting from the narrow side of the cones and secondary OH group from the wide side. As expected for carbohydrate molecules, all of them are soluble in water and the cavities normally fill with water molecules held in place by hydrogen bonds (6, 12, and 17 H_2O molecules for the α, β, and γ forms, respectively), but the insides of the cones are less polar than the outsides, so that nonpolar organic molecules readily displace the water. The polarity of such cavities has been probed by a chemical reaction: the solvolysis of benzoyl halides Reaction (**16**–**57**).[184] Thus the cyclodextrins form 1:1 cage complexes with many guests, ranging in size from the noble gases to large organic molecules. A guest molecule must not be too large or it will not fit, though many stable complexes are known in which one end of the guest molecule protrudes from the cavity (Fig. 3.4). On the other hand, if the guest is too small, it may go through the bottom hole (though some small polar molecules, e.g., methanol, do form complexes in which the cavity also contains some water molecules). Since the cavities of the three cyclodextrins are of different sizes (Fig. 3.3), a large variety of guests can be accommodated. Since

[183] See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***. For reviews, see in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Academic Press, NY, ***1984***, the reviews, by Saenger, W. Vol. 2, pp. 231–259, Bergeron, R.J. Vol. 3, pp. 391–443, Tabushi, I. Vol. 3, pp. 445–471, Breslow, R. Vol. 3, pp. 473–508; Croft, A.P.; Bartsch, R.A. *Tetrahedron* ***1983****, 39,* 1417; Tabushi, I.; Kuroda, Y. *Adv. Catal.,* ***1983****, 32,* 417; Tabushi, I. *Acc. Chem. Res.* ***1982****, 15,* 66; Saenger, W. *Angew. Chem. Int. Ed.* ***1980****, 19,* 344; Bergeron, R. *J. Chem. Ed.* ***1977****, 54,* 204; Griffiths, D.W.; Bender, M.L. *Adv. Catal.* ***1973****, 23,* 209.

[184] García-Río, L.; Hall, R.W.; Mejuto, J.C.; Rodriguez-Dafonte, P. *Tetrahedron* ***2007****, 63,* 2208.

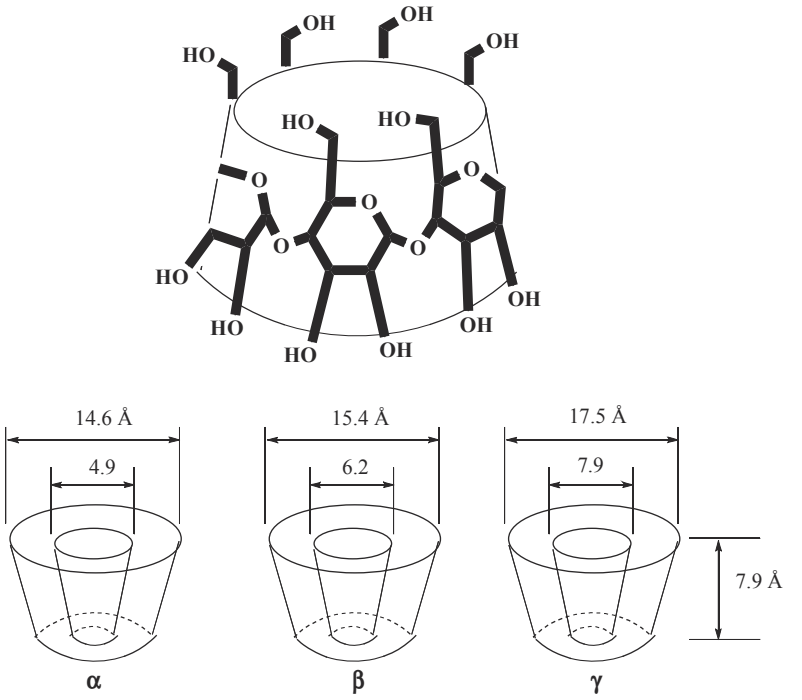


FIG. 3.3. Shape and dimensions of the α-, β-, and γ-cyclodextrin molecules.[185]

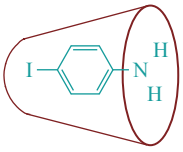


FIG. 3.4. Schematic drawing of the complex of α-cyclodextrin and *p*-iodoaniline.[186]

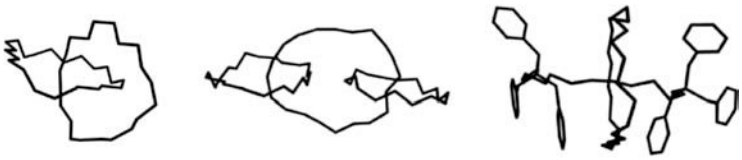
cyclodextrins are nontoxic (they are actually small starch molecules), they are now used industrially to encapsulate foods and drugs.[187]

The cyclodextrins also form channel-type complexes, in which the host molecules are stacked on top of each other, like coins in a row.[188] For example, α-cyclodextrin (cyclohexaamylose) forms cage complexes with acetic, propionic, and butyric acids, but channel complexes with valeric and higher acids. Capped cyclodextrins are known.[189]

[185] Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, p. 332; Nickon, A.; Silversmith, E.F. *The Name Game*, Pergamon, Elmsford, NY, p. 235.
[186] Modified from Saenger, W.; Beyer, K.; Manor, P.C. *Acta Crystallogr. Sect. B, **1976**, 32,* 120.
[187] For reviews, see Pagington, J.S. *Chem. Br., **1987**, 23,* 455; Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 331–390.
[188] See Saenger, W. *Angew. Chem. Int. Ed. **1980**, 19*, 344.
[189] Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev. **2003**, 103*, 4147.

3.D. CATENANES AND ROTAXANES[190]

These compounds contain two or more independent portions that are not bonded to each other by any valence forces, but nevertheless must remain linked. [*n*]-*Catenanes* (where *n* corresponds to the number of



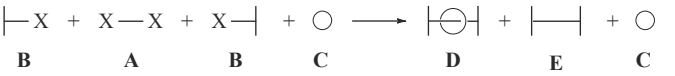
A [2]catenane A [3]catenane A rotaxane

linked rings) are made up of two or more rings held together as links in a chain, while in *rotaxanes* a linear portion is threaded through a ring and cannot get away because of bulky end groups. Among several types of bulky molecular units, porphyrin units have been used to cap rotaxanes[191] as have C_{60} fullerenes.[192] [2]Rotaxanes and [2]catenanes are quite common, and [3]catenanes are known having rather robust amide linkages.[193] More intricate variants [e.g., oligocatenanes,[194] molecular necklaces (a cyclic oligorotaxane in which a number of small rings are threaded onto a large ring),[195] and cyclic daisy chains (an interwoven chain in which each monomer unit acts as a donor and an acceptor for a threading interaction)][196] are known. Ring-in-ring complexes have also been reported.[197] Molecular thread, ribbon, and belt assemblies have been synthesized.[198] Rotaxanes have been used as the basis for molecular switches,[199] and a rotaxane eciplex has been generated that may have applications to molecular-scale photonic devices.[200]

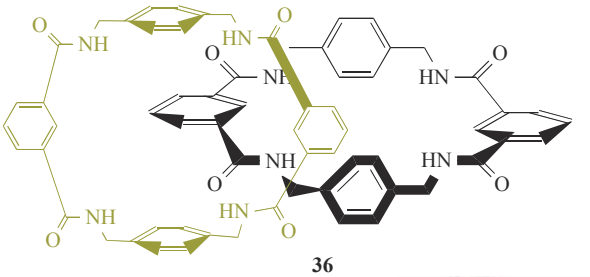
Transitional isomers are possible in [2]rotaxanes.[201] Catenanes and rotaxanes can be prepared by statistical methods or directed syntheses.[202] Catenanes can contain heteroatoms and heterocyclic units. In some cases, the catenane exists in equilibrium with the cyclic-non-catenane structures and in some cases this exchange is thought to proceed by

[190] For a monograph, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239.
[191] Solladié, N.; Chambron, J.-C.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999****, 121*, 3684.
[192] Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* ***2004****, 6*, 3957.
[193] Safarowsky, O.; Vogel, E.; Vögtle, F. *Eur. J. Org. Chem.* ***2000***, 499.
[194] Amabilino, D.B.; Ashton, P.R.; Balzani, V.; Boyd, S.E.; Credi, A.; Lee, J.Y.; Menzer, S.; Stoddart, J.F.; Venturi, M.; Williams, D.J. *J. Am. Chem. Soc.* ***1998****, 120,* 4295.
[195] Chiu, S.-H.; Rowan, S.J.; Cantrill, S.J.; Ridvan, L.; Ashton, R.P.; Garrell, R.L.; Stoddart, J.-F. *Tetrahedron* ***2002****, 58*, 807; Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed.* ***1999****, 38,* 638.
[196] See Onagi, H.; Easton, C.J.; Lincoln, S.F. *Org. Lett.* ***2001****, 3,* 1041; Cantrill, S.J.; Youn, G.J.; Stoddart, J.F.; Williams, D.J. *J. Org. Chem.* ***2001****, 66,* 6857.
[197] Chiu, S.-H.; Pease, A.R.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***2002****, 41,* 270.
[198] Schwierz, H.; Vögtle, F. *Synthesis* ***1999***, 295.
[199] Elizarov, A.M.; Chiu, S.-H.; Stoddart, J.-F. *J. Org. Chem.* ***2002****, 67,* 9175.
[200] MacLachlan, M. J.; Rose, A.; Swager, T. M. *J. Am. Chem. Soc.* ***2001****, 123,* 9180.
[201] Amabilino, D.B.; Ashton, P.R.; Boyd, S.E.; Gómez-López, M.; Hayes, W.; Stoddart, J.F. *J. Org. Chem.* ***1997****, 62*, 3062.
[202] For discussions, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239; Walba, D.M. *Tetrahedron* ***1985****, 41*, 3161.

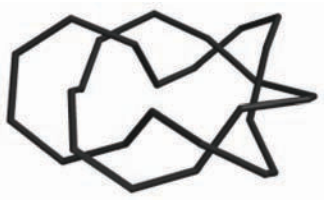
ligand exchange and a Möbius strip mechanism.[203] An example of a statistical synthesis of a rotaxane is a reaction where a compound **A** is bonded at two positions to another compound **B** in the presence of a large ring **C**. It is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.[204] In a directed synthesis,[205] the separate parts of the molecule are held together by other bonds that are later cleaved.



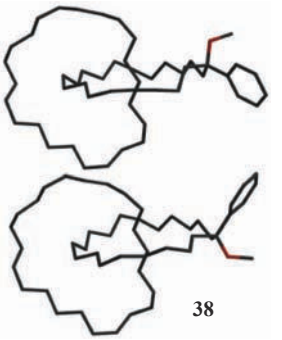
Rotation of one unit through the other catenanes is complex, often driven by making and breaking key hydrogen bonds or π–π interactions. In the case of the isophthaloyl [2]catenane (**36**), the rate-determining steps do not necessarily correspond to the passage of the bulkiest groups.[206]



36



37



38

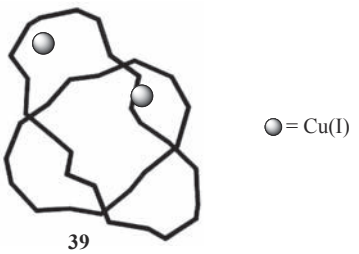
Singly and doubly interlocked [2]catenanes[207] can exist as *topological stereoisomers*[208] (see Sec. 4.G for a discussion of diastereomers). Catenanes **37** and **38** are such stereoisomers, and would be expected to have identical mass spectra. Analysis showed that

[203] Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* ***1996****, 118*, 899.
[204] Harrison, I.T.; Harrison, S. *J. Am. Chem. Soc.* ***1967****, 89,* 5723; Ogino, H. *J. Am. Chem. Soc.* ***1981****, 103,* 1303; Harrison, I.T. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 301; Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* ***1986****, 119,* 2647. See also, Agam, G.; Graiver, D.; Zilkha, A. *J. Am. Chem. Soc.* ***1976****, 98,* 5206.
[205] For a directed synthesis of a rotaxane, see Schill, G.; Zürcher, C.; Vetter, W. *Chem. Ber.* ***1973****, 106,* 228.
[206] Deleuze, M. S.; Leigh, D. A; Zerbetto, F. *J. Am. Chem. Soc.* ***1999****, 121,* 2364.
[207] For the synthesis of a doubly interlocking [2]catenane, see Ibukuro, F.; Fujita, M.; Yamaguchi, K.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999****, 121,* 11014.
[208] See Lukin, O.; Godt, A.; Vögtle, F. *Chem. Eur. J.,* ***2004****, 10*, 1879.

37 is more constrained and cannot readily accommodate an excess of energy during the mass spectrometry ionization process and, hence, breaks more easily.

Catenanes, molecular knots, and other molecules in these structural categories can exist as enantiomers. In other words, stereoisomers can be generated in some cases. This phenomenon was first predicted by Frisch and Wassermann,[209] and the first stereoisomeric catenanes and molecular knots were synthesized by Sauvage and Dietrich-Buchecker.[210] Enantiomeric resolution has been achieved.[211] A chiral [3]rotaxane containing two achiral wheels, mechanically bonded has been reported,[212] generating a cyclodiastereomeric compound, and the enantiomers were separated using chiral HPLC. The terms cycloenantiomerism and cyclodiastereomerism were introduced by Prelog et. al.[213] This type of stereoisomerism occurs in cyclic arrangements of several centrally chiral elements in combination with an orientation of the macrocycle.[212]

A rotaxane can also be an inclusion compound.[214] The molecule contains bulky end groups (or "stoppers," e.g., triisopropylsilyl groups, $i\text{Pr}_3\text{Si}$—) and a chain that consists of a series of —O—CH_2CH_2—O— groups, but also contains two benzene rings. Cyclodextrins have been threaded onto axle molecules.[215] The ring (or bead) around the chain is a macrocycle containing two benzene rings and four pyridine rings. It is preferentially attracted to one of the benzene rings in the chain. The benzene moiety serves as a "station" for the "bead." However, symmetry of the chain can make the two "stations" equivalent, so that the "bead" is equally attracted to them, and the "bead" actually moves back and forth rapidly between the two "stations," as shown by the temperature dependence of the NMR spectrum.[216] This molecule has been called a *molecular shuttle*. A copper(I) complexed rotaxane has been prepared with two fullerene (see Sec. 2.L) stoppers.[217]



39

[209] Frisch, H.L.; Wasserman, E. *J. Am. Chem. Soc.* ***1961****, 83,* 3789.

[210] *Molecular Catenanes, Rotaxanes and Knots* (Eds., Sauvage, J.-P.; Dietrich-Buchecker, C.O.) Wiley-VCH, Weinheim, ***1999***; Ashton, P.R.; Bravo, J.A.; Raymo, F.M.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Eur. J. Org. Chem.* ***1999***, 899; Mitchell, D.K.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1988****, 27,* 930; Nierengarten, J.-F.; Dietrich-Buchecker, C.O.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1994****, 116*, 375; Chen, C.-T.; Gantzel, P.; Siegel, J.S.; Baldridge, K.K.; English, R.B.; Ho, D.M. *Angew. Chem. Int. Ed.* ***1995****, 34,* 2657.

[211] Kaida, T.; Okamoto, Y.; Chambron, J.-C.; Mitchell, D.K.; Sauvage, J.-P. *Tetrahedron Lett.* ***1993****, 34,* 1019.

[212] Schmieder, R.; Hübner, G.; Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1999****, 38,* 3528.

[213] Prelog, V.; Gerlach, H. *Helv. Chim. Acta* ***1964****, 47,* 2288; Gerlach, H.; Owtischinnkow, J.A.; Prelog, V. *Helv. Chim. Acta* ***1964****, 47*, 2294; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds,* Wiley, NY, ***1994***, pp. 1176–1181; Chorev, M.; Goodman, M. *Acc. Chem. Res.* ***1993****, 26,* 266; Mislow, K. *Chimia,* ***1986****, 40,* 395.

[214] For an example, see Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991****, 113,* 5131.

[215] Oshikiri, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* ***2005****, 127,* 12186.

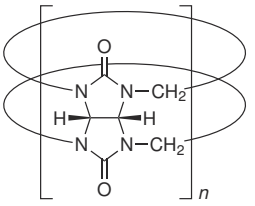
[216] Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991****, 113*, 5131. For a review of the synthesis and properties of molecules of this type, see Philp, D.; Stoddart, J.F. *Synlett* ***1991***, 445.

[217] Diederich, F.; Dietrich-Buchecker, C.O.; Nierengarten, S.-F.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* ***1995***, 781.

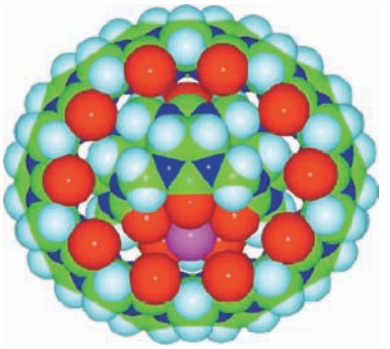
Another variation of these molecules is called molecular knots (e.g., **39)**, where the ● represents a metal [in this case, Cu(I)].[218] This is particularly interesting since knotted forms of deoxyribonucleic acid (DNA) have been reported.[219] There are mechanically interlocked molecules, and one example is known as suit[2]ane.[220]

3.E. CUCURBIT[*M*]URIL-BASED GYROSCANE

A new molecule known as gyroscane has been prepared, and proposed as a new supramolecular form.[221] The class of compounds known as cucurbit[*n*]urils, abbreviated Q_n (**40**),[222] are condensation products of glycoluril and formaldehyde. These macrocycles can act as molecular hosts. The new "supramolecular form is one in which a smaller macrocycle (Q5) is located inside a larger macrocycle (Q10), with facile rotation of one relative to the other in solution (see **41**).[221] The image of a ring rotating independently inside another ring, which resembles a gyroscope, suggests the name gyroscane for this new class of supramolecular system."[222]



40



41

[Reprinted with permission from Day, A.I, Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew Chem. Int. Ed.* ***2002****, 41*, 275, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***2002*** by Wiley-VCH Verlag.]

[218] Dietrich-Buchecker, C.O.; Nierengarten, J.-F.; Sauvage, J.-P. *Tetrahedron Lett.* ***1992****, 33*, 3625. See Dietrich-Buchecker, C.O.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1990****, 29*, 1154.

[219] Liu, L.F.; Depew, R.E.; Wang, J.C. *J. Mol. Biol.* ***1976****, 106*, 439.

[220] Williams, A.R.; Northrop, B.N.; Chang, T.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***2006****, 45,* 6665.

[221] Day, A.I.; Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew. Chem. Int. Ed,*. ***2002****, 41,* 275.

[222] Mock, W.L. *Top. Curr. Chem.* ***1995****, 175,* 1; Mock, W.L. in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D.; Vogtle, F.), Pergamon, Oxford, ***1996***, pp. 477–493; Day, A.; Arnold, A.P.; Blanch, R.J.; Snushall, B. *J. Org. Chem.* ***2001****, 66,* 8094. For cucurbit[10]uril, see Liu, S.; Zavalij, P.Y.; Isaacs, L. *J. Am. Chem. Soc.* ***2005****, 127*, 16798.

CHAPTER 4

Stereochemistry and Conformation

The discussions in Chapters 1–3 focused on electron distribution in organic molecules. In this chapter, the focus will be on the 3D structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same sequence of bonds, but having different 3D structures that are not interchangeable. These structures are called *configurations*.

4.A. OPTICAL ACTIVITY AND CHIRALITY[3]

Any material that rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the two structures constitute the same compound and the compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. The relationship between optical activity and chirality is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see Sec. 4.C). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This finding is both a necessary and a sufficient condition.[4] This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true. Note that parity violation

[1] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***; Sokolov, V.I. *Introduction to Theoretical Stereochemistry*, Gordon and Breach, NY, ***1991***; Nógrádi, M. *Sterochemistry*, Pergamon, Elmsford, NY, ***1981***; Kagan, H. *Organic Sterochemistry*, Wiley, NY, ***1979***; Testa, B. *Principles of Organic Stereochemistry*, Marcel Dekker, NY, ***1979***; Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd., Tokyo, ***1977***; Natta, G.; Farina, M. *Stereochemistry*, Harper and Row, NY, ***1972***; Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***; Mislow, K. *Introduction to Stereochemistry*, W.A. Benjamin, NY, ***1965***. For a historical treatment, see Ramsay, O.B. *Stereochemistry*, Heyden & Son, Ltd., London, ***1981***.

[2] See *Pure Appl. Chem.* ***1976***, *45*, 13 and in *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book).

[3] See Cintas, P. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4016.

[4] For a discussion of the conditions for optical activity in liquids and crystals, see O'Loane, J.K. *Chem. Rev.* ***1980***, *80*, 41. For a discussion of chirality as applied to molecules, see Quack, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 571.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

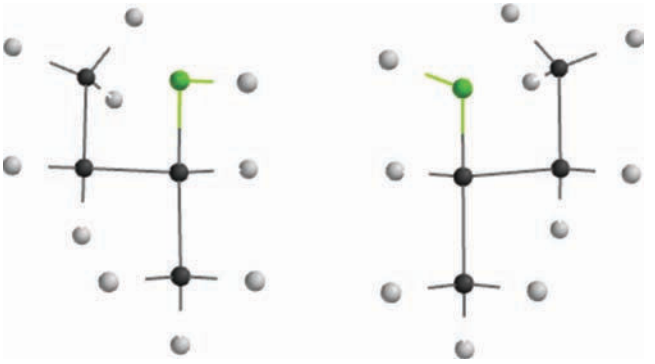


FIG. 4.1. Enantiomers of 2-butanol.

represents an essential property of particle and atomic handedness, and has been related to chirality.[5]

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity. In each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and right-handedness of their orientations (see the enantiomers for 2-butanol in Fig. 4.1). Enantiomers have identical[6] physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, although in equal amounts. The isomer that rotates the plane to the left (counterclockwise) is called the *levo isomer* and is designated (−), while the one that rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+). Because they differ in this property they are often called *optical antipodes*.
2. They may react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. This finding is the reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.[7]

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.[8] Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if an optically active *catalyst* is present; they may have different

[5] Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J.L.; Palacios, J.C. *Tetrahedron Asymm.* ***2000***, *11,* 2845.

[6] Interactions among electrons, nucleons, and certain components of nucleons (e.g., bosons), called *weak interactions*, violate parity; that is, mirror image interactions do not have the same energy. It has been contended that interactions of this sort cause one of a pair of enantiomers to be (slightly) more stable than the other. See Tranter, G.E. *J. Chem. Soc. Chem. Commun.* ***1986***, 60, and references cited therein. See also, Barron, L.D. *Chem. Soc. Rev.* ***1986****, 15*, 189.

[7] For a reported exception, see Hata, N. *Chem. Lett.* ***1991***, 155.

[8] See Craig, D.P.; Mellor, D.P. *Top. Curr. Chem.* ***1976***, *63*, 1.

solubilities in an optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, and so on. In most cases, these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive since the equal and opposite rotations cancel. Such mixtures are called *racemic mixtures*[9] or *racemates*.[10] Their properties are not always the same as those of the individual enantiomers. The properties in the gaseous or liquid state or in solution usually are the same, since such a mixture is nearly ideal, but properties involving the solid state[11] (e.g., melting points, solubilities, and heats of fusion), are often different. Thus racemic tartaric acid has a melting point of 204–206 °C and a solubility in water at 20 °C of 206 g L^{-1} while for the (+) or the (−) enantiomer, the corresponding figures are 170 °C and 1390 g L^{-1}. The separation of a racemic mixture into its two optically active components is called *resolution*. The presence of optical activity always proves that a given compound is chiral, but its absence does not prove that the compound is achiral. A compound that is optically inactive may be achiral, or it may be a racemic mixture (see also, Sec. 4.C).

4.A.i. Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[12] and concentration (for solutions), the pressure (for gases), and the wavelength of light.[13] Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. To make it possible for one value of α for a pure compound to be compared with another α for that compound taken under different circumstances, a physical property is defined, called the *specific rotation* [α], which is

$$[\alpha] = \frac{\alpha}{lc} \text{ for solutions} \quad [\alpha] = \frac{\alpha}{ld} \text{ for pure compounds}$$

where α is the observed rotation, *l* is the cell length in decimeters, *c* is the concentration in grams per milliliter, and *d* is the density in the same units. The specific rotation is usually given along with the temperature and wavelength of light used for the measurement, in this manner: $[\alpha]_{546}^{25}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; that is, λ = 589 nm. The *molar rotation* $[M]_\lambda^t$ is the specific rotation times the molecular weight divided by 100.

It must be emphasized that the value of α changes with conditions, but the molecular structure is unchanged. This finding is true even when the changes in conditions are

[9] Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book this expression refers to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

[10] See Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*, Wiley, NY, ***1981***.

[11] See Wynberg, H.; Lorand, J.P. *J. Org. Chem.* ***1981***, *46*, 2538 and references cited therein.

[12] A good example is found in Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3920.

[13] For a review of polarimetry see Lyle, G.G.; Lyle, R.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 13–27.

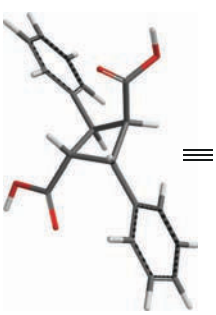
sufficient to change not only the amount of rotation, but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to $+4.36°$ at 20°C and $-1.86°$ at 90 °C, although the molecular structure is unchanged. A consequence of such cases is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior.

Other cases are known in which the direction of rotation is reversed by changes in wavelength, solvent, and even concentration.[14] In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute–solvent interactions often cause nonlinear behavior. For example, $[\alpha]_D^{24}$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is $-5.0°$ at $c = 16.5$ g 100 mL^{-1} (0.165 g mL^{-1}), $-0.7°$ at $c = 10.6$, $+1.7°$ at $c = 8.5$, and $+18.9°$ at $c = 2.2$.[15] Note that the concentration is sometimes reported in g 100 mL^{-1} (as shown) or as g dL^{-1} (decaliters) rather than the standard g mL^{-1}. One should always check the concentration term to be certain. Note that calculation of the optical rotation of (*R*)-(−)-3-chloro-1-butene found a remarkably large dependence on the C=C—C—C torsional angle.[16] However, the observed rotations are a factor of 2.6 smaller than the calculated values, independent of both conformation and wavelength from 589 to 365 nm.

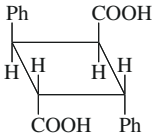
4.B. WHAT KINDS OF MOLECULES DISPLAY OPTICAL ACTIVITY?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used that are simpler to apply, but not always accurate. One such test is the presence of a *plane of symmetry*.[17] A plane of symmetry[18] (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry* (e.g., in α-truxillic acid), or an *alternating axis of symmetry* as in **1**.[19] A center of symmetry[18] is a point within an object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[18] of order *n* is an axis such that when an object containing such an axis is rotated by 360°/*n* about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained that is indistinguishable from the original one. Compounds that lack an alternating axis of symmetry are always chiral.

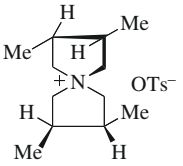
[14] For examples, see Shriner, R.L.; Adams, R.; Marvel, C.S. in Gilman, H. *Advanced Organic Chemistry*, Vol. 1, 2nd ed. Wiley, NY, ***1943***, pp. 291–301.
[15] Krow, G.; Hill, R.K. *Chem. Commun.* ***1968***, 430.
[16] Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J.R. *J. Am. Chem. Soc.* ***2003***, *125,* 1888.
[17] See Barron L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.
[18] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***, pp. 6,7. See also, Lemière, G.L.; Alderweireldt, F.C. *J. Org. Chem.* ***1980***, *45*, 4175.
[19] McCasland, G.E.; Proskow, S. *J. Am. Chem. Soc.* ***1955***, *77*, 4688.



≡



α-truxillic acid



1

≡



A molecule that contains just one *stereogenic carbon atom* (defined as a carbon atom connected to four different groups; also called a *chiral atom or* an *asymmetric carbon atom*) is always chiral, and hence optically active.[20] As seen in Fig. 4.1, such a molecule *cannot* have a plane of symmetry, whatever the identity of the four atoms or groups, as long as they are all different. However, optical activity may be present in molecules with no stereogenic atom.[21] Some molecules with two or more steroegenic carbon atoms, however, are superimposable on their mirror images (called *meso* compounds), and hence inactive principally because there is symmetry. Examples of such compounds will be discussed subsequently.

Optically active compounds may be classified into several categories.

1. *Compounds with a Stereogenic Carbon Atom.* If there is only one such atom, the molecule must be optically active, no matter how slight the differences are among the four groups. An example is 1,12-dibromo-6-methyldodecane, which has one stereogenic carbon and will be optically active. Optical activity has been detected even in cases[22] (e.g., 1-butanol-1-*d*), where one group is hydrogen and another deuterium:[23] The stereogenic carbon is connected to OH, H, D, and a propyl group.

   Although enantiomers will exhibit specific rotation of equal magnitude but opposite sign, the difference may be too small to be measured accurately. In optically active compounds, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities[24] and the optical activity of 5-ethyl-5-propylundecane is too low to be measurable at any wavelength between 280 and 580 nm.[25]
2. *Compounds with Other Quadrivalent Stereogenic Atoms.*[26] Any molecule with an atom that has four bonds pointing to the corners of a tetrahedron will be optically

[20] For discussions of the relationship between a chiral carbon and chirality, see Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* ***1984***, *106*, 3319; Brand, D.J.; Fisher, J. *J. Chem. Educ.* ***1987***, *64*, 1035.

[21] For a review of such molecules, see Nakazaki, M. *Top. Stereochem.* ***1984***, *15*, 199.

[22] See Barth, G.; Djerassi, C. *Tetrahedron* ***1981***, *24*, 4123; Verbit, L. *Prog. Phys. Org. Chem.* ***1970***, *7*, 51; Floss, H.G.; Tsai, M.; Woodard, R.W. *Top. Stereochem.* ***1984***, *15*, 253.

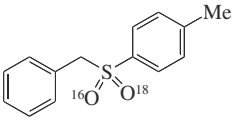
[23] Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1956***, *78*, 5597.

[24] For a discussion of optical activity in paraffins, see Brewster, J.H. *Tetrahedron* ***1974***, *30*, 1807.

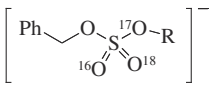
[25] Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2754.

[26] *For compounds with asymmetric atoms other than carbon, see Aylett, B.J.* Prog. Stereochem. **1969**, 4, *213; Belloli, R.* J. Chem. Educ. **1969**, 46, *640; Sokolov, V.I.; Reutov, O.A.* Russ. Chem. Rev. **1965**, 34, *1.*

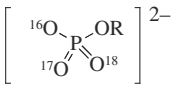
active if the four groups are different. Among atoms in this category are Si,[27] Ge, Sn,[28] and N (in quaternary salts or *N*-oxides).[29] In sulfones, the sulfur bonds have a tetrahedral array, but since two of the groups are always oxygen, no chirality results. However, the preparation[30] of an optically active sulfone (**2**) in which one oxygen is ^{16}O and the other is ^{18}O illustrates the point that slight differences in groups are all that is necessary. This point has been taken even further with the preparation of ester **3**, both enantiomers of which have been prepared.[31] Optically active chiral phosphates (**4**) have similarly been made.[32]



2



3



4

3. *Compounds with Tervalent Stereogenic Atoms.* Atoms with pyramidal bonding[33] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. For example, a secondary or tertiary amine



where X, Y, and Z are different and the fourth group is the electron pair would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until 1968 all of them failed because of *pyramidal inversion* (also called *fluxional inversion*), which is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer.[34] For ammonia, there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonia derivatives[35] (amines, amides, etc.). The interconversion barrier for endo versus exo methyl in *N*-methyl-2-azabicyclo[2.2.1]heptane, for example, is 0.3 kcal mol^{-1} (1.26 kJ mol^{-1}).[36] In this case, torsional strain plays a significant role, along with angle strain, in determining inversion barriers. Two types of nitrogen atom

[27] See Corriu, R.J.P.; Guérin, C.; Moreau, J.J.E. in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 1, Wiley, NY, ***1989***, pp. 305–370; *Top. Stereochem.* ***1984***, *15*, 43; Maryanoff, C.A.; Maryanoff, B.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 355–374.

[28] See Gielen, M. *Top. Curr. Chem.* ***1982***, *104*, 57; *Top. Stereochem.* ***1981***, *12*, 217.

[29] See Davis, F.A.; Jenkins Jr., R.H. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 313–353; Pope, W, J.; Peachey, S.J. *J. Chem. Soc.* ***1899***, *75*, 1127.

[30] Stirling, C.J.M. *J. Chem. Soc.* ***1963***, 5741; Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603; Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2057.

[31] Lowe, G.; Parratt, M.J. *J. Chem. Soc. Chem. Commun.* ***1985***, 1075.

[32] Abbott, S.J.; Jones, S.R.; Weinman, S.A.; Knowles, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 2558; Cullis, P.M.; Lowe, G. *J. Chem. Soc. Chem. Commun.* ***1978***, 512. See Lowe, G. *Acc. Chem. Res.* ***1983***, *16*, 244.

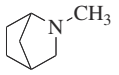
[33] For a review of the stereochemistry at trivalent nitrogen, see Raban, M.; Greenblatt, J. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 53–83.

[34] See Lambert, J.B. *Top. Stereochem.* ***1971***, *6*, 19; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400; Lehn, J.M. *Fortschr. Chem. Forsch.* ***1970***, *15*, 311.

[35] For example, see Stackhouse, J.; Baechler, R.D.; Mislow, K. *Tetrahedron Lett.* ***1971***, 3437, 3441.

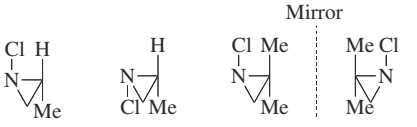
[36] Forsyth, D.A.; Zhang, W.; Hanley, J.A. *J. Org. Chem.* ***1996***, *61*, 1284. Also see, Adams, D.B. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 567.

invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an



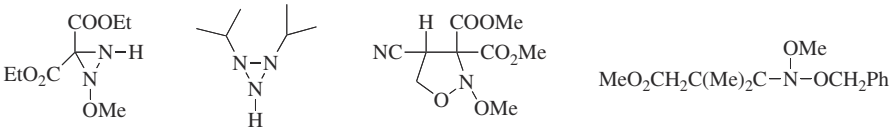
N-Methyl-2-azabicyclo[2.2.1]heptane

unshared pair. Even in such compounds, however, pyramidal inversion proved too rapid to permit isolation of separate isomers for many years. This goal was accomplished[29] only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**5** and **6**) were separated and do not interconvert at room temperature.[37] In suitable cases, this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For example, **7** has been resolved into its separate enantiomers.[38] Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for oxaziridines,[39] diaziridines (e.g., **8**),[40] triaziridines (e.g., **9**),[41] and 1,2-oxazolidines (e.g., **10**),[42] even though in this case the ring is five membered. However, note that the nitrogen atom in **10** is connected to two oxygen atoms.



trans *cis*

5 **6** **7**



8 **9** **10** **11**

[37] Brois, S.J. *J. Am. Chem. Soc.* ***1968***, *90*, 506, 508. See also, Shustov, G.V.; Kadorkina, G.K.; Kostyanovsky, R.G.; Rauk, A. *J. Am. Chem. Soc.* ***1988***, *110*, 1719; Lehn, J.M.; Wagner, J. *Chem. Commun.* ***1968***, 148; Felix, D.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 224. For a review, see Brois, S.J. *Trans. N.Y. Acad. Sci.* ***1969***, *31*, 931.

[38] Schurig, V.; Leyrer, U. *Tetrahedron Asymm.* ***1990***, *1*, 865.

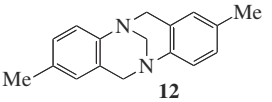
[39] Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1595. See also, Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L.; Di Silvestro, G.D. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 791. See Schmitz, E. *Adv. Heterocycl. Chem.* ***1979***, *24*, 63.

[40] Shustov, G.V.; Denisenko, S.N.; Chervin, I.I.; Asfandiarov, N.L.; Kostyanovsky, R.G. *Tetrahedron* ***1985***, *41*, 5719 and cited references. See also, Mannschreck, A.; Radeglia, R.; Gründemann, E.; Ohme, R. *Chem. Ber.* ***1967***, *100*, 1778.

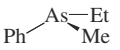
[41] Hilpert, H.; Hoesch, L.; Dreiding, A.S. *Helv. Chim. Acta* ***1985***, *68*, 1691; ***1987***, *70*, 381.

[42] See Wu, G.; Huang, M. *Chem. Rev.* ***2006***, *106,* 2596.

Compound **11** is another example in which nitrogen is connected to two oxygen atoms. In this case there is no ring at all, but it has been resolved into (+) and (−) enantiomers ($[\alpha]_D^{20} \approx \pm 3^\circ$).[43] This compound and several similar ones reported in the same paper are the first examples of compounds whose optical activity is solely due to an acyclic tervalent chiral nitrogen atom. However, **11** is not optically stable and racemizes at 20°C with a half-life of 1.22 h. A similar compound (**11**, with OCH_2Ph replaced by OEt) has a longer half-life, 37.5 h at 20°C.

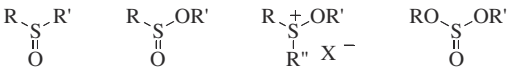


12



13

In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented. Such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **12** (*Tröger's base*) has been prepared.[44] Phosphorus inverts more slowly and arsenic still more slowly.[45] Nonbridgehead phosphorus,[46] arsenic, and antimony compounds have also been resolved (e.g., **13**).[47] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites. Examples of each of these have been resolved.[48] An interesting example is (+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C, but which has $[\alpha]_{280} = +0.71^\circ$.[49] A computational study indicates that base-catalyzed inversion at sulfur in sulfoxides is possible via a tetrahedral intermediate.[50]



4. *Suitably Substituted Adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has been resolved.[51] This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

[43] Kostyanovsky, R.G.; Rudchenko, V.F.; Shtamburg, V.G.; Chervin, I.I.; Nasibov, S.S. *Tetrahedron* ***1981***, *37*, 4245; Kostyanovsky, R.G.; Rudchenko, V.F. *Doklad. Chem.* ***1982***, *263*, 121. See also, Rudchenko, V.F.; Ignatov, S.M.; Chervin, I.I.; Kostyanovsky, R.G. *Tetrahedron* ***1988***, *44*, 2233.

[44] Prelog, V.; Wieland, P. *Helv. Chim. Acta* ***1944***, *27*, 1127.

[45] For reviews, see Yambushev, F.D.; Savin, V.I. *Russ. Chem. Rev.* ***1979***, *48*, 582; Gallagher, M.J.; Jenkins, I.D. *Top. Stereochem.* ***1968***, *3*, 1; Kamai, G.; Usacheva, G.M. *Russ. Chem. Rev.* ***1966***, *35*, 601.

[46] See Valentine, Jr., D.J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 263–312.

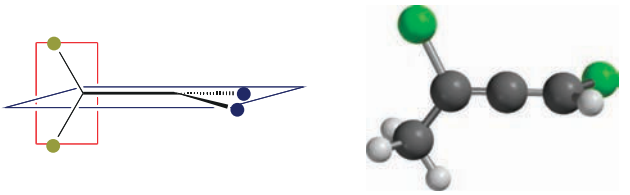
[47] Horner, L.; Fuchs, H. *Tetrahedron Lett.* ***1962***, 203.

[48] See Andersen, K.K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 55–94; and in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 229–312; Barbachyn, M.R.; Johnson, C.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 227–261; Cinquini, M.; Cozzi, F.; Montanari, F. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 355–407; Mikoł/ajczyk, M.; Drabowicz, J. *Top. Stereochem.* ***1982***, *13*, 333.

[49] Andersen, K.K.; Colonna, S.; Stirling, C.J.M. *J. Chem. Soc. Chem. Commun.* ***1973***, 645.

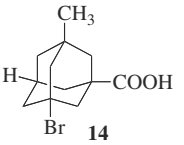
[50] Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* ***2004***, *6,* 2197.

[51] Hamill, H.; McKervey, M.A. *Chem. Commun.* ***1969***, 864; Applequist, J.; Rivers, P.; Applequist, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 5705.



I II

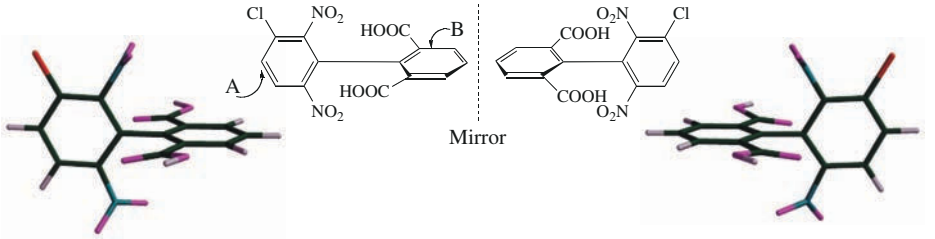
FIG. 4.2. Perpendicular dissymmetric planes and a chiral molecule with no stereogenic center.



14

5. *Restricted Rotation Giving Rise to Perpendicular Disymmetric Planes.* Certain compounds that do not contain asymmetric atoms are nevertheless chiral, as illustrated in Fig. 4.2. For such compounds, there are two perpendicular planes (see **I**), neither of which can be bisected by a plane of symmetry (as illustrated by **II**). If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

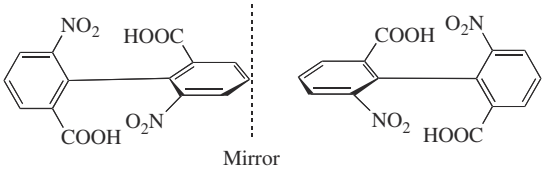
   Biphenyls that contain four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[52] For example, the activation energy (rotational barrier) for the enantiomerization process of the chiral 2-carboxy-2′-methoxy-6-nitrobiphenyl was determined, $\Delta G^{\ddagger} = 21.8 \pm 0.1$ kcal mol^{-1}(91.3 kJ mol^{-1}).[53] In such compounds, the two rings are in perpendicular planes. If either ring is symmetrically substituted, the molecule has a plane of symmetry. For example, consider the biaryls:



   Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; hence, it is a plane of symmetry and the compound is achiral. On the other hand, consider

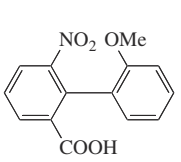
[52] When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, D.M. *Prog. Stereochem.* ***1969***, *4*, 1.

[53] Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron Asymm.* ***2003***, *14*, 3117.

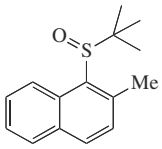


In this molecule, there is no plane of symmetry and the molecule is chiral; many such compounds have been resolved. Note that groups in the para position cannot cause lack of symmetry. Isomers that can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.[54] 9,9′-Bianthryls also show hindered rotation and exhibit atropisomers.[55] Low-temperature NMR is sometimes used to detect atropisomers in certain systems [1,2,4,5-tetra(*o*-tolyl) benzene, e.g.].[56] Configurationally stable atropisomers are known.[57]

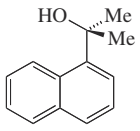
It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2′-bis-sulfonic acid.[58] In some cases, the groups may be large enough to slow rotation greatly, but not to prevent it completely. In such cases, optically active compounds can be prepared that slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.[59] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.[60]



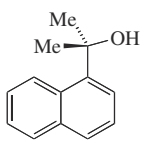
15



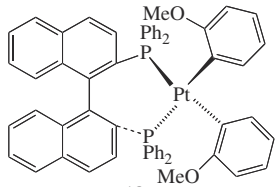
16



17a



17b



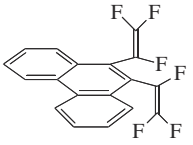
18

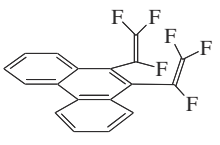
Atropisomerism occurs in other systems as well, including monopyrroles.[61] Sulfoxide (**16**), for example, forms atropisomers with an interconversion barrier with its atropisomer of 18–19 kcal mol^{-1} (75.4–79.5 kJ mol^{-1}).[62] The atropisomers of hindered naphthyl alcohols (e.g., **17**) exist as the *sp*-atropisomer (**17a**) and the *ap*-atropisomer (**17b**).[63] Atropisomers can also be formed in organometallic

[54] For a review, see Öki, M. *Top. Stereochem.* ***1983***, *14*, 1. Also see Miljanić, O.S.; Han, S.; Holmes, D.; Schaller, G.R.; Vollhardt, K.P.C. *Chem. Commun.* ***2005***, 2606.
[55] Becker, H.-D.; Langer, V.; Sieler, J.; Becker, H.-C. *J. Org. Chem.* ***1992***, *57*, 1883.
[56] Lunazzi, L.; Mazzanti, A.; Minzoni, M. *J. Org. Chem.* ***2005***, *70,* 10062.
[57] Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***2005***, *70,* 5098.
[58] Patterson, W.I.; Adams, R. *J. Am. Chem. Soc.* ***1935***, *57*, 762.
[59] Stoughton, R.W.; Adams, R. *J. Am. Chem. Soc.* ***1932***, *54*, 4426.
[60] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**.
[61] Boiadjiev, S.E.; Lightner, S.A. *Tetrahedron Asymm.* ***2002***, *13*, 1721.
[62] Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* ***1993***, *58*, 5674.
[63] See Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* ***2005***, *105*, 1801. For a review of BINOL, see Brunel, J.M. *Chem. Rev.* ***2005***, *105,* 857.

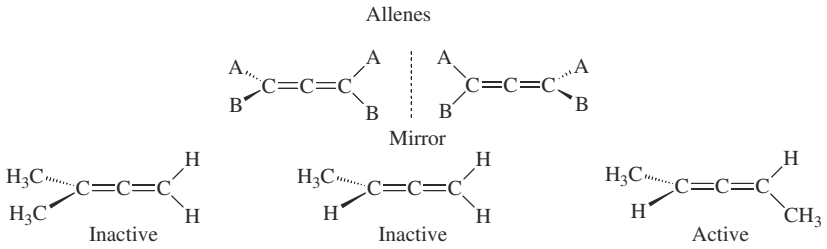
compounds, [e.g., the bis(phosphinoplatinum) complex (see **18**)] generated by reaction with (R)-BINAP [(2R_1 3*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphyl, see Reaction **19-36**].[64]

It is possible to isolate isomers in some cases, often due to restricted rotation. In 9,10-bis(trifluorovinyl)phenanthrene (**19**) torsional diastereomers (see Sec. 4.G) are formed. The value of *K* for interconversion of **19a** and **19b** is 0.48, with $\Delta G^0 = 15.1$ kcal mol^{-1}.[65] The ability to isolate atropisomers can depend on interactions with solvent, as in the isolation of atropisomeric colchicinoid alkaloids, which have been isolated, characterized, and their dichroic behavior described.[66]


19a


19b

In allenes, the central carbon is *sp* hybridized. The remaining two *p* orbitals are perpendicular to each other and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Fig. 4.2. Like biphenyls, allenes are chiral *only* if both sides are unsymmetrically substituted.[67] These cases are completely different from the cis–trans isomerism of compounds with one double bond (Sec. 4.K). In the latter cases, the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.



When a molecule has three, five, or any *odd* number of cumulative double bonds, orbital overlap causes the four groups to occupy one plane and cis–trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes and optical activity is possible. Compound **20** has been resolved.[68]

[64] Alcock, N.W.; Brown, J.M.; Pérez-Torrente, J.J. *Tetrahedron Lett.* ***1992***, *33*, 389. See also, Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J.J.; Yamanaka, M. *Synlett* ***2002***, 1561.

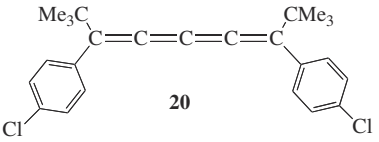
[65] Dolbier Jr., W.R.; Palmer, K.W. *Tetrahedron Lett.* ***1992***, *33*, 1547.

[66] Cavazza, M.; Zandomeneghi, M.; Pietra, F. *Tetrahedron Lett.* ***2000***, *41*, 9129.

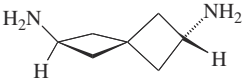
[67] For reviews of allene chirality, see Runge, W. in Landor, S.R. *The Chemistry of the Allenes*, Vol. 3, Academic Press, NY, ***1982***, pp. 579–678, and in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1, Wiley, NY, ***1980***, pp. 99–154; Rossi, R.; Diversi, P. *Synthesis* ***1973***, 25.

[68] Nakagawa, M.; Shingū, K.; Naemura, K. *Tetrahedron Lett.* ***1961***, 802.

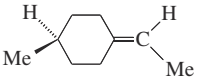
Other types of compounds that contain the system illustrated in Fig. 4.2 and that are similarly chiral if both sides are dissymmetric include spiranes (e.g., **21**), and compounds with exocyclic double bonds (e.g., **22**). Atropisomerism exists in (1,5)-bridgedcalix[8]arenes (see Sec. 3.C.ii).[69]



20

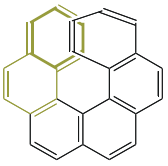


21

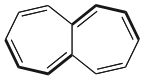


22

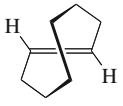
6. *Chirality due to a Helical Shape.*[70] Several compounds have been prepared that are chiral because they have a shape that is actually helical and can therefore be left or right handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right handedness. An example is hexahelicene,[71] in which one side of the molecule must lie above the other because of crowding.[72] The rotational barrier for helicene is ~22.9 kcal mol^{-1}(95.9 kJ mol^{-1}), and significantly higher when substituents are present.[73] It has been shown that the dianion of helicene retains its chirality.[74] Chiral discrimination of helicenes is possible.[75] 1,16-Diazo[6]helicene has also been prepared and, interestingly, does not act as a proton sponge (see Sec. 8.F) because the helical structure leaves the basic nitrogen atoms too far apart. Heptalene is another compound that is not planar (Sec. 2.I.iii). Its twisted structure makes it chiral, but the enantiomers rapidly interconvert.[76]



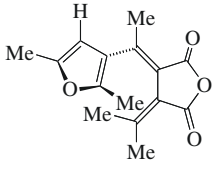
Hexahelicene



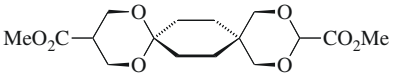
Heptalene



trans-Cyclooctene



23



24a



24b

[69] Consoli, G.M.L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* ***2002***, *4*, 2649.

[70] *For a review, see Meurer, K.P.; Vögtle, F.* Top. Curr. Chem. **1985**, 127*, 1. See also, Laarhoven, W.H.; Prinsen, W.J.C.* Top. Curr. Chem. **1984**, 125*, 63; Martin, R.H.* Angew. Chem. Int. Ed. **1974**, 13*, 649.*

[71] Martin, R.H.; Baes, M. *Tetrahedron* ***1975***, *31*, 2135; Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* ***1973***, *95*, 527; Defay, N.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 313; Bestmann, H.J.; Roth, W. *Chem. Ber.* ***1974***, *107*, 2923.

[72] For reviews of the helicenes, see Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.

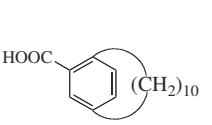
[73] Janke, R.H.; Haufe, G.; Würthwein, E.-U.; Borkent, J.H. *J. Am. Chem. Soc.* ***1996***, *118*, 6031.

[74] Frim, R.; Goldblum, A.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 267.

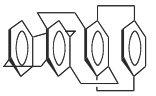
[75] Murguly, E.; McDonald, R.; Branda, N.R. *Org. Lett.* ***2000***, *2*, 3169.

[76] Staab, H.A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* ***1994***, *35*, 8357.

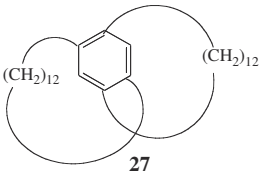
trans-Cyclooctene (see also, Sec. 4.K.i) also exhibits helical chirality because the carbon chain must lie above the double bond on one side and below it on the other.[77] Similar helical chirality also appears in fulgide **23**[78] and dispiro-1,3-dioxane (**24**), shows two enantiomers (**24a** and **24b**).[79]



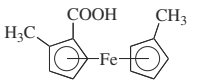
25



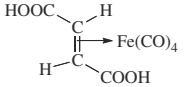
26



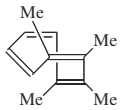
27



28



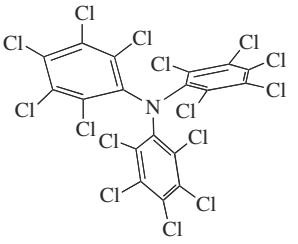
29



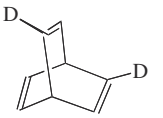
30

7. *Optical Activity Caused by Restricted Rotation of Other Types.* Substituted paracyclophanes may be optically active[80] and **25**, for example, has been resolved.[81] In this case, chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Many chiral layered cyclophanes (e.g., **26**), have been prepared.[82] Another cyclophane[83] with a different type of chirality is [12][12]paracyclophane (**27**), where the chirality arises from the relative orientation of the two rings attached to the central benzene ring.[84] An acetylenic cyclophane was shown to have helical chirality.[85] Metallocenes (Sec. 2.I.ii) substituted with at least two different groups on one ring are also chiral.[86] Several hundred such compounds have been resolved, one being **28**. Chirality is also found in other metallic complexes of suitable geometry.[87] Fumaric acid–iron tetracarbonyl (**29**) has been resolved,[88] and 1,2,3,4-tetramethylcyclooctatetraene (**30**) is also chiral.[89] This molecule, which exists in the tub form (Sec. 2.K), has

[77] Cope, A.C.; Ganellin, C.R.; Johnson, Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. Also see, Levin, C.C.; Hoffmann, R. *J. Am. Chem. Soc.* ***1972***, *94*, 3446.
[78] Yokoyama, Y.; Iwai, T.; Yokoyama, Y.; Kurita, Y. *Chem. Lett.* ***1994***, 225.
[79] Grosu, I.; Mager, S.; Plé, G.; Mesaros, E. *Tetrahedron* ***1996***, *52*, 12783.
[80] For an example, see Rajakumar, P.; Srisailas, M. *Tetrahedron* ***2001***, *57*, 9749.
[81] Blomquist, A.T.; Stahl, R.E.; Meinwald, Y.C.; Smith, B.H. *J. Org. Chem.* ***1961***, *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl, K. *Top. Curr. Chem.* ***1984***, *125*, 27.
[82] Nakazaki, M.; Yamamoto, K.; Tanaka, S.; Kametani, H. *J. Org. Chem.* ***1977***, *42*, 287. Also see, Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron Lett.* ***1996***, *37*, 1273. For an example of a chiral [2.2]-paracyclophane.
[83] For a treatise on the quantitative chirality of helicenes, see Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron Asymm.* ***2000***, *11*, 2695.
[84] Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-k. *J. Chem. Soc. Chem. Commun.* ***1994***, 1971.
[85] Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* ***2000***, *2*, 3189.
[86] For reviews on the stereochemistry of metallocenes, see Schlögl, K. *J. Organomet. Chem.* ***1986***, *300*, 219; *Top. Stereochem.* ***1967***, *1*, 39; *Pure Appl. Chem.* ***1970***, *23*, 413.
[87] For reviews of such complexes, see Paiaro, G. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 319.
[88] Paiaro, G.; Palumbo, R.; Musco, A.; Panunzi, A. *Tetrahedron Lett.* ***1965***, 1067. Also see, Paiaro, G.; Panunzi, A. *J. Am. Chem. Soc.* ***1964***, *86*, 5148.
[89] Paquette, L.A.; Gardlik, J.M.; Johnson, L.K.; McCullough, K.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5026.

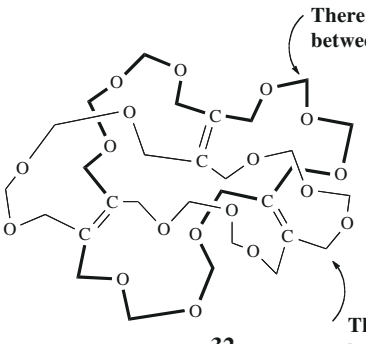


Perchlorotriphenylamine

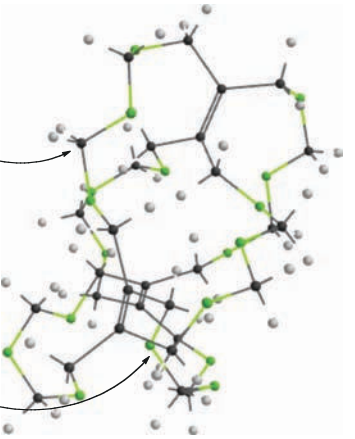


31

neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propeller-shaped perchlorotriphenylamine, which has been resolved.[90] The 2,5-dideuterio derivative (**31**) of barrelene is chiral, though the parent hydrocarbon and the monodeuterio derivative are not. Compound **25** has been prepared in optically active form[91] and is another case where chirality is due to isotopic substitution.



32



33

The main molecular chain in compound **32** has the form of a Möbius strip (see Fig. 15.7 and 3D model **33**).[92] This molecule has no stereogenic carbons, nor does it have a rigid shape, a plane, nor an alternating axis of symmetry. However, **32** has been synthesized and shown to be chiral.[93] Rings containing 50 or more members should be able to exist as knots (**34**, and see **39** on Sec. 3.D). Such a knot would be nonsuperimposable on its mirror image. Calixarenes,[94] crown ethers,[95] catenanes, and rotaxanes (see Sec. 3.D) can also be chiral if suitably substituted.[96] For example, **40** and **41** are nonsuperimposable mirror images.

[90] Okamoto, Y.; Yashima, E.; Hatada, K.; Mislow, K. *J. Org. Chem.* ***1984***, *49*, 557. See Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* ***2001***, *66*, 488.

[91] Lightner, D.A.; Paquette, L.A.; Chayangkoon, P.; Lin, H.; Peterson, J.R.*J. Org. Chem.* ***1988***, *53*, 1969.

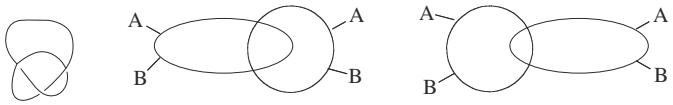
[92] See Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161.

[93] Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* ***1982***, *104*, 3219.

[94] Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* ***1995***, *36*, 8969.

[95] de Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; van der Gen, A. *J. Org. Chem.* ***1993***, *58*, 4315; Pappalardo, S.; Palrisi, M.F. *Tetrahedron Lett.* ***1996***, *37*, 1493; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 7627.

[96] See Schill, G. *Catenanes*, *Rotaxanes*, *and Knots*, Academic Press, NY, ***1971***, pp. 11–18.



34 **35** **36**

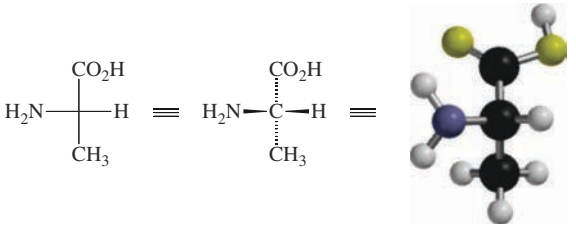
A stereogenic center may be created from an achiral molecule via a chemical reaction. One example is the α-bromination of a carboxylic acid (Hell–Volhardt–Zelenskii reaction, **12-05**) to form the α-bromo acid.

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

In this case, the α-carbon in the product is the stereogenic carbon. If there are no asymmetric components in the reaction, the product must be racemic. This means that no optically active material can be created if all starting materials and conditions are optically inactive.[97] This statement also holds when one begins with a racemic mixture, unless there is kinetic resolution (Sec. 4.I). Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

4.C. THE FISCHER PROJECTION

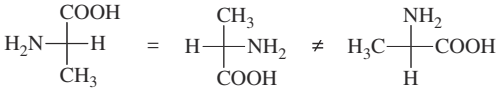
For a thorough understanding of stereochemistry, it is useful to examine molecular models (like those depicted in Fig. 4.1). However, this is not feasible when writing on paper. In 1891, Emil Fischer displayed amino acids and some carbohydrates in a particular way known as a *Fischer projection*. This is simply a method of representing and "edge-viewed" tetrahedral on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical, as shown for 2-aminopropanoic acid (alanine). With modern computers, molecular models are readily available, but the ability to write structures in two dimensions to represent a 3D form remains important.



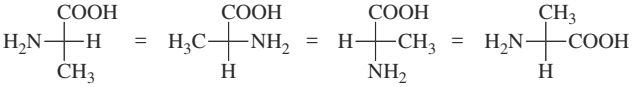
In order to obtain proper results with these formulas, remember that they are projections and must be treated differently from the models in testing for superimposability. Every

[97] There is one exception to this statement. In a very few cases, racemic mixtures may crystalize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock, R.E.; Wilson, K.R. *J. Chem. Educ.* ***1973***, *50*, 455.

plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also, they may not be rotated 90°, although 180° rotation is permissible:



It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):

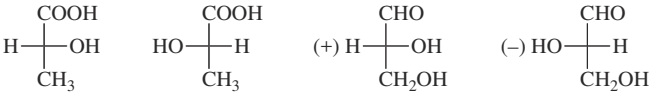


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models, as well as to the Fischer projections).

With these restrictions Fischer projections may be used instead of models to test whether a molecule containing a stereogenic carbon is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than chiral atoms (category 5 in Sec. 4.C).

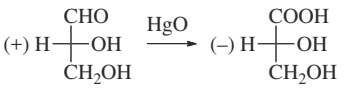
4.D. ABSOLUTE CONFIGURATION

Suppose there are two test tubes, one containing (−)-lactic acid and the other the (+) enantiomer. One test tube contains **37** and the other **38**. How can they be distinguished?



37 **38** **39** **40**

To generate a model to answer this question, Rosanoff proposed that one compound be chosen as a standard and a configuration arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **39** and given the label D. The (−) isomer, designated to be **39**, was given the label L. With a standard, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with

the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way, many thousands of compounds were related, indirectly, to D- or L-glyceraldehyde. It was determined that **37**, which has the D configuration, is the isomer that rotates the plane of polarized light to the left. Even compounds without asymmetric atoms (e.g., biphenyls and allenes), have been placed in the D or L series.[98] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.[99]

In 1951, it became possible to determine that Rosanoff's guess was right. Ordinary X-ray crystallography cannot distinguish between a D and a L isomer, but by use of a special technique, Bijvoet et al.[100] was able to examine sodium rubidium tartrate, compared it with glyceraldehyde, and found that Rosanoff had made the correct choice. It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. This method does not apply to all compounds that have a stereogenic center, but only those that can be structurally related to glyceraldehyde. The DL system is rarely used, therefore, except for certain groups of compounds (e.g., carbohydrates and amino acids). A more general model is required to distinguish the stereogenic centers of enantiomers.

4.D.i. The CAHN–INGOLD–PRELOG System

The system that is used universally is the *Cahn–Ingold–Prelog* system (or the CIP system), in which the four groups on a stereogenic carbon are ranked (prioritized) according to a set of sequence rules.[101] For the most part, only a few of these rules are sufficient to deal with the vast majority of chiral compounds.

1. Prioritize substituents in order of decreasing atomic number of the atom directly joined to the carbon.

[98] The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[99] For lists of absolute configurations of thousands of compounds, with references, mostly expressed as (*R*) or (*S*) rather than D or L, see Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*, 2nd ed., 2 Vols., Oxford University Press, Oxford, ***1978***; Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M.J.; Toullec, J. *Absolute Configurations* (Vol. 4 of Kagan, H. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***.

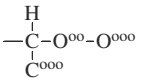
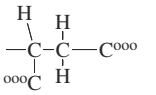
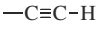
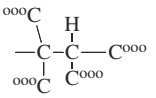
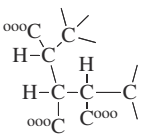
[100] Bijvoet, J.M.; Peerdeman, A.F.; van Bommel, A.J. *Nature (London)* ***1951***, *168*, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Neidle, S.; Rogers, D.; Allen, F.H. *J. Chem. Soc. C* ***1970***, 2340.

[101] For descriptions of the system and sets of sequence rules, see *Pure Appl. Chem.* ***19767***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book); Cahn, R.S.; Ingold, C.K.; Prelog, V. *Angew. Chem. Int. Ed.* ***1966***, *5*, 385; Cahn, R.S. *J. Chem. Educ.* ***1964***, *41*, 116; Fernelius, W.C.; Loening, K.; Adams, R.M. *J. Chem. Educ.* ***1974***, *51*, 735. See also, Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 567. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 101–147. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 15–23.

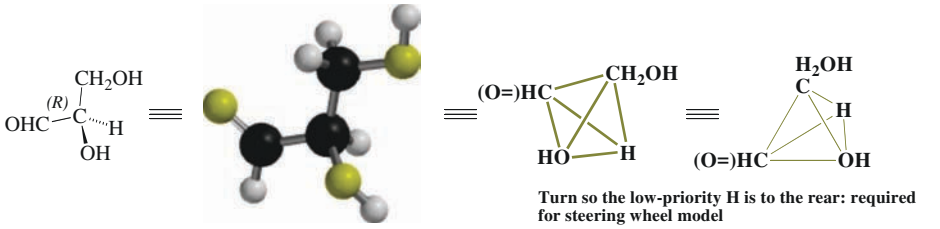
2. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (e.g., ^{14}C) takes precedence over any lower one.
3. Where two or more of the atoms connected to the stereogenic carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule $Me_2CH–CHBr–CH_2OH$, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even though there are two carbons in Me_2CH, and only one oxygen in CH_2OH. If two or more atoms connected to the second atom are the same, the third atom determines the precedence, and so on.
4. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms (designated by a subscript 0) are used to bring the valence up to 4. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $—^{+}NHMe_2$ ranks higher than $—NMe_2$.
5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in the examples in Table 4.1 (note the treatment of the phenyl group). Note that in a C=C double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

Using the four groups in Table 4.1 (aldehyde, vinyl, alkynyl, phenyl), the first atoms are connected, respectively, to (H, O, O), (H, C, C), (C, C, C), and (C, C, C). That is enough to establish that —CHO ranks first and $—CH=CH_2$ last, since even one oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups, proceed further along the chains. Note that $—C_6H_5$ has two of its (C, C, C) carbons connected to (C, C, H), while the third is $(_{000})$ and is thus preferred to —C≡CH, which has only one (C, C, H) and two $(_{000})$s.

TABLE 4.1 How Four Common Groups Are Treated in the Cahn–Ingold–Prelog System

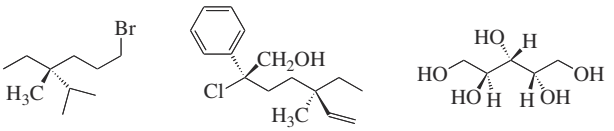
Group	Treated as if it Were	Group	Treated as if it Were
			
			

By application of the above rules, some groups in descending order of precedence are COOH, COPh, COMe, CHO, $CH(OH)_2$, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, C≡CH, *tert*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, and hydrogen. Using the CIP rules, the four groups of glyceraldehyde are arranged in the sequence: OH, CHO, CH_2OH, H.



Once the order is determined, a model is required to determine the absolute configuration (i.e., which structure correlates to which enantiomer). The model used is known as the *steering wheel model,* where the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Once the lowest priority group is held in that position, if the other groups, in the order listed, are oriented clockwise, the molecule is designated (*R*), and if counterclockwise (*S*). For glyceraldehyde, the (+) enantiomer is shown here and the CIP rules and the steering wheel model was used to assign an absolute configuration of (*R*).

The CIP rules and steering wheel model are used to assign an absolute configuration to the following molecules. In **A**, the isopropyl carbon is higher in priority than the bromine-containing chain, and the methyl group is the lowest priority. Turning the molecule to place the methyl group to the rear makes this an (*R*) configuration. In **B**, there are two stereogenic centers, where the (*S*) center has the chain containing the (*R*) center as the lowest priority, and the (*R*) center has the methyl group as the low priority. In **C**, there are two (*S*) centers, but the hydroxyl-bearing carbon in the middle of the molecule is *not* a stereogenic carbon. Close inspection of **C** shows that this carbon has two identical groups [$CH(OH)CH_2OH$].

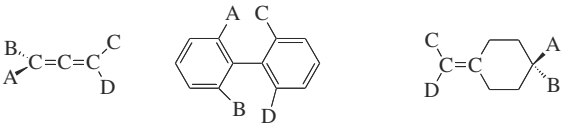


A **B** **C**

The CIP system is unambiguous and easily applicable in most cases. The CIP system also has been extended to chiral compounds that do not contain stereogenic centers, but rather have a chiral axis.[102] Compounds having a chiral axis include unsymmetrical allenes, biaryls that exhibit atropisomerism (see Sec. 4.C, category 5), and alkylidene cyclohexane derivatives, molecular propellers and gears, helicenes, cyclophanes, annulenes, *trans*-cycloalkenes, and metallocenes. A series of rules have been proposed to address these cases based on what is called an "extended tetrahedron mode", but the rules can be ambiguous in the case of cyclophanes and a few other systems.[103]

[102] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds,* Wiley, NY, ***1994***, pp. 1119–1190. See Krow, G. *Top. Stereochem.* ***1970***, *5*, 31.

[103] Mata, P.; Lobo, A.M.; Marshall, C.; Johnson, A.P. *Tetrahedron Asymm.* ***1993***, *4*, 657; Perdih, M.; Razinger, M. *Tetrahedron Asymm.* ***1994***, *5*, 835.



Allenes Biaryls Alkylidenecyclohexanes

4.D.ii. Methods of Determining Configuration[104]

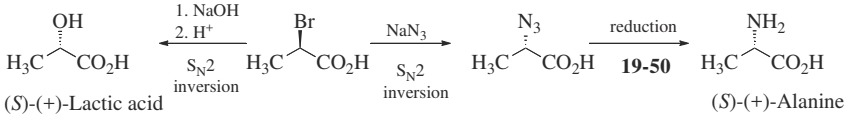
In all the methods,[105] it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this follow:

1. *Conversion of the Unknown to, or Formation of the Unknown from, a Compound of Known Configuration Without Disturbing the Stereogenic Center.* The glyceraldehyde–glyceric acid example above is



one example. The stereogenic center was not disturbed, and the configuration of the product (glyceric acid) is the same as the starting material (glyceraldehyde). Retention of the same absolute configuration such as with glyceraldehyde-to-glyceric acid is not always the case. If the reaction sequence does not disturb (change) the stereogenic center, the absolute configuration depends on the nature of the groups. For example, when (*R*)-1-bromo-2-butanol is reduced to 2-butanol without disturbing the stereogenic center, the product is the (*S*) enantiomer because CH_3CH_2 ranks lower than $BrCH_2$, but higher than CH_3.

2. *Conversion at the Stereogenic Center if the Mechanism is Known.* An S_N2 mechanism proceeds with inversion of configuration at a stereogenic carbon (Sec. 10.A.i). Indeed, a series of such transformations allowed the stereogenic center in lactic acid to be correlated to that in alanine.

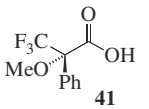


3. *Biochemical Methods.* In a series of similar compounds (e.g., amino acids or certain types of steroids), a given enzyme will usually attack only molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will demonstrate that it is also the L form.

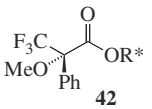
[104] See Kagan, H.B. *Determination of Configuration by Chemical Methods* (Vol. 3 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Brewster, J.H. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 1–249; Klyne, W.; Scopes, P.M. *Prog. Stereochem.* **1969**, *4*, 97; Schlenk, Jr., W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 139. Also see Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* ***1986***, *16*, 1.

[105] Except the X-ray method of Bijvoet.

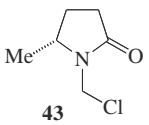
4. *Optical Comparison.* It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also, certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system (e.g., a steroid).
5. *The Special X-Ray Method of Bijvoet.* This method gives direct answers and has been used in a number of cases.[86]
6. *Derivatize the Alcohol with a Chiral Nonracemic Reagent and Examine the Ratio of Resulting Diastereomers by Gas Chromatography.*[106] This methods is one of the most useful for determining enantiomeric composition. Many derivatizing agents are available, but one class widely used are derivatives of α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, *Mosher's acid*, **41**).[107] Reaction with a chiral nonracemic alcohol (R^*OH) generates a *Mosher's ester* (**42**) that can be analyzed for diastereomeric composition by ^1H or ^{19}F NMR, as well as by chromatographic techniques.[108] Complexation with lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.[109] This NMR method, as well as other related methods,[110] are effective for determining the absolute configuration of an alcohol of interest (R^*OH, where R^* is a group containing a stereogenic center).[111] Two, of many other reagents that have been developed to determine the enantiopurity of alcohols and amines, include **43** and **44**. Chloromethyl lactam (**43**) reacts with R^*OH or R^*NHR (R^*NH_2),[112] forming derivatives that allow analysis by ^1H NMR and **44** reacts with alkoxides (R^*O^-)[113] to form a derivative that can be analyzed by ^{31}P NMR. For a more detailed discussion of methods to determine optical purity, see Section 4.J.



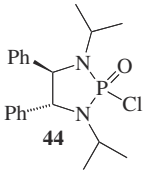
41



42



43



44

[106] *Parker, D.* Chem. Rev. **1991**, 91, *1441.*
[107] Dale, J. A.; Dull, D.L.; Mosher, H. S. *J. Org. Chem.* ***1969***, *34*, 2543; Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512.
[108] See Mori, K.; Akao, H. *Tetrahedron Lett.* ***1978***, 4127; Plummer, E.L.; Stewart, T.E.; Byrne, K.; Pearce, G.T.; Silverstein, R.M. *J. Chem. Ecol.* ***1976***, *2*, 307. See also, Seco, J.M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymm.* ***2000***, *11,* 2695.
[109] Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* ***1976***, *32*, 1363; Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* ***1980***, *21*, 2827; Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* ***1977***, 89.
[110] Latypov, S.K.; Ferreiro, M.J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* ***1998***, *120*, 4741; Latypov, S.K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* ***1995***, *60*, 1538.
[111] Seco, J.M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* ***2004***, *104*, 17.
[112] Smith, M.B.; Dembofsky, B.T.; Son, Y.C. *J. Org. Chem.* ***1994***, *59*, 1719; Latypov, S.K.; Riguera, R.; Smith, M. B.; Polivkova, J. *J. Org. Chem.* ***1998***, *63*, 8682. For a chiral compound used to determine the enantiomeric purity of primary amines, see Pérez-Fuertes, Y.; Kelly, A.M.; Johnson, A.L.; Arimori, S.; Bull, S.D.; James, T.D. *Org. Lett.* ***2006***, 8, *609.*
[113] Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* ***1992***, *57*, 1224.

7. *Other Methods.* Other method have also been used for determining absolute configuration in a variety of molecules, including optical rotatory dispersion,[114] circular dichroism (CD),[115] and asymmetric synthesis (Sec. 4.H). Optical rotatory dispersion (ORD) is a measurement of specific rotation [α] as a function of wavelength.[116] The change of specific rotation [α] or molar rotation [Φ] with wavelength is measured, and a plot of either versus wavelength is often related to the sense of chirality or the substance under consideration. In general, the absolute value of the rotation increases as the wavelength decreases. The plot of CD is the differential absorption of left and right circularly polarized radiation by a nonracemic sample, taking place only in spectral regions in which absorption bands are found in the isotropic UV or visible (vis) electronic spectrum.[117] The primary application of both ORD and CD is for the assignment of configuration or conformation.[118] Configurational and conformational analyses have been carried out using IR and vibrational circular dichroism (VCD) spectroscopies.[119]

   One example, and one of the more effective methods for derivatizing 1,2-diols, is the method employing dimolybdenum tetraacetate [$Mo_2(AcO)_4$] developed by Snatzke and Frelek.[120] Exposure of the resulting complex to air leads, in most cases, to a significant induced CD spectrum (known as ICD). The method can be used for a variety of 1,2-diols.[121]

8. *NMR Dabtabases.* Kishi and co-worker's[122] developed an NMR database[123] of various molecules in chiral solvents, for the assignment of relative and absolute stereochemistry without derivatization or degradation. Kishi referred to this database as a "universal NMR database."[124] The diagram provided for diols **45** illustrates the method (see Fig. 4.3). The graph presents the difference in

[114] See Ref. 277 for books and reviews on optical rotatory dispersion and CD. For predictions about anomalous ORD, see Polavarapu, P.L.; Zhao, C. *J. Am. Chem. Soc.* ***1999***, *121*, 246.

[115] Gawronski, J.; Grajewski, J. *Org. Lett.* ***2003***, *5*, 3301. See Ref. 277; Stephens, P.J.; Aamouche, A.; Devlin, F.J.; Superchi, S.; Donnoli, M.I.; Rosini, C. *J. Org. Chem.* ***2001***, *66*, 3671; McCann, D.M.; Stephens, P.J. *J. Org. Chem.* ***2006***, *71,* 6074.

[116] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1203, 999–1003.

[117] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1195, 1003–1007.

[118] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1007–1071; Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications*, VCH, NY, ***1994***; Purdie, N.; Brittain, H.G. *Analytical Applications of Circular Dichroism*, Elsevier, Amsterdam, The Netherlands, ***1994***.

[119] Devlin, F.J.; Stephens, P.J.; Osterle, C.; Wiberg, K.B.; Cheeseman, J.R.; Frisch, M.J. *J. Org. Chem.* ***2002***, *67,* 8090.

[120] Frelek, J.; Geiger, M.; Voelter, W. *Curr. Org. Chem.* ***1999***, *3,* 117–146 and references cited therein; Snatzke, G.; Wagner, U.; Wolff, H. P. *Tetrahedron* ***1981***, *37,* 349; Pakulski, Z.; Zamojski, A. *Tetrahedron Asymm.* ***1996***, *7,* 1363; Frelek, J.; Ikekawa, N.; Takatsuto, S.; Snatzke, G. *Chirality* ***1997***, *9,* 578.

[121] Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* ***2001***, *66*, 4819.

[122] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245; Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2249; Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2253.

[123] For another protocol, see Dambruoso, P.; Bassarello, C.; Bifulco, G.; Appendino, G.; Battaglia, A.; Fontana, G.; Gomez-Paloma, L. *Org. Lett.* ***2005***, *7,* 983.

[124] Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 2076.

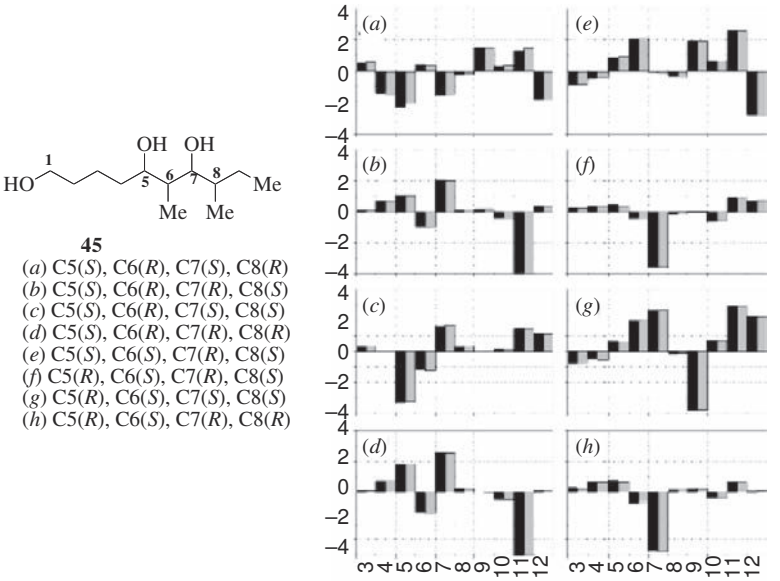


FIG. 4.3. Proton NMR analysis for assignment of stereochemistry.

carbon chemical shifts between the average and the values for **45** (100 MHz) in DMBA (*N*,α-dimethylbenzylamine). Spectra were recorded in both enantiomers of the solvent, where the solid bar was recorded in (*R*)-DMBA and the shaded bar in (*S*)-DMBA. The *x*- and *y*-axes represent the carbon number and Δδ ($\delta_{\mathbf{45a–h}}$ - δ_{ave} in ppm), respectively. The graphs are taken from "the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA, but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can be used for prediction of the relative stereochemistry of structural motifs in an intact form."[125]

A ^{1}H NMR analysis method has been developed that leads to the assignment of the stereochemistry of β-hydroxy ketones, by visual inspection of the ABX patterns for the (*R*)-methylene unit of the β-hydroxyketones.[126] Since β-hydroxy ketones are derived from the aldol reaction (**16-34**), this method is particularly useful in organic synthesis. A method has also been developed that uses ^{13}C NMR to determine the relative stereochemistry of 2,3-dialkylpentenoic acids.[127]

[125] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245.
[126] Roush, W.R.; Bannister, T.D.; Wendt, M.D.; VanNieuwenhze, M.S.; Gustin, D.J.; Dilley, G.J.; Lane, G.C.; Scheidt, K.A.; Smith, III, W.J. *J. Org. Chem.* ***2002***, *67*, 4284.
[127] Hong, S.-p.; McIntosh, M.C. *Tetrahedron* ***2002***, *57,* 5055.

4.E. THE CAUSE OF OPTICAL ACTIVITY

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known, and in a greatly simplified form may be explained as follows.[128]

Whenever any light hits any molecule in a transparent material, the light is slowed because of interactions with the molecule. This phenomenon on a gross scale is responsible for the refraction of light, and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left and the other is a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has a different polarizability depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other toward it, resulting in rotation of the plane. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been devised,[129] and have given fairly good results in many cases.

In liquids and gases, the molecules are randomly oriented. A molecule that is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane, but all others not oriented in that manner do rotate the plane, even though the molecules are achiral. There is no net rotation because even though the molecules are present in large numbers and randomly oriented, there will always be another molecule later on in the path of the light that is oriented exactly opposite and will rotate the plane back again. Even if nearly all molecules rotate the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present and there is a net rotation.

An interesting phenomenon was observed when the CD of chiral molecules was measured in achiral solvents. The chiral solvent contributed as much as 10–20% to the

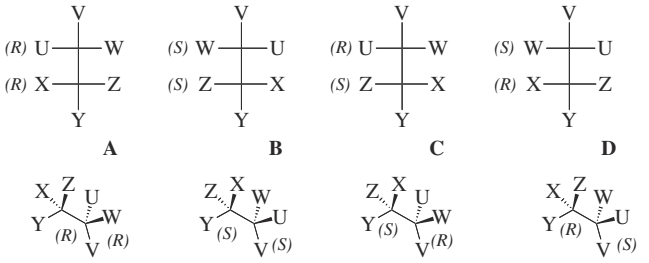
[128] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 93–94, 992–999; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 204–211; Caldwell, D.J.; Eyring, H. *The Theory of Optical Activity* Wiley, NY, ***1971***; Buckingham, A.D.; Stiles, P.J. *Acc. Chem. Res.* ***1974***, *7*, 258; Mason, S.F. *Q. Rev. Chem. Soc.* ***1963***, *17*, 20.

[129] Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Sathyanarayana, B. K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

CD intensity in some cases. Apparently, the chiral compound can induce a solvation structure that is chiral, even when the solvent molecules themselves are achiral.[130]

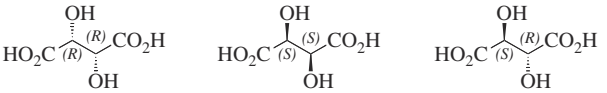
4.F. MOLECULES WITH MORE THAN ONE STEREOGENIC CENTER

When a molecule has two stereogenic centers, each has its own configuration and can be classified (*R*) or (*S*) by the CIP method. There are a total of four isomers, since the first center may be (*R*) or (*S*) and so may the second. Each is drawn as both the Fischer projection and in the extended conformation. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **A**. This enantiomer is **B** [the mirror image of an (*R*) center is *always* an (*S*) center]. Both **C** and **D** are a second pair of enantiomers and the relationship of **C** and **D** to **A** and **B** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers that are not enantiomers (they are stereoisomers that are not mirror images, and not superimposable)*. Since **C** and **D** are enantiomers, they must have identical properties, except as noted in Section 4.A, and the same is true for **A** and **B**. However, the properties of **A** and **B** are not identical with those of **C** and **D**. They are different compounds, which means that they have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. The properties are usually *similar*, but not *identical*. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (an example is presented below).



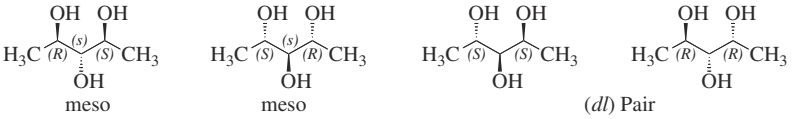
It is now possible to see why, as mentioned in Section 4.A, enantiomers react at different rates with other chiral molecules, but at the same rate with achiral molecules. In the latter case, the activated complex formed from the (*R*) enantiomer and the other molecule is the mirror image of the activated complex formed from the (*S*) enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an (*R*) enantiomer reacts with a chiral molecule that has, say, the (*R*) configuration, the activated complex has two chiral centers with configurations (*R*) and (*R*), while the activated complex formed from the (*S*) enantiomer has the configurations (*S)* and (*R*). The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

[130] Fidler, J.; Rodger, P.M.; Rodger, A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 235.



The three stereoisomers of tartaric acid

Although four is the maximum possible number of isomers when the compound has two stereogenic centers (chiral compounds without a stereogenic carbon, or with one stereogenic carbon and another type of stereogenic center, also follow the rules described here), some compounds have fewer. When the three groups on one stereogenic atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry, and hence is optically inactive, even though it has two stereogenic carbons. Tartaric acid is a typical case. As shown, there are only three isomers of tartaric acid: a pair of enantiomers and an inactive meso form. For compounds that have two stereogenic atoms, *meso forms are found only where the four groups on one of the chiral atoms are the same as those on the other chiral atom.*



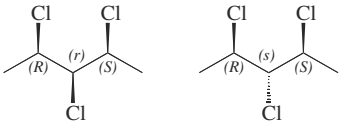
In compounds with two or more stereogenic centers, the maximum number of isomers can be calculated from the formula 2^n, where n is the number of stereogenic centers. The actual number may be less than this, owing to meso forms,[131] but never more. An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both (*R*) [or both (*S*)]; labeled the *dl* pair. The compound when one of them is (*R*) and the other (*S*) is asymmetric (labeled meso). The middle carbon in such compounds is called a *pseudoasymmetric* carbon. In such cases, there are four isomers: two *meso* forms and one *dl* pair. Remember that the meso forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers that have a different configuration at only one chiral center are called *epimers*.

The small letters used for the psuedoasymmetric center are assigned using established rules. An atom that is tetrahedrally substituted and bonded to four different entities, two and only two of which have opposite configurations, is stereogenic. The descriptors "*r*" and "*s*" are used to denote such centers; they are assigned in accordance with Sequence Rule 5, taking into consideration that "(*R*)" has precedence over "(*S*)" in the order of priority.[132] Step 1: configuration "(*R*)" or "(*S*)" is assigned to stereogenic centers C-2 and C-4; Using 1,2,3-trichloropentane as an example, Step 2: Configuration at C-3 is assigned by applying sequence rule, "(*R*)" precedes "(*S*)", and if (*R*) precedes (*S*), then Cl is the highest priority, followed by (*R*) and then (*S*): C-3 is *r*. The exchange of the

[131] For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse, J.G.; Carhart, R.E.; Smith, D.H.; Djerassi, C. *J. Am. Chem. Soc.* ***1979***, *101*, 1216; ***1980***, *102*, 6289.

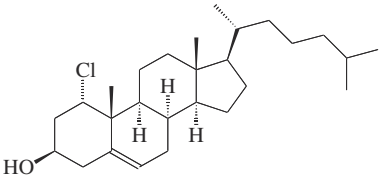
[132] Available at http://old.iupac.org/reports/provisional/abstract04/favre_310305.html, *Preferred IUPAC Names*, Chapter 9, September, 2004, p. 6.

Cl and H atoms at C-3 of the compound on the left generates the compound on the right, and "3*r*" becomes "3*s*"



In compounds with two or more steroegenic centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed in Section 4.E.ii, and then to relate the configuration at that center to the others in the molecule. One method is X-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any stereogenic center. This method does give *relative configurations* of all the stereogenic centers in a molecule, and if the absolute configuration of one stereogenic center is independently determined, the absolute configurations of all are then known. Other physical and chemical methods have also been used for this purpose.

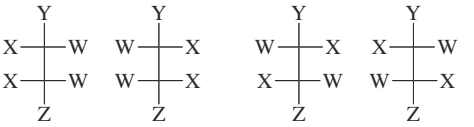
How to name the different stereoisomers of a compound when there are more than two is potentially a problem.[2] Enantiomers have the same IUPAC name, being distinguished by (*R*) and (*S*) or D and L or (+) or (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name or at least a different prefix (e.g., *epi-*, *peri-*, etc.). Thus the aldohexoses are called glucose, mannose, idose, and so on, although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge about which isomers had which configurations.[133] Today it is customary to describe *each chiral position* separately as either (*R*) or (*S*) or, in special fields, to use other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are typically used to depict β groups and dashed lines for α groups. An example is 1α-chloro-5-cholesten-3β-ol, showing the OH group on the top side of the molecule (up) and the chlorine atom on the bottom side (down).



1α-Chloro-5-cholesten-3β-ol

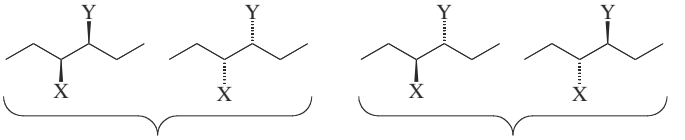
For many open-chain compounds, prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are *erythro-* and *threo-*, which are applied to systems containing two stereogenic carbons when two of the

[133] A method has been developed for the determination of stereochemistry in six-membered chair-like rings using residual dipolar couplings. See Yan, J.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Zartler, E. R. *J. Org. Chem.* ***2003***, *68,* 1786.



Erythro *dl* pair Threo *dl* pair

groups are the same and the third is different.[134] The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair. Another system[135] for designating stereoisomers[136] uses the terms *syn* and *anti*. The "main chain" of the molecule is drawn in the common zigzag manner. Then if two non-hydrogen substituents are on the same side of the plane defined by the main chain, the designation is syn; otherwise it is anti.



syn *dl* pair anti *dl* pair

4.G. ASYMMETRIC SYNTHESIS

Organic chemists often wish to synthesize a chiral compound in the form of a single enantiomer or diastereomer, rather than as a mixture of stereoisomers. There are two basic ways in which this can be done.[137] The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the stereogenic center (or centers). The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (Sec. 4.I). If possible, the starting material is obtained from Nature, since many compounds (e.g., amino acids, sugars, and steroids), are present in Nature in the form of a single enantiomer or diastereomer. These compounds have been referred to as a *chiral pool;* that is, readily available compounds that can be used as starting materials.[138] This term is not used much now.

[134] See Carey, F.A.; Kuehne, M.E. *J. Org. Chem.* ***1982***, *47*, 3811; Boguslavskaya, L.S. *J. Org. Chem. USSR* ***1986***, *22*, 1412; Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654; Brewster, J.H. *J. Org. Chem.* ***1986***, *51*, 4751. See also, Tavernier, D. *J. Chem. Educ.* ***1986***, *63*, 511; Brook, M.A. *J. Chem. Educ.* ***1987***, *64*, 218.

[135] For still another system, see Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654.

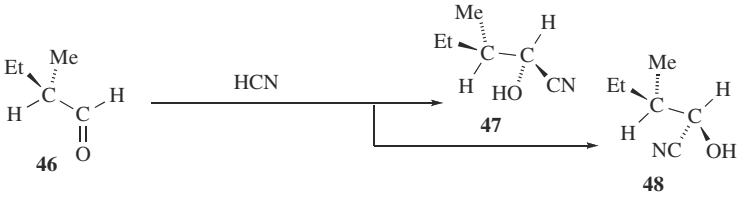
[136] Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* ***1982***, *104*, 5521.

[137] See Morrison, J.D.; Scott, J.W. *Asymmetric Synthesis*, Vol. 4; Academic Press, NY, ***1984***; Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon, Elmsford, NY, ***1989***; Crosby, J. *Tetrahedron* ***1991***, *47*, 4789; Mori, K. *Tetrahedron* ***1989***, *45*, 3233.

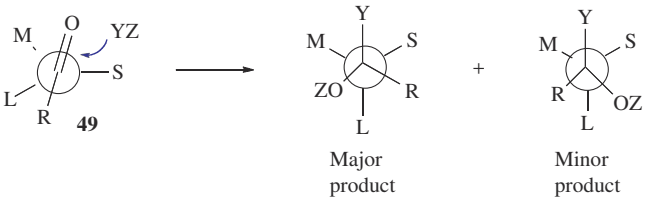
[138] See Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis*, Wiley, NY, ***1987***; Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Elmsford, NY, ***1983***; Hanessian, S. *Aldrichim. Acta* ***1989***, *22*, 3; Jurczak, J.; Gotebiowski, A. *Chem. Rev.* ***1989***, *89*, 149.

The other basic method is called *asymmetric synthesis*,[139] or *stereoselective synthesis*. As mentioned earlier, optically active materials cannot be created from inactive starting materials and conditions, except in the manner previously noted.[97] However, when a new stereogenic center is created, the two possible enantiomers need not be formed in equal amounts if anything is present that is not symmetric. Asymmetric synthesis may be categorized into four headings:

1. *Active Substrate.* If a new stereogenic center is created in a molecule that is already optically active, the product will generate diastereomers and the two diastereomers may not (except fortuitously) be formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon–oxygen double bond of ketones containing an asymmetric α carbon, *Cram's rule* predicts which of two diastereomers will predominate (diastereoselectivity).[140,141] The reaction of **46**, which has a stereogenic center at the α-carbon, and HCN can generate two possible diastereomers (**47** and **48**).



If **46** is observed along its axis, it may be represented as in **49** (Sec. 4.O.i), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl orients itself between the small- and the medium-sized groups. The rule requires that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **48** will be formed in larger amounts than **47**.

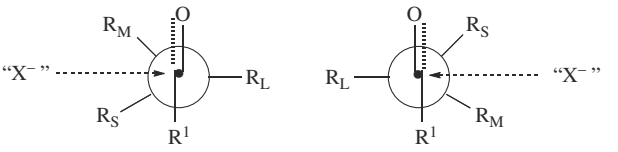


[139] See Morrison, J.D. *Asymmetric Synthesis* 5 Vols. [Vol. 4 coedited by Scott, J.W.], Academic Press, NY, ***1983–1985***; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***; Eliel, E.L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry,* American Chemical Society, Washington, ***1982***; Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, NJ, ***1971***, paperback reprint, American Chemical Society, Washington, ***1976***. For reviews, see Ward, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 1; Whitesell, J. K. *Chem. Rev.* ***1989***, *89*, 1581; Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* ***1989***, *45*, 1; Kochetkov, K.A.; Belikov, V.M. *Russ. Chem. Rev.* ***1987***, *56*, 1045; Oppolzer, W. *Tetrahedron* ***1987***, *43*, 1969; Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods*, ***1986***, *4*, 125; ApSimon, J.W.; Collier, T.L. *Tetrahedron* ***1986***, *42*, 5157.

[140] Leitereg, T.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4019. For discussions, see Anh, N.T. *Top. Curr. Chem*, ***1980***, *88*, 145, pp. 151–161; Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155. See Smith, R.J.; Trzoss, M; Bühl, M.; Bienz, S. *Eur. J. Org. Chem.* ***2002***, 2770.

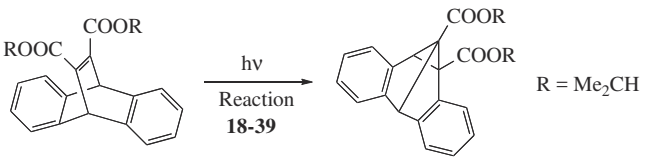
[141] See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, pp. 22–28; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

Another model uses transition state models **50** and **51** to predict diastereoselectivity in what is known as the *Felkin–Anh model*.[142]. This model assumes the favored transition state will be that with the greatest separation between the incoming group and any electronegative substituent at the α-carbon. The so-called *Cornforth model* has also been presented as a model for carbonyl addition to halogenated compounds,[143] and it assumes that the electron pairs on the carbonyl oxygen and on the halogen repel and assume an anti-conformation.



50 **51**

Many reactions of this type are known, and in some the extent of favoritism approaches 100% (e.g., see Reaction **12-12**).[144] The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed. There are many examples of asymmetric induction via nucleophilic acyl addition to carbonyl compounds (Reactions **16-24** and **16-25**). Enolborane addition to α-heteroatom substituted aldehydes has been evaluated using the Cornforth and the Felkin–Anh models.[145]



Not chiral Optically active

52 **53**

In a special case of this type of asymmetric synthesis, a compound (**52**) with achiral molecules, but whose crystals are chiral, was converted by UV light to a single enantiomer of a chiral product (**53**).[146]

It is often possible to convert an achiral compound to a chiral compound by (1) addition of a chiral group; (2) running an asymmetric synthesis, and (3) cleavage of the original chiral group. The original chiral group is called a *chiral auxiliary*.

[142] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* ***1968***, 2199; Chérest, M.; Felkin, H. *Tetrahedron Lett.* ***1968***, 2205; Anh, N.T.; Eisenstein, O. *Nov. J. Chem.* ***1977***, *1*, 61. For experiments that show explanations for certain systems based on the Felkin–Anh model to be weak, see Yadav, V.K.; Gupta, A.; Balamurugan, R.; Sriramurthy, V.; Kumar, N.V. *J. Org. Chem.* ***2006***, *71,* 4178.

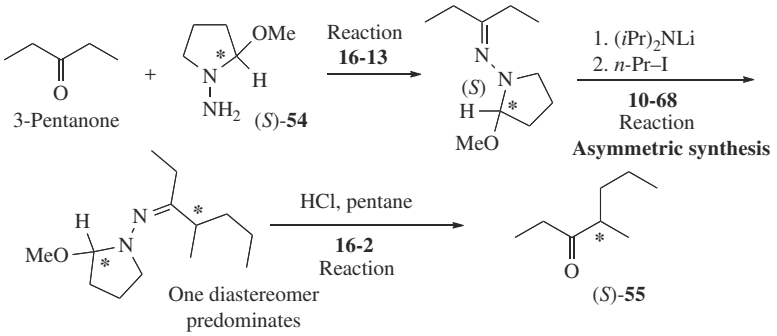
[143] Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* ***1959***, 112; Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1761.

[144] See Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155; Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* ***1978***, *100*, 1614; Still, W.C.; McDonald, J.H. *Tetrahedron Lett.* ***1980***, *21*, 1031; Still, W.C.; Schneider, J.A. *Tetrahedron Lett.* ***1980***, *21*, 1035.

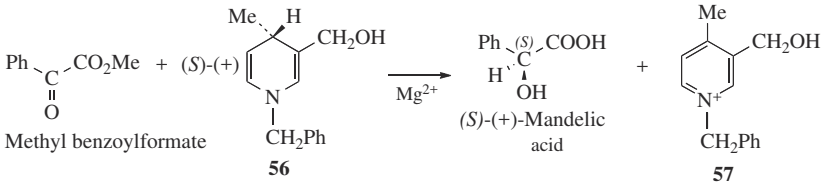
[145] Cee, V.J.; Cramer, C.J.; Evans, D.A. *J. Am. Chem. Soc.* ***2006***, *128,* 2920.

[146] Evans, S.V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* ***1986***, *108*, 5648; Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* ***1987***, *28*, 4789. For an earlier example, see Penzien, K.; Schmidt, G.M.J. *Angew. Chem. Int. Ed.* ***1969***, *8*, 608.

An example is conversion of the achiral 2-pentanone to the chiral 4-methyl-3-heptanone, (**55**).[147] In this case, >99% of the product was the (*S*) enantiomer. As noted, compound **54** is called a *chiral auxiliary* because it is used to induce asymmetry and is then removed.



2. *Active Reagent.* A pair of enantiomers can be separated by an active reagent that reacts faster with one of them than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and



by determining which diastereomer is preferentially formed.[148] Creation of a new stereogenic center in an inactive molecule can also be accomplished with an optically active reagent, although it is rare for 100% selectivity to be observed. An example[149,150] is the reduction of methyl benzoylformate with optically active *N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**56**) to produce mandelic acid (after hydrolysis) that contained ~97.5% of the (*S*)-(+) isomer and 2.5% of the (*R*)-(−) isomer (for another example, see Reaction **15-16**). Note that the other product, (**57**), is not chiral. Reactions like this, in which one reagent (in this case **56**) gives up its chirality to another, are called *self-immolative*.

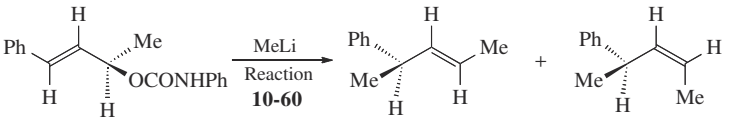
[147] Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K.A.M. *Tetrahedron* ***1984***, *40*, 1345.

[148] See Brockmann, Jr., H.; Risch, N. *Angew. Chem. Int. Ed.* ***1974***, *13*, 664; Potapov, V.M.; Gracheva, R.A.; Okulova, V.F. *J. Org. Chem. USSR* ***1989***, *25*, 311.

[149] Meyers, A.I.; Oppenlaender, T. *J. Am. Chem. Soc.* ***1986***, *108*, 1989. For reviews of asymmetric reduction, see Morrison, J.D. *Surv. Prog. Chem.* ***1966***, *3*, 147; Yamada, S.; Koga, K. *Sel. Org. Transform.*, ***1970***, *1*, 1. See also, Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***.

[150] See, in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

In another example:



chirality is transferred from one atom to another in the same molecule.[151]

A reaction in which an inactive substrate is converted selectively to one of two enantiomers is called an *enantioselective* reaction, and the process is called *asymmetric induction*. These terms apply to reactions in this category and in categories 3 and 4.

When an optically active substrate reacts with an optically active reagent to form two new stereogenic centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*[152] (for an example, see Reaction **16-34**).

3. *Optically Active Catalyst or Solvent.*[153] Many such examples are found in the literature, among them reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions **16-23** and **15-11**),[154] the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see Reaction **16-24**), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see Reaction **15-50**). In some instances, the ratio of enantiomers prepared in this way is 99:1 or more.[155] Other examples of the use of a chiral catalyst or solvent are the conversion of chlorofumaric acid (in the form of its diion) to the (−)-*threo* isomer of the diion of chloromalic acid by treatment with H_2O and the enzyme fumarase,[156] as well as the preparation of

[151] Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* ***1983***, *48*, 715.

[152] For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

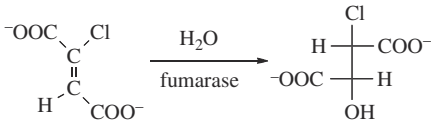
[153] For a monograph, see Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***. For reviews, see Tomioka, K. *Synthesis* ***1990***, 541; Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257; Brunner, H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 5, Wiley, NY, ***1989***, pp. 109–146; Noyori, R.; Kitamura, M. *Mod. Synth. Methods* ***1989***, *5*, 115; Pfaltz, A. *Mod. Synth. Methods* ***1989***, *5*, 199; Kagan, H.B. *Bull. Soc. Chim. Fr.* ***1988***, 846; Brunner, H. *Synthesis* ***1988***, 645; Wynberg, H. *Top. Stereochem.* ***1986***, *16*, 87.

[154] For reviews of these and related topics, see Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***; Brunner, H. *J. Organomet. Chem.* ***1986***, *300*, 39; Bosnich, B.; Fryzuk, M.D. *Top. Stereochem.* ***1981***, *12*, 119.

[155] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***. For random examples, see Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* ***2010***, *13*2, 11418; Berhal, F.; Wu, Z.; Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *J. Org. Chem.* ***2011***, *76*, 6320; He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* ***2011***, *13,* 936; Yang, H.-M.; Li, L.; Li, F.; Jiang, K.-Z.; Shang, J.-Y.; Lai, G.-Q.; Xu, L.-W. *Org. Lett.* ***2011***, *13,* 6508.

[156] Findeis, M.A.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2838; Réty, J.; Robinson, J.A. *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie, Deerfield Beach, FL, ***1982***. For reviews, see Klibanov, A.M. *Acc. Chem. Res.* ***1990***, *23*, 114; Jones, J.B. *Tetrahedron* ***1986***, *42*, 3351; Jones, J.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 309–344.

optically active aldols (aldol condensation, see Reaction **16-35**) by the condensation of enolate anions with optically active substrates.[157]

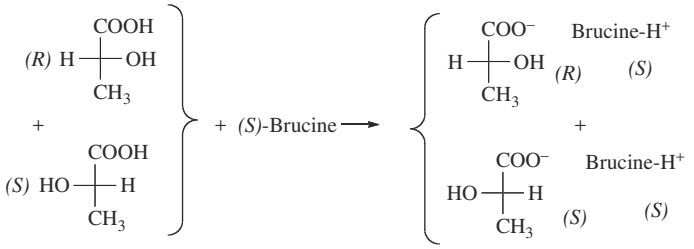


(–)-*threo* Isomer

4. *Reactions in the Presence of Circularly Polarized Light.*[158] If the light used to initiate a photochemical reaction (see Chap. 7) of achiral reagents is circularly polarized, then, in theory, a chiral product richer in one enantiomer might be obtained. However, such experiments have not proved fruitful. In certain instances, the use of left- and right-circularly polarized light *has* given products with opposite rotations[159] (showing that the principle is valid), but up to now the extent of favoritism has always been $<1\%$.

4.H. METHODS OF RESOLUTION[160]

A pair of enantiomers can be separated in several ways, but conversion to diastereomers and separation of these by fractional crystallization or chromatographic methods are used most often. In this method and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.



1. *Conversion to Diastereomers.* If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base. Since the base used is, say, the (*S*) form, there will be a mixture of two salts produced having the configurations (*SS*) and (*RS*). Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often used for separation is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent.

[157] Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* ***1979***, *101*, 7076.
[158] *For a review, See Buchardt, O.* Angew. Chem. Int. Ed. **1974**, 13, *179. For a discussion, see Barron L.D.* J. Am. Chem. Soc. **1986**, 108, *5539.*
[159] See Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* ***1973***, *95*, 527; Nicoud, J.F.; Kagan, J.F. *Isr. J. Chem.* ***1977***, *15*, 78. See also, Zandomeneghi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc.* ***1984***, *106*, 7261.
[160] Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Tetrahedron Asymm.* ***2008***, *19,* 519. See Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* ***1977***, *33*, 2725; Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 297–424; Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, aand Resolutions*, Wiley, NY, ***1981***.

Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubility is rarely if ever great enough to effect total separation with one crystallization. When fractional crystallizations must be used, the process is long and tedious. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids and the recovered base can be used again.

Most resolution of this type is done on carboxylic acids and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. Racemic compounds (e.g., 2-aminocylohexanol derivatives) react with carboxylic acids (e.g., optically active mandelic acid), to give diastereomers that are separated and then converted to enantiopure compounds.[161] Racemic bases can be converted to diastereomeric salts with active acids. The principle of conversion to diastereomers is not confined to carboxylic acids, and other functional groups[162] may be coupled to an optically active reagent.[163] Alcohols[164] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, and so on. Amino alcohols have been resolved using boric acid and chiral binaphthols.[165] Phosphine oxides[166] and chiral calix[4]arenes[167] have been resolved. Chiral crown ethers have been used to separate mixtures of enantiomeric alkylammonium and arylammonium ions, by the formation of diastereomeric complexes[168] (see also, category 3, below). Even hydrocarbons can be converted to diastereomeric inclusion compounds,[169] with urea. Urea is not chiral, but the cage structure is.[170] Racemic unsaturated hydrocarbons have been resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid.[171] *trans*-Cyclooctene (Sec. 4.C, category 6) was resolved by conversion to a Pt complex containing an optically active amine.[172]

[161] Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* ***2006***, *71,* 2320.
[162] See Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 322–424.
[163] For an extensive list of reagents that have been used for this purpose and of compounds resolved, see Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, University of Notre Dame Press, Notre Dame, IN, ***1972***.
[164] See Klyashchitskii, B.A.; Shvets, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 592.
[165] Periasamy, M.; Kumar, N.S.; Sivakumar, S.; Rao, V.D.; Ramanathan, C.R.; Venkatraman, L. *J. Org. Chem.* ***2001***, *66,* 3828.
[166] Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *J. Org. Chem.* ***2001***, *66*, 7478.
[167] Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron Asymm.* ***2000***, *11,* 3103.
[168] See Slingenfelter, D.S.; Helgeson, R.C.; Cram, D.J. *J. Org. Chem.* ***1981***, *46*, 393; Davidson, R.B.; Bradshaw, J.S.; Jones, B.A.; Dalley, N.K.; Christensen, J.J.; Izatt, R.M.; Morin, F.G.; Grant, D.M. *J. Org. Chem.* ***1984***, *49*, 353.
[169] See Prelog, V.; Kovačević, M.; Egli, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1147; Worsch, D.; Vögtle, F. *Top. Curr. Chem.* ***1987***, *140*, 21; Toda, F. *Top. Curr. Chem.* ***1987***, *140*, 43; Stoddart, J.F. *Top. Stereochem.* ***1987***, *17*, 207; Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. in Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 263–295.
[170] See Schlenk, Jr., W. *Liebigs Ann. Chem.* ***1973***, 1145, 1156, 1179, 1195. See Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* ***1983***, *105*, 4561.
[171] Miyamoto, H.; Sakamoto, M.; Yoskioka, K.; Takaoka, R.; Toda, F. *Tetrahedron Asymm.* ***2000***, *11,* 3045.
[172] For a review, see Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, see p. 220.

Fractional crystallization has always been the most common method for the separation of diastereomers. When it can be used, binary phase diagrams for the diastereomeric salts have been used to calculate the efficiency of optical resolution.[173] However, it is tedious and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but gas chromatography (GC)[174] and preparative liquid chromatography using chiral columns[175] have proved to be more useful. In many cases, they have supplanted fractional crystallization, especially where the quantities to be resolved are small.[176]

2. *Differential Absorption.* When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move along the column at different rates and should be separable without having to be converted to diastereomers.[176] This has been successfully accomplished with paper, column, thin-layer,[177] and gas and liquid chromatography.[178] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[179] Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.[180] Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.[181]
3. *Chiral Recognition.* The use of chiral hosts to form diastereomeric inclusion compounds was mentioned above. But in some cases it is possible for a host to form an inclusion compound with one enantiomer of a racemic guest, but not the other. This is called *chiral recognition*. One enantiomer fits into the chiral host cavity, the other does not. More often, both diastereomers are formed, but one forms more rapidly than the other, so that if the guest is removed it is already partially resolved (this is a form of kinetic resolution, see category 6). An example is use of the chiral crown ether (**58**) partially to resolve the racemic amine salt (**59**).[182] When an

[173] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.

[174] See Westley, J.W.; Halpern, B.; Karger, B.L. *Anal. Chem.* ***1968***, *40*, 2046; Kawa, H.; Yamaguchi, F.; Ishikawa, N. *Chem. Lett.* ***1982***, 745.

[175] See Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. *J. Org. Chem.* ***1979***, *44*, 2247; Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* ***1982***, *104*, 1093.

[176] See Lough, W.J. *Chiral Liquid Chromatography*; Blackie and Sons: London, ***1989***; Krstulović, A.M. *Chiral Separations by HPLC*, Ellis Horwood, Chichester, ***1989***; Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***. For a review, see Karger, B.L. *Anal. Chem.* ***1967***, *39*(8), 24A.

[177] Weinstein, S. *Tetrahedron Lett.* ***1984***, *25*, 985.

[178] See Allenmark, S.G. *Chromatographic Enantioseparation*, Ellis Horwood, Chichester, ***1988***; König, W.A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, ***1987***. For reviews, see Schurig, V.; Nowotny, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 939; Pirkle, W.H.; Pochapsky, T.C. *Chem. Rev.* ***1989***, *89*, 347; Blaschke, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 13; Rogozhin, S.V.; Davankov, V.A. *Russ. Chem. Rev.* ***1968***, *37*, 565. See also, many articles in the journal *Chirality*.

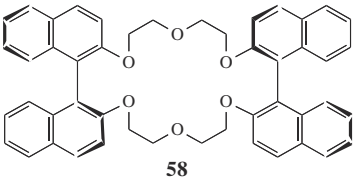
[179] Ohara, M.; Ohta, K.; Kwan, T. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 76. See also, Blaschke, G.; Donow, F. *Chem. Ber.* ***1975***, *108*, 2792; Hess, H.; Burger, G.; Musso, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 612.

[180] See Schurig, V.; Nowotny, H.; Schmalzing, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 736; Ôi, S.; Shijo, M.; Miyano, S. *Chem. Lett. 1990*, 59; Erlandsson, P.; Marle, I.; Hansson, L.; Isaksson, R.; Pettersson, C.; Pettersson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 4573.

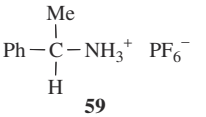
[181] See, for example, Pirkle, W.H.; Welch, C.J. *J. Org. Chem.* ***1984***, *49*, 138.

[182] Kanoh, S.; Hongoh, Y.; Katoh, S.; Motoi, M.; Suda, H. *J. Chem. Soc. Chem. Commun.* ***1988***, 405; Bradshaw, J.S.; Huszthy, P.; McDaniel, C.W.; Zhu, C.Y.; Dalley, N.K.; Izatt, R.M.; Lifson, S. *J. Org. Chem.* ***1990***, *55*, 3129.

aqueous solution of **59** was mixed with a solution of optically active **58** in chloroform, and the layers separated, the chloroform layer contained about twice as much of the complex between **58** and (*R*)-**59** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,[183] cholic acid,[184] and other kinds of hosts.[169] Of course, enzymes are generally very good at chiral recognition, and much of the work in this area has been an attempt to mimic the action of enzymes.



58

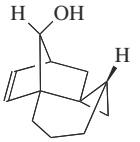


59

4. *Biochemical Processes.*[185] Reactions catalyzed by enzymes can be utilized for this kind of resolution.[186] Biological molecules may react at different rates with the two enantiomers. For example, a certain bacterium may digest one enantiomer, but not the other. Pig liver esterase has been used for the selective cleavage of one enantiomeric ester.[187] This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective. This process has been called chemoenzymatic dynamic kinetic resolution.[188]
5. *Mechanical Separation.*[189] This is the method by which Pasteur proved that racemic tartaric acid was actually a mixture of (+)- and (−)-tartaric acids.[190] In the case of racemic sodium ammonium tartrate, the enantiomers crystallize separately: all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical and a trained crystallographer can separate them with tweezers.[191] However, this is seldom a practical method, since few compounds crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized

[183] See, for example, Hamilton, J.A.; Chen, L. *J. Am. Chem. Soc.* ***1988***, *110*, 5833.
[184] See Miyata, M.; Shibakana, M.; Takemoto, K. *J. Chem. Soc. Chem. Commun.* ***1988***, 655.
[185] For a review, see Sih, C.J.; Wu, S. *Top. Stereochem.* ***1989***, *19*, 63.
[186] See Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1994***, *35*, 4375; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***1989***, *111*, 4953; Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.* ***69***, 1. For resolution with Subtilisin, see Savile, C.K.; Magloire, V.P.; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***2005***, *127,* 2104. For the chemoenzymatic kinetic resolution of primary amines, see Paetzold, J.; Bäckvall, J.E. *J. Am. Chem. Soc.* ***2005***, *127,* 17620.
[187] For an example, see Gais, H.-J.; Jungen, M.; Jadhav, V. *J. Org. Chem.* ***2001***, *66*, 3384.
[188] For an example of the resolution of acyloins, see Ödman, P.; Wessjohann, L.A.; Bornscheuer, U.T. *J. Org. Chem.* ***2005***, *70*, 9551.
[189] For reviews, see Collet, A.; Brienne, M.; Jacques, J. *Chem. Rev.* ***1980***, *80*, 215; *Bull. Soc. Chim. Fr.* ***1972***, 127; ***1977***, 494. For a discussion, see Curtin, D.Y.; Paul, I.C. *Chem. Rev.* ***1981***, *81*, 525 pp. 535–536.
[190] Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation (and, by extension, kinetic resolution).
[191] This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

<27°C. A more useful variation of the method, although still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.[192] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (Sec. 4.C. Category 7). One enantiomer of this

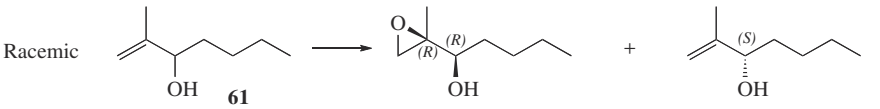


60

compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200°$ spontaneously crystallizes from benzene.[193] In the case of 1,1′-binaphthyl, optically active crystals can be formed simply by heating polycrystalline racemic samples of the compound at 76–150°C. A phase change from one crystal form to another takes place.[194] Note that 1,1′-binaphthyl is one of the few compounds that can be resolved by the Pasteur tweezer method. In some cases, resolution can be achieved by enantioselective crystallization in the presence of a chiral additive.[195] Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **60**, when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−) molecules into another.[196] In this case, the crystals are superimposable, unlike the situation with sodium ammonium tartrate, but the investigators were able to remove a single crystal, which proved optically active.

6. *Kinetic Resolution.*[197] Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed in Section 4.C, category 5. A method has been developed to evaluate the enantiomeric ratio of kinetic resolution using only the extent of substrate conversion.[198] An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,[199] since alkenes do not easily lend themselves to conversion to diastereomers if no

[192] For a review of the seeding method, see Secor, R.M. *Chem. Rev.* ***1963***, *63*, 297.
[193] Martin, R.H; Baes, M. *Tetrahedron* ***1975***, *31*, 2135. See also, Wynberg, H.; Groen, M.B. *J. Am. Chem. Soc.* ***1968***, *90*, 5339; McBride, J.M.; Carter, R.L. *Angew. Chem. Int. Ed.* ***1991***, *30*, 293.
[194] Kress, R.B.; Duesler, E.N.; Etter, M.C.; Paul, I.C.; Curtin, D.Y. *J. Am. Chem. Soc.* ***1980***, *102*, 7709. See also, Gottarelli, G.; Spada, G.P. *J. Org. Chem.* ***1991***, *56*, 2096. For a discussion and other examples, see Agranat, I.; Perlmutter-Hayman, B.; Tapuhi, Y. *Nouv. J. Chem.* ***1978***, *2*, 183.
[195] Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* ***1982***, *104*, 4610. See also, Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* ***1983***, *105*, 6615.
[196] Paquette, L.A.; Lau, C.J. *J. Org. Chem.* ***1987***, *52*, 1634.
[197] For reviews, see Pellissier, H. *Tetrahedron* ***2008***, *64,* 1563; Ward, R.S. *Tetrahedron Asymm.* ***1995***, *6*, 1475; Pellissier, H. *Tetrahedron* ***2003***, *59*, 8291.
[198] Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron Asymm.* ***1995***, *6*, 1093.
[199] Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* ***1964***, *86*, 397.



other functional groups are present. Another example is the resolution of allylic alcohols (e.g., **61)** with one enantiomer of a chiral epoxidation agent (see Reaction **15-50**).[200] In the case of **61**, the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor) being >100. Of course, in this method only one of the enantiomers of the original racemic mixture is obtained, but there are at least two possible ways of getting the other: (1) use of the other enantiomer of the chiral reagent and (2) conversion of the product to the starting compound by a reaction that preserves the stereochemistry.

Kinetic resolution of racemic allylic acetates[201] has been accomplished via asymmetric dihydroxylation (Reation **15-48**), and 2-oxoimidazolidine-4-carboxylates have been developed as new chiral auxiliaries for the kinetic resolution of amines.[202] A planar chiral cyclic ether was found to be stable at ambient temperatures, but resolved by kinetic resolution.[203]

7. *Deracemization.* In this type of process, one enantiomer is converted to the other, so that a racemic mixture is converted to a pure enantiomer, or to a mixture enriched in one enantiomer (*enantioenriched*). This finding is not quite the same as the methods of resolution previously mentioned, although an outside optically active substance is required. To effect the deracemization, two conditions are necessary: (1) the enantiomers must complex differently with the optically active substance and (2) they must interconvert under the conditions of the experiment. When racemic thioesters were placed in solution with a specific optically active amide for 28 days, the solution contained 89% of one enantiomer and 11% of the other.[204] In this case, the presence of a base (Et_3N) was necessary for the interconversion to take place. Biocatalytic deracemization processes induce deracemization of chiral secondary alcohols.[205] In a specific example, *Sphingomonas paucimobilis* NCIMB 8195 catalyzes the efficient deracemization of many secondary alcohols in up to 90% yield of the (*R*)-alcohol.[206]

[200] Carlier, P.R.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 2978; Discordia, R.P.; Dittmer, D.C. *J. Org. Chem.* ***1990***, *55*, 1414. For other examples, see Katamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron Asymm.* ***1990***, *1*, 1; Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1167.

[201] Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1993***, *34*, 3911.

[202] Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* ***1994***, *35*, 3107.

[203] Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* ***2005***, *127,* 12182.

[204] Pirkle, W.H.; Reno, D.S. *J. Am. Chem. Soc.* ***1987***, *109*, 7189. For another example, see Reider, P.J.; Davis, P.; Hughes, D.L.; Grabowski, E.J.J. *J. Org. Chem.* ***1987***, *52*, 955.

[205] Stecher, H.; Faber, K. *Synthesis* ***1997***, 1.

[206] Allan, G. R.; Carnell, A. J. *J. Org. Chem.* ***2001***, *66,* 6495.

4.I. OPTICAL PURITY[207]

An attempt to resolve a racemic mixture by one of the methods described in Section 4.I has given either a pure compound or a new mixture. How can the purity of the two enantiomers obtained be determined? If the (+) isomer is contaminated by, say, 20% of the (−) isomer, how can this be determined? If the value of [α] for the pure material ($[\alpha]_{max}$) is known, the purity of a sample is easily determined by measuring its rotation. For example, if $[\alpha]_{max}$ is +80° and the resolved (+) enantiomer contains 20% of the (−) isomer, [α] for the sample will be +48°.[208] *Optical purity* is defined as

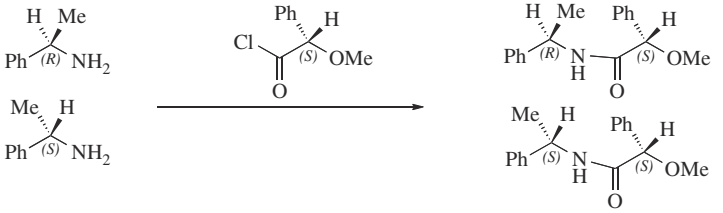
$$\text{Percent optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

Assuming a linear relationship between [α] and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{Optical purity} = \text{percent enantiomeric excess}(\%\text{ee})^{209} = \frac{[R] - [S]}{[R] + [S]} \times 100 = (\%R) - (\%S)$$

How is the value of $[\alpha]_{max}$ determined? It is plain that we have two related problems here; namely, what are the optical purities of our two samples and what is the value of $[\alpha]_{max}$. Finding the properties of one also gives the other. Several methods for solving these problems are known.

One of these methods involves the use of NMR[210] (see Sec. 4.E.ii, category 7). If there is a nonracemic mixture of two enantiomers and the proportions constitute an unknown, convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the NMR spectrum of the resulting mixture, for example,



[207] For a review, see Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[208] If a sample contains 80% (+) and 20% (−) isomer, the (−) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80° or 48°. This type of calculation, however, is not valid for cases in which [α] is dependent on concentration (Sec. 4.B); see Horeau, A. *Tetrahedron Lett.* ***1969***, 3121.

[209] For a method to measure %ee using electrooptics, see Walba, D.M.; Eshdat, L.; Korblova, E.; Shao, R.; Clark, N.A. *Angew. Chem. Int. Ed.* ***2007***, *46,* 1473.

[210] Raban, M.; Mislow, K. *Tetrahedron Lett.* ***1965***, 4249, ***1966***, 3961; Jacobus, J.; Raban, M. *J. Chem. Educ.* ***1969***, *46*, 351; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1988***, *29*, 6063. For a review, see Yamaguchi, S. in Morrison, J. D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 125–152. See also, Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

If the NMR spectrum of the starting mixture is examined, only one peak would be found (split into a doublet by the C—H) for the Me protons, since enantiomers give identical NMR spectra.[211] But the two amides are not enantiomers and each Me gives its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the "unsplit" OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),[212] as well as other cases, but it is obvious that sometimes corresponding groups in diastereomeric molecules will give NMR signals that are too close together for resolution. In such cases, one may resort to the use of a different optically pure reagent. The ^{13}C NMR can be used in a similar manner.[213] It is also possible to use these spectra to determine the absolute configuration of the original enantiomers by comparing the spectra of the diastereomers with those of the original enantiomers.[214] From a series of experiments with related compounds of known configurations it can be determined in which direction one or more of the ^{1}H or ^{13}C NMR peaks are shifted by formation of the diastereomer. It is then assumed that the peaks of the enantiomers of unknown configuration will be shifted the same way.

A closely related method does not require conversion of enantiomers to diastereomers, but relies on the fact that (in principle, at least) enantiomers have different NMR spectra *in a chiral solvent*, or when mixed with a chiral molecule (in which case transient diastereomeric species may form, see Sec. 4.E.ii). In such cases, the peaks may be separated enough to permit the proportions of enantiomers to be determined from their intensities.[215] Another variation, which gives better results in many cases, is to use an achiral solvent, but with the addition of a *chiral lanthanide shift reagent* [e.g., *tris*[3-trifluoroacetyl-*d*-camphorato]europium(III)].[216] Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds (e.g., alcohols, carbonyl compounds, and amines). Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving GC,[217] is similar in principle to the NMR chiral complex method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by GC and the ratios are determined from the peak areas. Once again, the

[211] Though enantiomers give identical NMR spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* ***1969***, *91*, 1871.

[212] Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199, see pp. 216–218.

[213] For a method that relies on diastereomer formation without a chiral reagent, see Feringa, B.L.; Strijtveen, B.; Kellogg, R.M. *J. Org. Chem.* ***1986***, *51*, 5484. See also, Pasquier, M.L.; Marty, W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 315; Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* ***1986***, *108*, 4873.

[214] See Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* ***1986***, *51*, 2370.

[215] For reviews of NMR chiral solvating agents, see Weisman, G.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 153–171; Pirkle, W.H.; Hoover, D.J. *Top. Stereochem.* ***1982***, *13*, 263. Sweeting, L.M.; Anet, F.A.L. *Org. Magn. Reson.* ***1984***, *22*, 539. See also, Pirkle, W.H.; Tsipouras, A. *Tetrahedron Lett.* ***1985***, *26*, 2989; Parker, D.; Taylor, R.J. *Tetrahedron* ***1987***, *43*, 5451.

[216] Sweeting, L.M.; Crans, D.C.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2273; Morrill, T.C. *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH, NY, ***1986***; Fraser, R.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 173–196; Sullivan, G.R. *Top. Stereochem.* ***1978***, *10*, 287.

[217] See Westley, J.W.; Halpern, B. *J. Org. Chem.* ***1968***, *33*, 3978.

ratio of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography has been used in a similar manner and has wider applicability.[218] The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.[219]

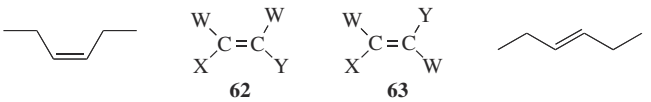
Other methods[220] involve isotopic dilution,[221] kinetic resolution,[222] ^{13}C NMR relaxation rates of diastereomeric complexes,[223] and circular polarization of luminescence.[224]

4.J. *cis–trans* ISOMERISM

Compounds in which rotation is restricted may exhibit cis–trans isomerism.[225] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

4.J.i. *cis-trans* Isomerism Resulting from Double Bonds

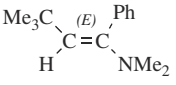
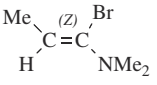
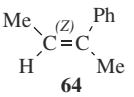
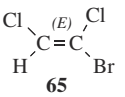
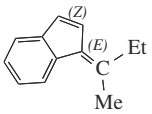
It has been mentioned (Sec. 1.D) that the two carbon atoms of a C=C d=ble bond and the four atoms directly attached to them are all in the same plane and that the presence of the π-bond prevents rotation around the double bond. This means that in the case of a molecule WXC=CYZ, stereoisomerism exists when $W \neq X$ and $Y \neq Z$. There are two and only two isomers (**62** and **63**), each superimposable on its mirror image unless one of the groups happens to carry a stereogenic center. Note that **62** and **63** are diastereomers, by the definition given in Section 4.E.i. There are two ways to name such isomers. In the older and less versatile method, one isomer is called *cis* and the other *trans*. When each carbon of the C=C unit has an *identical group* (W in **62** and **63**), but fits the substitution pattern of **62** and **63**, the *cis-trans* nomenclature system may be applied. When the two identical groups are on the same side (W and W in **62**), it is labeled cis. *cis*-3-Hexene is shown as an example. When the two identical groups are on opposite side (W and W in **63**) it is labeled trans. *trans*-3-Hexene is shown as an example. Unfortunately, there is no obvious way to apply this method when the four groups are different.



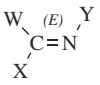
62 **63**

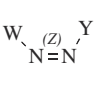
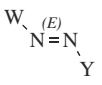
[218] For a review, see Pirkle, W.H.; Finn, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 87–124.
[219] For reviews, see in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, the articles by Schurig, V. pp. 59–86 and Pirkle, W.H.; Finn, J. pp. 87–124.
[220] See Hill, H.W.; Zens, A.P.; Jacobus, J. *J. Am. Chem. Soc.* ***1979***, *101*, 7090; Matsumoto, M.; Yajima, H.; Endo, R. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 4139.
[221] Berson, J.A.; Ben-Efraim, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4083; Andersen, K.K.; Gash, D.M.; Robertson, J.D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 45–57.
[222] Horeau, A.; Guetté, J.; Weidmann, R. *Bull. Soc. Chim. Fr.* ***1966***, 3513. For a review, see Schoofs, A.R.; Guetté, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 29–44.
[223] Hofer, E.; Keuper, R. *Tetrahedron Lett.* ***1984***, *25*, 5631.
[224] Schippers, P.H.; Dekkers, H.P.J.M. *Tetrahedron* ***1982***, *38*, 2089.
[225] *cis-trans* isomerism was formerly called *geometrical isomerism.*

The newer and more widely applicable method can be applied to all cases, and is based on the CIP system (Sec. 4.E.i). The two groups at each carbon of the C=C unit are ranked by the sequence rules. The isomer with the two higher ranking groups on the same side of the double bond is called (*Z*) (for the German word *zusammen* meaning *together*). The isomer with the two higher ranking groups on opposite sides of the double bond is called (*E*) (for *entgegen* meaning *opposite*).[226] A few examples are shown. Note that the (*Z*) isomer is not necessarily the one that would be called cis under the older system (e.g., **64** and **65**). Like cis and trans, (*E*) and (*Z*) are used as prefixes; for example, **65** is called (*E*)-1-bromo-1,2-dichloroethene.

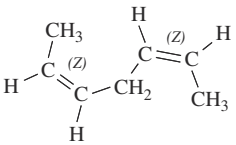
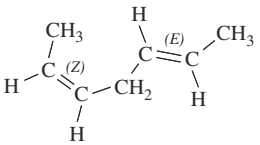
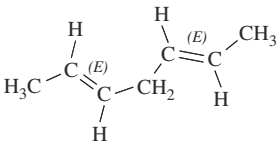



64

65


This type of isomerism is also possible with other double bonds (e.g., C=N,[227] N=N,[228] or even C=S),[229] although in these cases only two or three groups are connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **66** may be called syn and **67** anti, but (*E*) and (*Z*) are used here too.[230] In azo compounds there is no ambiguity. Compound **68** is always *syn* or (*Z*) regardless of the nature of W and Y.


66

67

68


If there is more than one double bond[231] in a molecule and if W ≠ X and Y ≠ Z for each, the number of isomers in the most general case is 2^n, although this number may be decreased if some of the substituents are the same, as in the three 2,5-heptadienes shown.

When a molecule contains a double bond and a stereogenic carbon, there are four isomers, a cis pair of enantiomers and a trans pair, shown for 4-methylhex-2-ene.

[226] For a complete description of the system, see *Pure Appl. Chem.* ***1976***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book).

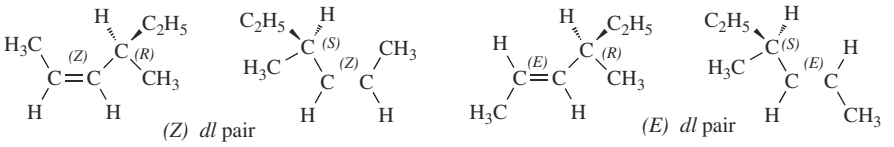
[227] See in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, the articles by McCarty, C.G. pp. 363–464 (pp. 364–408), and Wettermark, G. pp. 565–596 (pp. 574–582).

[228] Wang, Y.-N.; Bohle, D.S.; Bonifant, C.L.; Chmurny, G.N.; Collins, J.R.; Davies, K.M.; Deschamps, J.; Flippen-Anderson, J.L.; Keefer, L.K.; Klose, J.R.; Saavedra, J.E.; Waterhouse, D.J.; Ivanic, J. *J. Am. Chem. Soc.* ***2005***, *127,* 5388.

[229] King, J.F.; Durst, T. *Can. J. Chem.* ***1966***, *44*, 819.

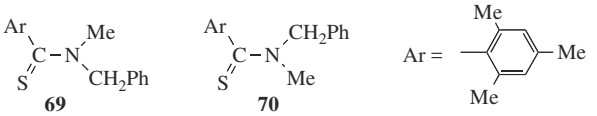
[230] A mechanism has been reported for the acid-catalyzed Z/E isomerization of imines. See Johnson, J.E.; Morales, N.M.; Gorczyca, A.M.; Dolliver, D.D.; McAllister, M.A. *J. Org. Chem.* ***2001***, *66*, 7979.

[231] This rule does not apply to allenes, which do not show *cis–trans* isomerism (see Sec. 4.C, category 5).



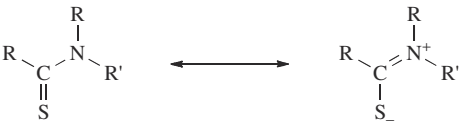
(*Z*) *dl* pair (*E*) *dl* pair

Double bonds in small rings are so constrained that they must be cis. From cyclopropene (a known system) to cycloheptene, double bonds in a stable ring *cannot* be trans. However, the cyclooctene ring is large enough to permit trans double bonds to exist (see Sec. 4.C, category 7), and for rings larger than 10- or 11-membered, trans isomers are more stable[232] (see also, Sec. 4.Q.ii).

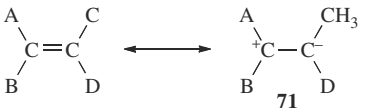


69 **70**

In a few cases, single-bond rotation is so slowed that cis and trans isomers can be isolated even where no double bond exists[233] (see also, Sec. 4.Q.iv). One example is *N*-methyl-*N*-benzylthiomesitylide (**69** and **70**).[234] The isomers are stable in the crystalline state, but interconvert with a half-life of ~25 h in $CDCl_3$ at 50°C.[235] This type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single-bond some double-bond character and slows rotation.[54] (For other examples of restricted rotation about single bonds, see Sec. 4.Q.iv.)



Conversely, there are compounds in which nearly free rotation is possible around what are formally C=C double bonds. These compounds, called *push–pull* or *captodative* ethylenes, have two electron-withdrawing groups on one carbon and two electron-donating groups on the other (**71**).[236] The contribution of diionic

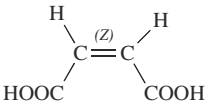


71

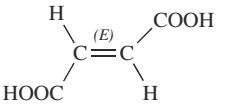
A, B = electron withdrawing
C, D = electron donating

[232] Cope, A.C.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1959***, *81*, 3153.
[233] Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 41–71.
[234] Mannschreck, A. *Angew. Chem. Int. Ed.* ***1965***, *4*, 985. See also, Völter, H.; Helmchen, G. *Tetrahedron Lett.* ***1978***, 1251; Walter, W.; Hühnerfuss, H. *Tetrahedron Lett.* ***1981***, *22*, 2147.
[235] This is another example of atropisomerism (Sec. 4.C, category 5).
[236] For reviews, see Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 111–125.

TABLE 4.2 Some Properties of Maleic and Fumaric Acids



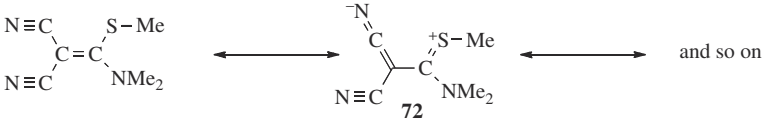
Maleic Acid



Fumaric Acid

Property	Maleic Acid	Fumaric Acid
Melting point (°C)	130	286
Solubility in water at 25 °C (g L^{-1})	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

canonical forms, such as the one shown, decreases the double-bond character and allows easier rotation. For example, compound **72** has a barrier to rotation of 13 kcal mol^{-1} (55 kJ mol^{-1}),[237] compared to a typical value of ~62–65 kcal mol^{-1}(260–270 kJ mol^{-1}) for simple alkenes.



72

Since they are diastereomers, *cis-trans* isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 4.2) that it is not surprising that they have different names. Since they generally have more symmetry than cis isomers, trans isomers in most cases have higher melting points and lower solubilities in inert solvents. The cis isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

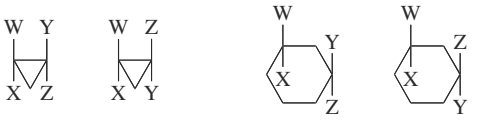
It is also important to note that *trans*-alkenes are often more stable than *cis*-alkenes due to diminished steric hindrance (Sec. 4.Q.iv), but this is not always the case. It is known, for example, that *cis*-1,2-difluoroethene is thermodynamically more stable than *trans*-1,2-difluoroethene. This appears to be due to delocalization of halogen lone-pair electrons and an antiperiplanar effect between vicinal antiperiplanar bonds.[238]

4.J.ii *cis–trans* Isomerism of Monocyclic Compounds

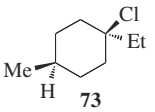
Although rings of four carbons and larger are not generally planar (see Sec. 4.O), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[239] and the principles are easier to visualize (see Sec. 4.O).

[237] Sandström, J.; Wennerbeck, I. *Acta Chem. Scand. Ser. B*, ***1978***, *32*, 421.
[238] Yamamoto, T.; Tomoda, S. *Chem. Lett.* ***1997***, 1069.
[239] See Leonard, J.E.; Hammond, G.S.; Simmons, H.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5052.

The presence of a ring, like that of a double bond, prevents rotation. *cis* and *trans* isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples follow:



In some cases, the two stereoisomers can interconvert. In cis- and trans-disubstituted cyclopropanones, for example, there is reversible interconversion that favors the more stable trans isomer. This fluxional isomerization occurs via ring opening to an unseen oxyallyl *valence bond* isomer.[240]



73

While cis and trans isomers are possible for rings, the restrictions are that W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z. There is an important difference from the double-bond case: The substituted carbons may be stereogenic carbons. This means that there may be more than two isomers. In the most general case, where W, X, Y, and Z are all different, there are four isomers since neither the cis nor the trans isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when W, X, Y, and Z are at opposite corners. Cyclohexane derivative **73**, for example, has no stereogenic carbons because there is a plane of symmetry. Imagine a focus on the chlorine-bearing carbon, and view each "arm" of the ring as a group. There are two identical groups so the carbon will not be stereogenic. When W = Y and X = Z, the cis isomer is always superimposable on its mirror image. Hence, this isomer is a meso compound, while the trans isomer consists of a *dl* pair, except in the case noted above. Again, the cis isomer has a plane of symmetry while the trans does not.

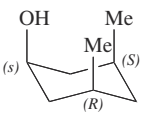


cis meso *trans dl* pair

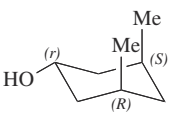
Rings with more than two differently substituted carbons can be dealt with using similar principles. In some cases, it is not easy to tell the number of isomers by inspection.[107] The best method may be to count the number n of differently substituted carbons (these will usually be asymmetric, but not always, e.g., in **73**), and then to draw 2^n structures, crossing out those that can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means, it can be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. Similar principles apply to heterocyclic rings as long as there are carbons (or other ring atoms) containing two different groups.

[240] Sorensen, T.S.; Sun, F. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1053.

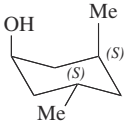
Cyclic stereoisomers containing only two differently substituted carbons are named either cis or trans, as previously indicated. The (*Z*, *E*) system is not used for cyclic compounds. However, *cis-trans* nomenclature will not suffice for compounds with more than two differently substituted atoms. For these compounds, a system is used in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest-numbered ring member bearing a substituent giving rise to *cis-trans* isomerism. The reference group is indicated by the symbol *r*. Three stereoisomers named according to this system are 3(*S*), 5(*R*)-dimethylcyclohexan-*s*-1-ol (**74**), 3(*S*), 5(*R*)-dimethylcyclohexan-*r*-1-ol (**75**), and 3(*S*), 5(*S*)-dimethylcyclohexan-*s*-1-ol (**76**). The last example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives the cis designation to the first substituent after the reference. Another example is 2(*S*), 4(*S*)-dimethyl-6*s*-ethyl-1,3-dioxane (**77**).



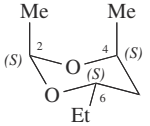
74



75



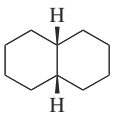
76



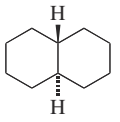
77

4.J.iii. *cis–trans* Isomerism of Fused and Bridged Ring Systems

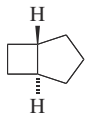
Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems, there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the trans configuration is impossible and the junction must be cis. The smallest trans junction that has been prepared when one ring is four membered is a four–five junction; *trans*-bicyclo[3.2.0]heptane (**78**) is known.[241] For the bicyclo[2.2.0] system (a four–four fusion), only cis compounds have been made. The smallest known trans junction when one ring is three membered is a six–three junction (a bicyclo[4.1.0] system). An example is **79**.[242] When one ring is three-membered and the other eight-membered (an eight–three junction), the trans-fused isomer is more stable than the corresponding cis-fused isomer.[243]



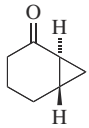
cis-Decalin



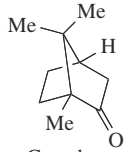
trans-Decalin



78



79

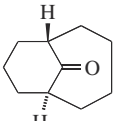


Camphor

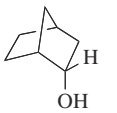
In *bridged* bicyclic ring systems, two rings share more than two atoms. In these cases, there may be fewer than 2^n isomers, because of the structure of the system. For example, there are only two isomers of camphor (a pair of enantiomers), although it has two stereogenic carbons. In both isomers, the methyl and hydrogen are cis. The trans pair of

[241] Meinwald, J.; Tufariello, J.J.; Hurst, J.J. *J. Org. Chem.* ***1964***, *29*, 2914.
[242] Paukstelis, J.V.; Kao, J. *J. Am. Chem. Soc.* ***1972***, *94*, 4783. For references to other examples, see Dixon, D.A.; Gassman, P.G. *J. Am. Chem. Soc.* ***1988***, *110*, 2309.
[243] Corbally, R.P.; Perkins, M.J.; Carson, A.S.; Laye, P.G.; Steele, W.V. *J. Chem. Soc. Chem. Commun.* ***1978***, 778.

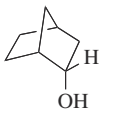
enantiomers is impossible in this case, since the bridge *must* be cis. The smallest bridged system so far prepared in which the bridge is trans is the [4.3.1] system; the trans ketone (**80**) has been prepared.[244] In this case, there are four isomers, since both the trans and the cis, which has also been prepared, are pairs of enantiomers.



80

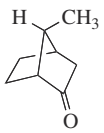


exo-2-Norborneol

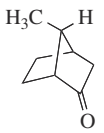


endo-2-Norborneol

When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges that do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix *endo-* is used when the substituent is closer to the longer of the two unsubstituted bridges; the prefix *exo-* is used when the substituent is closer to the shorter bridge; for example, When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made. For example, if one of the two bridges contains a functional group, the endo isomer is the one in which the substituent is closer to the functional group:



endo-7-Methyl-2-norcamphor

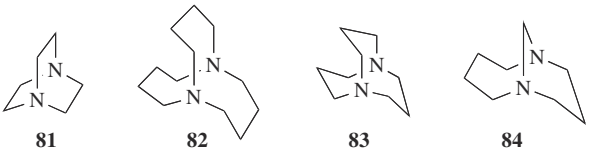


exo-7-Methyl-2-norcamphor

4.K. OUT–IN ISOMERISM

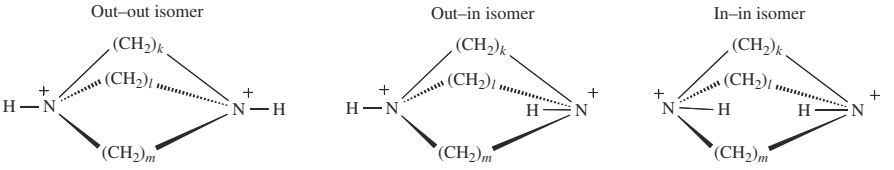
Another type of stereoisomerism, called *out–in* isomerism (or *in–out*),[245] is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In medium-sized bicyclic ring systems, *in–out* isomerism is possible,[246] and the bridgehead nitrogen atoms adopt the arrangement that is more stable.[247] A focus on the nitrogen lone pairs reveals that 1,4-diazabicyclo[2.2.2]octane (**81**) favors the *out–out* isomer, that 1,6-diazabicyclo[4.4.4] tetradecane (**82**) the *in–in*,[248] that 1,5-diazabicyclo[3.3.3]undecane (**83**) has nearly planar nitrogen atoms,[249] and that 1,9-diazabicyclo[7.3.1]tridecane (**84**) is *in–out*.[250] One can also focus on the NH unit in the case of ammonium salts.

[244] Winkler, J.D.; Hey, J.P.; Williard, P.G. *Tetrahedron Lett.* ***1988***, *29*, 4691.
[245] See Alder, R.W. *Acc. Chem. Res.* ***1983***, *16*, 321.
[246] Alder, R.W.; East, S.P. *Chem. Rev.* ***1996****, 96*, 2097.
[247] Alder, R.W. *Tetrahedron* ***1990****, 46*, 683.
[248] Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* ***1983***, 999.
[249] Alder, R.W.; Goode, N.C.; King, T.J.; Mellor, J.M.; Miller, B.W. *J. Chem. Soc., Chem. Commun.* ***1976***, 173; Alder, R.W.; Arrowsmith, R.J.; Casson, A.; Sessions, R.B.; Heilbronner, E.; Kovac, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* ***1981****, 103*, 6137.
[250] Alder, R.W.; Heilbronner, E.; Honegger, E.; McEwen, A.B.; Moss, R.E.; Olefirowicz, E.; Petillo, P.A.; Sessions, R.B.; Weisman, G.R.; White, J.M.; Yang, Z.-Z. *J. Am. Chem. Soc.* ***1993****, 115*, 6580.



81 **82** **83** **84**

In the examples **85–87**, when k, l, and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park[251] isolated several such isomers with k, l, and m varying from 6 to 10. In the 9,9,9 compound, the cavity of the in–in isomer is large enough to encapsulate a



85 **86** **87**

chloride ion that is hydrogen bonded to the two N—H groups. The species thus formed is a cryptate, but differs from the cryptates discussed at Section 3.C.ii in that there is a negative rather than a positive ion enclosed.[252] Even smaller ones (e.g., the 4,4,4 compound) have been shown to form mono-inside-protonated ions.[253] In compound **88**, which has four quaternary nitrogen atoms, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.[254] This ion does not display *in–out* isomerism. *Out–in* and *in–in* isomers have also been prepared in analogous all-carbon tricyclic systems.[255]

It is known that chiral phosphanes are more pyramidal and that inversion is more difficult, usually requiring temperatures well over 100°C for racemization.[256] Alder and Read[257] found that deprotonation of bis(phosphorane) **89,** which is known to have an *in–out* structure with significant P—P bonding, leads to a rearrangement and the *out–out* diphosphane **90**. Reprotonation gives **89**,[258] with inversion at the nonprotonated phosphorus atom occurring at room temperature.

[251] Simmons, H.E.; Park, C.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2428; Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1968***, *90*, 2429, 2431; Simmons, H.E.; Park, C.H.; Uyeda, R.T.; Habibi, M.F. *Trans. N.Y. Acad. Sci.* ***1970***, *32*, 521. See also, Dietrich, B.; Lehn, J.M.; Sauvage, J.P. *Tetrahedron* ***1973***, *29*, 1647; Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron* ***1973***, *29*, 1629.

[252] See Schmidtchen, F.P.; Gleich, A.; Schummer, A. *Pure. Appl. Chem.* ***1989***, *61*, 1535; Pierre, J.; Baret, P. *Bull. Soc. Chim. Fr.* ***1983***, II-367. See also, Hosseini, M.W.; Lehn, J. *Helv. Chim. Acta* ***1988***, *71*, 749.

[253] Dietrich, B.; Lehn, J.M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* ***1989***, *30*, 4125; Wallon, A.; Peter-Katalinić, J.; Werner, U.; Müller, W.M.; Vögtle, F. *Chem. Ber.* ***1990***, *123*, 375.

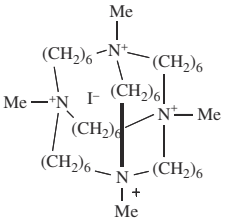
[254] Schmidtchen, F.P.; Müller, G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1115. See also, Schmidtchen, F.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8249, *Top. Curr. Chem.* ***1986***, *132*, 101.

[255] McMurry, J.E.; Hodge, C.N. *J. Am. Chem. Soc.* ***1984***, *106*, 6450; Winkler, J.D.; Hey, J.P.; Williard, P.G. *J. Am. Chem. Soc.* ***1986***, *108*, 6425.

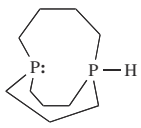
[256] See Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 3090; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400.

[257] Alder, R.W.; Read, D. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2879.

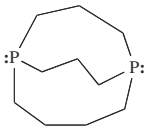
[258] Alder, R.W.; Ellis, D.D.; Gleiter, R.; Harris, C.J.; Lange, H.; Orpen, A.G.; Read, D.; Taylor, P.N. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 1657.



88



89

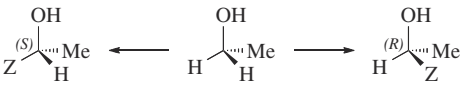


90

4.L. ENANTIOTOPIC AND DIASTEREOTOPIC ATOMS, GROUPS, AND FACES[259]

Many molecules contain atoms or groups that appear to be equivalent, but a close inspection will show them to be actually different. We can test whether two atoms are equivalent by replacing each of them in turn with some other atom or group. If the new molecules created by this process are identical, the original atoms are equivalent; otherwise they are not. There are three cases.

1. In the case of malonic acid [$CH_2(COOH)_2$], propane (CH_2Me_2), or any other molecule of the form CH_2Y_2,[260] replacing either of the CH_2 hydrogens by a group Z will give the identical compound. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent as are the two bromine atoms of 1,3-dibromopropane.
2. In the case of ethanol, replacing one of the CH_2 hydrogens by a group Z will give one enantiomer of the compound ZCHMeOH (**91**), while replacement of the other hydrogen gives the *other* enantiomer (**92**). Since the two compounds that result upon replacement of H by Z (**91** and **92**) are not identical but enantiomeric, the hydrogens are *not* equivalent. Two atoms or groups that upon replacement with a third group give enantiomers are defined as *enantiotopic*. In any symmetrical environment, the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. For example, in a reaction



91 **92**

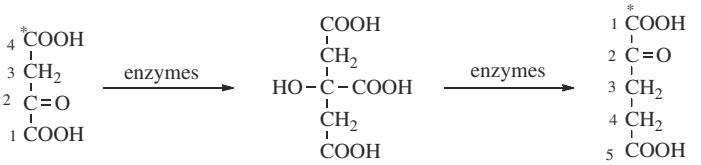
with a chiral reagent they may be attacked at different rates. This has important consequences in enzymatic reactions,[261] since enzymes are capable of much greater discrimination than ordinary chiral reagents. An example is found in the Krebs

[259] These terms were coined by Mislow. See Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1; Mislow, K.; Raban, M. *Top. Stereochem.* ***1967***, *1*, 1. See also, Jennings, W.B. *Chem. Rev.* ***1975***, *75*, 307.

[260] In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.

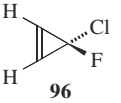
[261] For a review, see Benner, S.A.; Glasfeld, A.; Piccirilli, J.A. *Top. Stereochem.* ***1989***, *19*, 127. For a nonenzymatic example, see Job, R.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 809.

cycle, in biological organisms, where oxaloacetic acid (**93**) is converted to α-oxoglutaric acid (**95**) by a sequence that includes citric acid (**94**) as an intermediate. When **93** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **95**, despite the fact that **94** is not chiral. The two



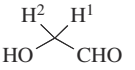
93 **94** **95**

CH_2COOH groups of **94** are enantiotopic and the enzyme easily discriminates between them.[262] Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic if neither W nor Y is chiral. However, enantiotopic atoms and groups may also be found in other molecules (e.g., the hydrogen atoms in 3-fluoro-3-chlorocyclopropene, **96**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.



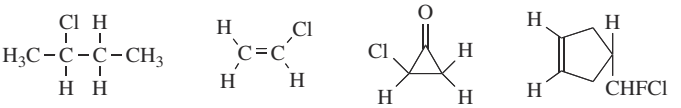
96

The term *prochiral*[263] is used for a compound or group that has two enantiotopic atoms or groups (e.g., CX_2WY). That atom or group X that would lead to an R compound if preferred to the other is called *pro*-(*R*). The other is *pro*-(*S*); for example,



H^2 = pro-(*S*)
H^1 = pro-(*R*)

3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**97**), vinyl chloride (**98**), and chlorocyclopropanone (**99**), as well as the two alkenyl hydrogens



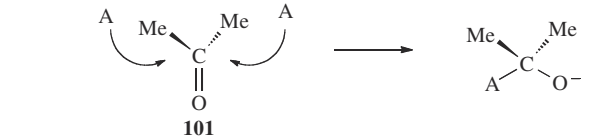
97 **98** **99** **100**

of **100**. Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react at different rates with achiral reagents, but an even

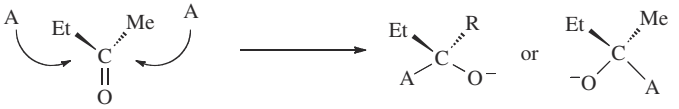
[262] The experiments were carried out by Evans Jr., E.A.; Slotin, L. *J. Biol. Chem.* ***1941***, *141*, 439; Wood, H.G.; Werkman, C.H.; Hemingway, A.; Nier, A.O. *J. Biol. Chem.* ***1942***, *142*, 31. The correct interpretation was given by Ogston, A.G. *Nature (London)* ***1948***, *162*, 963. For discussion, see Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1, pp. 5–7, 45–70.

[263] Hirschmann, H.; Hanson, K.R. *Tetrahedron* ***1974***, *30*, 3649.

more important consequence is that in NMR spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the NMR, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.[264] The term *isochronous* is used for hydrogens that are indistinguishable in the NMR.[265] In practice, the NMR signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents (Sec. 4.J) or by changing the solvent or concentration. Note that X atoms or groups (CX_2WY) are diastereotopic if either W or Y is chiral.

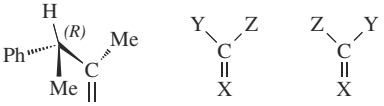


101



102

Just as there are enantiotopic and diastereotopic atoms and groups, *enantiotopic and diastereotopic faces* in trigonal molecules may be distinguished. Again, there are three cases: (1) In formaldehyde or acetone (**101**), attack by an achiral reagent A from either face of the molecule gives rise to the same transition state and product; the two faces are thus equivalent and there is only one product. (2) In 2-butanone (**102**) or acetaldehyde, attack by an achiral A at one face gives a chiral transition state and the enantiomeric products arise from attack at one or the other face. Such faces are *enantiotopic*. Attack at an enantiotopic face by a chiral reagent will generate another stereogenic center, which gives diastereomers that may not be formed in equal amounts. (3) In a case like **103**, the two faces are obviously not equivalent and are called *diastereotopic*. Enantiotopic and diastereotopic faces can be named by an extension of the CIP system (Sec. 4.E.i).[263] If the three groups as arranged by the sequence rules have the order X > Y > Z, that face in which the groups in this sequence are clockwise (as in **104**) is the *Re* face (from Latin *rectus*), whereas **105** shows the *Si* face (from Latin *sinister*).



103 **104** **105**

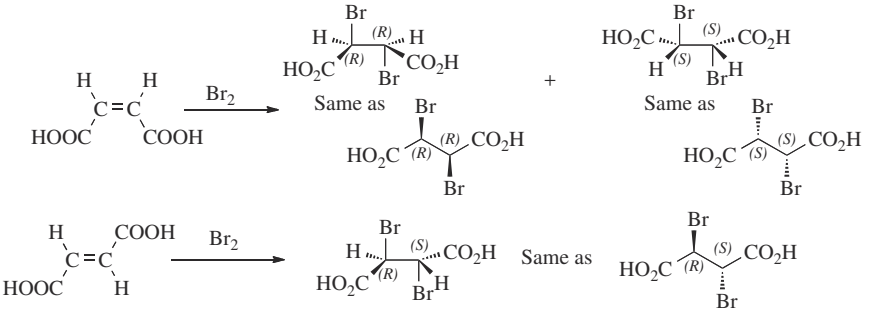
[264] Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 1837; Burlingame, T.G.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4294; Pirkle, W.H.; Burlingame, T.G. *Tetrahedron Lett.* ***1967***, 4039.

[265] For a review of isochronous and nonisochronous nuclei in NMR, see van Gorkom, M.; Hall, G.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 14. For a discussion, see Silverstein, R.M.; LaLonde, R.T. *J. Chem. Educ.* ***1980***, *57*, 343.

Note that new terminology has been proposed.[266] The concept of sphericity is used, and the terms homospheric, enantiospheric, and hemispheric have been coined to specify the nature of an orbit (an equivalent class) assigned to a coset representation.[267] Using these terms, prochirality can be defined: If a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral.[258]

4.M. STEREOSPECIFIC AND STEREOSELECTIVE SYNTHESES

Any reaction in which only one of a set of stereoisomers is formed predominantly is called a *stereoselective* synthesis.[268] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers, However, if both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective, but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective, not a stereospecific reaction.



4.N. CONFORMATIONAL ANALYSIS

For acyclic molecules with single covalent bonds, there is rotation about those bonds. As a practical matter, such rotation leads to different arrangements of the atoms with respect to a given bond, but all arrangements constitute the same molecule. The different

[266] Fujita, S. *J. Org. Chem.* ***2002****, 67,* 6055.
[267] Fujita, S. *J. Am. Chem. Soc.* ***1990***, *112,* 3390.
[268] For a further discussion of these terms and of stereoselective reactions in general, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 835–990.

arrangements for a molecule due to such rotation are called *rotamers*. In principle, there is rotation about every single bond and a near infinite number of rotamers. If two different 3D spatial arrangements of the atoms in an acyclic molecule are interconvertible merely by free rotation about bonds, they are called *conformations*.[269] If they are not interconvertible, they are called *configurations*.[270] Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus nonseparable. The terms "conformational isomer" or more commonly "rotamer"[271] are used to identify one of many structures that result from rotation about single covalent bonds. Typically, the conformation is the average of the collection of lower energy rotatmers for an acyclic compound. A number of methods have been used to determine conformations.[272] These include X-ray and electron diffraction, IR, Raman, UV, NMR,[273] and microwave spectra,[274] PES,[275] supersonic molecular jet spectroscopy,[276] and ORD and CD measurements.[277] Ring current NMR anisotropy has been applied to conformational analysis,[278] as has chemical shift simulation.[279] Some of these methods are useful only for solids. It must be kept in mind that the conformation of a molecule in the solid state is not necessarily the same as in solution.[280] Conformations can be *calculated* by a method called molecular mechanics (Sec. 4.P). A method was reported that characterized six-membered ring conformations as a linear combination of ideal basic conformations.[281] The term absolute conformation has been introduced for molecules where

[269] See Bonchev, D.; Rouvray, D.H. *Chemical Topology*, Gordon and Breach, Australia, ***1999***.

[270] See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

[271] Öki, M. *The Chemistry of Rotational Isomers*, Springer–Verlag, Berlin, ***1993***.

[272] For a review, see Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***, pp. 129–188.

[273] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Marshall, J.L. *Carbon–Carbon and Carbon–Proton NMR Couplings*, VCH, NY, ***1983***. For reviews, see Anet, F.A.L.; Anet, R. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 343–420; Kessler, H. *Angew. Chem. Int. Ed.* ***1970***, *9*, 219; Ivanova, T.M.; Kugatova-Shemyakina, G.P. *Russ. Chem. Rev.* ***1970***, *39*, 510; See also, Whitesell, J.K.; Minton, M. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*, Chapman and Hall, NY, ***1987***.

[274] For a review see Wilson, E.B. *Chem. Soc. Rev.* ***1972***, *1*, 293.

[275] For a review, see Klessinger, M.; Rademacher, P. *Angew. Chem. Int. Ed.* ***1979***, *18*, 826.

[276] Breen, P.J.; Warren, J.A.; Bernstein, E.R.; Seeman, J.I. *J. Am. Chem. Soc.* ***1987***, *109*, 3453.

[277] See Kagan, H.B. *Determination of Configurations by Dipole Moments*, *CD*, *or ORD* (Vol. 2 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Crabbé, P. *ORD and CD in Chemistry and Biochemistry*, Academic Press, NY, ***1972***; Snatzke, G. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Sadtler Research Laboratories, Philadelphia, ***1967***; Velluz, L.; Legrand, M.; Grosjean, M. *Optical Circular Dichroism*, Academic Press, NY, ***1965***. For reviews, see Smith, H.E. *Chem. Rev.* ***1983***, *83*, 359; Håkansson, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 67–120; Hudec, J.; Kirk, D.N. *Tetrahedron* ***1976***, *32*, 2475; Schellman, J.A. *Chem. Rev.* ***1975***, *75*, 323.

[278] Chen, J.; Cammers-Goodwin, A. *Eur. J. Org. Chem.* ***2003***, 3861.

[279] Iwamoto, H.; Yang, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* ***2001***, *42*, 49.

[280] See Kessler, H.; Zimmermann, G.; Förster, H.; Engel, J.; Oepen, G.; Sheldrick, W.S. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1053.

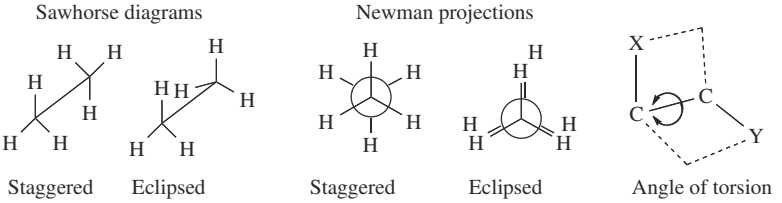
[281] Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* ***2001***, *57*, 477.

one conformation is optically inactive but, by internal rotation about a C(sp^3)—C(sp^3) bond, optically active conformers are produced.[282]

Note that "free" rotation about single bonds is not possible in cyclic molecules, but rather pseudorotation that leads to different conformations. This discussion will therefore separate rotation in acyclic molecules from pseudorotation in cyclic molecules.

4.N.i. Conformation in Open-Chain Systems[283]

For any open-chain molecule with a single bond that connects two sp^3 carbon atoms, an infinite number of rotatmers are possible, each of which has a certain energy associated with it, which leads to an infinite number of conformations. As a practical matter, the number of conformations is much less. If one ignores duplications due to symmetry, the number of conformations can be *estimated* as being $> 3^n$, where $n =$ the number of internal C—C bonds. For example, *n*-pentane, has 11, *n*-hexane 35, *n*-heptane 109, *n*-octane 347, *n*-nonane 1101, and *n*-decane 3263.[284] For ethane, there are two important rotamers that are taken as the extremes, a conformation of highest (marked eclipsed) and one of lowest (marked staggered) potential energy, depicted in two ways as sawhorse diagrams or Newman projections. In *Newman projection formulas*, the observer looks at the C—C bond head on. The three lines emanating from the center of the circle represent the bonds coming from the front carbon, with respect to the observer.



The staggered conformation is the conformation of lowest potential energy for ethane. As rotation about the bond occurs, the energy gradually increases until the eclipsed conformation is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 4.4 illustrates this finding. The *angle of torsion*, which is a dihedral angle, is the angle between the X—C—C and the C—C—Y planes, as shown in the diagram. For ethane, the difference in energy is $\sim$2.9 kcal mol^{-1} (12 kJ mol^{-1}).[285] This difference is called the *energy barrier or rotational barrier*,[286] since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. There was

[282] Öki, M.; Toyota, S. *Eur. J. Org. Chem.* ***2004***, 255.
[283] See Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* ***1989***, *25*, 1. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 597–664. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 35–47.
[284] Goto, H.; Osawa, E.; Yamato, M. *Tetrahedron* ***1993***, *49*, 387.
[285] Lide Jr., D.R. *J. Chem. Phys.* ***1958***, *29*, 1426; Weiss, S.; Leroi, G.E. *J. Chem. Phys.* ***1968***, *48*, 962; Hirota, E.; Saito, S.; Endo, Y. *J. Chem. Phys.* ***1979***, *71*, 1183.
[286] Mo, Y.; Gao, J. *Acc. Chem. Res.* ***2007***, *40*, 113.

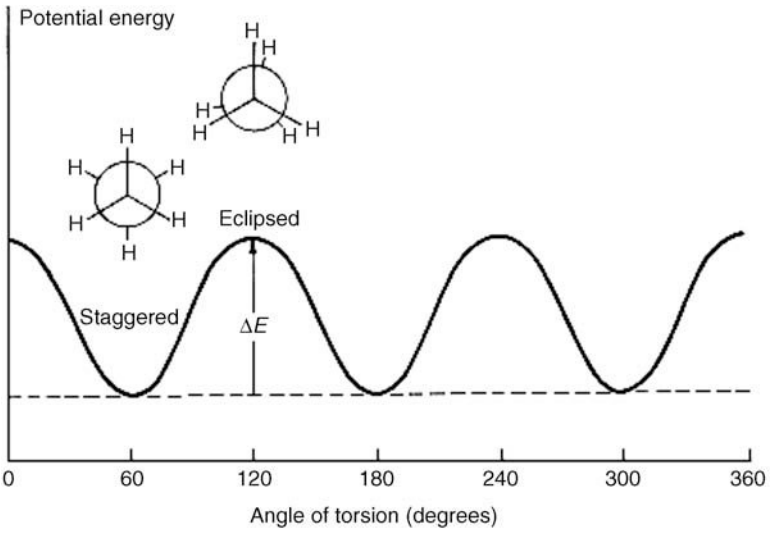


FIG. 4.4. Conformational energy diagram for ethane.

much speculation about the cause of the barriers and many explanations have been suggested.[287] It has been concluded from MO calculations (see Sec. 4.P) that the barrier is caused by repulsion between overlapping filled molecular orbitals.[288] The staggered conformation of ethane is lowest in energy because the orbitals of the C—H bonds in this conformation have the least amount of overlap with the C—H orbitals of the adjacent carbon.

At ordinary temperatures, enough rotational energy is present for the ethane molecule to rotate rapidly, but it spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers, presumably due to steric interactions between the larger units.[289] When the barriers are large enough, as in the case of suitably substituted biphenyls (Sec. 4.C, category 5) or the diadamantyl compound mentioned (see **107** and **108**) rotation at room temperature is completely prevented, which is described as a *q* configuration not *a* conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

A 1,2-disubstituted ethane (YCH_2–CH_2Y or YCH_2–CH_2X,[290] e.g., *n*-butane),[291] is somewhat more complicated. There are four extremes: a fully staggered conformation, called *anti, trans,* or *antiperiplanar*; another staggered conformation, called *gauche* or *synclinal*; and two types of eclipsed conformations, called *synperiplanar* and *anticlinal*.

[287] See Lowe, J.P. *Prog. Phys. Org. Chem.* ***1968***, *6*, 1; Oosterhoff, L.J. *Pure Appl. Chem.* ***1971***, *25*, 563; Wyn-Jones, E.; Pethrick, R.A. *Top. Stereochem.* ***1970***, *5*, 205; Pethrick, R.A.; Wyn-Jones, E. *Q. Rev. Chem. Soc.* ***1969***, *23*, 301; Brier, P.N. *J. Mol. Struct.* ***1970***, *6*, 23; Lowe, J.P. *Science*, ***1973***, *179*, 527.

[288] See Pitzer, R.M. *Acc. Chem. Res.* ***1983***, *16*, 207. See, however, Bader, R.F.W.; Cheeseman, J.R.; Laidig, K.E.; Wiberg, K.B.; Breneman, C. *J. Am. Chem. Soc.* ***1990***, *112*, 6530.

[289] See Bader, W.; Cortés-Guzmán, F. *Can. J. Chem.* ***2009***, *87*, 1583.

[290] See Wiberg, K.B.; Murcko, M.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8029; Allinger, N.L.; Grev, R.S.; Yates, B.F.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 114.

[291] Cormanich, R.A.; Freitas, M.P. *J. Org. Chem.* ***2009***, *74*, 8384; Mo, Y. *J. Org. Chem.* ***2010***, *75*, 2733.

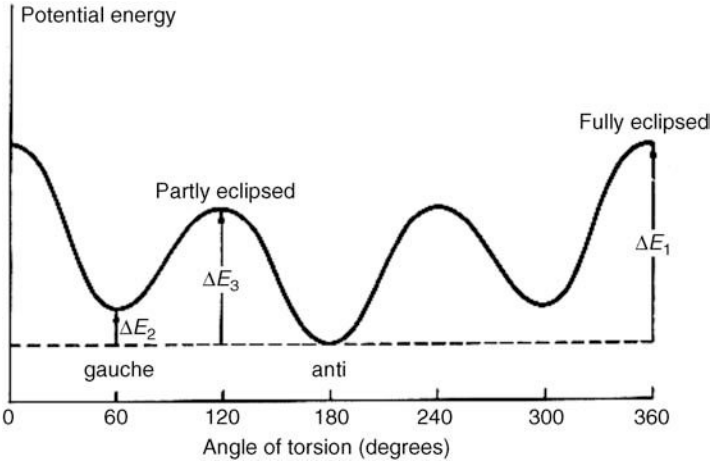
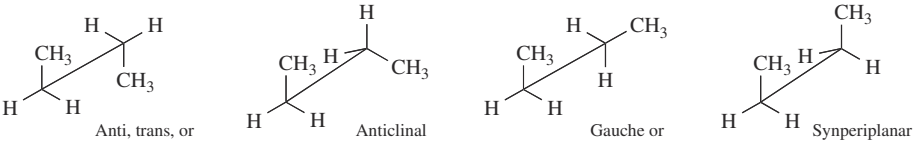


FIG. 4.5. Conformational energy for $YCH_2—CH_2Y$ or $YCH_2—CH_2X$. For *n*-butane, $\Delta E_1 = 4–6$, $\Delta E_2 = 0.9$, and $\Delta E_3 = 3.4\,\text{kcal mol}^{-1}$ (17–25, 3.8, $14\,\text{kJ mol}^{-1}$, respectively).



106

An energy diagram for this system is given in Fig. 4.5. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, a consideration of dipole moment and polarizability measurements led to the conclusion that for 1,2-dichloroethane in CCl_4 solution at 25°C ~ 70% of the molecules are in the *anti* and ~ 30% in the *gauche* conformation.[292] The corresponding figures for 1,2-dibromoethane are 89% *anti* and 11% *gauche*.[293] The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

It may be observed that the *gauche* conformation of butane (see **106**), or any other similar molecule, appears to be chiral. It is not. The lack of optical activity in such compounds arises from the fact that **106** is not a static molecule, but is in dynamic equilibrium with many other conformations, including its mirror image. In effect, they interconvert too rapidly for separation.

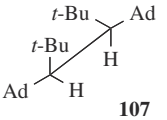
For butane and for most other molecules of the forms $YCH_2—CH_2Y$ and $YCH_2—CH_2X$, the *anti* conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially

[292] Le Fèvre, R.J.W.; Orr, B.J. *Aust. J. Chem.* ***1964***, *17*, 1098.
[293] See Schrumpf, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 146.

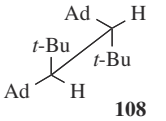
fluorine and oxygen. Thus 2-fluoroethanol,[294] 1,2-difluoroethane,[295] and 2-fluoroethyl trichloroacetate ($FCH_2CH_2OCOCCl_3$)[296] exist predominantly in the *gauche* form and compounds, such as, 2-chloroethanol and 2-bromoethanol,[294] also prefer the *gauche* form. It has been proposed that the preference for the *gauche* conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*; that is, a tendency to adopt that structure that has the maximum number of *gauche* interactions between adjacent electron pairs or polar bonds.[297] It was believed that the favorable *gauche* conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation does not do for molecules like 2-fluoroethyl trichloroacetate. It has in fact been ruled out for 2-fluoroethanol as well.[298] The effect of β-substituents in Y—C—C—OX systems where Y = F or SiR_3 has been examined and there is a small bond shortening effect on C—OX that is greatest when OX is a good leaving group. Bond lengthening was also observed with the β-silyl substituent.[299] Other exceptions are known, where small electronegative atoms are absent. For example 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the *gauche* conformation,[300] even though 1,1,2,2-tetrafluoroethane prefers the *anti*.[301] Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the *gauche* conformation,[302] and 2,3-dimethylbutane shows no preference for either.[303] Furthermore, the solvent can exert a powerful effect. For example, the compound 2,3-dinitro-2,3-dimethylbutane exists entirely in the *gauche* conformation in the solid state, but in benzene, the *gauche*/*anti* ratio is 79:21; while in CCl_4 the *anti* form is actually favored (*gauche*/*anti* ratio 42:58).[304] In many cases, there are differences in the conformation of these molecules between the gas and the liquid phase (as when X = Y = OMe) because of polar interactions with the solvent.[305]

In one case, two conformational isomers of a single aliphatic hydrocarbon, 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane, have proven stable enough for isolation at room temperature.[306] The two isomers **107** and **108** were separately crystallized, and the structures were proven by X-ray crystallography. The actual dihedral angles are distorted from the 60° angles shown in the drawings, due to steric hindrance between the large adamantyl and *tert*-butyl groups.

[294] See Davenport, D.; Schwartz, M. *J. Mol. Struct.* ***1978***, *50*, 259; Huang, J.; Hedberg, K. *J. Am. Chem. Soc.* ***1989***, *111*, 6909.
[295] See Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* ***1980***, *102*, 3987; Fernholt, L.; Kveseth, K. *Acta Chem. Scand. Ser. A* ***1980***, *34*, 163.
[296] Abraham, R.J.; Monasterios, J.R. *Org. Magn. Reson.* ***1973***, *5*, 305.
[297] See Wolfe, S. *Acc. Chem. Res.* ***1972***, *5*, 102. See also, Phillips, L.; Wray, V. *J. Chem. Soc. Chem. Commun.* ***1973***, 90; Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2371; Zefirov, N.S. *J. Org. Chem. USSR* ***1974***, *10*, 1147; Juaristi, E. *J. Chem. Educ.* ***1979***, *56*, 438.
[298] Griffith, R.C.; Roberts, J.D. *Tetrahedron Lett.* ***1974***, 3499.
[299] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.
[300] Kagarise, R.E. *J. Chem. Phys.* ***1956***, *24*, 300.
[301] Brown, D.E.; Beagley, B. *J. Mol. Struct.* ***1977***, *38*, 167.
[302] Ritter, W.; Hull, W.; Cantow, H. *Tetrahedron Lett.* ***1978***, 3093.
[303] Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K.U. *J. Am. Chem. Soc.* ***1977***, *99*, 4573.
[304] Tan, B.; Chia, L.H.L.; Huang, H.; Kuok, M.; Tang, S. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1407.
[305] Smith, G.D.; Jaffe, R.L.; Yoon, D.Y. *J. Am. Chem. Soc.* ***1995***, *117*, 530. For an analysis of *N,N*-dimethylacetamide, see Mack, H.-G.; Oberhammer, H. *J. Am. Chem. Soc.* ***1997***, *119*, 3567.
[306] Flamm-ter Meer; Beckhaus, H.; Peters, K.; von Schnering, H.; Fritz, H.; Rüchardt, C. *Chem. Ber.* ***1986***, *119*, 1492; Rüchardt, C.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529.

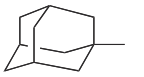


107



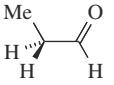
108

Ad =



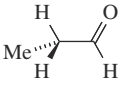
All the conformations so far discussed have involved rotation about sp^3–sp^3 bonds. Many studies have also been made of compounds with sp^3–sp^2 bonds.[307] For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal, the eclipsing conformations have lower energy than the other two, with **109** favored over **110** by $\sim$1 kcal mol^{-1} (4 kJ mol^{-1}).[308] As already pointed out (Sec. 4.K.i), for a few of these compounds, rotation is slow enough to permit *cis-trans* isomerism, although for simple compounds rotation is rapid. The cis conformer of acetic acid was produced in solid Ar,[309] and it was reported that acetaldehyde has a lower rotational barrier ($\sim$1 kcal mol^{-1} or 4 kJ mol^{-1}) than ethane.[310] Calculations have examined the rotational barriers around the CO and CC bonds in formic acid, ethanedial, and glycolaldehyde molecules.[311]

Eclipsing



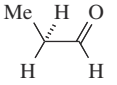
109

Eclipsing

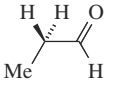


110

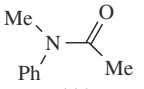
Bisecting



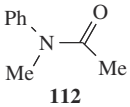
Bisecting



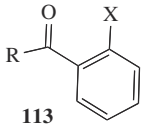
Other carbonyl compounds exhibit rotation about sp^3–sp^3 bonds, including amides.[312] In *N*-acetyl-*N*-methylaniline, the cis- conformation (**111**) is more stable than the trans- (**112**) by 3.5 kcal mol^{-1} (14.6 kJ mol^{-1}).[313] This is due to destabilization of (*S*) due to steric hindrance between two methyl groups, and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons in the twisted phenyl orientation.[313]



111



112



113

[307] See Sinegovskaya, L.M.; Keiko, V.V.; Trofimov, B.A. *Sulfur Rep.* ***1987***, *7*, 337 (for enol ethers and thioethers); Karabatsos, G.J.; Fenoglio, D.J. *Top. Stereochem.* ***1970***, *5*, 167; Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* ***1973***, *18*, 1 (for carboxylic esters). See also, Cossé-Barbi, A.; Massat, A.; Dubois, J.E. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 919; Dorigo, A.E.; Pratt, D.W.; Houk, K.N. *J. Am. Chem. Soc.* ***1987***, *109*, 6591.

[308] Allinger, N.L.; Hickey, M.J. *J. Mol. Struct.* ***1973***, *17*, 233; Gupta, V.P. *Can. J. Chem.* ***1985***, *63*, 984.

[309] Macoas, E.M.S.; Khriachtchev, L.; Pettersson, M.; Fausto, R.; Rasanen, M. *J. Am. Chem. Soc.* ***2003***, *125,* 16188.

[310] Davidson, R.B.; Allen, L.C. *J. Chem. Phys.* ***1971***, *54*, 2828.

[311] Ratajczyk, T.; Pecul, M.; Sadlej, J. *Tetrahedron* ***2004***, *60*, 179.

[312] Avalos, M.; Babiano, R.; Barneto, J.L.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2001***, *66*, 7275. Also see Modarresi-Alam, A.R.; Najafi, P.; Rostamizadeh, M.; Keykha, H.; Bijanzadeh, H.-R.; Kleinpeter, E. *J. Org. Chem.* ***2007***, *72,* 2208.

[313] Saito, S.; Toriumi, Y.; Tomioka, A.; Itai, A. *J. Org. Chem.* ***1995***, *60*, 4715.

A similar conformational analysis has been done with formamide derivatives,[314] with secondary amides,[315] and for hydroxamide acids.[316] It is known that thioformamide has a larger rotational barrier than formamide, which can be explained by a traditional picture of amide "resonance" that is more appropriate for the thioformamide than formamide itself.[317] Torsional barriers in α-keto amides have been reported,[318] and the C—N bond of acetamides,[319] thioamides,[320] enamides[321] carbamates ($R_2N—CO_2R'$),[322] and enolate anions derived from amides[323] have been examined. It is known that substituents influence rotational barriers.[324]

In Section 4.C, category 5, atropisomerism was possible when ortho substituents on biphenyl derivatives and certain other aromatic compounds prevented rotation about the $C^{sp^3}—C^{sp^3}$ bond. The presence of ortho-substituents can also influence the conformation of certain groups.[325] In **113**, R = alkyl and the carbonyl unit is planar, with the *trans* C=O···F conformer is more stable when X = F. When $X = CF_3$, the cis and trans are planar and the trans predominates.[326] When R = alkyl, there is one orthogonal conformation, but there are two interconverting nonplanar conformations when R = *O*-alkyl.[326] In 1,2-diacylbenzenes, the carbonyl units tend to adopt a twisted conformation to minimize steric interactions.[327]

4.N.ii. Conformation in Six-Membered Rings[328]

For cyclic compounds, complete rotation (360°) about a single bond is impossible. However, repulsion between atoms and groups leads to motion about each bond called pseudorotation. Pseudorotation leads to a variety of different conformations, depending on the size of the ring. In many such conformations, the ring is said to be puckered. For cyclohexane, there are two extreme conformations in which all the angles are tetrahedral (the C—C—C angles in cyclohexane are actually 111.5°).[329] These are called the *boat* and the *chair* conformations. The chair conformation is the low-energy structure that participates in a dynamic equilibrium (there are two chair conformations that are

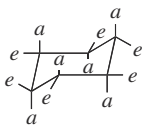
[314] Axe, F.U.; Renugopalakrishnan, V.; Hagler, A.T. *J. Chem. Res.* ***1998***, 1. For an analysis of DMF see Wiberg, K.B.; Rablen, P.R.; Rush, D.J.; Keith, T.A. *J. Am. Chem. Soc.* ***1995***, *117*, 4261.
[315] Avalos, M.; Babiano, R.; Barneto, J.L.; Cintas, P.; Clemente, F.R.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2003****, 68*, 1834.
[316] Kakkar, R.; Grover, R.; Chadha, P. *Org. Biomol. Chem.* ***2003***, *1*, 2200.
[317] Wiberg, K.B.; Rablen, P.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2201.
[318] Bach, R.D.; Mintcheva, I.; Kronenberg, W.J.; Schlegel, H.B. *J. Org. Chem.* ***1993***, *58*, 6135.
[319] Ilieva, S.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* ***2002***, *67*, 6210.
[320] Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* ***2001***, *123,* 2038; *J. Org. Chem.* ***2002***, *67*, 826.
[321] Rablen, P.R.; Miller, D.A.; Bullock, V.R.; Hutchinson, P.H.; Gorman, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 218.
[322] Deetz, M.J.; Forbes, C.C.; Jonas, M.; Malerich, J.P.; Smith, B.D.; Wiest, O. *J. Org. Chem.* ***2002***, *67,* 3949.
[323] Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* ***1999***, *1*, 2069.
[324] Smith, B.D.; Goodenough-Lashua, D.M.; D'Souza, C.J.E.; Norton, K.J.; Schmidt, L.M.; Tung, J.C. *Tetrahedron Lett.* ***2004****, 45*, 2747.
[325] For an analysis of barriers to rotation in such compounds, see Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J.E. *J. Org. Chem.* ***2006****, 71,* 5474.
[326] Abraham, R.J.; Angioloni, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 41.
[327] Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.
[328] See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 54–67.
[329] See Geise, H.J.; Buys, H.R.; Mijlhoff, F.C. *J. Mol. Struct.* ***1971***, *9*, 447; Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* ***1973***, *18*, 163.

equivalent in energy for cyclohexane), and the boat form is a higher energy form[330] in equilibrium with a somewhat more stable form



Boat Chair Twist

known as the *twist* conformation. The twist form is $\sim$1.5 kcal mol^{-1} (6.3 kJ mol^{-1}) more stable than the boat because it has less eclipsing interaction (see below).[331] The chair form is more stable than the twist form by $\sim$5 kcal mol^{-1} (21 kJ mol^{-1}).[332] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely as equilibrating chair forms.[333] It is known that the boat or twist form exists transiently. In some cases, chair and twist–boat conformations have actually been observed (*cis*-1,4-di-*tert*-butylcyclohexane, e.g.).[334]



Axial and equatorial bonds
in chair cyclohexane

An inspection of the chair form shows that six of its bonds are directed differently from the other six. On each carbon, one bond is directed up or down and the other more or less in the "plane" of the ring. The up or down bonds are called *axial* and the others are *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. This result is incorrect, however, as it has never been possible to isolate isomers of this type at room temperature.[335] In order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only if the boat or twist conformations are transient species. Conversion of one chair form to another requires an activation energy of $\sim$10 kcal mol^{-1} (42 kJ mol^{-1})[336] and is very rapid at room temperature.[337] However, by working at low temperatures, Jensen and Bushweller[338] were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution. Equatorial chlorocyclohexane has a half-life of 22 years in solution at -160°C.

[330] See Dunitz, J.D. *J. Chem. Educ.* ***1970***, *47*, 488.
[331] For a review of nonchair forms, see Kellie, G.M.; Riddell, F.G. *Top. Stereochem.* ***1974***, *8*, 225.
[332] Squillacote, M.; Sheridan, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3244.
[333] See Wiberg, K.B.; Castejon, H.; Bailey, W.F.; Ochterski, J. *J. Org. Chem.* ***2000***, *65*, 1181.
[334] Gill, G.; Pawar, D.M.; Noe, E.A. *J. Org. Chem.* ***2005***, *70*, 10726.
[335] See Wehle, D.; Fitjer, L. *Tetrahedron Lett.* ***1986***, *27*, 5843.
[336] See Anet, F.A.L.; Bourn, A.J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 760. See also, Strauss, H.L. *J. Chem. Educ.* ***1971***, *48*, 221.
[337] See Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 287–307; Anderson, J.E. *Top. Curr. Chem.* ***1974***, *45*, 139.
[338] See Jensen, F.R.; Bushweller, C.H.; *J. Chem. Soc.* ***1969***, *91*, 3223.


Norbornane


Twistane

In some molecules, the twist conformation is actually preferred.[339] Of course, in certain bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.

In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position because there is an interaction between the substituent and the axial hydrogens in the axial 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group.[340] Alkyl groups have a greater preference for the equatorial position than polar groups. For alkyl groups, the preference increases with size, although size seems to be unimportant for polar groups. Both the large HgBr[341] and HgCl[342] groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 4.3 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial (these are called *A* values),[343] although it must be kept in mind that they vary somewhat with physical state, temperature, and solvent.[344] Values for other groups in kcal mol^{-1} include D[345] (0.008), NH_2[346] (1.4), $CH{=}CH_2$[347] (1.7), CH_3[348] (1.74), C_6H_{11}[349] (2.15), $Si(CH_3)$,[350] (2.4–2.6), OCH_3[351] (0.75), C_6H_5[352] (2.7), and t-$(CH_3)_3C$[353] (4.9).

For alkyl groups in disubstituted compounds, the conformation is such that as many groups as possible adopt the equatorial position. This conformation will minimize the axial interactions (known as $A^{1,3}$-strain), and will be the lower energy conformation. The preference for one chair conformation over the other depends on the groups attached to the cyclohexane ring, and their relative positions on that ring. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2,

[339] Weiser, J.; Golan, O.; Fitjer, L.; Biali, S.E. *J. Org. Chem.* ***1996***, *61*, 8277.
[340] For a study of thioether, sulfoxide and sulfone substituents, see Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.,* ***2000***, *65*, 969.
[341] Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 6337.
[342] Anet, F.A.L.; Krane, J.; Kitching, W.; Dodderel, D.; Praeger, D. *Tetrahedron Lett.* ***1974***, 3255.
[343] These values are from Corey, E.J.; Feiner, N.F. *J. Org. Chem.* ***1980***, *45*, 765. Also see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139. See also, Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579 and see Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 54–67.
[344] See Ford, R.A.; Allinger, N.L. *J. Org. Chem.* ***1970***, *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139.
[345] Anet, F.A.L.; O'Leary, D.J. *Tetrahedron Lett.* ***1989***, *30*, 1059.
[346] Buchanan, G.W.; Webb, V.L. *Tetrahedron Lett.* ***1983***, *24*, 4519.
[347] Eliel, E.L.; Manoharan, M. *J. Org. Chem.* ***1981***, *46*, 1959.
[348] Booth, H.; Everett, J.R. *J. Chem. Soc. Chem. Commun.* ***1976***, 278.
[349] Hirsch, J.A. *Top. Stereochem.* ***1967***, *1*, 199.
[350] Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* ***1982***, *47*, 5153.
[351] Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579.
[352] Squillacote, M.E.; Neth, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 198. Values of 2.59–2.92 kcal mol^{-1}(10.84–12.23 kJ mol^{-1}) were determined for 4-X-C_6H_4— substituents (X = NO_2, Cl, MeO): see Kirby, A.J.; Williams, N. H. *J. Chem. Soc. Chem. Commun.* ***1992***, 1285, 1286.
[353] Manoharan, M.; Eliel, E.L. *Tetrahedron Lett.* ***1984***, *25*, 3267.

TABLE 4.3 Free-Energy Differences between Equatorial and Axial Substituents on a Cyclohexane Ring[a,b]

Group	*A* (kcal mol $^{-1}$)	kJ mol^{-1}	Group	*A* (kcal mol^{-1})	kJ mol^{-1}
H	0		N=	0.5	2.09
F	0.2	0.84	N≡	0.2	0.84
Cl	0.4	1.67	NO_2	1.1	4.61
Br	0.4	1.67	C≡	0.2	0.84
I	0.4	1.67	aryl	3.0	12.56
PR_3	1.6	6.7	CO_2^-	2.0	8.37
SR	0.8	3.35	CHO	0.8	3.35
S(O)R	1.9	7.95	C=	1.3	5.44
$S(O_2)R$	2.5	10.47	CR_3	6.0	25.11
OR	0.8	3.35	CHR_2	2.1	8.79
NH_3^+	2.0	8.37	CH_2R	1.8	7.54
NR_3^+	2.1	8.79			
NHR	1.3	5.44			

[Reprinted with permission from Corey, E.J.; Feiner, N.F. *J. Org. Chem.* ***1980****, 45,* 765. Copyright © ***1980*** American Chemical Society.]

[a]See Ref. 343.

[b]The *A* values or $A^{1,3}$-strain.

compound both may be equatorial or both axial. This finding is also true for 1,4-disubstituted cyclohexanes, but the reverse holds for 1,3-compounds: the trans isomer must have the *age* conformation and the cis isomer may be *a* or *ee*. For alkyl groups, the *ee* conformation predominates over the *a*, but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *a* conformations about equally populated[354] and most *trans*-1,2-dihalocyclohexanes exist predominantly in the *a* conformation.[355] Note that in the latter case the two halogen atoms are anti in the *a* conformation, but *gauche* in the *ee* conformation.[356]

Since compounds with alkyl equatorial substituents are generally more stable, trans-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their cis-1,2 isomers, which must exist in the *age* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is ∼2 kcal mol^{-1} (8 kJ mol^{-1}). Similarly, trans-1,4 and cis-1,3 compounds are more stable than their stereoisomers.

An interesting anomaly is *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, in which the six isopropyl groups prefer the axial position, although the six ethyl groups of the corresponding hexaethyl compound prefer the equatorial position.[357] The alkyl groups of these compounds can of course only be all axial or all equatorial, and it is likely that the molecule prefers the all-axial conformation because of unavoidable strain in the other conformation.

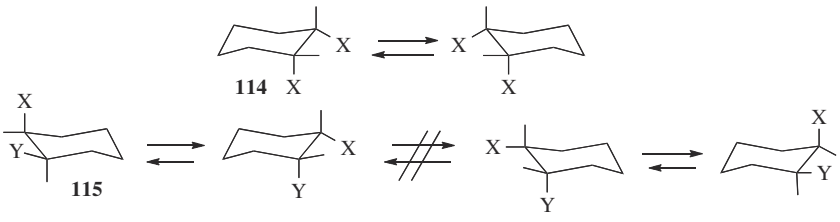
[354] Abraham, R.J.; Rossetti, Z.L. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 582. See also, Hammarström, L.; Berg, U.; Liljefors, T. *Tetrahedron Lett.* ***1987***, *28*, 4883.

[355] Abraham, M.H.; Xodo, L.E.; Cook, M.J.; Cruz, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1503; Samoshin, V.V.; Svyatkin, V.A.; Zefirov, N.S. *J. Org. Chem. USSR* ***1988***, *24*, 1080, and references cited therein. See Zefirov, N.S.; Samoshin, V.V.; Subbotin, O.A.; Sergeev, N.M. *J. Org. Chem. USSR* ***1981***, *17*, 1301.

[356] For a case of a preferential diaxial conformation in 1,3 isomers, see Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 4606.

[357] Golan, O.; Goren, Z.; Biali, S.E. *J. Am. Chem. Soc.* ***1990***, *112*, 9300.

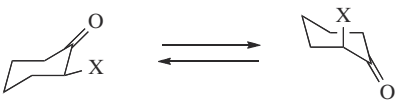
Incidentally, it is now apparent, at least in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even though they are not planar (Sec. 4.K.ii). In the case of both a *cis*-1,2-X,X-disubstituted and a *cis*-1,2-X,Y-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case (**114**) conversion of one chair form to the other which of course happens rapidly, turns the molecule into its mirror image, while in the latter case (**115**) rapid interconversion does not give the mirror image, but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **114** is not due to a plane of symmetry, but to a rapid interconversion of the molecule and its mirror image. A similar situation holds for cis-1,3 compounds. However, for cis-1,4 isomers (both X,X and X,Y) optical inactivity arises from a plane of symmetry in both conformations. All *trans*-1,2- and *trans*-1,3-disubstituted cyclohexanes are chiral (whether X,X or X,Y), while trans-1,4 compounds (both X,X and X,Y) are achiral, since all conformations have a plane of symmetry. It has been shown that the equilibrium is very dependent on both the solvent and the concentration of the disubstituted cyclohexane.[358] A theoretical study of the 1,2-dihalides showed a preference for the diaxial form with X = Cl, but predicted that the energy difference between diaxial and diequatorial was small when X = F.[359]



The conformation of a group can be frozen into a desired position by putting a large alkyl group into the ring (most often *tert*-butyl), which introduces significant $A^{1,3}$-strain and leads to a preference for the chair with the groups in the equatorial position.[360] It is known that silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane, some monosilyloxycyclohexanes and some silylated sugars have unusually large populations of chair conformations with axial substituents.[361] Adjacent silyl groups in the 1,2-disubstituted series show a stabilizing interaction in all conformations, generally leading to unusually large axial populations.

[358] Abraham, R.J.; Chambers, E.J.; Thomas, W.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1061.
[359] Wiberg, K.B. *J. Org. Chem.* ***1999***, *64,* 6387.
[360] This idea was suggested by Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955***, *77*, 5561. See Saunders, M.; Wolfsberg, M.; Anet, F.A.L.; Kronja, O. *J. Am. Chem. Soc.* ***2007***, *129,* 10276.
[361] Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* ***2003***, *125,* 15163.

TABLE 4.4 Proportion of Axial Conformation in 2-Substituted Cyclohexanones, in $CDCl_3$[a]



X	% Axial Conformation
F	17 ± 3
Cl	45 ± 4
Br	71 ± 4
I	88 ± 5
MeO	28 ± 4
MeS	85 ± 7
MeSe	(92)
Me_2N	44 ± 3
Me	(26)

Reprinted with permission from Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* ***1993****, 58,* 7865. Copyright © 1993 American Chemical Society.

[a]See Ref. 366.

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms. For example, cyclohexanone and cyclohexene, are similar.[362–364] The barrier to interconversion in cyclohexane has been calculated to be 8.4–12.1 kcal mol^{-1}(35.2–50.7 kJ mol^{-1}).[365] Cyclohexanone derivatives also assume a chair–conformation. Substituents at C-2 can assume an axial or equatorial position depending on steric and electronic influences. The proportion of the conformation with an axial X group is shown in Table 4.4 for a variety of substituents (X) in 2-substituted cyclohexanones.[366]

[362] See Rabideau, P.W. The *Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH, NY, ***1989***; Vereshchagin, A.N. *Russ. Chem. Rev.* ***1983***, *52*, 1081; Johnson, F. *Chem. Rev.* ***1968****, 68*, 375. See also, Lambert, J.B.; Clikeman, R.R.; Taba, K.M.; Marko, D.E.; Bosch, R.J.; Xue, L. *Acc. Chem. Res.* ***1987****, 20*, 454.

[363] See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

[364] See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 61–65.

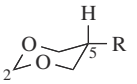
[365] Laane, J.; Choo, J. *J. Am. Chem. Soc.* ***1994***, *116*, 3889.

[366] Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* ***1993***, *58*, 7865.

4.N.iii. Conformation in Six-Membered Rings Containing Heteroatoms

In six-membered rings containing heteroatoms,[367] the basic principles are the same; that is, there are chair, twist, and boat forms, axial, and equatorial groups. The conformational equilibrium for tetrahydropyridines, for example, has been studied.[368] In certain compounds, a number of new factors enter the picture. Only two of these will be examined.[369]

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[370] the $A^{1,3}$-strain is much lower. This fact indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. There is some evidence of a homoanomeric interaction in these systems.[371] Similar behavior is found in the 1,3-dithianes,[372] and 2,3-disubstituted-1,4-dithianes have also been examined.[373] With certain non-alkyl substituents (e.g., F, NO_2, SOMe,[374] NMe_3^+) the axial position is actually preferred.[375]



Substituted 1,3-dioxanes

2. An alkyl group located on a carbon α to a heteroatom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this phenomenon, known as the *anomeric effect*,[376] is the greater stability of α-glucosides over β-glucosides. A number of explanations have been offered for the anomeric

[367] See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycle*, VCH, NY, ***1988***; Riddell, F.G. *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, NY, ***1980***; Juaristi, *E. Acc. Chem. Res.* ***1989***, *22*, 357; Crabb, T.A.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1984***, *36*, 1; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739; *Pure Appl. Chem.* ***1971***, *25*, 509; *Acc. Chem. Res.* ***1970***, *3*, 1; Lambert, J.B. *Acc. Chem. Res.* ***1971***, *4*, 87.

[368] Bachrach, S.M.; Liu, M. *Tetrahedron Lett.* ***1992***, *33*, 6771.

[369] These factors are discussed by Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739.

[370] Riddell, F.G.; Robinson, M.J.T. *Tetrahedron* ***1967***, *23*, 3417; Eliel, E.L.; Knoeber, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 3444. See also, Eliel, E.L.; Alcudia, F. *J. Am. Chem. Soc.* ***1974***, *96*, 1939. See Cieplak, P.; Howard, A.E.; Powers, J.P.; Rychnovsky, S.D.; Kollman, P.A. *J. Org. Chem.* ***1996***, *61*, 3662 for conformational energy differences in 2,2,6-trimethyl-4-alkyl-1,3-dioxane.

[371] Cai, J.; Davies, A.G.; Schiesser, C.H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1151.

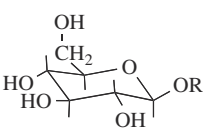
[372] Hutchins, R.O.; Eliel, E.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2703. See also, Juaristi, E.; Cuevas, G. *Tetrahedron* ***1999***, *55*, 359.

[373] Strelenko, Y.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.E.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* ***1994***, *50*, 10107.

[374] Gordillo, B.; Juaristi, E.; Matínez, R.; Toscano, R.A.; White, P.S.; Eliel, E.L. *J. Am. Chem. Soc.* ***1992***, *114*, 2157.

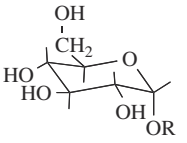
[375] Kaloustian, M.K.; Dennis, N.; Mager, S.; Evans, S.A.; Alcudia, F.; Eliel, E.L. *J. Am. Chem. Soc.* ***1976***, *98*, 956. See also, Eliel, E.L.; Kandasamy, D.; Sechrest, R.C. *J. Org. Chem.* ***1977***, *42*, 1533.

[376] See Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Szarek, W.A.; Horton, D. *Anomeric Effect*, American Chemical Society, Washington, ***1979***; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Elmsford, NY, ***1983***, pp. 4–26; Zefirov, N.S. *Tetrahedron* ***1977***, *33*, 3193; Lemieux, R.U. *Pure Appl. Chem.* ***1971***, *27*, 527.



A β-glucoside

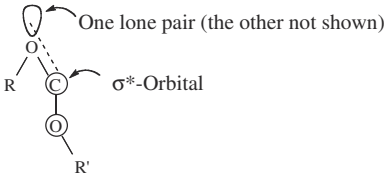
116



An α-glucoside

117

effect.[377] The one[378] that has received the most acceptance[379] is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **117**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom:



This can happen only if the two orbitals are in the positions shown. The situation can also be represented by this type of hyperconjugation (called "negative hyperconjugation," see Sec. 2.M):



It is possible that simple repulsion between parallel dipoles in **116** also plays a part in the greater stability of **117**. It has been shown that aqueous solvation effects reduce anomeric stabilization in many systems, particularly for tetrahydropyranosyls.[380] In contrast to cyclic acetals, simple acyclic acetals rarely adopt the anomeric conformation, apparently because the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon–oxygen bonds.[381] In all *cis*-2,5-di-*tert*-butyl-1,4-cyclohexanediol, hydrogen bonding stabilizes the otherwise high-energy form[382] and 1,3-dioxane (**118**) exists largely as the twist conformation shown.[383] The conformational preference of 1-methyl-1-silacyclohexane (**121**) has been studied.[384] A strongly decreased activation barrier in

[377] Juaristi, E.; Cuevas, G. *Tetrahedron* ***1992***, *48*, 5019.

[378] See Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39, pp. 73–77; Wolfe, S.; Whangbo, M.; Mitchell, D.J. *Carbohydr. Res.* ***1979***, *69*, 1.

[379] See Praly, J.; Lemieux, R.U. *Can. J. Chem.* ***1987***, *65*, 213; Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron* ***1987***, *43*, 4699. For evidence against it, see Box, V.G.S. *Heterocycles* ***1990***, *31*, 1157.

[380] Cramer, C.J. *J. Org. Chem.* ***1992***, *57*, 7034; Booth, H.; Dixon, J.M.; Readshaw, S.A. *Tetrahedron* ***1992***, *48*, 6151.

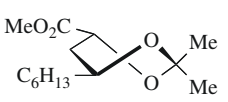
[381] Anderson, J.E. *J. Org. Chem.* ***2000***, *65*, 748.

[382] Stolow, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2170; Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *J. Am. Chem. Soc.* ***1964***, *86*, 2165. Also see Fitjer, L.; Scheuermann, H.; Klages, U.; Wehle, D.; Stephenson, D.S.; Binsch, G. *Chem. Ber.* ***1986***, *119*, 1144.

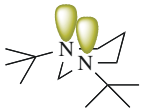
[383] Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* ***1993***, *58*, 5251.

[384] Arnason, I.; Kvaran, A.; Jonsdottir, S.; Gudnason, P. I.; Oberhammer, H. *J. Org. Chem.* ***2002***, *67,* 3827.

silacyclohexane was observed, as compared to that in the parent ring, and is explained by the longer endocyclic Si—C bonds.



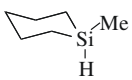
118



119



120

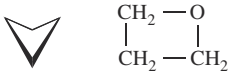


121

Second-row heteroatoms are known to show a substantial anomeric effect.[385] There appears to be evidence for a reverse anomeric effect in 2-aminotetrahydropyrans,[386] but it has been called into question whether a reverse anomeric effect exists at all.[387] In **119**, the lone-pair electrons assume an axial conformation and there is an anomeric effect.[388] In **120**, however, the lone-pair electron orbitals are oriented *gauche* to both the axial and equatorial α-CH bond and there is no anomeric effect.[388]

4.N.iv. Conformation in Other Rings[389]

Three-membered saturated rings are usually planar, but other small rings can have some flexibility. Cyclobutane[390] is not planar, but exists as in **122**, with an angle between the planes of ∼35°.[391] The deviation from planarity is presumably caused by eclipsing in the planar form (see Sec. 4.Q.i). Oxetane is closer to



122 Oxetane

planarity because there is less eclipsing, with an angle between the planes of ∼10°.[392] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects.[393] There are two puckered conformations for cyclopentane, the *envelope* and the *half-chair*. There is little energy difference between these two forms and many five-membered ring systems have

[385] Salzner, U.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1993***, *115*, 10231; Aggarwal, V.K.; Worrall, J.M.; Adams, H.; Alexander, R.; Taylor, B.F. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 21.
[386] Salzner, U.; Schleyer, P.v.R. *J. Org. Chem.* ***1994***, *59*, 2138.
[387] Perrin, C.L. *Tetrahedron* ***1995***, *51*, 11901.
[388] Anderson, J.E.; Cai, J.; Davies, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 2633. For some controversy concerning the anomeric effect a related system, see Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem. Soc.* ***1994***, *116*, 715; Salzner, U. *J. Org. Chem.* ***1995***, *60*, 986.
[389] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 675–685 and 754–770.
[390] For reviews of the stereochemistry of four-membered rings, see Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231; Moriarty, R.M. *Top. Stereochem.* ***1974***, *8*, 271; Cotton, F.A.; Frenz, B.A. *Tetrahedron* ***1974***, *30*, 1587.
[391] Miller, F.A.; Capwell, R.J.; Lord, R.C.; Rea, D.G. *Spectrochim. Acta Part A*, ***1972***, *28*, 603. However, see Margulis, T.N. *J. Am. Chem. Soc.* ***1971***, *93*, 2193.
[392] Luger, P.; Buschmann, J. *J. Am. Chem. Soc.* ***1984***, *106*, 7118.
[393] See Fuchs, B. *Top. Stereochem.* ***1978***, *10*, 1; Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231.

conformations somewhere in between them.[394] Although in the envelope conformation one carbon is shown above the others,



Envelope Half-chair

ring motions cause each of the carbons in rapid succession to assume this position. The puckering rotates around the ring in what is called a *pseudorotation*[395] (see Sec. 4.O.ii). In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents [e.g., tetrahydrofuran (THF), cyclopentanone, C_3- and C_7-monosubstituted and disubstituted hexahydroazepin-2-ones (caprolactams),[396] tetrahydrothiophene *S*-oxide[397]], one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal mol^{-1} (22 kJ mol^{-1}).[398] Contrary to previous reports, there is only weak stabilization (<2 kcal mol^{-1}; <8 kJ mol^{-1}) of three-, four-, and five-membered rings by *gem*-dialkoxycarbonyl substituents (e.g., COOR).[399]

Rings larger than six-membered are always puckered[400] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, Sec. 4.Q.ii). The energy and conformations of the alkane series cycloheptane to cyclodecane has been reported.[401] The conformation shown for oxacyclooctane (**123**), for example, appears to be the most abundant one.[402] The conformations of other large-ring compounds have been studied, including cycloundecane,[403] 11-membered ring lactones,[404] 10- and 11-membered ring ketones,[405] and 11- and 14-membered ring lactams.[406] Dynamic NMR was used to determine the conformation large-ring cycloalkenes and lactones,[407] and C—H coupling constants have been used for conformational analysis.[408] Strain estimates have been made

[394] Willy, W.E.; Binsch, G.; Eliel, E.L. *J. Am. Chem. Soc.* ***1970***, *92*, 5394; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 423.

[395] Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 411; Poupko, R.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* ***1982***, *104*, 5307; Riddell, F.G.; Cameron K.S.; Holmes, S.A.; Strange, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 7555.

[396] Matallana, A.; Kruger, A.W.; Kingsbury, C.A. *J. Org. Chem.* ***1994***, *59*, 3020.

[397] Abraham, R.J.; Pollock, L.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2329.

[398] Carreira, L.A.; Jiang, G.J.; Person, W.B.; Willis, Jr., J.N. *J. Chem. Phys.* ***1972***, *56*, 1440.

[399] Verevkin, S.P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* ***1998***, 579.

[400] See Arshinova, R.P. *Russ. Chem. Rev.* ***1988***, *57*, 1142; Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* ***1987***, *64*, 568; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 307–321; Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 911; Anet, F.A.L. *Top. Curr. Chem.* ***1974***, *45*, 169; Dunitz, J.D. *Pure Appl. Chem.* ***1971***, *25*, 495. See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles* VCH, NY, ***1988***.

[401] Wiberg, K.B. *J. Org. Chem.* ***2003***, *68*, 9322.

[402] Meyer, W.L.; Taylor, P.W.; Reed, S.A.; Leister, M.C.; Schneider, H.-J.; Schmidt, G.; Evans, F.E.; Levine, R.A. *J. Org. Chem.* ***1992***, *57*, 291.

[403] Pawar, D.M.; Brown II, J.; Chen, K.-H.; Allinger, N.L.; Noe, E.A. *J. Org. Chem.* ***2006***, *71,* 6512.

[404] Spracklin, D.K.; Weiler, L. *J. Chem. Soc. Chem. Commun.* ***1992***, 1347; Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* ***1988***, *110*, 7858.

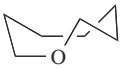
[405] Pawar, D.M.; Smith, S.V.; Moody, E.M.; Noe, E.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8241.

[406] Borgen, G.; Dale, J.; Gundersen, L.-L.; Krivokapic, A.; Rise, F.; Øverås, A.T. *Acta Chem. Scand. B*, ***1998***, *52*, 1110.

[407] Pawar, D.M.; Davids, K.L.; Brown, B.L.; Smith, S.V.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4580; Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4586.

[408] Kleinpeter, E.; Koch, A.; Pihlaja, K. *Tetrahedron* ***2005***, *61,* 7349.

for small-ring cyclic allenes and butatrienes.[409] Note that axial and equatorial hydrogens are found only in the chair conformations of six-membered rings. In rings of other sizes, the hydrogens protrude at angles that generally do not lend themselves to classification in this way,[410] although in some cases the terms "pseudo-axial" and "pseudo-equatorial" have been used to classify hydrogens in rings of other sizes.[411]



123

4.O. MOLECULAR MECHANICS[412]

Molecular Mechanics[413] describes a molecule in terms of a collection of bonded atoms that have been distorted from some idealized geometry due to nonbonded van der Waals (steric) and Coulombic (charge–charge) interactions. This approach is fundamentally different from MO theory that is based on quantum mechanics and that make no reference whatsoever to chemical bonding. The success of molecular mechanics depends on the ability to represent molecules in terms of unique valence structures, on the notion that bond lengths and angles may be transferred from one molecule to another and on a predictable dependence of geometrical parameters on the local atomic environment.

The molecular mechanics energy of a molecule is given as a sum of contributions arising from distortions from ideal bond distances (stretch contributions), bond angles (bend contributions) and torsion angles (torsion contributions), together with contributions from non-bonded interactions. This energy is commonly referred to as a *strain energy*, meaning that it reflects the inherent strain in a real molecule relative to a hypothetical idealized (strain-free) form.

$$\boldsymbol{E}^{\text{strain}} = \boldsymbol{E}_{\text{A}}^{\text{stretch}} + \boldsymbol{E}_{\text{A}}^{\text{bend}} + \boldsymbol{E}_{\text{A}}^{\text{torsion}} + \boldsymbol{E}_{\text{AB}}^{\text{nonboned}} \tag{4.1}$$

Stretch and bend terms are most simply given in terms of quadratic (Hooke's law) forms:

$$\boldsymbol{E}^{\text{strain}}(r) = \frac{1}{2} k^{\text{stretch}} (r - r^{\text{eq}})^2 \tag{4.2}$$

$$\boldsymbol{E}^{\text{bend}}(\alpha) = \frac{1}{2} k^{\text{bend}} (r - r^{\text{eq}})^2 \tag{4.3}$$

[409] Daoust, K.J.; Hernandez, S.M.; Konrad, K.M.; Mackie, I.D.; Winstanley, Jr., J.; Johnson, R.P. *J. Org. Chem.* ***2006***, *71,* 5708.

[410] For definitions of axial, equatorial, and related terms for rings of any size, see Anet, F.A.L. *Tetrahedron Lett.* ***1990***, *31*, 2125.

[411] For a discussion of the angles of the ring positions, see Cremer, D. *Isr. J. Chem.* ***1980***, *20*, 12.

[412] Thanks to Dr. Warren Hehre, Wavefunction, Inc., Irvine, CA. Personal communication. See Hehre, W.J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*, Wavefunction, Inc., Irvine, CA, ***2003***, pp. 56–57.

[413] For a review, see Rappe, A.K.; Casewit, C.J. *Molecular Mechanics Across Chemistry,* University Science Books, Sausalito, CA, ***1997***.

r and α are the bond distance and angle, respectively, and r^{eq} and α^{eq} are the ideal bond length and angle, respectively.

Torsion terms need to properly reflect the inherent periodicity of the particular bond involved in a rotation. For example, the threefold periodicity of the carbon–carbon bond in ethane may be represented by a simple cosine form.

$$\boldsymbol{E}^{\text{torsion}}(\omega) = k^{\text{torsion3}}[1 - \cos 3(\omega - \omega^{\text{eq}})] \tag{4.4}$$

Ω is the torsion angle, ω^{eq} is the ideal torsion angle and k^{torsion} is a parameter. Torsion contributions to the strain energy usually will also need to include contributions that are onefold and twofold periodic. These can be represented in the same manner as the threefold term.

$$\begin{aligned}\boldsymbol{E}^{\text{torsion}}(\omega) = {} & k^{\text{torsion1}}[1 - \cos(\omega - \omega^{\text{eq}})] + k^{\text{torsion2}}[1 - \cos 2(\omega - \omega^{\text{eq}})] \\ & + k^{\text{torsion3}}[1 - \cos 3(\omega - \omega^{\text{eq}})]\end{aligned} \tag{4.5}$$

Nonbonded interactions involve a sum of van der Waals (VDW) interactions and Coulombic interactions. The Coulombic term accounts for charge–charge interactions.

$$\boldsymbol{E}^{\text{nonbonded}}(r) = \boldsymbol{E}^{\text{VDW}}(r) + \boldsymbol{E}^{\text{Coulombic}}(r) \tag{4.6}$$

The VDW is made up of two parts, the first to account for strong repulsion on nonbonded atoms as they closely approach, and the second to account for weak long-range attraction, r is the nonbonded distance.

Molecular mechanics methods differ both in the form of the terms that make up the strain energy and in their detailed parameterization. Older methods (e.g., SYBYL[414]) use very simple forms and relatively few parameters, while newer methods (e.g., MM3,[415] MM4,[416] and MMFF[417]) use more complex forms and many more parameters. In general, the more complex the form of the strain energy terms and the more extensive the parameterization, the better the results. Of course, more parameters mean that more (experimental) data will be needed in their construction. Because molecular mechanics is not based on "physical fundamentals," but rather is essentially an interpolation scheme, its success depends on the availability of either experimental or high-quality theoretical data for parameterization. A corollary is that molecular mechanics would not be expected to lead to good results for "new" molecules, that is, molecules outside the range of their parameterization.

The two most important applications of molecular mechanics are geometry calculations on very large molecules (e.g., on proteins) and conformational analysis on molecules for which there may be hundreds, thousands, or even tens of thousands of distinct structures. It is here that methods based on quantum mechanics are simply not (yet) practical. It should be no surprise that equilibrium geometries obtained from molecular mechanics are generally in good accord with experimental values. There are ample data with which to

[414] Clark, M.; Cramer, III, R.D.; van Opdenbosch, N. *J. Computational Chem.* ***1989***, *10,* 982.
[415] Allinger, N.L.; Li, F.; Yun, Y.H. *J. Computational Chem.* ***1990***, *11,* 855, and later papers in this series.
[416] Allinger, N.L.; Chen, K.; Lii, J.-H. *J. Computational Chem.* ***1996***, *17,* 642, and later papers in this series.
[417] Halgren, T.A. *J. Computational Chem* ***1996***, *17,* 490, and later papers in this series.

parameterize and evaluate the methods. However, because there are very few experimental data relating to the equilibrium conformations of molecules and energy differences among different conformations, molecular mechanics calculations for these quantities need to be viewed with a very critical eye. In time, high-quality data from quantum mechanics will provide the needed data and allow more careful parameterization (and assessment) than now possible.

The most important limitation of molecular mechanics is its inability to provide thermochemical data. The reason for this is that the mechanics strain energy is specific to a given molecule (it provides a measure of how much this molecule deviates from an ideal arrangement), and different molecules have different ideal arrangements. For example, acetone and methyl vinyl ether have different bonds and would be referenced to different standards. The only exception occurs for conformational energy differences or, more generally, for energy comparisons among molecules with exactly the same bonding (e.g., *cis*- and *trans*-2-butene).

Because a molecular mechanics calculation reveals nothing about the distribution of electrons or distribution of charge in molecules, and because mechanics methods have not (yet) been parameterized to reproduce transition state geometries, they are of limited value in describing either chemical reactivity or product selectivity. There are, however, situations where steric considerations associated with either the product or reactants are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Because of the different strengths and limitations of molecular mechanics and quantum chemical calculations, it is now common practice to combine the two, for example, to use molecular mechanics to establish conformation (or at least a set of reasonable conformations) and then to quantum calculations to evaluate energy differences.

In practical terms, molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upward of a hundred atoms. Modern graphical based programs for desktop computers make the methods available to all chemists.

4.P. STRAIN

Steric strain[418] exists in a molecule when bonds are forced to make abnormal angles, usually due to repulsion of large atoms or groups attached to those bonds, but not always. This repulsion results in a higher energy than would be the case in the absence of the angle distortions. It has been shown that there is a good correlation between the $^{13}C—H$ coupling constants in NMR and the bond angles and bond force angles in strained organic molecules.[419] There are, in general, two kinds of structural features that result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap.[420] Such strain is called *small-angle strain or Baeyer strain*. The other arises when nonbonded

[418] See Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***; Wiberg, K.B. *Angew. Chem. Int. Ed.* ***1986***, *25*, 312; Greenberg, A.; Stevenson, T.A. *Mol. Struct. Energ.* ***1986***, *3*, 193; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1976***, *76*, 311; Cremer, D.; Kraka, E. *Mol. Struct. Energ.* ***1988***, *7*, 65.
[419] Zhao, C.-Y.; Duan, W.-S.; Zhang, Y.; You, X.-Z. *J. Chem. Res. (S)* ***1998***, 156.
[420] Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.

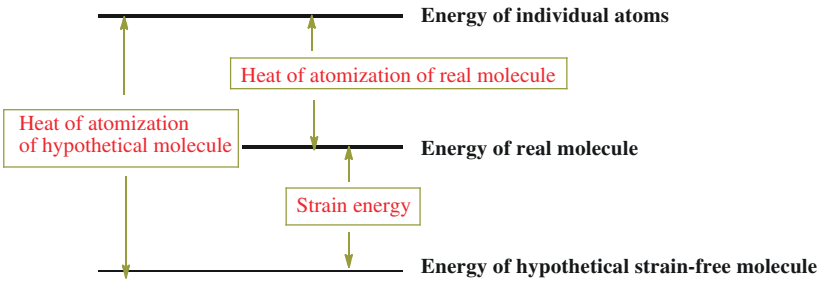


FIG. 4.6. Strain energy calculation.

atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions*. This latter type of strain is most often associated with the term steric strain.

Strained molecules possess *strain energy*. That is, their potential energies are higher than they would be if strain were absent.[421] The strain energy for a particular molecule can be estimated from heat of atomization or heat of combustion data. A strained molecule has a lower heat of atomization than it would have if it were strain-free (Fig. 4.6). As in the similar case of resonance energies (Sec. 2.B), strain energies cannot be known exactly, because the energy of a real molecule can be measured, but not the energy of a hypothetical unstrained model. It is also possible to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.[422]

4.P.i Strain in Small Rings

Three-membered rings have a great deal of angle strain (also called *Baeyer strain*), since 60° angles represent a large departure from the "normal" tetrahedral angles. Calculations have been interpreted to say that Baeyer strain in small ring systems originates from a decrease in nucleus–electron attraction compared to acyclic compounds,[423] but this has been challenged in later work.[424] However, in sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see Sec. 10.G.iii). Ring opening, of course, relieves the strain.[425] Cyclopropane,[426] which is even more strained[427] than ethylene oxide, is also cleaved more easily than would be expected for an alkane.[428] Thus,

[421] For discussions, see Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.
[422] For a review, see Rüchardt, C.; Beckhaus, K. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529. See also, Burkert, U.; Allinger, N.L. *Molecular Mechanisms*, American Chemical Society, Washington, ***1982***, pp. 169–194; Allinger, N. L. *Adv. Phys. Org. Chem.* ***1976***, *13*, 1, 45–47.
[423] Barić, D.; Maksić, Z.B. *Theor. Chem. Acc.* **2005**, 114, 222.
[424] Hohlneicher, G.; Packschies, L. *Tetrahedron Lett.* ***2007***, *48,* 6429. However, see Barić, D.; Maksić, Z.B. *Tetrahedron Lett.* ***2008***, *49,* 1428.
[425] For reviews of reactions of cyclopropanes and cyclobutanes, see Trost, B.M. *Top. Curr. Chem.* ***1986***, *133*, 3; Wong, H.N.C.; Lau, C.D.H.; Tam, K. *Top. Curr. Chem.* ***1986***, *133*, 83.
[426] For a treatise, see Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts.; Wiley, NY, ***1987***.
[427] See in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts, Wiley, NY, ***1987***, the papers by Wiberg, K.B. pt. 1., pp. 1–26; Liebman, J.F.; Greenberg, A. pt. 2, pp. 1083–1119; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1989***, *89*, 1225.
[428] See Wong, H.N.C.; Hon, M.; Ts, C.e; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165; Reissig, H. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 375–443.

pyrolysis at 450–500°C converts it to propene, bromination gives 1,3-dibromopropane,[429] and it can be hydrogenated to propane (though at high pressure).[430] Other three-membered rings are similarly reactive.[431] Alkyl substituents influence the strain energy of small ring compounds,[432] and carbonyl substitution also influences the strain energy.[433] *gem*-Dimethyl substitution, for example, "lowers the strain energy of cyclopropanes, cyclobutanes, epoxides, and dimethyldioxirane by 6–10 kcal mol^{-1} (25–42 kJ mol^{-1}) relative to an unbranched acyclic reference molecule."[432] The CH bond dissociation energy also tends to increase ring strain in small-ring alkenes.[434] Computation of the ring strain energy of 1,1-dimethylcyclobutane, however, shows "no significant enthalpic component of the *gem*-dimethyl effect as measured by the ring strain energy."[435]

There is much evidence, chiefly derived from NMR coupling constants, that the bonding in cyclopropanes is not the same as in compounds that lack small-angle strain.[436] For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals, each containing ~25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have ~33% *s* character, so that they are ~sp^2 orbitals, while the internal orbitals have ~17% *s* character, so that they may be called ~sp^5 orbitals.[437] Each of the three carbon–carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular-orbital calculations show that such bonds are not completely *s* in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring.[438] Figure 4.7 shows the direction of orbital overlap.[439] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[439] Molecular orbital calculations also show that the maximum electron densities of the C—C σ orbitals are bent away from the ring, with $\theta = 9.4°$ for cyclopropane and 3.4° for cyclobutane.[440] The bonds in cyclopropane are called *bent bonds* (sometimes, *banana bonds*), and are intermediate

[429] Ogg, Jr., R.A.; Priest, W.J. *J. Am. Chem. Soc.* ***1938***, *60*, 217.
[430] Shortridge, R.W.; Craig, R.A.; Greenlee, K.W.; Derfer, J.M.; Boord, C.E. *J. Am. Chem. Soc.* ***1948***, *70*, 946.
[431] See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147.
[432] Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* ***2002***, *67,* 2588.
[433] Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2006***, *128,* 4598.
[434] Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2004***, *126*, 4444; Tian, Z.; Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* ***2006***, *128,* 17087.
[435] Bachrach, S.M. *J. Org. Chem.* ***2008***, *73*, ***2466***. Also see Ringer, A.L.; Magers, D.H. *J. Org. Chem.* ***2007***, *72,* 2533.
[436] See Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 3811; Slee, T.S. *Mol. Struct. Energ.* ***1988***, *5*, 63; Casaarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.
[437] Randić, M.; Maksić, Z. *Theor. Chim. Acta* ***1965***, *3*, 59; Weigert, F.J.; Roberts, J.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5962.
[438] Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.
[439] See Hoffmann, R.; Davidson, R.B. *J. Am. Chem. Soc.* ***1971***, *93*, 5699. See also Ref. 438
[440] Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.

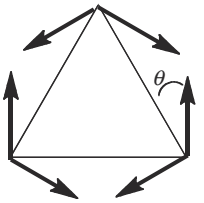
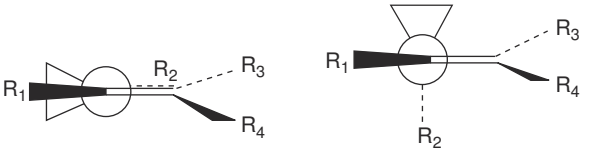


FIG. 4.7. Orbital overlap in cyclopropane. The arrows point toward the center of electron density.



(*a*) (*b*)

FIG. 4.8. Conformations of α-cyclopropylalkenes. Conformation (*a*) leads to maximum conjugation and conformation (*b*) to minimum conjugation

in character between σ and π, so that cyclopropanes behave in some respects like double-bond compounds.[441] For one thing, there is much evidence, chiefly from UV spectra,[442] that a cyclopropane ring is conjugated with an adjacent double bond. The conjugation is greatest for the conformation shown in Fig. 4.8*a* and is least or absent for the conformation shown in 4.8*b*, since overlap of the double-bond π orbital with two of the *p*-like orbitals of the cyclopropane ring is greatest in conformation *a*. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.[443] For other examples of the similarities in behavior of a cyclopropane ring and a double bond (see Sec. 4.O.iv).

Four-membered rings also exhibit angle strain, but much less than three-membered rings, and for that reason are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and although it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420°C gives two molecules of ethylene. As mentioned earlier (Sec. 4.O.iv), cyclobutane is not planar.

Many highly strained compounds containing small rings in fused systems have been prepared,[444] showing that organic molecules can exhibit much more strain than simple cyclopropanes or cyclobutanes.[445] Table 4.5 shows a few of these compounds.[446]

[441] See Tidwell, T.T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Groups,* pt. 1, Wiley, NY, ***1987***, pp. 565–632; Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, pp. 511–610, Wiley, NY, ***1970***.

[442] See Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1806; Drumright, R.E.; Mas, R.H.; Merola, J.S.; Tanko, J.M. *J. Org. Chem.* ***1990***, *55*, 4098.

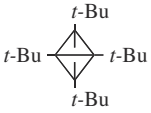
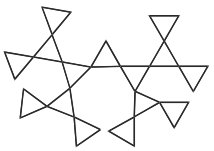
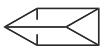
[443] Staley, S.W. *J. Am. Chem. Soc.* ***1967***, *89*, 1532; Pews, R.G.; Ojha, N.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5769. See, however, Noe, E.A.; Young, R.M. *J. Am. Chem. Soc.* ***1982***, *104*, 6218.

[444] See the reviews in *Chem. Rev.* ***1989***, *89*, 975, and the following: Jefford, C.W. *J. Chem. Educ.* ***1976***, *53*, 477; Seebach, D. *Angew. Chem. Int. Ed.* ***1965***, *4*, 121; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 210–220; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, ***1994***, pp. 771–811.

[445] For a useful classification of strained polycyclic systems, see Gund, P.; Gund, T.M. *J. Am. Chem. Soc.* ***1981***, *103*, 4458.

[446] For a computer program that generates IUPAC names for complex bridged systems, see Rücker, G.; Rücker, C. *Chimia* ***1990***, *44*, 116.

TABLE 4.5 Some Strained Small-Ring Compounds

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name if Any	Reference
	Bicyclo[1.1.0]butane	Bicyclobutane	447
	$\Delta^{1,4}$-Bicyclo[2.2.0]hexene		448
	Tricyclo[1.1.0.$0^{2,4}$]butane	Tetrahedrane	449
	Pentacyclo[5.1.0.$0^{2,4}$.$0^{3,5}$.$0^{6,8}$]octane	Octabisvalene	450
	Tricyclo[1.1.1.$0^{1,3}$]pentane	a [1.1.1] Propellane	364
	Tetradecaspiro [2.0.2.0.0.0.0.0.2.0.2.0.0.0.2.0.2. 0.0.1.0.0.2.0.2.0.0.0]untriacontane	[15] Triangulane	451
	Tetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]hexane	Prismane	452
	Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane	Cubane	453

[447] Lemal, D.M.; Menger, F.M.; Clark, G.W. *J. Am. Chem. Soc.* ***1963***, *85*, 2529; Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett*. ***1963***, 2173; Hoz, S. in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1121–1192; Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. For a review of [*n*.1.1] systems, see Meinwald, J.; Meinwald, Y.C. *Adv. Alicyclic Chem.* ***1966***, *1*, 1.

[448] Casanova, J.; Bragin, J.; Cottrell, F.D. *J. Am. Chem. Soc.* ***1978***, *100*, 2264.

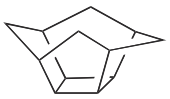
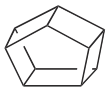
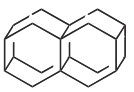
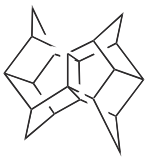
[449] Irngartinger, H.; Goldmann, A.; Jahn, R.; Nixdorf, M.; Rodewald, H.; Maier, G.; Malsch, K.; Emrich, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 993; Maier, G.; Fleischer, F. *Tetrahedron Lett.* ***1991***, *32*, 57. Also see Maier, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 309; Maier, G.; Rang, H.; Born, D. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 219–259; Maier, G.; Born, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1050.

[450] Rücker, C.; Trupp, B. *J. Am. Chem. Soc.* ***1988***, *110*, 4828.

[451] Von Seebach, M.; Kozhushkov, S.I.; Boese, R.; Benet-Buchholz, J.; Yufit, D.S.; Howard, J.A.K.; de Meijere, A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2495.

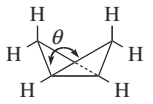
[452] Katz, T.J.; Acton, N. *J. Am. Chem. Soc.* ***1973***, *95*, 2738. See also, Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004.

TABLE 4.5 (*Continued*)

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name if Any	Reference
	Pentacyclo[5.4.1.0^{3,1}.0^{5,9}.0^{8,11}] dodecane	4[Peristylane]	454
	Hexacyclo[5.3.0.0^{2,6}.0^{3,10}.0^{4,9}.0^{5,8}] decane	Pentaprismane	455
	Tricyclo[3.1.1.1^{2,4}]octane	Diasterane	456
	Hexacyclo[4.4.0.0^{2,4}.0^{3,9}.0^{5,8}.0^{7,10}] decane		457
	Nonacyclo[10.8.0^{2,11}.0^{4,9}.0^{4,19}.0^{6,17}.-0^{7,16}.0^{9,14}.0^{14,19}]eicosane	A double tetraesterane	458
	Undecacyclo[9.9.0.0^{1,5}.0^{2,12}.0^{2,18}.0^{3,7}.-0^{6,10}.0^{8,12}.0^{11,15}.0^{13,17}.0^{16,20}]eicosane	Pagodane	459

[453] Hedberg, L.; Hedberg, K.; Eaton, P.E.; Nodari, N.; Robiette, A.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1514. For a review of cubanes, see Griffin, G.W.; Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 997.
[454] Paquette, L.A.; Fischer, J.W.; Browne, A.R.; Doecke, C.W. *J. Am. Chem. Soc.* ***1985***, *105*, 686.
[455] Eaton, P.E.; Or, Y.S.; Branca, S.J.; Shankar, B.K.R. *Tetrahedron* ***1986***, *42*, 1621. See also, Dauben, W.G.; Cunningham Jr., A.F. *J. Org. Chem.* ***1983***, *48*, 2842.
[456] Otterbach, A.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 554.
[457] Allred, E.L.; Beck, B.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2393.
[458] Hoffmann, V.T.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1006.
[459] Rihs, G. *Tetrahedron Lett.* ***1983***, *24*, 5857. See Mathew, T.; Keller, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* ***1996***, *37*, 4491 for the synthesis of azapagodanes (also called azadodecahedranes).

Perhaps the most interesting are cubane, prismane,[460] and the substituted tetrahedrane, since preparation of these ring systems had been the object of much endeavor. Prismane is tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane and many derivatives are known,[461] including bis (homohexaprismane) derivatives.[462] The bicyclobutane molecule is bent, with the angle θ between the planes equal to $126 \pm 3°$.[463] The rehybridization effect, described above for cyclopropane, is even more extreme in this molecule. Calculations have shown that the central bond is essentially formed by overlap of two *p* orbitals with little or no

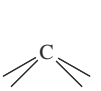


Angle between planes

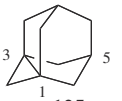
s character.[464] *Propellanes* are compounds in which two carbons, directly connected, are also connected by three other bridges. [1.1.1]Propellane is in the table and it is the smallest possible propellane.[465] It is in fact more stable than the larger [2.1.1]propellane and [2.2.1] propellane, which have been isolated only in solid matrixes at low temperature.[466] The bicyclo[1.1.1]pentanes are related to the propellanes except that the central connecting bond is missing, and several derivatives are known.[467] Even more complex systems are known.[468]

In certain small-ring systems, including small propellanes, the geometry of one or more carbon atoms is so constrained that all four of their valences are directed to the same side of a plane (inverted tetrahedron), as in **124**.[469] An example is 1,3-dehydroadamantane, **125,** which is also a propellane.[470] X-ray crystallography of the 5-cyano derivative of **125** shows that the four carbon valences at C-1 and C-3 are all directed "into" the molecule and none point outside.[471] Compound **125** is quite reactive; it is unstable in air, readily adds hydrogen, water, bromine, or acetic acid to the C-1—C-3 bond, and is easily polymerized. When two such atoms are connected by a bond (as in **125**), the bond is very long (the C-1—C-3 bond length in the 5-cyano derivative of **125** is 1.64 Å), as the atoms try to compensate in this way for their enforced angles. The high reactivity of the C-1—C-3 bond of **125** is not only caused by strain, but also by the fact that reagents find it easy to approach these atoms since there are no bonds (e.g., C—H bonds on C-1 or C-3) to get in the way.

[460] Gribanova, T.N.; Minyaev, R.M.; Minkin, V.I. *Russ. J. Org. Chem.* ***2007***, *43*, 1144.
[461] Gleiter, R.; Treptow, B.; Irngartinger, H.; Oeser, T. *J. Org. Chem.* ***1994***, *59*, 2787.
[462] Golobish, T.D.; Dailey, W.P. *Tetrahedron Lett.* ***1996***, *37*, 3239.
[463] Haller, I.; Srinivasan, R. *J. Chem. Phys.* ***1964***, *41*, 2745.
[464] Newton, M.D.; Schulman, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 767.
[465] Wiberg, K.B.; Waddell, S.T. *J. Am. Chem. Soc.* ***1990***, *112*, 2194; Seiler, S.T. *Helv. Chim. Acta* ***1990***, *73*, 1574; Bothe, H.; Schlüter, A. *Chem. Ber.* ***1991***, *124*, 587; Lynch, K.M.; Dailey, W.P. *J. Org. Chem.* ***1995***, *60*, 4666. See Wiberg, K.B. *Chem. Rev.* ***1989***, *89*, 975; Ginsburg, D. in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1193–1221; Ginsburg, D. *Top. Curr. Chem.* ***1987***, *137*, 1. For a discussion of charge density and bonding, see Coppens, P. *Angew. Chem. Int. Ed.* ***2005***, *44,* 6810.
[466] Wiberg, K.B.; Walker, F.H.; Pratt, W.E.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 3638.
[467] Della, E.W.; Taylor, D.K. *J. Org. Chem.* ***1994***, *59*, 2986.
[468] See Kuck, D.; Krause, R.A.; Gestmann, D.; Posteher, F.; Schuster, A. *Tetrahedron* ***1998***, *54*, 5247.
[469] For a review, see Wiberg, K.B. *Acc. Chem. Res.* ***1984***, *17*, 379.
[470] Scott, W.B.; Pincock, R.E. *J. Am. Chem. Soc.* ***1973***, *95*, 2040.
[471] Gibbons, C.S.; Trotter, J. *Can. J. Chem.* ***1973***, *51*, 87.



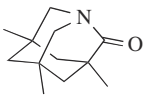
124



125

4.P.ii. Strain in Other Rings[472]

In rings larger than four-membered, there is no strain due to small bond angles, but there are three other kinds of strain. In the chair form of cyclohexane, which does not exhibit any of the three kinds of strain, all six carbon–carbon bonds have the two attached carbons in the *gauche* conformation. However, in five-membered rings and in rings containing from 7 to 13 carbons, any conformation in which all the ring bonds are *gauche* contains transannular interactions, that is, interactions between the substituents on C-1 and C-3 or C-1 and C-4, and so on. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon–carbon bonds must adopt eclipsed or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice, each ring adopts conformations that minimize both sorts of strain as much as possible. For cyclopentane, as seen in Section 4.O. iv, this means that the molecule is not planar. In rings larger than nine-membered, Pitzer strain seems to disappear, but transannular strain is still present.[473] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115–120° have been found in X-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[474]



126

Strain can exert other influences on molecules. 1-Aza-2-adamantanone (**126**) is an extreme case of a twisted amide.[475] The overlap of the lone-pair electrons on nitrogen with the π-system of the carbonyl is prevented.[475] In chemical reactions, **126** reacts more or less like a ketone, giving a Wittig reaction (**16-44**) and it can form a ketal (**16-7**). A twisted biadamantylidene compound has been reported.[476]

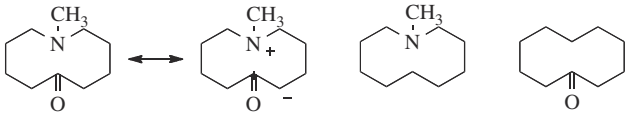
The amount of strain in cycloalkanes is shown in Table 4.6,[477] which lists heats of combustion per CH_2 group. As can be seen, cycloalkanes > 13-membered are as strain-free as cyclohexane.

[472] See Raphael, R.A. *Proc. Chem. Soc.* ***1962***, 97; Sicher, J. *Prog. Stereochem.* ***1962***, *3*, 202.
[473] Huber-Buser, E.; Dunitz, J.D. *Helv. Chim. Acta* ***1960***, *43*, 760.
[474] Dunitz, J.D.; Venkatesan, K. *Helv. Chim. Acta* ***1961***, *44*, 2033.
[475] Kirby, A.J.; Komarov, I.V.; Wothers, P.D.; Feeder, N. *Angew. Chem. Int. Ed.*, ***1998***, *37*, 785. Also see Madder, R.D.; Kim, C.-Y.; Chandra, P.P.; Doyon, J.B.; Barid, Jr., T.A.; Fierke, C.A.; Christianson, D.W.; Voet, J.G.; Jain, A. *J. Org. Chem.* ***2002***, *67*, 582.
[476] Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2002***, *67*, 5981.
[477] Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218.

TABLE 4.6 Heats of Combustion in the Gas Phase for Cycloalkanes, per CH_2 Group[a]

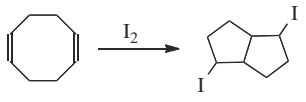
	$-\Delta H_c$ (g)			$-\Delta H_c$ (g)	
Size of Ring	kcal mol^{-1}	kJ mol^{-1}	Size of Ring	kcal mol^{-1}	kJ mol^{-1}
3	166.3	695.8	10	158.6	663.6
4	163.9	685.8	11	158.4	662.7
5	158.7	664.0	12	157.8	660.2
6	157,4	658.6	13	157.7	659.8
7	158.3	662.3	14	157.4	658.6
8	158.6	663.6	15	157.5	659.0
9	158.8	664.4	16	157.5	659.0

[Reprinted with permission. Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218].
[a]See Ref. 472.

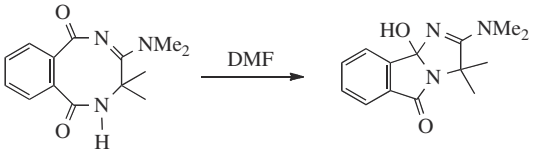


127a **127b** **128** **129**

Transannular interactions can exist across rings from 8- to 11-membered and even larger.[478] Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **127a** is affected by the nitrogen (**127b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen *n* and C=O π orbitals in **127** differ from those of the two comparison molecules **128** and **129**.[479] It is significant that when **127** donates electrons to a proton, it goes to the oxygen rather than to the nitrogen. Many examples of transannular reactions are known, including the following:



Ref. 480



Ref. 481

where DMF = *N*, *N*-dimethylformamide (Solvent)

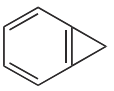
[478] For a review, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119.
[479] Spanka, G.; Rademacher, P. *J. Org. Chem.* ***1986***, *51*, 592. See also, Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 2119.

In summary, saturated rings may be divided into four groups, of which the first and third are more strained than the other two.[482]

1. *Small rings* (three- and four-membered). Small-angle strain predominates.
2. *Common rings* (five-, six-, and seven-membered). Largely unstrained. The strain that is present is mostly Pitzer strain.
3. *Medium rings* (8- to 11-membered). Considerable strain; Pitzer, transannular, and large-angle strain.
4. *Large rings* (12-membered and larger). Little or no strain.[483]

4.P.iii. Unsaturated Rings[484]

Double bonds can exist in rings of any size. As expected, the most highly strained are the three-membered rings (e.g., cyclopropene). Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene[485] because the ideal angle is more distorted. In cyclopropane, the bond angle is forced to be 60°, ∼50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also ∼60°, is now ∼60° smaller than the ideal angle of 120° for an alkene Thus, the angle of cyclopropene is ∼10° more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing strain present in cyclopropane. Cyclopropene has been prepared[486] and is stable at liquid-nitrogen temperatures, although on warming even to −80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[464] The highly strained benzocyclopropene,[487] in which the cyclopropene ring is fused to a benzene ring, has been prepared[488] and is stable for weeks at room temperature, although it decomposes on distillation at atmospheric pressure.



Benzocyclopropene

[482] See Granik, V.G. *Russ. Chem. Rev.* ***1982***, *51*, 119.

[483] An example is the calculated strain of 1.4–3.2 kcal mol^{-1}(5.9–13.4 kJ mol^{-1}) in cyclotetradecane. See Chickos, J.S.; Hesse, D.G.; Panshin, S.Y.; Rogers, D.W.; Saunders, M.; Uffer, P.M.; Liebman, J.F. *J. Org. Chem.* ***1992***, *57*, 1897.

[484] For a review of strained double bonds, see Zefirov, N.S.; Sokolov, V.I. *Russ. Chem. Rev.* ***1967***, *36*, 87. For a review of double and triple bonds in rings, see Johnson, R.P. *Mol. Struct. Energ.* ***1986***, *3*, 85.

[485] See Baird, M.S. *Top. Curr. Chem.* ***1988***, *144*, 137; Halton, B.; Banwell, M.G. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1223–1339; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53; For a discussion of the bonding and hybridization, see Allen, F.H. *Tetrahedron* ***1982***, *38*, 645.

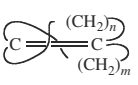
[486] Dem'yanov, N.Ya.; Doyarenko, M.N. *Ber.* ***1923***, *56*, 2200; Schlatter, M.J. *J. Am. Chem. Soc.* ***1941***, *63*, 1733; Stigliani, W.M.; Laurie, V.W.; Li, J.C. *J. Chem. Phys.* ***1975***, *62*, 1890.

[487] See Halton, B. *Chem. Rev.* ***1989***, *89*, 1161; ***1973***, *73*, 113; Billups, W.E.; Rodin, W.A.; Haley, M.M. *Tetrahedron* ***1988***, *44*, 1305; Billups, W.E. *Acc. Chem. Res.* ***1978***, *11*, 245.

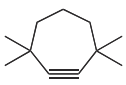
[488] Vogel, E.; Grimme, W.; Korte, S. *Tetrahedron Lett.* ***1965***, 3625. Also see Müller, P.; Bernardinelli, G.; Thi, H. C.G. *Chimia* ***1988***, *42*, 261; Neidlein, R.; Christen, D.; Poignée, V.; Boese, R.; Bläser, D.; Gieren, A.; Ruiz-Pérez, C.; Hübner, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 294.

As previously mentioned, double bonds in relatively small rings must be cis. A stable trans double bond[489] first appears in an eight-membered ring (*trans*-cyclooctene, Sec. 4.C, category 6), although the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.[490] Above ~11 members, the trans isomer is more stable than the cis.[232] It has proved possible to prepare compounds in which a trans double bond is shared by two cycloalkene rings (e.g., **130**). Such compounds have been called *[m.n] betweenanenes*, and several have been prepared with *m* and *n* values from 8 to 26.[491] The double bonds of the smaller betweenanenes, as might be expected from the fact that they are deeply buried within the bridges, are much less reactive than those of the corresponding cis–cis isomers.

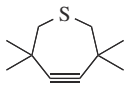
The smallest unstrained cyclic triple bond is found in cyclononyne.[492] Cyclooctyne has been isolated,[493] but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in seven-membered rings. 3,3,7,7-Tetramethylcycloheptyne (**131**) is known and dimerizes within 1 h at room temperature,[494] but the thia derivative (**132**), in which the C—S bonds are longer than the corresponding C—C bonds in **131**, is indefinitely stable even at 140°C.[495] Cycloheptyne itself has not been isolated, although its transient existence has been shown.[496] Cyclohexyne[497] and its 3,3,6,6-tetramethyl derivative[498] have been trapped at 77 K, and in an Ar π matrix at 12 K, respectively. Its IR spectra have also been



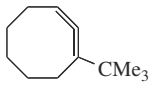
130



131



132



133

obtained. Transient six- and even five-membered rings containing triple bonds have also been demonstrated.[499] A derivative of cyclopentyne has been trapped in a matrix.[500] Although cycloheptyne and cyclohexyne have not been isolated at room temperatures, Pt(0) complexes of these compounds have been prepared and are stable.[501] The smallest

[489] For reviews of *trans* cycloalkenes, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213.

[490] Wallraff, G.M.; Michl, J. *J. Org. Chem.* ***1986***, *51*, 1794; Squillacote, M.; Bergman, A.; De Felippis, J. *Tetrahedron Lett.* ***1989***, *30*, 6805.

[491] Marshall, J.A.; Flynn, K.E. *J. Am. Chem. Soc.* ***1983***, *105*, 3360. For reviews, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213. For a review of these and similar compounds, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095.

[492] See Meier, H. *Adv. Strain Org. Chem.* ***1991***, *1*, 215; Krebs, A.; Wilke, J. *Top. Curr. Chem.* ***1983***, *109*, 189; Nakagawa, M. in Patai, S. *The Chemistry of the C≡C Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 635–712; Krebs, A. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 987–1062. See Meier, H.; Hanold, N.; Molz, T.; Bissinger, H.J.; Kolshorn, H.; Zountsas, J. *Tetrahedron* ***1986***, *42*, 1711.

[493] Blomquist, A.T.; Liu, L.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2153. See also, Bühl, H.; Gugel, H.; Kolshorn, H.; Meier, H. *Synthesis* ***1978***, 536.

[494] Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* ***1974***, 1471.

[495] Krebs, A.; Kimling, H. *Tetrahedron Lett.* ***1970***, 761.

[496] Bottini, A.T.; Frost II, K.A.; Anderson, B.R.; Dev, V. *Tetrahedron* ***1973***, *29*, 1975.

[497] Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* ***1988***, *110*, 1874.

[498] See Sander, W.; Chapman, O.L. *Angew. Chem. Int. Ed.* ***1988***, *27*, 398.

[499] See Bolster, J.M.; Kellogg, R.M. *J. Am. Chem. Soc.* ***1981***, *103*, 2868; Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 664.

[500] Chapman, O.L.; Gano, J.; West, P.R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* ***1981***, *103*, 7033.

[501] Bennett, M.A.; Robertson, G.B.; Whimp, P.O.; Yoshida, T. *J. Am. Chem. Soc.* ***1971***, *93*, 3797.

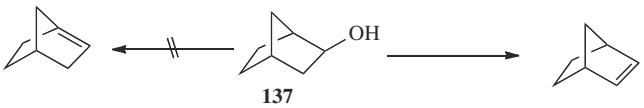
cyclic allene[502] so far isolated is 1-*tert*-butyl-1,2-cyclooctadiene (**133**).[503] The parent 1,2-cyclooctadiene has not been isolated. It has been shown to exist as a transient species, but rapidly dimerizes.[504] Incorporation of the *tert*-butyl group apparently prevents this. The transient existence of 1,2-cycloheptadiene has also been shown,[505] and both 1,2-cyclooctadiene and 1,2-cycloheptadiene have been isolated in Pt complexes.[506] 1,2-Cyclohexadiene has been trapped at low temperatures, and its structure has been proved by spectral studies.[507] Cyclic allenes in general are less strained than their acetylenic isomers.[508] The cyclic cumulene 1,2,3-cyclononatriene also has been synthesized and is reasonably stable in solution at room temperature in the absence of air.[509]



134 **135** **136**

There are many examples of polycyclic molecules and bridged molecules that have one or more double bonds. There is flattening of the ring containing the C=C unit, and this can have a significant effect on the molecule. Norbornene (bicyclo[2.2.1]hept-2-ene, **134**) is a simple example and it has been calculated that it contains a distorted π-face.[510] The double bond can appear away from the bridgehead carbon atoms, as in bicyclo[4.2.2]dec-3-ene (**135**), which flattens that part of the molecule. The C=C units in pentacyclo [8.2.1.1^{2,5}.1^{4,7}.1^{8,11}]hexadeca-1,7-diene (**136**) are held in a position where there is significant π–π interactions across the molecule.[511]

Double bonds at the bridgehead of bridged bicyclic compounds are impossible in small systems. This result is the basis of *Bredt's rule*,[512] which states that elimination to give a double bond in a bridged bicyclic system (e.g., **137**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough. In



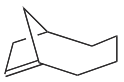
137

[502] See Johnson, R.P. *Chem. Rev.* ***1989***, *89*, 1111; Thies, R.W. *Isr. J. Chem.* ***1985***, *26*, 191; Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*; Wiley, NY, ***1984***, pp. 38–56.
[503] Price, J.D.; Johnson, R.P. *Tetrahedron Lett.* ***1986***, *27*, 4679.
[504] See Marquis, E.T.; Gardner, P.D. *Tetrahedron Lett.* ***1966***, 2793.
[505] Wittig, G.; Dorsch, H.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 55.
[506] Visser, J.P.; Ramakers, J.E. *J. Chem. Soc. Chem. Commun.* ***1972***, 178.
[507] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed.* ***1983***, *22*, 542. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare, W.C.; Johnson, R.P. *J. Am. Chem. Soc.* ***1990***, *112*, 8578.
[508] Moore, W.R.; Ward, H.R. *J. Am. Chem. Soc.* ***1963***, *85*, 86.
[509] Angus Jr., R.O.; Johnson, R.P. *J. Org. Chem.* ***1984***, *49*, 2880.
[510] Ohwada, T. *Tetrahedron* ***1993***, *49*, 7649.
[511] Lange, H.; Schäfer, W.; Gleiter, R.; Camps, P.; Vázquez, S. *J. Org. Chem.* ***1998***, *63*, 3478.
[512] See Shea, K.J. *Tetrahedron* ***1980***, *36*, 1683; Buchanan, G.L. *Chem. Soc. Rev.* ***1974***, *3*, 41; Köbrich, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 464. See Billups, W.E.; Haley, M.M.; Lee, G. *Chem. Rev.* ***1989***, *89*, 1147; Warner, P.M. *Chem. Rev.* ***1989***, *89*, 1067; Keese, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 528. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 553–555.

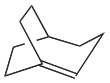
determining whether a bicyclic system is large enough to accommodate a bridgehead double bond, the most reliable criterion is the size of the ring in which the double bond is located.[513] Bicyclo[3.3.1]non-1-ene[514] (**138**) and bicyclo[4.2.1]non-1(8)ene[515] (**139**) are stable compounds. Both can be looked upon as derivatives of *trans*-cyclooctene, which is of course a known compound. Compound **138** has been shown to have a strain



138



139

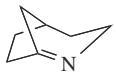


140



(E) Isomer

141



(Z) Isomer

142



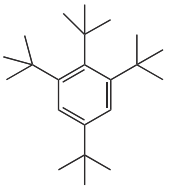
143

energy of the same order of magnitude as that of *trans*-cyclooctene.[516] On the other hand, in bicyclo[3.2.2]non-1-ene (**140**), the largest ring that contains the double bond is a *trans*-cycloheptene, which is as yet unknown. Compound **140** has been prepared, but dimerized before it could be isolated.[517] Even smaller systems ([3.2.1] and [2.2.2]), but with imine double bonds (**141–143**), have been obtained in matrixes at low temperatures.[518] These compounds are destroyed on warming. Compounds **141** and **142** are the first reported example of (*E–Z*) isomerism at a strained bridgehead double bond.[519]

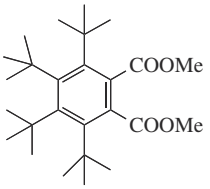
4.P.iv. Strain Due to Unavoidable Crowding[520]

In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing *ortho tert*-butyl groups. Two examples that have been prepared, of several, are 1,2,3-tri-*tert*-butyl compound **144**[521] and the 1,2,3,4-tetra-*tert*-butyl compound **145**.[522] That these molecules are strained is demonstrated by UV and IR spectra, which show that the ring is not planar in 1,2,4-tri-*tert*-butylbenzene, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which show that the 1,2,4 compound possesses $\sim$22 kcal mol^{-1} (92 kJ mol^{-1}) more strain energy than its isomer[523] (see also Reaction **18-27**). Although $SiMe_3$ groups are larger

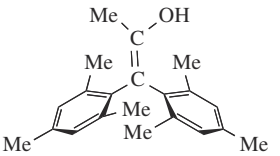
[513] See Maier, W.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 1891.
[514] Kim, M.; White, J.D. *J. Am. Chem. Soc.* ***1975***, *97*, 451; Becker, K.B. *Helv. Chim. Acta* ***1977***, *60*, 81. See Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* ***1979***, *44*, 2438.
[515] Wiseman, J.R.; Chan, H.; Ahola, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 2812; Carruthers, W.; Qureshi, M.I. *Chem. Commun.* ***1969***, 832; Becker, K.B. *Tetrahedron Lett.* ***1975***, 2207.
[516] Lesko, P.M.; Turner, R.B. *J. Am. Chem. Soc.* ***1968***, *90*, 6888; Burkert, U. *Chem. Ber.* ***1977***, *110*, 773.
[517] Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 7775.
[518] Sheridan, R.S.; Ganzer, G.A. *J. Am. Chem. Soc.* ***1983***, *105*, 6158; Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.
[519] Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.
[520] See Tidwell, T.T. *Tetrahedron* ***1978***, *34*, 1855; Mosher, H.S.; Tidwell, T.T. *J. Chem. Educ.* ***1990***, *67*, 9. For a review of van der Waals radii, see Zefirov, Yu.V.; Zorkii, P.M. *Russ. Chem. Rev.* ***1989***, *58*, 421.
[521] Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803.
[522] Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. For another example, see Krebs, A.; Franken, E.; Müller, S. *Tetrahedron Lett.* ***1981***, *22*, 1675.
[523] Arnett, E.M.; Sanda, J.C.; Bollinger, J.M.; Barber, M. *J. Am. Chem. Soc.* ***1967***, *89*, 5389;. See also, Barclay, L.R.C.; Brownstein, S.; Gabe, E.J.; Lee, F.L. *Can. J. Chem.* ***1984***, *62*, 1358.



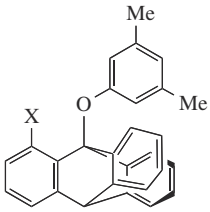
144



145

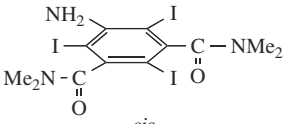


146

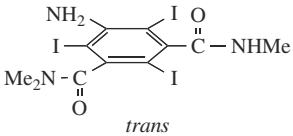


147

than CMe_3 groups, it has proven possible to prepare $C_6(SiMe_3)_6$. This compound has a chair-shaped ring in the solid state, and a mixture of chair and boat forms in solution.[524] Even smaller groups can sterically interfere in ortho positions. In hexaisopropylbenzene, the six isopropyl groups are so crowded that they cannot rotate, but are lined up around the benzene ring, all pointed in the same direction.[525] This compound is an example of a *geared molecule*.[526] The isopropyl groups fit into each other in the same manner as interlocked



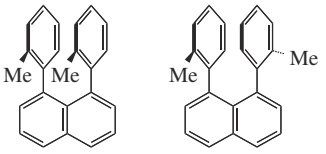
cis



trans

gears. Another example is **146**, which is a stable enol.[527] In this case, each ring can rotate about its C–aryl bond only by forcing the other to rotate as well. In the case of triptycene derivatives (e.g., **147**), a complete 360° rotation of the aryl group around the O–aryl bond requires the aryl group to pass over three rotational barriers; one of which is the C—X bond and the other two the "top" C—H bonds of the other two rings. As expected, the C—X barrier is the highest, ranging from 10.3 kcal mol^{-1} (43.1 kJ mol^{-1}) for X = F to 17.6 kcal mol^{-1} (73.6 kJ mol^{-1}) for X = *tert*-butyl.[528] In another instance, it has proved possible to prepare cis and trans isomers of 5-amino-2,4,6-triiodo-*N,N,N′,N′*-tetramethylisophthalamide because there is no room for the $CONMe_2$ groups to rotate, caught as they are between two bulky iodine atoms.[529] The trans isomer is chiral and has been resolved, while the cis isomer is a meso form. Another example of *cis-trans* isomerism resulting from restricted rotation about single bonds[530] is found in 1,8-di-*o*-tolylnapthalene[531] (see also, Sec. 4.K.i).

[524] Sakurai, H.; Ebata, K.; Kabuto, C.; Sekiguchi, A. *J. Am. Chem. Soc.* ***1990***, *112*, 1799.
[525] Siegel, J.; Gutiérrez, A.; Schweizer, W.B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* ***1986***, *108*, 1569. Also see Kahr, B.; Biali, S.E.; Schaefer, W.; Buda, A.B.; Mislow, K. *J. Org. Chem.* ***1987***, *52*, 3713.
[526] See Iwamura, H.; Mislow, K. *Acc. Chem. Res.* ***1988***, *21*, 175; Mislow, K. *Chemtracts: Org. Chem.* ***1989***, *2*, 151; Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* ***1985***, *18*, 80.
[527] Nugiel, D.A.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 3357.
[528] Yamamoto, G.; Öki, M. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3597. See Yamamoto, G. *Pure Appl. Chem.* ***1990***, *62*, 569; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 269–284.
[529] Ackerman, J.H.; Laidlaw, G.M.; Snyder, G.A. *Tetrahedron Lett.* ***1969***, 3879; Ackerman, J.H.; Laidlaw, G.M. *Tetrahedron Lett.* ***1969***, 4487. See also, Cuyegkeng, M.A.; Mannschreck, A. *Chem. Ber.* ***1987***, *120*, 803.
[530] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1977***, *16*, 429; Öki, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 87.
[531] Clough, R.L.; Roberts, J.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1018. For a study of rotational barriers in this system, see Cosmo, R.; Sternhell, S. *Aust. J. Chem.* ***1987***, *40*, 1107.



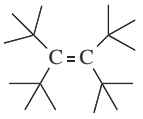
cis *trans*

There are many other cases of intramolecular crowding that result in the distortion of bond angles. Hexahelicene (Sec. 4.C, category 6) and bent benzene rings (Sec. 2.G) have been mentioned previously. The compounds tri-*tert*-butylamine, and tetra-*tert*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved and it is questionable whether this compound can ever be made. In tri-*tert*-butylamine, the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*tert*-butylcarbinol, coplanarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[532] Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol and it should be possible to prepare it.[533] The tetra-*tert*-butylphosphonium cation $(t\text{-Bu})_4P^+$ has been prepared.[534] Although steric effects are nonadditive in crowded molecules, a quantitative measure has been proposed by DeTar, based on molecular mechanics calculations. This is called *formal steric enthalpy* (FSE), and values have been calculated for alkanes, alkenes, alcohols, ethers, and methyl esters[535] For example, some FSE values for alkanes are butane 0.00; 2,2,3,3-tetramethylbutane 7.27; 2,2,4,4,5-pentamethylhexane 11.30; and tri-*tert*-butylmethane 38.53.

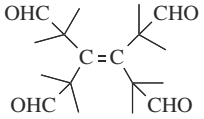
The two carbon atoms of a C=C double bond and the four groups attached to them are normally in a plane, but if the groups are large enough, significant deviation from planarity can result.[536] The compound tetra-*tert*-butylethene (**148**) has not been prepared,[537] but the tetraaldehyde (**149**), which should have about the same amount of strain, has been made. X-ray crystallography shows that **149** is twisted out of a planar shape by an angle of 28.6°.[538] Also, the C=C double bond distance is 1.357 Å, significantly longer than normal C=C bond of 1.32 Å (Table 1.5). (*Z*)-1,2-Bis(*tert*-butyldimethylsilyl)-1,2-bis (trimethylsilyl)ethene (**150**) has an even greater twist, but could not be made to undergo conversion to the (*E*) isomer, probably because the groups are too large to slide past each other.[539] A different kind of double-bond strain is found in tricyclo[4.2.2.$2^{2,5}$]dodeca-1,5-

[532] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.
[533] See Back, T.G.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans 1*, ***1977***, 924; Kopka, I.E.; Fataftah, Z.A.; Rathke, M.W. *J. Org. Chem.* ***1980***, *45*, 4616.
[534] Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* ***1980***, *113*, 1612.
[535] DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1985***, *50*, 2826, 5298, 5304.
[536] For reviews, see Luef, W.; Keese, R. *Top. Stereochem.* ***1991***, *20*, 231; Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83, pp. 160–169.
[537] For a list of crowded alkenes that have been made, see Drake, C.A.; Rabjohn, N.; Tempesta, M.S.; Taylor, R.B. *J. Org. Chem.* ***1988***, *53*, 4555. See also, Garratt, P.J.; Payne, D.; Tocher, D.A. *J. Org. Chem.* ***1990***, *55*, 1909.
[538] Krebs, A.; Nickel, W.; Tikwe, L.; Kopf, J. *Tetrahedron Lett.* ***1985***, *26*, 1639.
[539] Sakurai, H.; Ebata, K.; Kabuto, C.; Nakadaira, Y. *Chem. Lett*. ***1987***, 301.

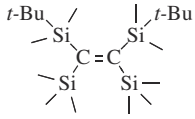
diene (**151**),[540] cubene (**152**),[541] and homocub-4(5)-ene (**153**).[542] In these molecules, the four groups on the



148

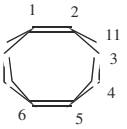


149



150

double bond are all forced to be on one side of the double-bond plane.[543] In **151**, the angle between the line C1–C2 (extended) and the plane defined by C2, C3, and C11 is 27°. An additional source of strain in this molecule is the fact that the two double bonds are pushed into close proximity by the four bridges. In an effort to alleviate this sort of strain, the bridge bond distances (C-3—C-4) are 1.595 Å, which is considerably longer than the 1.53 Å expected for a normal sp^3–sp^3 C—C bond (Table 1.5). Compounds **152** and **153** have ***not*** been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.[541,542]



151



152



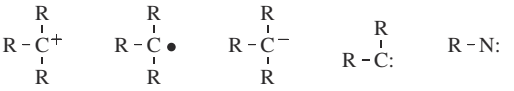
153

[540] Wiberg, K.B.; Matturo, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 2194; Wiberg, K.B.; Adams, R.D.; Okarma, P.J.; Matturo, M.G.; Segmuller, B. *J. Am. Chem. Soc.* ***1984***, *106*, 2200.
[541] Eaton, P.E.; Maggini, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7230.
[542] Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 7229.
[543] For a review of such molecules, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095. See also, Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4710.

CHAPTER 5

Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes

There are four types of organic species in which a carbon atom has a valence of only 2 or 3.[1] They are usually very short-lived, and most exist only as intermediates that are quickly converted to more stable molecules. However, some are more stable than others and fairly stable examples have been prepared for three of the four types. The four types of species are *carbocations* (**A**), *carbon radicals* (**B**), *carbanions* (**C**), and *carbenes* (**D**). Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but only *nitrenes* (**E**), the nitrogen analogues of carbenes, will be discussed. Each of these five types is discussed in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated for the appropriate specific reactions in Part II.



A **B** **C** **D** **E**

5.A. CARBOCATIONS[2]

5.A.i. Nomenclature

First, the nomenclature of carbocations (**A**) is discussed. For many years, these species were called "carbonium ions," although it was suggested[3] as long ago as 1902 that this was

[1] For general references, see Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***; McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***. Two serial publications devoted to review articles on this subject are *Reactive Intermediates (Wiley)* and *Reactive Intermediates (Plenum)*.

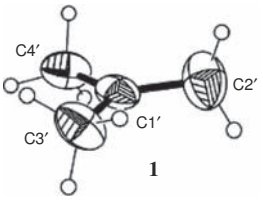
[2] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, 5 Vols., Wiley, NY, ***1968–1976***; Vogel, P. *Carbocation Chemistry*, Elsevier, NY, ***1985***. See Saunders, M.; Jiménez-Vázquez, H.A. *Chem. Rev.* ***1991***, *91*, 375; Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1987***, *3*, 189. For reviews of dicarbocations, see Lammertsma, K.; Schleyer, P.v.R.; Schwarz, H. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1321. See also, the series *Advances in Carbocation Chemistry*.

[3] Gomberg, M. *Ber.* ***1902***, *35*, 2397.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

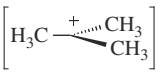
inappropriate because "-onium" usually refers to a covalency higher than that of the neutral atom. Nevertheless, the name "carbonium ion" was well established and created few problems[4] until some years ago, when Olah and co-workers[2,5] found evidence for another type of intermediate in which there is a positive charge at a carbon atom, but in which the formal covalency of the carbon atom is five rather than three. The simplest example is the methanonium ion (CH_5^+; see Reaction **12-01**). Olah[5] proposed that the name "carbonium ion" be henceforth reserved for pentacoordinated positive ions, and that **A** be called a "carbenium ions." He also proposed the term "carbocation" to encompass both types. IUPAC has accepted these definitions.[6] For the most part, intermediates such as **A** are called *carbenium ions* or *carbocations*, but the latter term will be used more often in this book.

5.A.ii. Stability and Structure of Carbocations



1

≡



[Reprinted with permission from Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2908, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***2004*** by Wiley–VCH Verlag]

Carbocations are intermediates in several kinds of reactions.[7] The more stable ones have been prepared in solution and in some cases even as solid salts. X-ray crystallographic structures also have been obtained in some cases.[8] The X-ray of the *tert*-butyl cation complexed with dichloromethane was reported,[9] for example, and is presented as **1** with the solvent molecules removed for clarity. The IR spectrum of the *tert*-butyl cation has been recorded in the gas phase.[10] An isolable dioxa-stabilized pentadienylium ion was isolated and its structure was determined by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR.[11] A β-fluoro substituted 4-methoxyphenethyl cation has been observed directly by laser flash photolysis.[12] In solution, the carbocation may be free (this is more likely in polar solvents,

[4] For a history of the term "carbonium ion", see Traynham, J.G. *J. Chem. Educ.* ***1986***, *63*, 930.
[5] Olah, G.A. *CHEMTECH* ***1971***, *1*, 566; *J. Am. Chem. Soc.* ***1972***, *94*, 808.
[6] Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *Compendium of Chemical Terminology, IUPAC Recommendations*, Blackwell Scientific Publications, Oxford, ***1987***.
[7] Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 5943. See Olah, G.A.; Prakash, G.K.S. (Eds.), *Carbocation Chemistry*, Wiley Intersience, Hoboken, NJ, ***2004***.
[8] See Laube, T. *J. Am. Chem.* ***2004***, 126, 10904 and references therein. For the X-ray of a vinyl carbocation see Müller, T.; Juhasz, M.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1543.
[9] Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2908.
[10] Douberly, G.E.; Ricks, A.M.; Ticknor, B.W.; Schleyer, P.v.R.; Duncan, M.A. J. *Am. Chem. Soc.* ***2007***, *129*, 13782.
[11] Lüning, U.; Baumstark, R. *Tetrahedron Lett.* ***1993***, *34*, 5059.
[12] McClelland, R.A.; Cozens, F.L.; Steenken, S.; Amyes, T.L.; Richard, J.P. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1717.

in which it is solvated) or it may exist as an ion pair,[13] which means that it is closely associated with a negative ion, called a *counterion* or *gegenion*. Ion pairs are more likely in nonpolar solvents.

Among simple alkyl carbocations,[14] the order of stability is tertiary > secondary > primary. There are many known examples of rearrangements of primary or secondary carbocations to tertiary, both in solution and in the gas phase (see Sec. 18.A.ii). Since simple alkyl cations are unstable in ordinary strong-acid solutions (e.g., H_2SO_4), the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely as stable solutions in mixtures of fluorosulfuric acid and antimony pentafluoride. Such mixtures, usually dissolved in SO_2 or SO_2ClF, are among the strongest acidic solutions known and are often called *superacids*.[15] The original experiments involved the addition of alkyl fluorides to SbF_5.[16]

$$RF + SbF_5 \longrightarrow R^+SbF_6^-$$

Subsequently, it was found that the same carbocations could also be generated from alcohols in superacid–SO_2 at $-60\,^\circ C$[17] and from alkenes by the addition of a proton from superacid or HF—SbF_5 in SO_2 or SO_2ClF at low temperatures.[18] Even alkanes give carbocations in superacid by loss of H^-. For example,[19] 2-methylpropane gives the *tert*-butyl cation.

$$Me_3CH \xrightarrow{FSO_3H-SbF_5} Me_3C^+SbF_5FSO_3^- + H_2$$

No matter how they are generated, study of the simple alkyl carbocations has provided dramatic evidence for the stability order.[20] Both propyl fluorides gave the isopropyl cation; all four butyl fluorides[21] gave the *tert*-butyl cation, and all seven of the pentyl fluorides examined gave the *tert*-pentyl cation. *n*-Butane, in superacid, gave only the *tert*-butyl cation. To date, no primary cation has survived long enough for detection. Neither methyl nor ethyl fluoride gave the corresponding carbocations when treated with SbF_5. At low temperatures, methyl fluoride gave chiefly the methylated sulfur dioxide salt $[(CH_3OSO)^+SbF_6^-]$,[22] while ethyl fluoride rapidly formed the *tert*-butyl and *tert*-hexyl cations by addition of the initially formed ethyl cation to ethylene molecules also formed.[23] At room temperature, methyl fluoride also gave the *tert*-butyl cation.[24] In accord with the

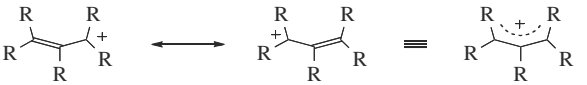
[13] For a treatise, see Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, 2 Vols., Wiley, NY, ***1972–1974***.
[14] For a review, see Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, WIley, NY, ***1969***, pp. 715–782. Also see, Farcasiu, D.; Norton, S.H. *J. Org. Chem.* ***1997***, *62*, 5374.
[15] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. in *Superacids*, Wiley, NY, ***1985***, pp. 65–175.
[16] Olah, G.A.; Baker, E.B.; Evans, J.C.; Tolgyesi, W.S.; McIntyre, J.S.; Bastien, I.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1360; Kramer, G.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4819.
[17] Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576.
[18] Olah, G.A.; Halpern, Y. *J. Org. Chem.* ***1971***, *36*, 2354. See also, Herlem, M. *Pure Appl. Chem.* ***1977***, *49*, 107.
[19] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.
[20] See Amyes, T.L.; Stevens, I.W.; Richard, J.P. *J. Org. Chem.* ***1993***, *58*, 6057 for a recent study.
[21] See Saunders, M.; Hagen, E.L.; Rosenfeld, J. *J. Am. Chem. Soc.* ***1968***, *90*, 6882; Saunders, M.; Cox, D.; Lloyd, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6656; Myhre, P.C.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1981***, *103*, 230.
[22] Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5163.
[23] Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, p. 722.
[24] Bacon, J.; Gillespie, R.J. *J. Am. Chem. Soc.* ***1971***, *91*, 6914.

stability order, hydride ion is abstracted from alkanes by superacid most readily from tertiary and least readily from primary positions.

$$\underset{\mathbf{2}}{(CD_3)_3C^+} + (CH_3)_3CH \rightleftharpoons \underset{\mathbf{3}}{(CH_3)_3C^+} + (CD_3)_3CH \quad K_{298} = 1.97 \pm 0.20$$

The stability order can be explained by the polar effect and by hyperconjugation (Sec. 2.M). In the polar effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Since a tertiary carbocation has more carbon substituents on the positively charged carbon, relative to a primary, there is a greater polar effect that leads to great stability. In the hyperconjugation explanation,[25] a primary carbocation is compared with a tertiary, and "*the hyperconjugation concept arises from model-building procedures* (see Sec. 2.M). In general, this means that the model must be corrected by including some delocalization in order to get a good enough description."[26] Evidence used to support the hyperconjugation explanation is that the equilibrium constant for this reaction involving **2** and **3** is 1.97, showing that **3** is more stable than **2**.[27] Due to a β secondary isotope effect, there is less hyperconjugation in **2** than in **3** (see Sec. 6.J.V.ii for isotope effects).[28] The field effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be. There are several structural types of delocalization, as summarized in Table 5.1.[29]

The most stable of the simple alkyl cations is the *tert*-butyl cation. Even the relatively stable *tert*-pentyl and *tert*-hexyl cations fragment at higher temperatures to produce the *tert*-butyl cation, as do all other alkyl cations with four or more carbons to date studied.[30] Methane,[31] ethane, and propane, in superacid, also yield *tert*-butyl cations as the main product (see Reaction **12-20**). Even paraffin wax and polyethylene give a *tert*-butyl cation. Solid salts of *tert*-butyl and *tert*-pentyl cations, [e.g., $Me_3C^+\ SbF_6^-$], have been prepared from superacid solutions and are stable below −20 °C.[32]



4

[25] See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426.

[26] Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd ed.*, HarperCollins, NY, ***1987***, p. 68.

[27] Meot-Ner, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7947.

[28] If only the field effect were operating, **2** would be more stable than **3**, since deuterium is electron-donating with respect to hydrogen (Sec. 1.J), assuming that the field effect of deuterium could be felt two bonds away.

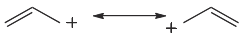
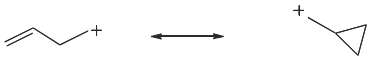
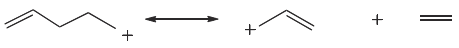
[29] Lambert, J.B.; Ciro, S.M. *J. Org. Chem.* ***1996***, *61*, 1940.

[30] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739; Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, pp. 750–764.

[31] Olah, G.A.; Klopman, G.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 3261. See also, Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 319.

[32] Olah, G.A.; Svoboda, J.J.; Ku, A.T. *Synthesis* ***1973***, 492; Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.

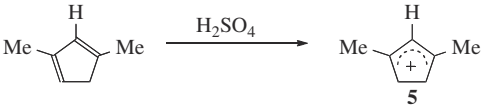
TABLE 5.1 Structural Types of Delocalization[a]

Valence Structures	Abbreviation	Name
	ππ	Simple conjugation
	σπ	Hyperconjugation
	πσ	Homoconjugation
	σσ	Homohyperconjugation
	σπ/ππ	Hyperconjugation/ conjugation
	σπ/σπ	Double hyperconjugation

[Reprinted with permission from Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***1976*** by Wiley–VCH Verlag].

[a]See Ref. 25.

In carbocations, where the positive carbon is in conjugation with a double bond, as in allylic cations (the allyl cation is **4**, R = H), the stability is greater because of increased delocalization due to resonance[33] where the positive charge is spread over several atoms instead of being concentrated on one (see the molecular orbital picture of **4** in Sec. 2.C, category 2). Each of the terminal atoms in **4** has a charge of $\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable cyclic and acyclic allylic-type carbocations[34] have been prepared by dissolving conjugated dienes in concentrated sulfuric acid; the cyclopentadienyl cation, (**5**) is an example.[35]



5

Stable allylic carbocations have also been obtained by the reaction between alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.[36] *Bis*(allylic) cations[37] are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[38] Arenium ions (Sec. 11.A.i) are

[33] See Barbour, J.B.; Karty, J.M. *J. Org. Chem.* ***2004****, 69,* 648; Mo, Y. *J. Org. Chem.* ***2004****, 69*, 5563 and references cited therein.

[34] For reviews, see Deno, N.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2 Wiley, NY, ***1970***, pp. 783–806; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 39–114.

[35] Deno, N.C.; Richey, Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.

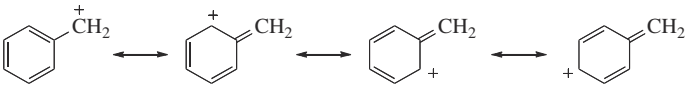
[36] Olah, G.A.; Spear, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 1539 and references cited therein.

[37] For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, T.S. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 807–835.

[38] Deno, N.C.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1964***, *86*, 1871.

familiar examples of this type. Propargyl cations ($RC{\equiv}CC^{+}R_2$) have also been prepared.[39]

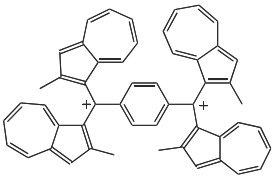
Canonical forms can be drawn for benzylic carbocations, as shown,[40] and they are similar to those shown above for allylic cations.



A number of benzylic carbocations have been obtained in solution as SbF_6^- salts.[41] Diarylmethyl and triarylmethyl cations are even more stable because more canonical forms are possible (i.e., there is more extensive delocalization, hence greater stability). Chlorotriphenylmethane ionizes in polar solvents to give the stable triphenylmethyl cation (trityl cation, see **18**), for example, because the solvent does not react with the ion,

$$Ph_3CCl \rightleftharpoons Ph_3C^+ + C^-$$

whereas water does react with the ion. In liquid SO_2, for example, the ion remains stable for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts.[42] In fact, $Ph_3C^+\ BF_4^-$ and related salts are available commercially. Arylmethyl cations are further stabilized if they have electron-donating substituents in ortho or para positions.[43] Dications[44] and trications are also possible, including the particularly stable dication (**6**), where each positively charged benzylic carbon is stabilized by two azulene rings.[45] A related trication is known where two azulene rings stabilize each benzylic cationic center.[46]

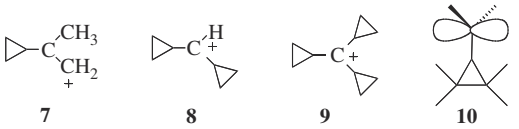


6

Cyclopropylmethyl carbocations[47] are even more stable than benzylic carbocations. Carbocations **7**, **8**, and similar ions have been prepared by dissolution of the alcohols in $FSO_3H{-}SO_2{-}SbF_5$,[48] and **9** has been prepared from the corresponding alcohol in

[39] Olah, G.A.; Spear, R.J.; Westerman, P.W.; Denis, J. *J. Am. Chem. Soc.* ***1974***, *96*, 5855.
[40] For a review of benzylic, diarylmethyl, and triarymethyl cations, see Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1971***, pp. 1501–1578.
[41] Olah, G.A.; Porter, R.D.; Jeuell, C.L.; White, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2044.
[42] Volz, H.; Schnell, H.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 873.
[43] Deno, N.C.; Schriesheim, A. *J. Am. Chem. Soc.* ***1955***, *77*, 3051.
[44] Prakash, G.K.S. *Pure Appl. Chem.* ***1998***, *70*, 2001.
[45] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.
[46] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1994***, *35*, 751.
[47] For reviews, see in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***: Richey, Jr., H.G. pp. 1201–294; Wiberg, K.B.; Hess, Jr., B.A.; Ashe, III, A.H. pp. 1295–1345.
[48] Pittman, Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 2998; Deno, N.C.; Liu, J.S.; Turner, J.O.; Lincoln, D.N.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* ***1965***, *87*, 3000.

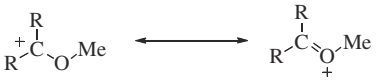
96% H_2SO_4.[49] This special stability, which increases with each additional cyclopropyl group, is



7 **8** **9** **10**

a result of conjugation between the bent orbitals of the cyclopropyl rings (Sec. 4.Q.i) and the vacant *p* orbital of the cationic carbon (see **10**). Nuclear magnetic resonance and other studies have shown that the vacant *p* orbital lies parallel to the C-2—C-3 bond of the cyclopropane ring and not perpendicular to it.[50] In this respect, the geometry is similar to that of a cyclopropane ring conjugated with a double bond (Sec. 4.Q.i). Cyclopropylmethyl cations are further discussed in Section 10.C.i, category 4. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbocation as ordinary alkyl groups.[51]

Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair[52] (e.g., oxygen,[53] nitrogen,[54] or halogen).[55] Such ions are stabilized by resonance, as with the oxocarbenium ion ($R_2C{=}O^+Me$).



This methoxymethyl cation can be obtained as a stable solid, $MeOCH_2{}^+$ $SbF_6{}^-$.[56] Carbocations containing either α, β, or γ silicon atom are also stabilized,[57] relative to similar ions without the silicon atom. γ-Silyl cyclobutylcarbocations are known.[58] In superacid solution, ions [e.g., $CX_3{}^+$ (X = Cl, Br, I)] have been prepared.[59] Vinyl-stabilized halonium ions are also known.[60]

[49] Deno, N.C.; Richey, Jr., H.G.; Liu, J.S.; Hodge, J.D.; Houser, H.J.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1962***, *84*, 2016.

[50] See Poulter, C.D.; Spillner, C.J. *J. Am. Chem. Soc.* ***1974***, *96*, 7591; Childs, R.F.; Kostyk, M.D.; Lock, C.J.L.; Mahendran, M. *J. Am. Chem. Soc.* ***1990***, *112*, 8912.

[51] Sorensen, T.S.; Miller, I.J.; Ranganayakulu, K. *Aust. J. Chem.* ***1973***, *26*, 311.

[52] See Hevesi, L. *Bull. Soc. Chim. Fr.* ***1990***, 697; Olah, G.A.; Liang, G.; Mo, Y.M. *J. Org. Chem.* ***1974***, *39*, 2394; Borch, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5303; Rabinovitz, M.; Bruck, D. *Tetrahedron Lett.* ***1971***, 245.

[53] For a review of ions of the form R_2C^+—OR', see Rakhmankulov, D.L.; Akhmatdinov, R.T.; Kantor, E.A. *Russ. Chem. Rev.* ***1984***, *53*, 888. For a review of ions of the form $R'C^+(OR)_2$ and $C^+(OR)_3$, see Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75.

[54] For a review of such ions where nitrogen is the heteroatom, see Scott, F.L.; Butler, R.N. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1643–1696.

[55] See Allen, A.D.; Tidwell, T.T. *Adv. Carbocation Chem.* ***1989***, *1*, 1. See also, Teberekidis, V.I.; Sigalas, M.P. *Tetrahedron* ***2003***, *59*, 4749.

[56] Olah, G.A.; Svoboda, J.J. *Synthesis* ***1973***, 52.

[57] See Lambert, J.B. *Tetrahedron* ***1990***, *46*, 2677; Lambert, J.B.; Zhao, Y.; Emblidge, R.W.; Salvador, L.A.,;Liu, X.; So, J.-H.; Chelius, E.C. *Acc. Chem. Res.* **1999**, 32, 183. See also, Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* ***1990***, *112*, 8120.

[58] Creary, X.; Kochly, E.D. *J. Org. Chem.* ***2009***, *74*, 9044.

[59] Olah, G.A.; Heiliger, L.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8020.

[60] Haubenstock, H.; Sauers, R.R. *Tetrahedron* ***2004***, *60*, 1191.

Simple acyl cations (RCO^+) have been prepared[61] in solution and the solid state.[62] The acetyl cation (CH_3CO^+) is about as stable as the *tert*-butyl cation (see Table 5.1). The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4.[63] These ions, often referred to as *acylium ions*, are stabilized by a canonical form containing a triple bond (**12**), although the positive charge is principally located on the carbon,[64] so that **11** contributes more than **12**.

$$\underset{\textbf{11}}{R-\overset{+}{C}=O} \longleftrightarrow \underset{\textbf{12}}{R-C\equiv O^+}$$

The stabilities of many other stable carbocations can also be attributed to resonance. Among these are the tropylium, cyclopropenium,[65] and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl ($C_6H_5^+$) or vinyl cations,[66] the ion, if formed at all, is usually very short lived.[67] Neither a vinyl[68] nor a phenyl cation has as yet been prepared as a stable species in solution.[69] However, stable alkenyl carbocations have been generated on Zeolite Y,[70] and the phenyl cation has been observed in cryogenic argon matrices.[71]

Various quantitative methods have been developed to express the relative stabilities of carbocations.[72] One of the most common of these, although useful only for relatively stable carbocations that are formed by ionization of alcohols in acidic solutions, is based on the equation[73]

$$H_R = pK_{R^+} - \log \frac{C_{R^+}}{C_{ROH}}$$

[61] see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1; Olah, G.A.; Germain, A.; White, A.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2049–2133; Lindner, E. *Angew. Chem. Int. Ed.* ***1970***, *9*, 114.

[62] See Olah, G.A.; Dunne, K.; Mo, Y.K.; Szilagyi, P. *J. Am. Chem. Soc.* ***1972***, *94*, 4200; Olah, G.A.; Svoboda, J.J. *Synthesis* ***1972***, 306.

[63] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651.

[64] Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706.

[65] See Komatsu, K.; Kitagawa, T. *Chem. Rev.* ***2003***, *103*, 1371. Also see, Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. *J. Org. Chem.* ***2000***, *65,* 1422.

[66] See Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* ***2002***, *67,* 693. For a discussion of aryl substituted vinyl cations, see Müller, T.; Margraf, D.; Syha, Y. *J. Am. Chem. Soc.* ***2005***, *127, 10852*.

[67] For a review of destabilized carbocations, see Tidwell, T.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 20.

[68] See Abram, T.S.; Watts, W.E. *J. Chem. Soc. Chem. Commun*,. ***1974***, 857; Siehl, H.; Carnahan, Jr., J.C.; Eckes, L.; Hanack, M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 675. Also see Franke, W.; Schwarz, H.; Stahl, D. *J. Org. Chem.* ***1980***, *45*, 3493. See also, Siehl, H.; Koch, E. *J. Org. Chem.* ***1984***, *49*, 575.

[69] See Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979; Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Acc. Chem. Res.* ***1976***, *9*, 364; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Richey, Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 899–957; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 42–49; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64,* 902.

[70] Yang, S.; Kondo, J.N.; Domen, K. *Chem. Commun.* ***2001***, 2008.

[71] Winkler, M.; Sander, W. *J. Org. Chem.* ***2006***, *71,* 6357.

[72] For reviews, see Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313; Bethell, D.; Gold, V. *Carbonium Ionds*, Academic Press, NY, ***1967***, pp. 59–87.

[73] Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

TABLE 5.2 $R—H \rightarrow R^+ + H^-$ Dissociation Energies in the Gas Phase

	$D(R^+—H^-)$		
Ion	kcal mol^{-1}	kJ mol^{-1}	Reference
CH_3^+	314.6	1316	76
$C_2H_5^+$	276.7	1158	76
$(CH_3)_2CH^+$	249.2	1043	76
$(CH_3)_3C^+$	231.9	970.3	76
$C_6H_5^+$	294	1230	77
$H_2C{=}CH^+$	287	1200	77,78
$H_2C{=}CH—CH_2^+$	256	1070	77
Cyclopentyl	246	1030	77
$C_6H_5CH_2^+$	238	996	77
CH_3CHO	230	962	77

pK_{R^+} is the pK value for the reaction $R^+ + 2\,H_2O \rightleftarrows ROH + H_3O^+$ and is a measure of the stability of the carbocation. The H_R parameter is an easily obtainable measurement of the stability of a solvent (Sec. 8.C) and approaches pH at low concentrations of acid. In order to obtain pK_{R^+}, for a cation R^+, one dissolves the alcohol ROH in an acidic solution of known H_R. Then, the concentration of R^+ and ROH are obtained, generally from spectra, and pK_{R+} is easily calculated.[74] A measure of carbocation stability that applies to less stable ions is the dissociation energy [$D(R^+—H^-)$] for the cleavage reaction $R—H \rightarrow R^+ + H^-$, which can be obtained from PES (Sec. 1.E) and other measurements. Some values of $D(R^+—H^-)$ are shown in Table 5.2.[75–78] Within a given class of ion, (primary, secondary, allylic, aryl, etc.), $D(R^+—H^-)$ has been shown to be a linear function of the logarithm of the number of atoms in R^+, with larger ions being more stable.[77]

Since the central carbon of tricoordinated carbocations has only three bonds and no other valence electrons, the bonds are sp^2 and should be planar.[79] Raman, IR, and NMR spectroscopic data on simple alkyl cations show this to be so.[80] In methylcycohexyl cations, there are two chair conformations where the carbon bearing the positive charge is planar (**13** and **14**), and there is evidence that **14** is more stable due to a difference in

[74] For a list of stabilities of 39 typical carbocations, see Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.* ***1983****, 105*, 2889. See also, Schade, C.; Mayr, H.; Arnett, E.M. *J. Am. Chem. Soc.* ***1988****, 110*, 567; Schade, C.; Mayr, H. *Tetrahedron* ***1988****, 44*, 5761.

[75] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651; Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* ***1978***, *100*, 5408; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329.

[76] Schultz, J.C.; Houle, F.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3917.

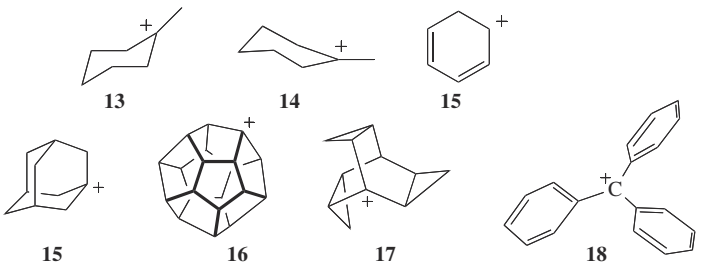
[77] Lossing. F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[78] Vinyl cations are generated by photolysis of vinyl iodonium salts. See Slegt, M.; Gronheid, R.; van der Vlugt, D.; Ochiai, M.; Okuyama, T.; Zuilhof, H.; Overkleeft, H.S.; Lodder, G. *J. Org. Chem.* ***2006*** *, 71,* 2227.

[79] See Schleyer, P.v.R. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, p. 241; Hehre, W. J. *Acc. Chem. Res.* ***1975***, *8*, 369; Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions,* Vol. 4, Wiley, NY, ***1974***, pp. 1561–574.

[80] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459; Yannoni, C.S.; Kendrick, R.D.; Myhre, P.C.; Bebout, D.C.; Petersen, B.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6440.

hyperconjugation.[81] Arenonium ions (**15**) are also known, and are relatively stable.[82] Other evidence is that carbocations are difficult to form at bridgehead atoms in [2.2.1] systems,[83] where they cannot be planar (see Sec. 10.A.ii).[84] Bridgehead carbocations are known, however, as in [2.1.1]hexanes[85] and cubyl carbocations.[86] However, larger bridgehead ions can exist. For example, the adamantyl cation (**15**) has been synthesized, as the SF_6^- salt.[87] The relative stability of 1-adamantyl cations is influenced by the number and nature of substituents. For example, the stability of the 1-adamantyl cation increases with the number of isopropyl substituents at C-3, C-5, and C-7.[88] Among other bridgehead carbocations that have been prepared in superacid solution at –78 °C are the dodecahydryl cation (**16**)[89] and the 1-trishomobarrelyl cation (**17**).[90] In the latter case, the instability of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.



Triarylmethyl cations (e.g., the triphenylmethyl carbocation, **18**),[91] are propeller-shaped, although the central carbon and the three ring carbons connected to it are in a plane:[92] The three benzene rings cannot be all in the same plane due to steric hindrance, although increased resonance energy would be gained if they could.

An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge.[93] This shift approximately correlates with electron density on the carbon. The ^{13}C chemical shifts for a

[81] Rauk, A.; Sorensen, T.S.; Maerker, C.; de M. Carneiro, J.W.; Sieber, S.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1996***, *118*, 3761.
[82] Lawlor, D.A.; More O'Ferrall, R.A.; Rao, S.N. *J. Am. Chem. Soc.* ***2008****, 130,* 17997.
[83] For a review of bridgehead carbocations, see Fort, Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1783–1835.
[84] Della, E.W.; Schiesser, C.H. *J. Chem. Soc. Chem. Commun.* ***1994***, 417.
[85] Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc. Chem. Commun.* ***1994***, 2785.
[86] Della, E.W.; Head, N.J.; Janowski, W.K.; Schiesser, C.H. *J. Org. Chem.* ***1993***, *58*, 7876.
[87] Olah, G.A.; Prakash, G.K.S.; Shih, J.G.; Krishnamurthy, V.V.; Mateescu, G.D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1985***, *107*, 2764. See also, Kruppa, G.H.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2162; Laube, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 349.
[88] Takeuchi, K.; Okazaki, T.; Kitagawa, T.; Ushino, T.; Ueda, K.; Endo, T.; Notario, R. *J. Org. Chem.* ***2001***, *66,* 2034.
[89] Olah, G.A.; Prakash, G.K.S.; Fessner, W.; Kobayashi, T.; Paquette, L.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8599.
[90] de Meijere, A.; Schallner, O. *Angew. Chem. Int. Ed.* ***1973***, *12*, 399.
[91] See Sundaralingam, M.; Chwang, A.K. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2427–2476.
[92] Schuster, I.I.; Colter, A.K.; Kurland, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4679.
[93] For reviews of the NMR spectra of carbocations, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.*, ***1979***, *12*, 261; Farnum, D.G. *Adv. Phys. Org. Chem.* ***1975***, *11*, 123.

TABLE 5.3 The ^{13}CNMRChemical-Shift Values, in Parts per Million from $^{13}CS_2$, for the Charged Carbon Atom of Some Carbocations in $SO_2ClF—SbF_5$, $SO_2—FSO_3H—SbF_6$, or $SO_2—SbF_5$[a]

Ion	Chemical Shift	Temperature (°C)	Ion	Chemical Shift	Temperature (°C)
Et_2MeC^+	−139.4	−20	$C(OH)_3^+$	+28.0	−50
Me_2EtC^+	−139.2	−60	$PhMe_2C^+$	−61.1	−60
Me_3C^+	−135.4	−20	$PhMeCH^+$	−40[91]	
Me_2CH^+	−125.0	−20	Ph_2CH^+	−5.6	−60
Me_2COH^+	−55.7	−50	Ph_3C^+	−18.1	−60
$MeC(OH)_2^+$	−1.6	−30	Me_2(cyclopropyl)C^+	−86.8	−60
$HC(OH)_2^+$	+17.0	−30			

Reprinted with permission from Olah, G.A.; White, A.M. *J. Am. Chem. Soc*. ***1968***, *90*, 1884, Copyright © 1968 American Chemical Society. Reprinted with permission from Olah, G.A.; White, A.M. *J. Am. Chem. Soc*. ***1969***, *91*, 5801, Copyright © 1969 American Chemical Society.

[a]See Ref. 94.

number of ions are given in Table 5.3.[94] As shown in Table 5.3, the substitution of an ethyl for a methyl or a methyl for a hydrogen atom causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbocation stabilities, as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, although the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of −86.8 and −61.1, respectively, although we have seen that according to other criteria a cyclopropyl group is better than a phenyl group at stabilizing a carbocation.[95] The reasons for this discrepancy are not fully understood.[88,96]

Nonclassical carbocations are discussed in section 10.C.i.

5.A.iii. The Generation and Fate of Carbocations

A number of methods are available to generate carbocations, stable or unstable.

1. A direct ionization, in which a leaving group attached to a carbon atom leaves with its pair of electrons, as in solvolysis reactions of alkyl halides (see Sec. 10.G.i) or sulfonate esters (Reaction **10-04**):

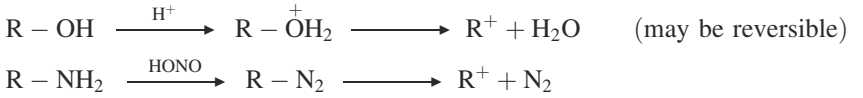
$$R-X \longrightarrow R^+ + X^- \qquad \text{(may be reversible)}$$

[94] Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1884; ***1969***, *91*, 5801. For ^{13}C NMR data for additional ions, see Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5026; Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Org. Chem.* ***1977***, *42*, 2666.

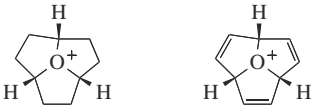
[95] Olah, G.A.; Porter, R.D.; Kelly, D.P. *J. Am. Chem. Soc.* ***1971***, *93*, 464.

[96] See Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1977***, *99*, 1712; Kitching, W.; Adcock, W.; Aldous, G. *J. Org. Chem.* ***1979***, *44*, 2652. See also, Larsen, J.W.; Bouis, P.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4418; Volz, H.; Shin, J.; Streicher, H. *Tetrahedron Lett*. ***1975***, 1297; Larsen, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 330.

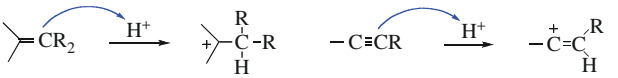
2. Ionization after an initial reaction that converts one functional group into a leaving group, as in protonation of an alcohol to give an oxonium ion (ROH_2^+) or conversion of a primary amine to a diazonium salt, both of which ionize to the corresponding carbocation:



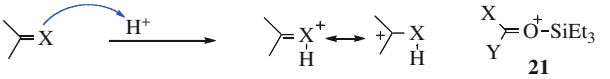
Oxonium ions are also generated by protonation of ethers,[97] including epoxides.[98] However, these ions do not always lead to carbocations via ionization, but often undergo substitution reactions (see Chap 10). Oxatriquinane, (**19**) is a fused, tricyclic alkyl oxonium ion that is remarkably stable. Oxonium ion **19** has been heated to reflux in water, can be chromatographed, and does not react with alcohols or alkyl thiols.[99] The X-ray crystal structure shows longer C—O bond distances and more acute C—O—C bond angles than any reported alkyloxonium salt. Oxatriquinene (**20**) has also been synthesized.



3. A proton or other positive species adds to one atom of an alkene or alkyne, leaving the adjacent carbon atom with a positive charge (see Chapters 11 and 15).



4. A proton or other positive species adds to one atom of a C=X bond, where X = O, S, N in most cases, leaving the adjacent carbon atom with a positive charge (see Chapter 16). When X = O, S, this ion is a resonance stabilized oxocarbenium ion (X = O) or thiacarbenium ion (X = S), as shown. When X = NR, protonation leads to an iminium ion (X = N), with the charge localized on the nitrogen. A silylated carboxonium ion (e.g., **21**) has been reported.[100]



When formed by any of the processes 1–3, carbocations are most often short-lived transient species and react further without being isolated. Oxocarbenium ions are more stable and may be longer lived, but even oxocarbenium ions are transient intermediates. The intrinsic barriers to formation and reaction of carbocations have been studied.[101]

[97] Peterson, P.E.; Slama, F.J. J. *Am. Chem. Soc.*, ***1968***, *90*, 6516.
[98] Carlier, P.R.; Deora, N.; Crawford, T.D. *J. Org. Chem.* ***2006***, *71*, 1592.
[99] Mascal, M.; Hafezi, N.; Meher N.K.; Fettinger, J.C. *J. Am. Chem. Soc.* ***2008***, *130,* 13532.
[100] Prakash, G.K.S.; Bae, C.; Rasul, G.; Olah, G.A. *J. Org. Chem.* ***2002***, *67*, 1297.

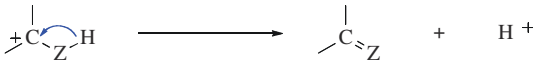
There are two principal pathways by which carbocations react to give stable products that are effectively the reverse of the two pathways just described.

1. *A carbocation may combine with a species possessing an electron pair* (essentially a Lewis acid–base reaction, see Chapter 8). This reaction occurs by an atom or group donating electrons to the positive carbon of the carbocation. The atom or group that donates the electrons to carbon is called a *nucleophile* (see Chapter 10):

$$R^+ + Y^- \rightarrow R - X$$

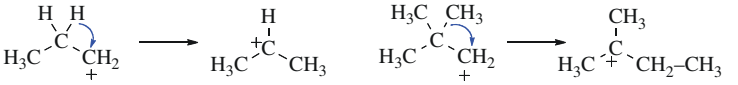
Any reasonable nucleophile will react with the carbocation, but the nucleophile may also be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, and 16). These reactions are very fast. A recent study measured k_s (the rate constant for reaction of a simple tertiary carbocation) to be $3.5 \times 10^{12}\,s^{-1}$.[102]

2. *The carbocation may have a proton* (or much less often, another positive ion) *removed* from the adjacent atom (see Chapters 11 and 17):



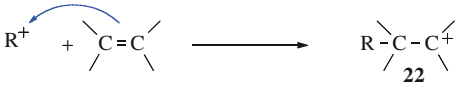
Carbocations can also adopt two other pathways that lead not to stable products, but to other carbocations:

3. *Rearrangement*. An alkyl or aryl group or a hydrogen atom (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chap 18):



A novel rearrangement has been observed. The 2-methyl-2-butyl-1-^{13}C cation (^{13}C-labeled *tert*-amyl cation) shows an interchange of the inside and outside carbons with a barrier of 19.5 kcal mol^{-1} (81.6 kJ mol^{-1}) (±2.0 kcal mol^{-1}, 8.4 kJ mol^{-1}).[103] Another unusual migratory process has been observed for the nonamethylcyclopentyl cation. It has been shown that "four methyl groups undergo rapid circumambulatory migration with a barrier <2 kcal mol^{-1} (8.4 kJ mol^{-1}) while five methyl groups are fixed to ring carbons. The process that equalizes the two sets of methyls has a barrier of 7.0 kcal mol^{-1} (29.3 kJ mol^{-1})."[104]

4. *Addition*. A carbocation may add to a double bond, generating a positive charge at a new position (see Chaps 11 and 15). This means that the π bond donates two electrons to a positive atom, generating positive charge on the carbon as shown:



22

[101] Richard, J.P.; Amyes, T.L.; Williams, K.B. *Pure. Appl. Chem.* ***1998***, *70*, 2007.
[102] Toteva, M.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 11434.
[103] Vrcek, V.; Saunders, M.; Kronja, O. *J. Am. Chem. Soc.* ***2004***, *126,* 13703.
[104] Kronja, O.; Kohli, T.-P.; Mayr, H.; Saunders, M. *J. Am. Chem. Soc.* ***2000***, *122,* 8067.

Whether formed by pathway 3 or 4, the new carbocation normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **22** can add to another alkene molecule, and this product can add to still another, and so on. This is one of the mechanisms for vinyl polymerization.

5.B. CARBANIONS

5.B.i. Stability and Structure[105]

Formally, a carbanion is a trivalent carbon atom with an unshared electron pair, and a formal charge of −1. In fact, there are few carbanions that do not have an anion-stabilizing group attached to the carbon atom. Stabilization may be by resonance delocalization or by orbital participation of an atom with *d* orbitals or orbitals associated withy a metal.

By definition, every carbanion possesses an unshared pair of electrons and is formally a base. When a carbanion donates an electron to a proton, it is converted to its conjugate acid (an acid–base reaction, see Chapter 8). If the carbanion ($R_3C:^-$) were available, reaction with an acid generates the conjugate acid ($R_3C—H$), an alkane. The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker that conjugate acid, the greater the base strength of the carbanion, and the lower the stability of the carbanion.[106] Stability here is judged by diminished reactivity (lower electron-donating ability) with a proton. The greater the stability, the lower the electron-donating ability (lower reactivity) for reaction of the carbanion with a proton (any acid that is sufficiently strong), and hence the longer lived the carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the inverse order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths (e.g., Table 8.1).

While formation of simple carbanions (e.g, CH_3^-) is rare, formation of a carbon–metal bond often generates a molecule (e.g., $R_3C—M$, where M = a metal atom) that has a polarized bond in which the carbon is electron rich (δ^-). An organic molecule that contains a carbon–metal bond is called an *organometallic compound*. Organometallic compounds where the metal is Mg, Li, or other metals are carbanion surrogates, and in much of their chemistry they react as if they were carbanions (see Reactions **12-22–12.39**). Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. This section will discuss carbanions with little reference to a metal. Section 5.B.ii will discuss the structures of organometallic compounds, which are often carbanion surrogates.

Carbanions are very strong bases, and the conjugate acids of simple unsubstituted carbanions are very weak acids, with very few exceptions. Unfortunately, it is not easy to measure acid strengths of very weak acids. There is little doubt that carbanions are very

[105] See Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier, NY, ***1980***, ***1984***, ***1987***; Bates, R.B.; Ogle, C.A. *Carbanion Chemistry*, Springer, NY, ***1983***; Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***; Staley, S.W. *React. Intermed. (Wiley)* ***1985***, *3*, 19; Staley, S.W.; Dustman, C.K. *React. Intermed. (Wiley)* ***1981***, *2*, 15. For reviews of NMR spectra of carbanions, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261. For a review of dicarbanions, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223.

[106] See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, Elmsford, NY, ***1978***; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116.

unstable in solution, and in contrast to the situation with carbocations, efforts to prepare solutions in which carbanions (e.g., ethyl or isopropyl) exist in a relatively free state have not yet been successful. It has also not been possible to form these carbanions in the gas phase. Indeed, there is evidence that simple carbanions (e.g., ethyl and isopropyl) are unstable, losing an electron, which converts them to radicals.[107] Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[108] studied the position of equilibrium for the reaction:

$$RLi + R'I \rightleftharpoons RI + R'Li$$

This reaction was done in ether or an ether–pentane mixture. The reasoning in these experiments was that the R group that forms the more stable carbanion would be more likely to be bonded to lithium than to iodine. Carbanion stability was found to be in the order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy et al.[109] treated a number of alkylmagnesium compounds with a number of alkylmercury compounds in THF, setting up the equilibrium:

$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R_2Mg$$

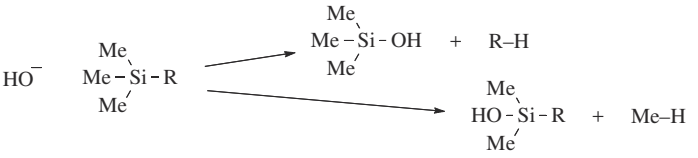
where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined this way was phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible to determine the position of *tert*-butyl by the experiments reported by Dessy et al.[109], but there seems little doubt that it is still less stable. This stability order can be interpreted as solely a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien[108] show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see Sec. 5.B.i, category 2). Strongly electron-withdrawing groups (e.g., trifluoromethylsulfonyl) provide exceptional stability to carbanions.[110]

A different approach to the problem of hydrocarbon acidity, and hence carbanion stability, is that of Shatenshtein and Shapiro, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[111] The experiments did not measure *thermodynamic* acidity, since rates were measured, not positions of equilibria. They measured *kinetic* acidity; that is, which compounds gave up protons most rapidly (see Sec. 6.F for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured

[107] See Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.
[108] Applequist, D.E.; O'Brien, D.F. *J. Am. Chem. Soc.* ***1963***, *85*, 743.
[109] Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.
[110] Terrier, F.; Magnier, E.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* ***2005***, *127,* 5563.
[111] For reviews, see Jones, J.R. *Surv. Prog. Chem.* ***1973***, *6*, 83; Shatenshtein, A.I.; Shapiro, I.O. *Russ. Chem. Rev.* ***1968***, *37*, 845.

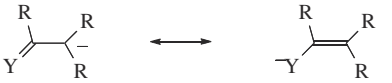
because they lie too far to the side of the starting materials; that is, where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic and kinetic acidity is far from perfect,[112] the results of the rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.[111]

Experiments described above were done in solution, and experiments in the gas phase gave different results. In reactions of $^{-}$OH with alkyltrimethylsilanes, it is possible to cleave either R or Me. Since the R or Me come off as a carbanion or incipient carbanion, the product ratio RH/MeH can be used to establish the relative stabilities of various R groups. From these experiments a stability order of neopentyl > cyclopropyl > *tert*-butyl > *n*-propyl > methyl > isopropyl > ethyl was found.[113] On the other hand, in a different kind of gas-phase experiment, Graul and Squires[114] were able to observe CH_3^- ions, but not the ethyl, isopropyl, or *tert*-butyl ions.

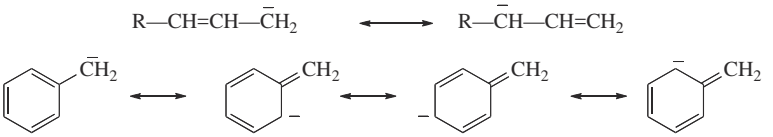


As mentioned above, carbanion-stabilizing groups can increase the stability of carbanions, which influences their ease of formation. Six structural features that lead to improved stability are listed:

1. *Conjugation of the Unshared Pair with an Unsaturated Bond.*



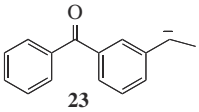
In cases where a double or triple bond is located α to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic[115] and benzylic[116] types of carbanions:



Diphenylmethyl and triphenylmethyl anions are still more stable due to extensive delocalization into the benzene rings, and can be kept in solution indefinitely if

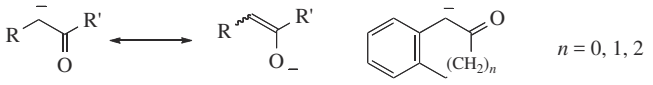
[112] See Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. *J. Am. Chem. Soc.* ***1975***, *97*, 442.
[113] DePuy, C.H.; Gronert, S.; Barlow, S.E.; Bierbaum, V.M.; Damrauer, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1968. The same order (for *t*-Bu, Me, *i*Pr, and Et) was found in gas-phase cleavages of alkoxides (Reaction **12-41**): Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1984***, *106*, 4053.
[114] Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.
[115] See Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 67–77.
[116] See Bockrath, B.; Dorfman, L.M. *J. Am. Chem. Soc.* ***1974***, *96*, 5708.

water is rigidly excluded.[117] X-ray crystallographic structures have been obtained for Ph_2CH^- and Ph_3C^- enclosed in crown ethers.[118] Carbanion **23** has a lifetime of several minutes (hours in a freezer at $-20\,^\circ C$) in dry THF.[119] Condensed aromatic rings fused to a cyclopentadienyl anion are known to stabilize the carbanion.[120]



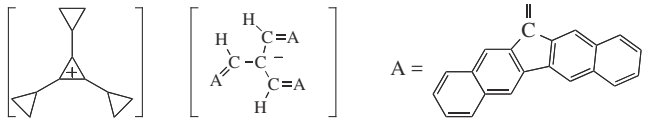
23

Where the carbanionic carbon is conjugated with a carbon–oxygen or carbon–nitrogen multiple bond (Y = O or N), the stability of the ion is greater than that of the triarylmethyl anions, since these electronegative atoms are more capable of bearing a negative charge than carbon. However, it is questionable whether ions of this type should be called a carbanion at all, since in the case of enolate ions, for example, **25** contributes more to the hybrid than **24** although such ions react more often at the carbon than at the oxygen. In benzylic enolate anions (e.g., **26**), the conformation of the enolate can be coplanar with the aromatic ring or bent out of plane if the strain is too great.[121] Enolate ions can also be maintained in solution in many cases, at least for minutes or hours at lower temperatures. In the case of carbanions at a carbon α to a nitrile, the "enolate" resonance form would be a ketene imine nitranion, but the existence of this species has been called into question.[122] A nitro group is particularly effective in stabilizing a negative charge on an adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus the pK_a for nitromethane is 10.2. Dinitromethane is even more acidic (p$K_a = 3.6$). In contrast to the stability of cyclopropylmethyl cations (Sec. 5.A.ii), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.[123]



24 **25** **26** $n = 0, 1, 2$

By combining a very stable carbanion with a very stable carbocation, Okamoto et al.[124] were able to isolate the salt (**27**), as well as several similar salts, as stable solids. These are salts that consist entirely of carbon and hydrogen atoms.



27

[117] See Buncel, E.; Menon, B. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C, Elsevier, NY, ***1980, 1984, 1987***, pp. 97–124.

[118] Olmstead, M.M.; Power, P.P. *J. Am. Chem. Soc.* ***1985***, *107*, 2174.

[119] Laferriere, M.; Sanrame, C. N.; Scaiano, J. C. *Org. Lett.* ***2004***, *6,* 873.

[120] Kinoshita, T.; Fujita, M.; Kaneko, H.; Takeuchi, K-i.; Yoshizawa, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1145.

[121] Eldin, S.; Whalen, D.L.; Pollack, R.M. *J. Org. Chem.* ***1993***, *58*, 3490.

[122] Abbotto, A.; Bradamante, S.; Pagani, G.A. *J. Org. Chem.* ***1993***, *58*, 449.

[123] Perkins, M.J.; Peynircioglu, N.B. *Tetrahedron* ***1985***, *41*, 225.

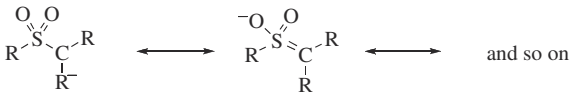
[124] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

2. *Carbanions Increase in Stability with an Increase in the Amount of s Character at the Carbanionic Carbon*. Thus the order of stability is

$$RC{\equiv}C^- > R_2C{=}CH^- \sim Ar^- > R_3C{-}CH_2{}^-$$

Acetylene, where the carbon is *sp* hybridized with 50% *s* character, is much more acidic than ethylene[125] (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus, and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (see Sec. 4.Q.i).

3. *Stabilization by Sulfur*[126] *or Phosphorus*. Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty *d* orbital[127] ($p\pi$–$d\pi$ bonding, see Sec. 2.H). For example, a carbanion containing the SO_2R group would be written as follows:



However, there is evidence against *d*-orbital overlap; and the stabilizing effects have been attributed to other causes.[128] In the case of a PhS substituent, carbanion stabilization is thought to be due to a combination of the inductive and polarizability effects of the group, and *d*–pπ resonance and negative hyperconjugation play a minor role, if any.[129] An α silicon atom also stabilizes carbanions.[130]

4. *Field Effects*. Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, although it is difficult to separate the field effect from the resonance effect. However, in a nitrogen (ylid $R_3N^+{-}CR_2$, see Sec. 2.H), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylids are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any heteroatom (O, N, or S) connected to the carbanionic carbon, provided that the heteroatom bears a positive charge in at least one important canonical form,[131] for example,

[125] See Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 49–56.

[126] See Oae, S.; Uchida, Y. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 583–664; Wolfe, S. in Bernardi, F.; Csizmadia, I.G.; Mangini. A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 133–190; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 42–56; Durst, T.; Viau, R. *Intra-Sci. Chem. Rep.* ***1973***, *7* (3), 63. Also see, Reich, H.J. in Liotta, DC. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 243–276.

[127] See Wolfe, S.; LaJohn, L.A.; Bernardi, F.; Mangini, A.; Tonachini, G. *Tetrahedron Lett.* ***1983***, *24*, 3789; Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* ***1983***, *24*, 4071.

[128] See Borden, W.T.; Davidson, E.R.; Andersen, N.H.; Denniston, A.D.; Epiotis, N.D. *J. Am. Chem. Soc.* ***1978***, *100*, 1604; Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* ***1986***, *108*, 8171.

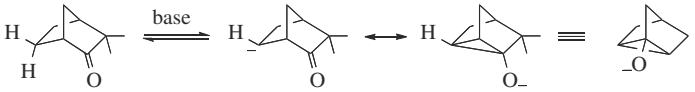
[129] Bernasconi, C.F.; Kittredge, K.W. *J. Org. Chem.* ***1998***, *63*, 1944.

[130] Wetzel, D.M.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 8333.

[131] For a review of such carbanions, see Beak, P.; Reitz, D.B. *Chem. Rev.* ***1978***, *78*, 275. See also, Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekhar, J.; Schleyer, P.v.R. *J. Org. Chem.* ***1981***, *46*, 4108.



5. Certain Carbanions Are Stable because They Are Aromatic. See the cyclopentadienyl anion in Section 2.I.ii, and other aromatic anions in Chapter 2.
6. *Stabilization by a Nonadjacent π Bond.*[132] In contrast to the situation with carbocations (see Sec. 2.C.i), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **30**, formed when optically active camphenilone (**28**) was treated with a strong base (potassium *tert*-butoxide).[133] That **30** was truly formed was shown by the following facts: (1) A proton was abstracted: ordinary CH_2 groups are not acidic enough for this base; (2) recovered **28** was racemized: **30** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **28** contained up to three atoms of deuterium per molecule, although if **29** were the only ion, no more than two could be taken up. Ions of this type, in which a negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.



28 **29** **30**

Based on these four categories, functional groups in the α position stabilize carbanions in the following order: $NO_2 > RCO > COOR > SO_2 > CN \sim CONH_2 >$ halogen $> H > R$.

It is unlikely that free carbanions exist in solution, although some of the stabilized carbanions noted above have reasonable lifetimes in solution. Like carbocations, they usually exist as either ion pairs or they are solvated.[134] Among experiments that demonstrate ion pairing or solvation was the treatment of $PhCOCHMe^- M^+$ with ethyl iodide, where M^+ was Li^+, Na^+, or K^+. The half-lives of the reaction were[135] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Similar results[136] were obtained with Li, Na, and Cs triphenylmethides ($Ph_3C^- M^+$).[137] Where ion pairs are unimportant, carbanions are solvated. Cram[105] demonstrated

[132] See Werstiuk, N.H. *Tetrahedron* ***1983***, *39*, 205; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 410–437.

[133] See Werstiuk, N.H.; Yeroushalmi, S.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 1945; Lee, R.E.; Squires, R.R. *J. Am. Chem. Soc.* ***1986***, *108*, 5078; Peiris, S.; Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.* ***1987***, *65*, 789; Shiner, C. S.; Berks, A.H.; Fisher, A.M. *J. Am. Chem. Soc.* ***1988***, *110*, 957.

[134] For reviews of carbanion pairs, see Hogen-Esch, T.E. *Adv. Phys. Org. Chem.* ***1977***, *15*, 153; Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737. See also, Laube, T. *Acc. Chem. Res.* ***1995***, *28*, 399.

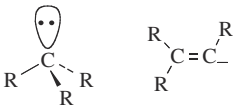
[135] Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386.

[136] Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1981***, *17*, 381. See also, Solov'yanov, A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1964.

[137] See DePalma, V.M.; Arnett, E.M. *J. Am. Chem. Soc.* ***1978***, *100*, 3514; Buncel, E.; Menon, B. *J. Org. Chem.* ***1979***, *44*, 317; O'Brien, D.H.; Russell, C.R.; Hart, A.J. *J. Am. Chem. Soc.* ***1979***, *101*, 633; Streitwieser, Jr., A.; Shen, C.C.C. *Tetrahedron Lett.* ***1979***, 327; Streitwieser, Jr., A. *Acc. Chem. Res.* ***1984***, *17*, 353.

solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more localized in solution in order to maximize the electrostatic attraction to the counterion.[138]

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it is likely that the central carbon is sp^3 hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions are expected to have pyramidal structures (e.g., **31**, similar to those of amines.



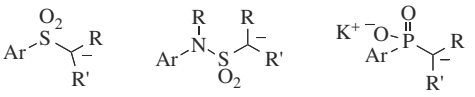
31 **32**

The methyl anion (CH_3^-) has been observed in the gas phase and reported to have a pyramidal structure.[139] If this is taken as a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this principle, but without success.[140] A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, although extremely reluctant to undergo reactions in which they must be converted to carbocations, easily undergo reactions in which they must be carbanions and stable bridgehead carbanions are known.[141] Also, reactions at vinylic carbons proceed with retention,[142] indicating that the intermediate **32** has sp^2 hybridization and not the sp hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.[143]

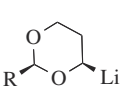
Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, although unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[144] Cram[144] showed that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (see Sec. 12.A.ii). This result is

[138] See Schade, C.; Schleyer, P.v.R.; Geissler, M.; Weiss, E. *Angew. Chem. Int. Ed.* ***1986***, *21*, 902.
[139] Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc. 1978*, *100*, 2556.
[140] Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see Sec. 12.A.ii).
[141] See Peoples, P.R.; Grutzner, J.B. *J. Am. Chem. Soc.* ***1980***, *102*, 4709.
[142] See Feit, B.; Melamed, U.; Speer, H.; Schmidt, R.R. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 775; Chou, P.K.; Kass, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 4357.
[143] Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* ***1988***, *110*, 6925; Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***. For a review, see Boche, G.; Walborsky, H.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 701–808.
[144] See Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

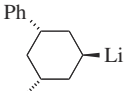
explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, for example, are inherently chiral, since retention of configuration is observed where



they are generated, even in solvents that cause racemization or inversion with other carbanions.[145] It is known that in THF, PhCH(Li)Me behaves as a prochiral entity,[146] and **33** has been prepared as an optically pure α-alkoxylithium reagent.[147] Cyclohexyllithium (**34**) shows some configurational stability, and it is known that isomerization is slowed by an increase in the strength of lithium coordination and by an increase in solvent polarity.[148] It is known that a vinyl anion is configurationally stable whereas a vinyl radical is not. This is due to the instability of the radical anion that must be an intermediate for conversion of one isomer of vinyllithium to the other.[149] The configuration about the carbanionic carbon, at least for some of the α-sulfonyl carbanions, seems to be planar,[150] and the inherent chirality is caused by lack of rotation about the C—S bond.[151]



33



34

5.B.ii. The Structure of Organometallic Compounds[152]

Whether a carbon–metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon–sodium bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of Na, K,

[145] Bordwell, F.G.; Phillips, D.D.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 426; Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* ***1981***, 1005; Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.* ***1982***, *232*, 293; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 105–113; Hirsch, R.; Hoffmann, R.W. *Chem. Ber.* ***1992***, *125*, 975.

[146] Hoffmann, R.W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* ***1992***, 719.

[147] Rychnovsky, S.D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* ***1994***, *35*, 6799.

[148] Reich, H.J.; Medina, M.A.; Bowe, M.D. *J. Am. Chem. Soc.* ***1992***, *114*, 11003.

[149] Jenkins, P.R.; Symons, M.C.R.; Booth, S.E.; Swain, C.J. *Tetrahedron Lett.* ***1992***, *33*, 3543.

[150] Gais, H.; Müller, J.; Vollhardt, J.; Lindner, H.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4002. For a contrary view, see Trost, B.M.; Schmuff, N.R. *J. Am. Chem. Soc.* ***1985***, *107*, 396.

[151] Grossert, J.S.; Hoyle, J.; Cameron, T.S.; Roe, S.P.; Vincent, B.R. *Can. J. Chem.* ***1987***, *65*, 1407.

[152] See Elschenbroich, C.; Salzer, A. *Organometallics*, VCH, NY, ***1989***; Oliver, J.P. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 789–826; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 1, Methuen: London, ***1967***; Grovenstein, Jr., E. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. C, Elsevier, NY, ***1987***, pp. 175–221.

Rb, and Cs[153] are nonvolatile solids[154] insoluble in benzene or other organic solvents, while alkyllithium reagents are soluble, although they too are generally nonvolatile solids. Organolithium reagents with alkyl units (alkyllithium reagents) do not exist as monomeric species in hydrocarbon solvents or ether.[155] In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithium reagents are normally hexameric unless steric interactions favor tetrameric aggregates.[156] Nuclear magnetic resonance studies, especially measurements of $^{13}C—^{6}Li$ coupling, have also shown aggregation in hydrocarbon solvents.[157] Boiling-point-elevation studies have been performed in ether solutions, where alkyllithium reagents exist in two- to fivefold aggregates.[158] Even in the gas phase[159] and in the solid state,[160] alkyllithium reagents exist as aggregates. X-ray crystallography has shown that methyllithium has the same tetrahedral structure in the solid state as in ether solution.[160] However, *tert*-butyllithium is monomeric in THF, although dimeric in ether and tetrameric in hydrocarbon solvents.[161] Neopentyllithium exists as a mixture of monomers and dimers in THF.[162]

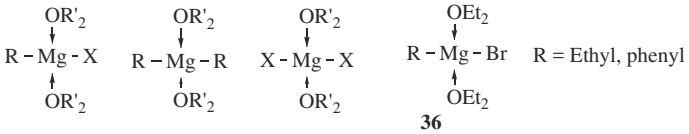
The C—Mg bond in *Grignard reagents* is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[163] In 1929, it was discovered[164] that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R_2Mg in ether; (i.e., there can be no RMgX in the solution since there is no halide). The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \underset{\mathbf{35}}{R_2Mg{\cdot}MgX_2}$$

in which **35** is a complex. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium depends on the identity of R, X, the

[153] See Schade, C.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1987***, *27*, 169.
[154] For X-ray crystallography studies, see Weiss, E.; Sauermann, G. *Chem. Ber.* ***1970***, *103*, 265; Weiss, E.; Köster, H. *Chem. Ber.* ***1977***, *110*, 717.
[155] See Setzer, W.N.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1985***, *24*, 353; Schleyer, P.v.R. *Pure Appl. Chem.* ***1984***, *56*, 151; Brown, T.L. *Pure Appl. Chem.* ***1970***, *23*, 447, *Adv. Organomet. Chem.* ***1965***, *3*, 365; Kovrizhnykh, E.A.; Shatenshtein, A.I. *Russ. Chem. Rev.* ***1969***, *38*, 840. For reviews of the structures of lithium enolate anions and related compounds, see Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 277; Seebach, D. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1624. Also see Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1212; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.
[156] Lewis, H.L.; Brown, T.L. *J. Am. Chem. Soc.* ***1970***, *92*, 4664; Brown, T.L.; Rogers, M.T. *J. Am. Chem. Soc.* ***1957***, *79*, 1859; Weiner, M.A.; Vogel, G.; West, R. *Inorg. Chem.* ***1962***, *1*, 654.
[157] Thomas, R.D.; Jensen, R.M.; Young, T.C. *Organometallics* ***1987***, *6*, 565. See also, Kaufman, M.J.; Gronert, S.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1988***, *110*, 2829.
[158] Wittig, G.; Meyer, F.J.; Lange, G. *Liebigs Ann. Chem.* ***1951***, *571*, 167. See also, Bates, T.F.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5109.
[159] Plavš ić, D.; Srzić, D.; Klasinc, L. *J. Phys. Chem.* ***1986***, *90*, 2075.
[160] Weiss, E.; Sauermann, G.; Thirase, G. *Chem. Ber.* ***1983***, *116*, 74.
[161] Bauer, W.; Winchester, W.R.; Schleyer, P.v.R. *Organometallics* ***1987***, *6*, 2371.
[162] Fraenkel, G.; Chow, A.; Winchester, W.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6190.
[163] For reviews, see Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Wakefield, B. J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.
[164] Schlenk, W.; Schlenk, Jr., W. *Ber.* ***1929***, *62B*, 920.

solvent, the concentration, and the temperature.[165] It has been known for many years that the magnesium in a solution of a Grignard reagent, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds to generate the solvent-coordinated species shown.



36

Rundle and Guggenberger[166] performed X-ray diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the solids crystallized. They found that the structures were magnesium bromides (e.g., **36**). These solids still contained ether. When ordinary ethereal Grignard solutions[167] prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at $\sim$100 °C under vacuum so that the solid remaining contained no ether, X-ray diffraction showed *no* RMgX, but a mixture of R_2Mg and MgX_2.[168] These results indicate that in the presence of ether, $RMgX{\cdot}2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in THF at all concentrations and in ether at low concentrations (up to $\sim$0.1 M) Grignard reagents prepared from alkyl bromides and iodides are monomeric, (i.e., there are few or no molecules with two Mg atoms).[169] Thus, part of the Schlenk equilibrium is operating but not the other part (i.e., **35** is not present in measurable amounts). This was substantiated by ^{25}Mg NMR spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr, Et_2Mg, and $MgBr_2$.[170] That the equilibrium between RMgX and R_2Mg lies far to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker,[171] who mixed 0.1 M ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal mol^{-1} (15 kJ mol^{-1}) of Et_2Mg, and that the product was *monomeric* (by boiling-point elevation measurements). When either solution was added little by little to the other, there was a linear output of heat until almost a 1 : 1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX

[165] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206; Salinger, R.M.; Mosher, H.S. *J. Am. Chem. Soc.* ***1964***, *86*, 1782.
[166] Guggenberger, L.J.; Rundle, R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 5375.
[167] See Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* ***2001***, *3*, 1793.
[168] Weiss, E. *Chem. Ber.* ***1965***, *98*, 2805.
[169] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363; Vreugdenhil, A.D.; Blomberg, C. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 453, 461.
[170] Benn, R.; Lehmkuhl, H.; Mehler, K.; Rufińska, A. *Angew. Chem. Int. Ed.* ***1984***, *23*, 534.
[171] Smith, M.B.; Becker, W.E. *Tetrahedron* ***1966***, *22*, 3027.

(coordinated with solvent), but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

For some aryl Grignard reagents, it is possible to distinguish separate NMR chemical shifts for ArMgX and Ar_2Mg.[172] From the area under the peaks, it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the Schlenk equilibrium. These data show[172] that the position of the equilibrium depends very markedly on the aryl group and the solvent, but that conventional aryl Grignard reagents in ether are largely ArMgX. In THF the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate NMR chemical shifts have also been found for alkyl RMgBr and R_2Mg in HMPA[173] and in ether at low temperatures.[174] When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX.[175] Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N, higher in ether, and still higher in THF.[176]

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5–1 M) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,[177] so that **35** is in solution, probably in equilibrium with RMgX and R_2Mg (i.e., the complete Schlenk equilibrium seems to be present).

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the Mg containing carbon (demonstrated by NMR; this compound is not chiral).[178] The mechanism of this inversion is not completely known. Despite the mechanistic ambiguity, in almost all cases, it is not possible to retain the configuration of a stereogenic carbon while forming a Grignard reagent.

Organolithium reagents (RLi) are very important reagents in organic chemistry. In recent years, a great deal has been learned about their structure[179] in both the solid state and in solution. X-ray analysis of complexes of *n*-butyllithium with tetramethylethylenediamine (TMEDA), THF, and 1,2-dimethoxyethane (DME) shows them to be dimers and tetramers [e.g., $(BuLi{\cdot}DME)_4$];[180] they are aggregates.[181] X-ray analysis of isopropyllithium shows it to be a hexamer [$(i$PrLi$)_6$],[182] and unsolvated lithium aryls are tetramers.[183] α-Ethoxyvinyllithium [$CH_2{=}C(OEt)Li$] shows a polymeric structure with tetrameric subunits.[184] Aminomethyl aryllithium reagents have been shown to be

[172] Evans, D.F.; Fazakerley, V. *Chem. Commun.* ***1968***, 974.
[173] Ducom, J. *Bull. Chem. Soc. Fr.* ***1971***, 3518, 3523, 3529.
[174] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971****, 93*, 1206.
[175] Ashby, E.C.; Walker, F. *J. Org. Chem.* ***1968***, *33*, 3821.
[176] Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971****, 93*, 1206.
[177] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964****, 86*, 4363.
[178] Fraenkel, G.; Cottrell, C.E.; Dix, D.T. *J. Am. Chem. Soc.* ***1971***, *93*, 1704; Pechhold, E.; Adams, D.G.; Fraenkel, G. *J. Org. Chem.* ***1971***, *36*, 1368; Maercker, A.; Geuss, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 270.
[179] See Pratt, L.M.; Kass, S.R. *J. Org. Chem.* ***2004****, 69,* 2123.
[180] Nichols, M.A.; Williard, P.G. *J. Am. Chem. Soc.* ***1993***, *115*, 1568.
[181] See Jones, A.C.; Sanders, A.W.; Bevan, M.J.; Reich, H.J. *J. Am. Chem. Soc.* ***2007****, 129,* 3492.
[182] Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* ***1994***, *116*, 5507.
[183] Ruhlandt-Senge, K.; Ellison, J.J.; Wehmschulte, R.J.; Pauer, F.; Power, P.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11353. Also see Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* ***2000****, 2*, 3805.
[184] Sorger, K.; Bauer, W.; Schleyer, P.v.R.; Stalke, D. *Angew. Chem. Int. Ed.*, ***1995***, *34*, 1594.

chelated and dimeric in solvents (e.g., THF).[185] There are several functionalized organolithium reagents.[186]

The dimeric, tetrameric, and hexameric structures of organolithium reagents[187] in the solid state is often retained in solution, but this is dependent on the solvent and complexing additives, if any. A tetrahedral organolithium compound is known,[188] and the X-ray of an α,α-dilithio hydrocarbon has been reported.[189] Phenyllithium is a mixture of tetramers and dimers in diethyl ether, but stoichiometric addition of THF, DME, or TMEDA leads to the dimer.[190] The solution structures of mixed aggregates of butyllithium and amino-alkaloids has been determined[191] as well as the solution structure of sulfur-stabilized allyllithium compounds.[192] Vinyllithium is an 8:1 mixture of tetramer/dimer in THF at −90 °C, but addition of TMEDA changes the ratio of tetramer/dimer to 1 : 13 at −80 °C.[193] Internally solvated allylic lithium compounds have been studied, showing the coordinated lithium to be closer to one of the terminal allyl carbons.[194] A relative scale of organolithium stability has been established,[195] and the issue of configurational stability of enantioenriched organolithium reagents has been examined.[196]

Enolate anions are an important class of carbanions that appear in a variety of important reactions, including alkylation α to a carbonyl group and the aldol (**16-34**) and *Claisen condensation* (**16-85**) reactions. Metal enolate anions of aldehydes, ketones, esters, and other acid derivatives exist as aggregates in ether solvents.[197] There is evidence that the lithium enolate of isobutyrophenone is a tetramer in THF,[198] but a dimer in DME.[199] X-ray crystallography of ketone enolate anions have shown that they can exist as tetramers and hexamers.[200] There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species. Lithium enolate anions derived from esters are as dimers in the solid state[201] that contain four THF molecules. It has also been established that the reactivity of enolate anions in alkylation and condensation reactions is influenced by the aggregate state of the enolate. It is also true that the relative proportions of (*E*) and (*Z*) enolate anions are influenced by the extent of solvation and the aggregation state.

[185] Reich, H.J.; Gudmundsson, B.O.; Goldenberg, W.S.; Sanders, A.W.; Kulicke, K.J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* ***2001****, 123,* 8067.
[186] Nájera, C.; Yus, M. *Tetrahedron* ***2005****, 61*, 3137.
[187] See Parisel, O.; Fressigne, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* ***2003****, 68,* 1290.
[188] Sekiguchi, A.; Tanaka, M. *J. Am. Chem. Soc.* ***2003****, 125,* 12684.
[189] Linti, G.; Rodig, A.; Pritzkow, H. *Angew. Chem. Int. Ed.* ***2002****, 41*, 4503.
[190] Reich, H.J.; Green, D.P.; Medina, M.A.; Goldenberg, W.S.; Gudmundsson, B.Ö.; Dykstra, R.R.; Phillips. N.H. *J. Am. Chem. Soc.* ***1998***, *120*, 7201.
[191] Sun, X.; Winemiller, M.D.; Xiang, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123,* 8039. See also, Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002****, 124,* 264.
[192] Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* ***2000****, 65*, 5942.
[193] Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* ***1993***, *115*, 10871.
[194] Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* ***2004****, 126,* 3983.
[195] Graña, P.; Paleo, M.R.; Sardina, F.J. *J. Am. Chem. Soc.* ***2002****, 124,* 12511.
[196] Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* ***2002****, 41*, 717. See also, Fraenkel, G.; Duncan, J.H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* ***1999****, 121*, 10538.
[197] Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4464; Bernstein, M.P.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 789; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.
[198] Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.
[199] Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737.
[200] Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462; Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 3345 and references cited therein.
[201] Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* ***1985***, *107*, 5403.

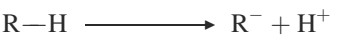
Addition of LiBr to a lithium enolate anion in THF suppresses the concentration of monomeric enolate.[202] *Ab initio* studies confirm the aggregate state of acetaldehyde.[203] It is also known that α-Li benzonitrile [PhCH(Li)CN] exists as a dimer in ether and with TMEDA.[204] Mixed aggregates of *tert*-butyllithium and lithium *tert*-butoxide are known to be hexameric.[205]

It might be mentioned that matters are much simpler for organometallic compounds with less-polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former is a liquid and the latter is a solid. Organocalcium reagents are also known, and are formed from alkyl halides via a single electron transfer (SET) mechanism with free radical intermediates.[206]

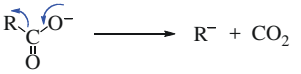
5.B.iii. The Generation and Fate of Carbanions

There are two principal ways in which most carbanions are generated.

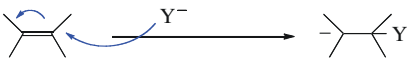
1. *A Group Attached to a Carbon Leaves Without Its Electron Pair*



The "leaving group" is most often a proton. In fact, the proton is removed by a suitable base, and this is a simple acid–base reaction.[207] However, other leaving groups are known (see Chap 12), such as carboxyl:

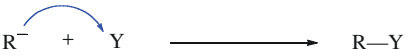


2. *A Negative Ion Adds to a Carbon–Carbon Double or Triple Bond* (see Chapter 15)



The addition of a negative ion to a carbon–oxygen double bond (C=O) does not give a carbanion, but an alkoxide ($R—O^-$), since the negative charge resides on the oxygen.

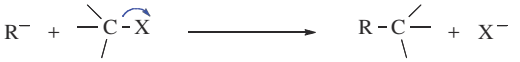
The most common reaction of carbanions is to donate electrons to a positive species, often a proton, or with another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):



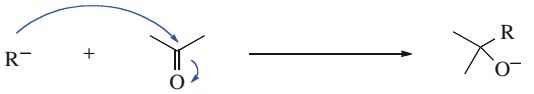
This means that carbanions react with electrophilic atoms (those functionalized so there is a δ^+ carbon atom); see Chapter 16.

[202] Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* ***1996***, *118*, 8136.
[203] Abbotto, A.; Streitwieser, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1997***, *119*, 11255.
[204] Carlier, P.R.; Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 11602.
[205] DeLong, G.T.; Pannell, D.K.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1993***, *115*, 7013.
[206] Walborsky, H.M.; Hamdouchi, C. *J. Org. Chem.* ***1993***, *58*, 1187.
[207] For a review of such reactions, see Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry,* pt. B, Elsevier, NY, **1984**, pp. 239–291.

Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):



Like carbocations, carbanions can also react in ways in which they are converted to species that are still charged. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



or rearrange, although this is rare (see Chapter 18),

$$Ph_3C\bar{C}H_2 \longrightarrow Ph_2\bar{C}CH_2Ph$$

or they are oxidized to free radicals.[208] A system in which a carbocation [$Ph(p\text{-}Me_2NC_6H_4)_2C^+$] oxidizes a carbanion [$(p\text{-}NO_2C_6H_4)_3C^-$] to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.[209,210]

Organometallic compounds that are not ionic but polar–covalent behave very much as if they were ionic and give similar reactions.

5.C. FREE RADICALS

5.C.i. Stability and Structure[211]

A *free radical* (usually just called a *radical*) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO_2), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive and are usually transient species. For the most part, their lifetimes are extremely short in solution, but they can be kept frozen for relatively long periods of time within the crystal lattices of other

[208] For a review, see Guthrie, R.D. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, pp. 197–269.

[209] Arnett, E.M.; Molter, K.E.; Marchot, E.C.; Donovan, W.H.; Smith, P. *J. Am. Chem. Soc.* ***1987***, *109*, 3788.

[210] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

[211] See Alfassi, Z.B. *N-Centered Radicals*, Wiley, Chichester, ***1998***; Alfassi, Z.B. *Peroxyl Radicals*, Wiley, Chichester, ***1997***; Alfassi, Z.B. *Chemical Kinetics of Small Organic Radicals*, 4 Vols., CRC Press: Boca Raton, FL, ***1988***; Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, Cambridge, ***1974***; Kochi, J.K. *Free Radicals*, 2 Vols., Wiley, NY, ***1973***; Hay, J.M. *Reactive Free Radicals*, Academic Press, NY, ***1974***;. For reviews, see Kaplan, L. *React. Intermed. (Wiley)* ***1985***, *3*, 227; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1976***, *9*, 13.

molecules.[212] There are, however, many stable radicals,[213] some of which will be noted below. Many spectral[214] measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10–15 min in a methanol lattice at 77 K.[215] Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not be very stable.

Radicals can be characterized by several techniques (e.g., mass spectrometry[216] or the characterization of alkoxycarbonyl radicals by Step–Scan Time-Resolved Infrared Spectroscopy).[217] Another technique makes use of the magnetic moment that is associated with the spin of an electron, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the *Pauli principle*, any two electrons occupying the same orbital must have opposite spins, so the total magnetic moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required.

A much more important technique is *electron spin resonance* (ESR), also called *electron paramagnetic resonance* (EPR).[218] The principle of ESR is similar to that of NMR, except that electron spin is involved rather than nuclear spin. The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = -\frac{1}{2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in NMR, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio frequency signal. Inasmuch as two electrons paired in one orbital must have opposite spins that cancel, an ESR spectrum arises only from species that have one or more unpaired electrons (i.e., free radicals).

Since only free radicals give an ESR spectrum, the method can be used to detect the presence of radicals and to determine their concentration.[219] Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the ESR spectrum (ESR peaks are split by nearby

[212] See Dunkin, I.R. *Chem. Soc. Rev.* ***1980***, *9*, 1; Jacox, M.E. *Rev. Chem. Intermed.* ***1978***, *2*, 1. For a review of the study of radicals at low temperatures, see Mile, B. *Angew. Chem. Int. Ed.* ***1968***, *7*, 507.

[213] See. Hicks, R.G. *Org. Biomol. Chem.* ***2007***, *5,* 1321. See also, Hioe, J.; Zipse, H. *Org. Biomol. Chem.* ***2010***, *8,* 3609.

[214] See Andrews, L. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 109.

[215] Sullivan, P.J.; Koski, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 384.

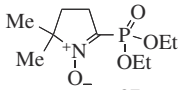
[216] Sablier, M.; Fujii, T. *Chem. Rev.* ***2002***, *102*, 2855.

[217] Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* ***2001***, 545.

[218] See Wertz, J.E.; Bolton, J.R. *Electron Spin Resonance*, McGraw-Hill, NY, ***1972*** [reprinted by Chapman and Hall, NY, and Methuen: London, ***1986***]; Assenheim, H.M. *Introduction to Electron Spin Resonance*, Plenum, NY, ***1967***; Bersohn, R.; Baird, J.C. *An Introduction to Electron Paramagnetic Resonance*, W.A. Benjamin, NY, ***1966***. For reviews, see Bunce, N.J. *J. Chem. Educ.* ***1987***, *64*, 907; Hirota, N.; Ohya-Nishiguchi, H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2, Wiley, NY, ***1986***, pp. 605–655; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 193; Norman, R.O.C. *Chem. Soc. Rev.* ***1980***, *8*, 1; Fischer, H. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 435–491; Turro, N.J.; Kleinman, M.H.; Karatekin, E. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4437; Kurreck, H.; Kirste, B.; Lubitz, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 173. See also, Poole, Jr., C.P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed., Wiley, NY, ***1983***.

[219] Davies, A.G. *Chem. Soc. Rev.* ***1993***, *22*, 299.

protons).[220] Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an ESR spectrum to be obtained. Electron spin resonance spectra have been observed for radicals with lifetimes considerably <1 s. Failure to observe an ESR spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases, the *spin-trapping* technique can be used.[221] In this technique, a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by ESR. Azulenyl nitrones have been developed as chromotropic spin-trapping agents.[222] An important class of spin-trapping compounds are nitroso compounds, which react with radicals to give stable nitroxide radicals:[223] $RN{=}O + R'\cdot \rightarrow RR'N{-}O\cdot$. An *N*-oxide spin trap has been developed [**37**; 2(diethylphosphino)-5,5-dimethyl-1-pyrroline-*N*-oxide], and upon trapping a reactive free radical, ^{31}P NMR can be used to identify it.[224] This technique is effective, and short-lived species (e.g., the oxiranylmethyl radical) have been detected by spin trapping.[225] Other molecules have been used to probe the intermediacy of radicals via SET processes. They are called SET probes.[226]



37

Because there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, radicals are observed as a single line in an ESR spectrum unless they interact with other electronic or nuclear spins or possess magnetic anisotropy, in which case two or more lines may appear in the spectrum.[227]

Another magnetic technique for the detection of free radicals uses an ordinary NMR instrument. It was discovered[228] that if an NMR spectrum is taken during the course of a reaction, certain signals might be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically induced dynamic nuclear polarization*[229] (CIDNP), is found in the NMR spectrum of the product of a reaction, it

[220] See Walton, J.C. *Rev. Chem. Intermed.* ***1984***, *5*, 249; Kochi, J.K. *Adv. Free-Radical Chem.* ***1975***, *5*, 189; Bielski, B.H.J.; Gebicki, J.M. *Atlas of Electron Spin Resonance Spectra*, Academic Press, NY, ***1967***.

[221] See Janzen, E.G.; Haire, D.L. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 253; Perkins, M.J. *Adv. Phys. Org. Chem.* ***1980***, *17*, 1; Zubarev, V.E.; Belevskii, V.N.; Bugaenko, L.T. *Russ. Chem. Rev.* ***1979***, *48*, 729; Evans, C.A. *Aldrichimica Acta* ***1979***, *12*, 23; Janzen, E.G. *Acc. Chem. Res.* ***1971***, *4*, 31. See also, the collection of papers on this subject in *Can. J. Chem.* ***1982***, *60*, 1379.

[222] Becker, D.A.; Natero, R.; Echegoyen, L.; Lawson, R.C. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1289. Also see, Klivenyi, P.; Matthews, R.T.; Wermer, M.; Yang, L.; MacGarvey, U.; Becker, D.A.; Natero, R.; Beal, M.F. *Experimental Neurobiology* ***1998***, *152*, 163.

[223] For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* ***1990***, *62*, 177.

[224] Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* ***1995***, *60*, 5441. For the preparation of a new but structurally related spin trap see Karoui, H.; Nsanzumuhire, C.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* ***1999***, *64,* 1471.

[225] Grossi, L.; Strazzari, S. *Chem. Commun.* ***1997***, 917.

[226] Timberlake, J.W.; Chen, T. *Tetrahedron Lett.* ***1994***, *35*, 6043; Tanko, J.M.; Brammer, Jr., L.E.; Hervas', M.; Campos, K. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1407.

[227] Harry Frank, University of Connecticut, Storrs, CT., Personal Communication.

[228] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R. *J. Am. Chem. Soc.* ***1969***, *91*, 749; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748.

[229] See Lepley, R.L.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***. Bargon, J. *Helv. Chim. Acta 2006,* ***89***, 2082. For reviews, see Adrian, F.J. *Rev. Chem. Intermed.* ***1986***, *7*, 173; Closs, G.L.; Miller, R.J.; Redwine, O.D. *Acc. Chem. Res.* ***1985***, *18*, 196; Closs, G.L. *Adv. Magn. Reson.* ***1974***, *7*, 157; Lawler, R.G. *Acc. Chem. Res.* ***1972***, *5*, 25; Kaptein, R. *Adv. Free-Radical Chem.* ***1975***, *5*, 319.



FIG. 5.1.[231] (*a*) The NMR spectrum taken during reaction between EtI and EtLi in benzene (the region between 0.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0–1.6 δ are due to butane, some of which is also formed in the reaction. (*b*) Reference spectrum of EtI. [Reprinted with permission from Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc*. ***1969***, *91*, 746. Copyright © 1969 American Chemical Society.]

means that *at least a portion of that product was formed via the intermediacy of a free radical*.[230] For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (Reaction **12-39**):

$$\mathrm{EtI} + \mathrm{EtLi} \rightleftharpoons \mathrm{EtLi} + \mathrm{EtI}$$

Curve *a* in Fig. 5.1[231] shows an NMR spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\delta = 1.85$; CH_2 protons at $\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP and so was formed via a free radical intermediate. Chemically induced dynamic nuclear polarization results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products. Although the presence of CIDNP almost always means that a free radical is involved,[232] its absence does not prove that a free radical intermediate is

[230] A related technique is called CIDEP. For a review, see Hore, P.J.; Joslin, C.G.; McLauchlan, K.A. *Chem. Soc. Rev.* ***1979***, *8*, 29.

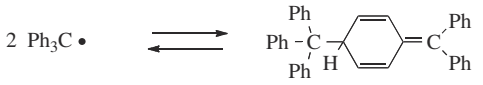
[231] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746.

[232] It has been shown that CIDNP can also arise in cases where para hydrogen (H_2 in which the nuclear spins are opposite) is present: Eisenschmid, T.C.; Kirss, R.U.; Deutsch, P.P.; Hommeltoft, S.I.; Eisenberg, R.; Bargon, J.; Lawler, R.G.; Balch, A.L. *J. Am. Chem. Soc.* ***1987***, *109*, 8089.

necessarily absent, since reactions involving free radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free radical intermediate, only that some of it was. Note that dynamic nuclear polarization (DNP) enhances signal intensities in the NMR spectra of solids and liquids. In a contemporary DNP experiment, a diamagnetic sample is doped with a paramagnet and the large polarization of the electron spins is transferred to the nuclei via microwave irradiation of the EPR spectrum.[233] Dynamic nuclear polarization has been used to examine biradicals.[234]

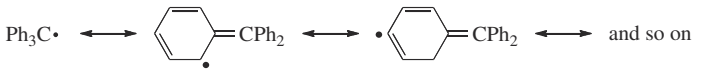
As with carbocations, the stability order of free radicals is tertiary > secondary > primary, explainable by field effects and hyperconjugation, analogous to that in carbocations (Sec. 5.A.ii).[235]

With resonance possibilities, the stability of free radicals increases;[236] some can be kept indefinitely.[237] Benzylic and allylic[238] radicals for which canonical forms can be drawn similar to those shown for the corresponding cations (Sec. 5.A.ii) and anions (Sec. 5.B.i, category 1) are more stable than simple alkyl radicals, but still have only a transient existence under ordinary conditions. Note that 2-phenylethyl radicals have been shown to exhibit bridging of the phenyl group.[239]



38

The triphenylmethyl and similar radicals[240] are stable enough to exist in solution at room temperature, although they are in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution is ~2% at room temperature. For many years, it was assumed that $Ph_3C\cdot$, the first stable free radical known,[241] dimerized to hexaphenylethane ($Ph_3C—CPh_3$),[242] but UV and NMR investigations have shown that the true structure is **38**.[243] Although triphenylmethyl-type radicals are stabilized by resonance:



[233] Wind, R.A.; Duijvestijn, M.J.; van der Lugt, C.; Manenschijn, A.; Vriend, J. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1985****, 17,* 33.

[234] Hu, K.-N.; Yu, H.-h.; Swager, T. M.; Griffin, R. G. *J. Am. Chem. Soc.* ***2004****, 126,* 10844. A discussion of electronic effects is found in Wagner, P.J.; Wang, L. *Org. Lett.* ***2006****, 8*, 645.

[235] For a discussion of the role of alkyl substitution with respect to radical stabilization, see Gronert, S. *J. Org. Chem.* ***2006****, 71*, 7045. For a discussion concerning data that hyperconguation stabilizes alkyl radicals, see Gronert, S. *Org. Lett.* ***2007****, 9,* 2211.

[236] For a discussion, see Robaugh, D.A.; Stein, S.E. *J. Am. Chem. Soc.* ***1986***, *108*, 3224.

[237] See Forrester, A.R.; Hay, J.M.; Thomson, R.H. *Organic Chemistry of Stable Free Radicals*, Academic Press, NY, ***1968***.

[238] For an electron diffraction study of the allyl radical, see Vajda, E.; Tremmel, J.; Rozsondai, B.; Hargittai, I.; Maltsev, A.K.; Kagramanov, N.D.; Nefedov, O.M. *J. Am. Chem. Soc.* ***1986***, *108*, 4352.

[239] Asensio, A.; Dannenberg, J. J. *J. Org. Chem.* ***2001****, 66,* 5996.

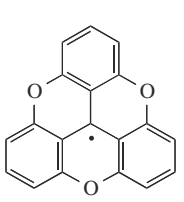
[240] For a review, see Sholle, V.D.; Rozantsev, E.G. *Russ. Chem. Rev.* ***1973***, *42*, 1011.

[241] Gomberg, M. *J. Am. Chem. Soc.* ***1900***, *22*, 757, *Ber.* ***1900***, *33*, 3150.

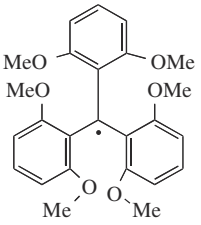
[242] For hexaphenylethane derivatives, see Stein, M.; Winter, W.; Rieker, A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 692; Yannoni, N.; Kahr, B.; Mislow, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6670.

[243] Volz, H.; Lotsch, W.; Schnell, H. *Tetrahedron* ***1970***, *26*, 5343; McBride, J. *Tetrahedron* ***1974***, *30*, 2009. See Guthrie, R.D.; Weisman, G.R. *Chem. Commun.* ***1969***, 1316; Takeuchi, H.; Nagai, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 753; Peyman, A.; Peters, K.; von Schnering, H.G.; Rüchardt, C. *Chem. Ber.* ***1990***, *123*, 1899.

steric hindrance to dimerization and not resonance is the major cause of their stability.[244] This was demonstrated by the preparation of the radicals **39** and **40**.[245] These radicals are electronically very similar, but **39**, being planar, has much less steric hindrance to dimerization than $Ph_3C^{\cdot}$, while **40**, with six groups in ortho positions, has much more. On the other hand, the planarity of **35** means that it has a maximum amount of



39



40

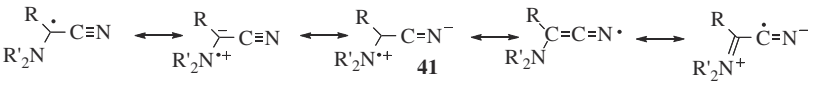
resonance stabilization, while **40** must have much less, since its degree of planarity should be even less than $Ph_3C^{\cdot}$, which itself is propeller shaped and not planar. Thus if resonance is the chief cause of the stability of $Ph_3C^{\cdot}$, **40** should dimerize and **39** should not, but if steric hindrance is the major cause, the reverse should happen. It was found[233] that **40** gave no evidence of dimerization, even in the solid state, while **39** existed primarily in the dimeric form, which is dissociated to only a small extent in solution.[246] This result indicates that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals. A similar conclusion was reached in the case of $(NC)_3C^{\cdot}$, which dimerizes readily although it is considerably stabilized by resonance.[247] Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the facts that (1) the radical *t*-$Bu(Ph)_2C^{\cdot}$ dimerizes more than $Ph_3C^{\cdot}$, while *p*-$PhCOC_6H_4(Ph_2)C^{\cdot}$ dimerizes less.[248] The latter has more canonical forms than $Ph_3C^{\cdot}$, but steric hindrance should be about the same (for attack at one of the two rings). (2) A number of radicals $(p\text{-}XC_6H_4)_3C^{\cdot}$, with X = F, Cl, O_2N, CN, and so on, do not dimerize, but are kinetically stable.[249] Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.[250]

Allylic radical are relatively stable, and the pentadienyl radical is particularly stable, but (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-stereoisomers can form. It has been calculated that the (*Z,Z*)-pentadienyl radical is 5.6 kcal mol^{-1} less stable than the (*E,E*)-pentadienyl radical.[251] Note that vinyl radicals have (*E*)- and (*Z*)-forms and the inversion barrier from one to the other increases as the electronegativity of substituents increase.[252] Conjugated propargylic radicals are calculated to have diminished stability as the

[244] For a review of steric effects in free radical chemistry, see Rüchardt, C. *Top. Curr. Chem.* ***1980***, *88*, 1.
[245] Sabacky, M.J.; Johnson, Jr., C.S.; Smith, R.G.; Gutowsky, H.S.; Martin, J.C. *J. Am. Chem. Soc.* ***1967***, *89*, 2054.
[246] Müller, E.; Moosmayer, A.; Rieker, A.; Scheffler, K. *Tetrahedron Lett.* ***1967***, 3877. See also, Neugebauer, F. A.; Hellwinkel, D.; Aulmich, G. *Tetrahedron Lett.* ***1978***, 4871.
[247] Kaba, R.A.; Ingold, K.U. *J. Am. Chem. Soc.* ***1976***, *98*, 523.
[248] Zarkadis, A.K.; Neumann, W.P.; Marx, R.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 450; Zarkadis, A.K.; Neumann, W.P.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 1183.
[249] Dünnebacke, D.; Neumann, W.P.; Penenory, A.; Stewen, U. *Chem. Ber.* ***1989***, *122*, 533.
[250] For reviews, see Ballester, M. *Adv. Phys. Org. Chem.* ***1989***, *25*, 267, pp. 354–405; *Acc. Chem. Res.* ***1985***, *18*, 380. See also, Hegarty, A.F.; O'Neill, P. *Tetrahedron Lett.* ***1987***, *28*, 901.
[251] Fort, Jr., R.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***1993***, *58*, 211.
[252] Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* ***1997***, *62*, 4072.

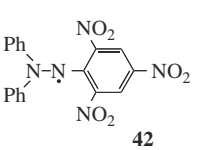
conjugation increases, in contrast to the behavior of alkenes.[253] Cyclopropyl alkynes have been used as mechanistic probes to distinguish between vinyl radicals and ionic intermediates.[254] Enolate radicals are also known.[255]

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of *both* an electron-donating and an electron-withdrawing group.[256] This finding is called the *push–pull* or *captodative effect* (see also, Sec. 4.K.i). The effect arises from increased resonance, as in **41**.

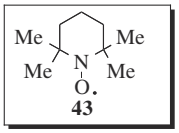


41

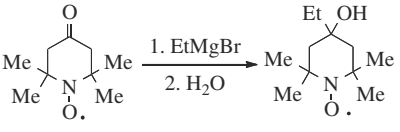
There is some evidence in favor[257] of the captodative effect, some of it from ESR studies.[258] However, there is also experimental[259] and theoretical[260] evidence against it. There is evidence that while $FCH_2^{\cdot}$ and $F_2CH^{\cdot}$ are more stable than $CH_3^{\cdot}$, the radical $CF_3^{\cdot}$ is less stable; that is, the presence of the third F destabilizes the radical.[261]



42
Diphenylpicrylhydrazyl



43

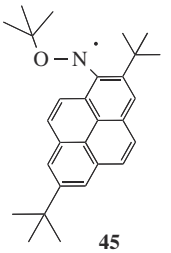


44

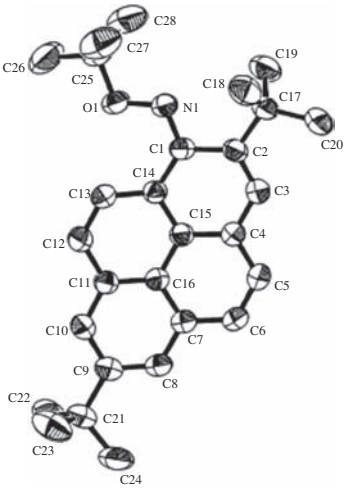
Certain radicals with unpaired electron on a carbon are also very stable.[262] Radicals can be stabilized by intramolecular hydrogen bonding.[263] Diphenylpicrylhydrazyl (**42**) is a solid that can be kept for years, and stable neutral azine radicals have been prepared.[264] Nitroxide radicals were mentioned previously,[265] and the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) free radical (**43**) is a stable nitroxyl radical used in

[253] Rogers, D.W.; Matsunaga, N.; Zavitsas, A.A. *J. Org. Chem.* ***2006****, 71*, 2214.
[254] Gottschling, S.E.; Grant, T.N.; Milnes, K.K.; Jennings, M.C.; Baines, K.M. *J. Org. Chem.* ***2005****, 70,* 2686.
[255] Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* ***1993***, *34*, 5885.
[256] For reviews, see Sustmann, R.; Korth, H. *Adv. Phys. Org. Chem.* ***1990***, *26*, 131; Viehe, H.G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* ***1985***, *18*, 148.
[257] See Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164. See also, Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; Bell, N.A. *Educ. Chem.* ***1973***, 143.
[258] See Sakurai, H.; Kyushin, S.; Nakadaira, Y.; Kira, M. *J. Phys. Org. Chem.* ***1988***, *1*, 197; Rhodes, C.J.; Roduner, E. *Tetrahedron Lett.* ***1988***, *29*, 1437; Viehe, H.G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* ***1988***, *60*, 1635; Bordwell, F.G.; Lynch, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7558.
[259] See Bordwell, F.G.; Bausch, M.J.; Cheng, J.P.; Cripe, T.H.; Lynch, T.-Y.; Mueller, M.E. *J. Org. Chem.* ***1990***, *55*, 58; Bordwell, F.G.; Harrelson, Jr., J.A. *Can. J. Chem.* ***1990***, *68*, 1714.
[260] See Pasto, D.J. *J. Am. Chem. Soc.* ***1988****, 110*, 8164.
[261] Jiang, X.; Li, X.; Wang, K. *J. Org. Chem.* ***1989***, *54*, 5648.
[262] For reviews of radicals with the unpaired electron on atoms other than carbon, see, in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, the reviews by Nelson, S.F. pp. 527–593 (*N*-centered); Bentrude, W.G. pp. 595–663 (*P*-centered); Kochi, J.K. pp. 665–710 (*O*-centered); Kice, J.L. pp. 711–740 (*S*-centered); Sakurai, H. pp. 741–807 (Si, Ge, Sn, and Pb centered).
[263] Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* ***2001****, 123,* 3371.
[264] Jeromin, G.E. *Tetrahedron Lett.* ***2001****, 42*, 1863.
[265] See Novak, I.; Harrison, L.J.; Kovač, B.; Pratt, L.M. *J. Org. Chem.* ***2004****, 69,* 7628.

chemical reactions (e.g., oxidations),[266] or as a spin trap.[267] Nitroxyl radical **44** is a nitroxide radical so stable that reactions can be performed on it (e.g., the *Grignard reaction* shown with **44**; see Reaction **16-24**) without affecting the unpaired electron[268] (the same is true for some of the chlorinated triarylmethyl radicals mentioned above[269]). Several nitrogen-containing groups are known to stabilize radicals, and the most effective radical stabilization is via spin delocalization.[270] A number of persistent *N*-*tert*-butoxy-1-aminopyrenyl radicals (e.g., **45**) have been isolated as monomeric radical crystals (see **46**, the X-ray crystal



45



structure of **45**),[271] and monomeric *N*-alkoxyarylaminyls have been isolated.[272] α-Trichloromethylbenzyl(*tert*-butyl)aminoxyl (**47**) is extremely stable.[273] In aqueous media it is stable for > 30 days, and in solution in an aromatic hydrocarbon solvent it has survived for >90 days.[273] Although the stable nitroxide radicals have the α-carbon blocked to prevent radical formation there, stable nitroxide radicals are also known with hydrogen at the α-carbon,[274] and long-lived vinyl nitroxide radicals are known.[275] A stable

[266] See Anelli, P.L.; Montanari, F.; Quici, S. *Org. Synth.* ***1990****, 69,* 212; Fritz-Langhals, E. *Org. Process Res. Dev.* ***2005****, 9,* 577. See also, Rychnovsky, S.D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P.J. *J. Org. Chem.* ***1999****, 64,* 6745.

[267] Volodarsky, L.B.; Reznikov, V.A.; Ovcharenko, V.I. *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, FL, ***1994***; Keana, J.F.W. *Chem. Rev.* ***1978****, 78,* 37; Aurich, H.G. *Nitroxides. In Nitrones, Nitronates, Nitroxides*, Patai, S.; Rappoport, Z., Eds., Wiley, NY, ***1989***; Chap. 4.

[268] Neiman, M.B.; Rozantsev, E.G.; Mamedova, Yu.G. *Nature* (*London*) ***1963***, *200*, 256. See Breuer, E.; Aurich, H.G.; Nielsen, A. *Nitrones*, *Nitronates*, *and Nitroxides*, Wiley, NY, ***1989***, pp. 313–399; Rozantsev, E.G.; Sholle, V.D. *Synthesis* ***1971***, 190, 401.

[269] See Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc. Chem. Commun.* ***1983***, 982.

[270] Adam, W.; Ortega Schulte, C. M. *J. Org. Chem.* ***2002****, 67,* 4569.

[271] Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* ***2002****, 67*, 8764. For another stable nitroxide radical, see Huang, W.-l.; Chiarelli, R.; Rassat, A. *Tetrahedron Lett.* ***2000****, 41*, 8787.

[272] Miura, Y.; Tomimura, T.; Matsuba, N.; Tanaka, R.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* ***2001****, 66,* 7456. See also, Miura, Y.; Muranaka, Y.; Teki, Y. *J. Org. Chem.* ***2006****, 71,* 4786; Miura, Y.; Mu, Y. *Chem. Lett.* ***2005****, 34,* 48

[273] Janzen, E.G.; Chen, G.; Bray, T.M.; Reinke, L.A.; Poyer, J.L.; McCay, P.B. *J. Chem. Soc. Perkin Trans. 2.* ***1993***, 1983.

[274] Reznikov, V.A.; Volodarsky, L.B. *Tetrahedron Lett.* ***1994***, *35*, 2239.

[275] Reznikov, V.A.; Pervukhina, N.V.; Ikorskii, V.N.; Ovcharenko, V.I..; Grand, A. *Chem. Commun.* ***1999***, 539.

TABLE 5.4 The D_{298} Values for Some R—H Bonds[a,b]

R	Reference	D_{298} kcal mol^{-1}	D_{298} kJ mol^{-1}
Ph·	279	111	464
CF_3·		107	446
CH_2=CH·		106	444
Cyclopropyl	280	106	444
Me·		105	438
Et·		100	419
Me_3CCH_2·		100	418
Pr·		100	417
Cl_3C·		96	401
Me_2CH·		96	401
Me_3C·	281	95.8	401
Cyclohexyl		95.5	400
$PhCH_2$·		88	368
HCO·		87	364
CH_2=CH—CH_2·		86	361

Reprinted with permission from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, ***2007***, pp. 9-60–9-61. Copyright © 2007, with permission from Taylor & Francis Group LLC.

[a]See Ref. 278.

[b]Free radical stability is in the reverse order.

organic radical lacking resonance stabilization has been prepared (**48**), and its X-ray crystal structure was obtained.[276] Dissociation energies (*D* values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.[277] Table 5.4 lists such values.[278–281] The higher the *D* value, the less stable the radical. Bond-dissociation energies also have been reported for the C—H bond of alkenes and dienes[282] and for the C—H bond in radical precursors XYC—H, where X,Y can be H, alkyl, COOR, COR, SR, CN, NO_2, and so on.[283] Bond dissociation energies for the C—O bond in hydroperoxide radicals (ROO·) have also been reported.[284] However, note that basing radical

[276] Apeloig, Y.; Bravo-Zhivotovskii, D.; Bendikov, M.; Danovich, D.; Botoshansky, M.; Vakulrskaya, T.; Voronkov, M.; Samoilova, R.; Zdravkova, M.; Igonin, V.; Shklover, V.; Struchkov, Y. *J. Am. Chem. Soc.* ***1999***, *121,* 8118.

[277] It has been claimed that relative *D* values do not provide such a measure: Nicholas, A.M. de P.; Arnold, D.R. *Can. J. Chem.* ***1984***, *62*, 1850, 1860.

[278] Except where noted, these values are from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, ***2007***, pp. 9-60–9-61. For another list of *D* values, see McMillen, D.F.; Golden, D.M. *Annu. Rev. Phys. Chem.* ***1982***, *33*, 493. See also, Holmes, J.L.; Lossing, F.P.; Maccoll, A. *J. Am. Chem. Soc.* ***1988***, *110*, 7339; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7343; Roginskii, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 403.

[279] For the IR of a matrix-isolated phenyl radical, see Friderichsen, A. V.; Radziszewski, J. G.; Nimlos, M. R.; Winter, P. R.; Dayton, D. C.; David, D. E.; Ellison, G. B. *J. Am. Chem. Soc.* ***2001***, *123,* 1977.

[280] For a review of cyclopropyl radicals, see Walborsky, H.M. *Tetrahedron* ***1981***, *37*, 1625. See also, Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***.

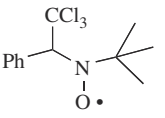
[281] This value is from Gutman, D. *Acc. Chem. Res.* ***1990***, *23*, 375.

[282] Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.

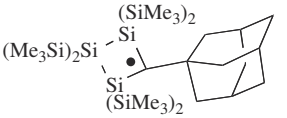
[283] Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.

[284] Pratt, D.A.; Porter, N.A. *Org. Lett.* ***2003***, *5*, 387.

stabilization energy on the difference between the bond dissociation energy (BDE) of CH_3—H, as a reference point, and of R—H has been observed to have shortcomings.[285] The problem is that these values are only applicable to carbon-centered radicals, and the stabilization energies are not transferable and cannot be used to estimate BDE of R—R′, R—R, or any R—X compounds.[282]

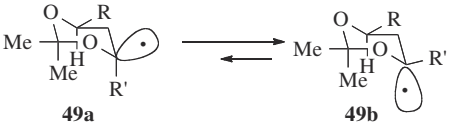


47



48

There are two possible structures for simple alkyl radicals.[286] They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a *p* orbital, or the bonding might be sp^3, which would make the structure pyramidal and place the odd electron in an sp^3 orbital. The ESR spectra of $^{\cdot}CH_3$ and other simple alkyl radicals as well as other evidence indicate that these radicals have planar structures.[287] This finding is in accord with the known loss of optical activity when a free radical is generated at a stereogenic carbon.[288] In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near planar.[289] The IR spectra of $^{\cdot}CH_3$ trapped in solid argon led to a similar conclusion.[290] Despite the usual loss of optical activity noted above, asymmetric radicals can be prepared in some cases. For example, asymmetric nitroxide radicals are known.[291] An anomeric effect was observed in alkoxy radical **49**, where the ratio of **49a/49b** was 1:1.78.[292]



49a **49b**

Evidence from studies on bridgehead compounds shows that although a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.[293] In sum, the available evidence indicates that

[285] Zavitsas, A.A.; Rogers, D.W.; Matsunaga, N. *J. Org. Chem.* ***2010****, 75*, 5697.

[286] For a review, see Kaplan, L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 361–434.

[287] See Giese, B.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 594; Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978****, 100*, 2556. See, however, Paddon-Row, M.N.; Houk, K.N. *J. Am. Chem. Soc.* ***1981***, *103*, 5047.

[288] There are a few exceptions. See Section 14.A.iv.

[289] Herzberg, G. *Proc. R. Soc. London*, *Ser. A* ***1961***, *262*, 291. See also, Tan, L.Y.; Winer, A.M.; Pimentel, G.C. *J. Chem. Phys.* ***1972***, *57*, 4028; Yamada, C.; Hirota, E.; Kawaguchi, K. *J. Chem. Phys.* ***1981***, *75*, 5256.

[290] Andrews, L.; Pimentel, G.C. *J. Chem. Phys.* ***1967***, *47*, 3637; Milligan, D.E.; Jacox, M.E. *J. Chem. Phys.* ***1967***, *47*, 5146.

[291] Tamura, R.; Susuki, S.; Azuma, N.; Matsumoto, A.; Todda, F.; Ishii, Y. *J. Org. Chem.* ***1995***, *60*, 6820.

[292] Rychnovsky, S.D.; Powers, J.P.; LePage, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 8375.

[293] Danen, W.C.; Tipton, T.J.; Saunders, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5186; Fort, Jr., R.C.; Hiti, J. *J. Org. Chem.* ***1977***, *42*, 3968; Lomas, J.S. *J. Org. Chem.* ***1987***, *52*, 2627.

although simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity (e.g., $\cdot CF_3$), prefer a pyramidal shape;[294] increasing the electronegativity increases the deviation from planarity.[295] Cyclopropyl radicals are also pyramidal.[296] Free radicals with resonance are definitely planar, although triphenylmethyl-type radicals are propeller shaped,[297] like the analogous carbocations (Sec. 5.A.i). Radicals possessing simple alkyl substituents attached to the radical carbon (C$\cdot$) that have $C^{sp3}—C^{sp3}$ bonds, and rotation about those bonds is possible. The internal rotation barrier for the *tert*-butyl radical ($Me_3C\cdot$), for example, was estimated to be $\sim$1.4 kcal mol^{-1} 6 kJ mol^{-1}.[298]

A number of diradicals (also called biradicals) are known,[299] and the thermodynamic stability of diradicals has been examined.[300] Orbital phase theory has been applied to the development of a theoretical model of localized 1,3-diradicals, and used to predict the substitution effects on the spin preference and S–T gaps, and to design stable localized carbon-centered 1,3-diradicals.[301] When the unpaired electrons of a diradical are widely separated, for example, as in $\cdot CH_2CH_2CH_2CH_2\cdot$, the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system (as in trimethylenemethane),[302] they can have total spin numbers of +1, 0, or -1, since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically they are called *triplets*,[303] since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet molecules, the two unpaired electrons have the same spin. Not all diradicals have a triplet ground state. In 2,3-dimethylelecycohexane-1,4-diyl (**50**), the singlet and triplet states were found to be almost degenerate.[304] Diradicals (e.g., **51**) are very stable with a triplet ground state.[305] Diradicals are generally short-lived species. The lifetime of **52** was measured to be <0.1 ns and other diradicals were found to have lifetimes

[294] Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* ***1965***, *43*, 2704; Rogers, M.T.; Kispert, L.D. *J. Chem. Phys.* ***1967***, *46*, 3193; Pauling, L. *J. Chem. Phys.* ***1969***, *51*, 2767.

[295] See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201. For a discussion, see Krusic, P.J.; Bingham, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 230.

[296] See Deycard, S.; Hughes, L.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1987***, *109*, 4954.

[297] Adrian, F.J. *J. Chem. Phys.* ***1958***, *28*, 608; Andersen, P. *Acta Chem. Scand.* ***1965***, *19*, 629.

[298] Kubota, S.; Matsushita, M.; Shida, T.; Abu-Raqabah, A.; Symons, M.C.R.; Wyatt, J.L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 140.

[299] See Borden, W.T. *Diradicals*, Wiley, NY, ***1982***; Johnston, L.J.; Scaiano, J.C. *Chem. Rev.* ***1989***, *89*, 521; Doubleday Jr., C.; Turro, N.J.; Wang, J. *Acc. Chem. Res.* ***1989***, *22*, 199; Scheffer, J.R.; Trotter, J. *Rev. Chem. Intermed.* ***1988***, *9*, 271; Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339; Borden, W.T. *React. Intermed. (Wiley)* ***1985***, *3*, 151; ***1981***, *2*, 175; Borden, W.T.; Davidson, E.R. *Acc. Chem. Res.* ***1981***, *14*, 69. See also, Döhnert, D.; Koutecky, J. *J. Am. Chem. Soc.* ***1980***, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* ***1982***, *38*, 735. For a stable hydrocarbon diradical, see Rajca, A.; Shiraishi, K.; Vale, M.; Han, H.; Rajca, S. *J. Am. Chem. Soc.* ***2005***, *127,* 9014.

[300] Zhang, D. Y.; Borden, W. T. *J. Org. Chem.* ***2002***, *67,* 3989.

[301] Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* ***2004***, *69,* 4245

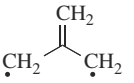
[302] For reviews of trimethylenemethane, see Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125; Bergman, R.G. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 141–149.

[303] See Turro, N.J. *J. Chem. Educ.* ***1969***, *46*, 2; Wasserman, E.; Hutton, R.S. *Acc. Chem. Res.* ***1977***, *10*, 27; Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.A.; Helms, A.M. *J. Org. Chem.* ***1998***, *63*, 3176.

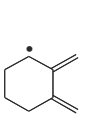
[304] Matsuda, K.; Iwamura, H. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1023. Also see, Roth, W.R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lenmartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber.* ***1993***, *126*, 2701.

[305] Inoue, K.; Iwamura, H. *Angew. Chem. Int. Ed.* ***1995***, *34*, 927. Also see, Ulrich, G.; Ziessel, R.; Luneau, D.; Rey, P. *Tetrahedron Lett.* ***1994***, *35*, 1211.

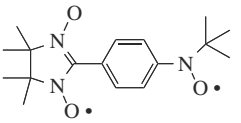
in the 4–316-ns range.[306] Diradical **53** [3,5-di-*tert*-butyl-3′-(*N*-*tert*-butyl-*N*-aminoxy)-4-oxybiphenyl] was found to have a lifetime of weeks even in the presence of oxygen, and survived brief heating in toluene up to ∼60 °C.[307] Radicals with both unpaired electrons on the same carbon are discussed under carbenes. 1,4-Biradicals are known, and α-carbonyl substituents increase the lifetime of the radical, and negative α-hyperconjugation (see Sec. 2.M) has been suggested as the cause.[308]



Trimethylenemethane



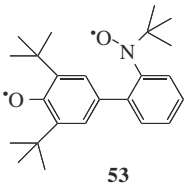
50



51



52

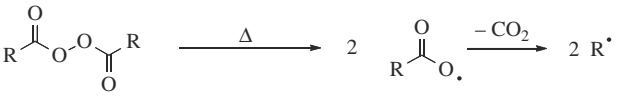


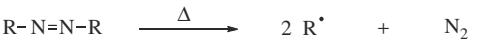
53

5.C.ii. The Generation and Fate of Free Radicals[309]

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.[310,311] The energy necessary to break the bond is supplied in one of two ways.

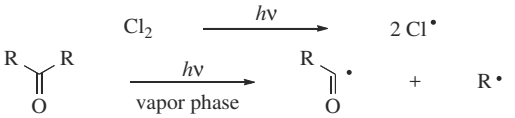
1. *Thermal Cleavage*. Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with *D* values or 20–40 kcal mol^{-1} (80–170 kJ mol^{-1}), cleavage can be caused in the liquid phase. Two common examples are cleavage of diacyl peroxides to acyl radicals that decompose to alkyl radicals[312] and cleavage of azo compounds to alkyl radicals[313]





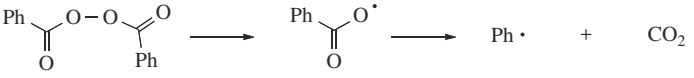
[306] Engel, P.S.; Lowe, K.L. *Tetrahedron Lett.* ***1994***, *35*, 2267.
[307] Liao, Y.; Xie, C.; Lahti, P.M.; Weber, R.T.; Jiang, J.; Barr, D.P. *J. Org. Chem.* ***1999***, *64,* 5176.
[308] Cai, X.; Cygon, P.; Goldfuss, B.; Griesbeck, A.G.; Heckroth, H.; Fujitsuka, M.; Majima, T. *Chemistry: European J.* ***2006***, *12,* 4662.
[309] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 267–281; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 44–61.
[310] See Harmony, J.A.K. *Methods Free-Radical Chem.* ***1974***, *5*, 101.
[311] See Barker, P.J.; Winter, J.N. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 151–218.
[312] Matsuyama, K.; Sugiura, T.; Minoshima, Y. *J. Org. Chem.* ***1995***, *60*, 5520; Ryzhkov, L.R. *J. Org. Chem.* ***1996***, *61*, 2801. See Howard, J.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 235–258; Batt, L.; Liu, M.T.H. in the same volume, pp. 685–710.
[313] See Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99; Adams, J.S.; Burton, K.A.; Andrews, B.K.; Weisman, R.B.; Engel, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 7935; Schmittel, M.; Rüchardt, C. *J. Am. Chem. Soc.* ***1987***, *109*, 2750.

2. *Photochemical Cleavage (see Sec. 7.A.v).* Light energy of 600–300 nm is 48–96 kcal mol^{-1} (200–400 kJ mol^{-1}), which is on the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of alkyl halides in the presence of triethylamine,[314] alcohols in the presence of mercuric oxide and iodine,[315] alkyl 4-nitrobenzenesulfenates,[316] chlorine and of ketones:



Photolytic decomposition of *N*-hydroxypyridin-2-thione is a method that generates hydroxyl radicals.[317] The photochemistry of radicals and biradicals has been reviewed.[318]

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical[319] to give another radical, for example, the decomposition of benzoyl peroxide to give the benzoyl radical:



55

Radicals can also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give nonradical products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple coupling of similar or different radicals:

$$R^{\bullet} + R'^{\bullet} \rightarrow R{-}R'$$

Another termination process is disproportionation:[320]

A propagation reaction is one in which a radical reacts to give at least one radical product, which continues the radical reaction sequence. There are four principal propagation reactions, of which the first two are most common:

$$2\,CH_3{-}CH_2^{\bullet} \rightarrow CH_3{-}CH_3 + CH_2{=}CH_2$$

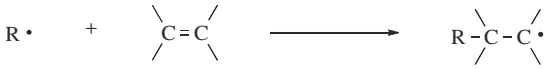
[314] Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* ***1994***, *35*, 8161.
[315] Courtneidge, J.L. *Tetrahedron Lett.* ***1992***, *33*, 3053.
[316] Pasto, D.J.; Cottard, F. *Tetrahedron Lett.* ***1994***, *35*, 4303.
[317] Halliwell, B.; Gutteridge, J.M.C. in *Free Radicals in Biology and Medicine*, Oxford University Press, Oxford, ***1999***, pp 246–350; DeMatteo, M.P.; Poole, J.S.; Shi, X.; Sachdeva, R.; Hatcher, P.G.; Hadad, C.M.; Platz, M.S. *J. Am. Chem. Soc.* ***2005***, *127*, 7094.
[318] Johnston, L.J. *Chem. Rev.* ***1993***, *93*, 251.
[319] See Costentin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* ***2003***, *125*, 105.
[320] See Pilling, M.J. *Int. J. Chem. Kinet.* ***1989***, *21*, 267; Khudyakov, I.V.; Levin, P.P.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 982; Gibian, M.J.; Corley, R.C. *Chem. Rev.* ***1973***, *73*, 441.

1. *Abstraction of Another Atom or Group, Usually a Hydrogen Atom (also see Chap 14).*

$$R^{\bullet} + R'— H \rightarrow R—H + R'^{\bullet}$$

A radical may abstract hydrogen atoms from a second molecule, or by an intramolecular process. A bromine radical ($Br^{\bullet}$) reacts with an alkane, for example, to give HBr and a carbon radical. This type of reaction is known as hydrogen-atom transfer. Water is an excellent hydrogen atom source for many reactions involving metals.[321] The reduction of a carbon radical with Bu_3SnH is an example of a hydrogen-transfer reaction (see Sec. 14.A.i). Indeed, carbon radicals react as hydrogen-bond acceptors.[322] Other atoms may be removed by a radical via atom-transfer reactions. A halogen atom can be transferred in some cases, including the transfer of an iodine atom from an aryl iodide to give an aryl radical.[323] Solvent effects play a role in hydrogen-atom transfer (hydrogen abstraction), and hydrogen-bonding plays a role.[324]

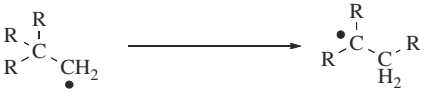
2. *Addition to a Multiple Bond (see Chap 15).*



The radical formed from an alkene may add to the double bond of a second equivalent of alkene, and so on. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition.* This process can be illustrated by the decomposition of the benzoxy radical (see **55**).

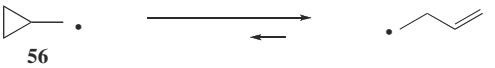
4. *Rearrangement.*



This reaction is less common than rearrangement of carbocations, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18). Perhaps the best-known rearrangement is that of cyclopropylcarbinyl radicals to a butenyl radical.[325] The rate constant for this rapid ring opening has been measured in certain functionalized cyclopropylcarbinyl radicals by picosecond radical kinetics.[326] Substituent effects on the kinetics of ring opening in substituted cyclopropylcarbinyl radicals have been studied.[327] "The cyclopropylcarbinyl

[321] Cuerva, J.M.; Campaña, A.G.; Justicia, J.; Rosales, A.; Oller-López, J.L.; Robles, R.; Cárdenas, D.J.; Buñuel, E.; Oltra, J.E. *Angew. Chem. Int. Ed.* ***2006****, 45*, 5522.
[322] Hammerum, S. *J. Am. Chem. Soc.* ***2009****, 131,* 8627.
[323] Dolenc, D.; Plesniar, B. *J. Org. Chem.* ***2006****, 71,* 8028.
[324] Bietti, M.; Salamone, M. *Org. Lett.* ***2010****, 12,* 3654.
[325] See Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* ***2002****, 124,* 4271.
[326] LeTadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1467. See also, Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* ***2000****, 65,* 4447; Cooksy, A. L.; King, H. F.; Richardson, W. H. *J. Org. Chem.* ***2003****, 68,* 9441; Tian, F.; Dolbier, Jr., W.R. *Org. Lett.* ***2000****, 2*, 835.
[327] Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* ***2000****, 122,* 2988.

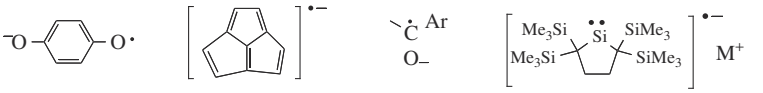
radical (**56**) has found an important application as a radical clock.[328] Various radical processes can be clocked by the competition of direct reaction with the cyclopropylcarbinyl radical (k_t) and opening of that radical to the 1-buten-4-yl radical (k_r) followed by trapping. Relative rates (k_t/k_r) can be determined from yields of 4-X-1-butene and cyclopropylcarbinyl products as a function of the radical trap[329] (X—Y) concentration. Absolute rate constants have been determined for a number of radicals with various radical traps by laser flash photolysis methods.[330] From these absolute rate constants, reasonably accurate values of k_t can be estimated, and with the relative rate (k_t/k_r), a value for k_r can be calculated. From the calibrated radical-clock reaction rate (k_r), rates (k_t) of other competing reactions can be determined from relative rate data (k_t/k_r)."[326] Other radical clocks are known.[331]



56

Free radicals can also be oxidized to carbocations or reduced to carbanions.[332]

5.C.iii. Radical Ions[333]



57 **58** **59** **60** M = Cs, Rb, Na, Li

Several types of radical anions are known with the unpaired electron or the charge or both on atoms other than carbon. Examples include semiquinones[334] (**57**), acepentalenes (**58**),[335] ketyls[336] (**59**) and the radical anion of the isolable dialkylsilylene (**60**).[337] Radical anions are formed by the reaction of carbene anions with chloromethanes.[338] Reactions in

[328] Newcomb, M.; Choi, S.-Y.; Toy, P. H. *Can. J. Chem.* ***1999****, 77,* 1123; Nevill, S. M.; Pincock, J. A. *Can. J. Chem.* ***1997****, 75,* 232.

[329] See Barton, D.H.R.; Jacob, M.; Peralez, E. *Tetrahedron Lett.* ***1999****, 40,* 9201.

[330] Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000****, 65,* 4447; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997****, 62,* 1210.

[331] See Leardini, R.; Lucarini, M.; Pedulli, G.F.; Valgimigli, L. *J. Org. Chem.* ***1999****, 64,* 3726; Roschek, Jr., B.; Tallman, K.A.; Rector, C.L.; Gillmore, J.G.; Pratt, D.A.; Punta, C.; Porter, N.A. *J. Org. Chem.* ***2006****, 71,* 3527.

[332] See Khudyakov, I.V.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 22.

[333] See Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***; Gerson, F.; Huber, W. *Acc. Chem. Res.* ***1987***, *20*, 85; Todres, Z.V. *Tetrahedron* ***1985***, *41*, 2771; Holy, N.L.; Marcum, J.D. *Angew. Chem. Int. Ed.* ***1971***, *10*, 115. See Chanon, M.; Rajzmann, M.; Chanon, F. *Tetrahedron* ***1990***, *46*, 6193. For a series of papers on this subject, see *Tetrahedron* ***1986***, *42*, 6097.

[334] See Depew, M.C.; Wan, J.K.S. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 963–1018; Huh, C.; Kang, C.H.; Lee, H.W.; Nakamura, H.; Mishima, M.; Tsuno, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1999****, 72,* 1083.

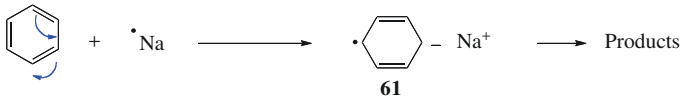
[335] de Meijere, A.; Gerson, F.; Schreiner, P.R.; Merstetter, P.; Schüngel, F.-M. *Chem. Commun.* ***1999***, 2189.

[336] See Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 471–512. See Davies, A.G.; Neville, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 163, 171.

[337] Ishida, S.; Iwamoto, T.; Kira, M. *J. Am. Chem. Soc.* ***2003****, 125*, 3212; Sekiguchi, A.; Tanaka, T.; Ichinohe, M.; Akiyama, K.; Tero-Kubota, S. *J. Am. Chem. Soc.* ***2003****, 125*, 4962; Inoue, S.; Ichinohe, M.; Sekiguchi, A. *J. Am. Chem. Soc.* ***2007****, 129,* 6096.

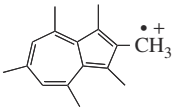
[338] Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***2008****, 130,* 7214.

which alkali metals are reducing agents often involve radical anion intermediates (*Birch reduction*, e.g., Reaction **15-13**) that proceed via radical anion **61**.

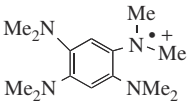


61

Several types of radical cation are also known.[339] Typical examples include alkyl azulene cation radicals (**62**),[340] trialkyl amine radical cations,[341] 1,2-bis(dialkylamino)benzenes radical cations (e.g., **63**),[342] dimethylsulfonium cation radicals ($Me_2S^{\bullet+}$),[343] *N*-alkyl substituted imine cation radicals ($Ph_2C{=}NEt^{\bullet+}$),[344] dibenzo[*a,e*]cyclooctene (**64**, a non-planar cation radical),[345] and [*n.n*]paracyclophane cation radicals.[346] A twisted radical cation derived from bicyclo[2.2.2]oct-2-ene has been reported.[347]



62



63



64

5.D. CARBENES

5.D.i. Stability and Structure[348]

Carbenes are highly reactive species, and practically all have lifetimes considerably < 1 s. With exceptions noted below (Sec. 5.D.ii), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).[349] The parent species (CH_2) is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, although it can also be called dichloromethylene.

[339] See Roth, H.D. *Acc. Chem. Res.* ***1987***, *20*, 343; Courtneidge, J.L.; Davies, A.G. *Acc. Chem. Res.* ***1987***, *20*, 90; Symons, M.C.R. *Chem. Soc. Rev.* ***1984***, *13*, 393; Marchetti, F.; Pinzino, C.; Zacchini. S.; Guido, G. *Angew. Chem. Int. Ed.* ***2010***, *49*, 5268.

[340] Gerson, F.; Scholz, M.; Hansen, H.-J.; Uebelhart, P. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 215.

[341] de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* ***1999***, *64*, 6951.

[342] Neugebauer, F.A.; Funk, B.; Staab, H.A. *Tetrahedron Lett.* ***1994***, *35*, 4755. See Stickley, K.R.; Blackstock, S.C. *Tetrahedron Lett.* ***1995***, *36*, 1585.

[343] Dauben, W.G.; Cogen, J.M.; Behar, V.; Schultz, A.G.; Geiss, W.; Taveras, A.G. *Tetrahedron Lett.* ***1992***, *33*, 1713.

[344] Rhodes, C.J.; AgirBas H. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 397.

[345] Gerson, F.; Felder, P.; Schmidlin, R.; Wong, H.N.C. *J. Chem. Soc. Chem. Commun.* ***1994***, 1659.

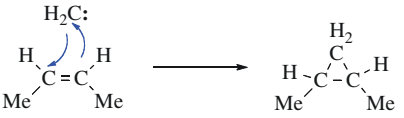
[346] Wartini, A.R.; Valenzuela, J.; Staab, H.A.; Neugebauer, F.A. *Eur. J. Org. Chem.* ***1998***, 139.

[347] Nelson, S.F.; Reinhardt, L.A.; Tran, H.Q.; Clark, T.; Chen, G.-F.; Pappas, R.S.; Williams, F. *Chem. Eur. J.* ***2002***, *8*, 1074.

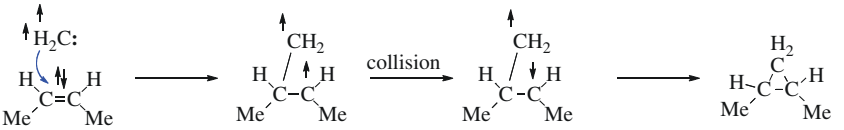
[348] See Jones, Jr., M.; Moss, R.A. *Carbenes*, 2 Vols., Wiley, NY, ***1973–1975***; Rees, C.W.; Gilchrist, T.L. *Carbenes, Nitrenes, and Arynes*, Nelson, London, ***1969***; Minkin, V.I.; Simkin, B.Ya.; Glukhovtsev, M.N. *Russ. Chem. Rev.* ***1989***, *58*, 622; Moss, R.A.; Jones, Jr., M. *React. Intermed. (Wiley)* ***1985***, *3*, 45; Liebman, J.F.; Simons, J. *Mol. Struct. Energ.* ***1986***, *1*, 51.

[349] See Nefedov, O.M.; Maltsev, A.K.; Mikaelyan, R.G. *Tetrahedron Lett.* ***1971***, 4125; Wright, B.B. *Tetrahedron* ***1985***, *41*, 1517. For reviews, see Zuev, P.S.; Nefedov, O.M. *Russ. Chem. Rev.* ***1989***, *58*, 636; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 196–216; Trozzolo, A.M. *Acc. Chem. Res.* ***1968***, *1*, 329.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as seen above (Sec. 5.C.i), two unpaired electrons appear as a *triplet*. An ingenious



method of distinguishing between the two possibilities was developed by Skell,[350] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (Reaction **15-51**). If the singlet species adds to *cis*-2-butene, the resulting cyclopropane should be the cis isomer since the movements of the two pairs of electrons



should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by *Hund's rule* they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once, but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[351]

The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (MO calculations[352] and experimental determinations show that the difference in energy between singlet and triplet CH_2 is ~8–10 kcal mol^{-1} or 33–42 kJ mol^{-1})[353]. However, it is possible to prepare triplet CH_2 directly by a photosensitized decomposition of diazomethane.[354] The CH_2 group is so reactive[355] that it generally reacts as the singlet before it has a chance to decay to the triplet state.[356] As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. There are, however, molecules that generate persistent triplet carbenes.[357]

[350] Skell, P.S. *Tetrahedron* ***1985***, *41*, 1427.

[351] See Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193, pp. 203–210; Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153, p. 194; Hoffmann, R. *J. Am. Chem. Soc.* ***1968***, *90*, 1475.

[352] Richards, Jr., C.A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 10104.

[353] See Lengel, R.K.; Zare, R.N. *J. Am. Chem. Soc.* ***1978***, *100*, 7495; Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125, see pp. 128–134; Leopold, D.G.; Murray, K.K.; Lineberger, W.C. *J. Chem. Phys.* ***1984***, *81*, 1048.

[354] Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. *J. Am. Chem. Soc.* ***1961***, *83*, 2397; ***1962***, *84*, 1015; Duncan, F.J.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3593.

[355] For a review of the kinetics of CH_2 reactions, see Laufer, A.H. *Rev. Chem. Intermed.* ***1981***, *4*, 225.

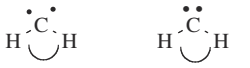
[356] See Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* ***1987***, *109*, 2101.

[357] Tomioka, H. *Acc. Chem. Res.* ***1997***, *30*, 315; Kirmse, W. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2117; Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* ***2009***, *109*, 3275.

Indeed, remarkably stable diaryl triplet carbenes have been prepared,[358] and protected diphenylcarbenes are particularly stable.[359] There are also persistent singlet carbenes, although radical fragmentation is a problem.[360]

There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.[361] When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy (i.e., it is in an excited state). It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis–trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[362]

Studies of the IR spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.[363] The geometrical structure of triplet methylene can be investigated by ESR measurements,[364] since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of $\sim 136°$.[365] The EPR measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis[366] of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of $\sim 103°$.[367] Singlet CCl_2[300] and CBr_2[368] are also bent, with angles of 100 and 114°, respectively. It has long been known that triplet aryl carbenes are bent.[369]

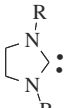


136° Triplet methylene

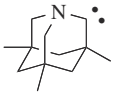
103° Singlet methylene

[358] Woodcock, H.L.; Moran, D.; Schleyer, P.v.R.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***2001****, 123*, 4331.
[359] Itoh, T.; Nakata, Y.; Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* ***2006****, 128,* 957.
[360] Cattoën, X.; Miqueu, K.; Gornitzka, H.; Bourissou, D.; Bertrand, G. *J. Am. Chem. Soc.* ***2005****, 127,* 3292.
[361] For other methods of distinguishing singlet from triplet carbenes, see Hendrick, M.E.; Jones, Jr., M. *Tetrahedron Lett.* ***1978***, 4249; Creary, X. *J. Am. Chem. Soc.* ***1980***, *102*, 1611.
[362] Rabinovitch, B.S.; Tschuikow-Roux, E.; Schlag, E.W. *J. Am. Chem. Soc.* ***1959***, *81*, 1081; Frey, H.M. *Proc. R. Soc. London*, *Ser. A* ***1959***, *251*, 575; Lambert, J.B.; Larson, E.G.; Bosch, R.J. *Tetrahedron Lett.* ***1983***, *24*, 3799.
[363] Andrews, L. *J. Chem. Phys.* ***1968***, *48*, 979.
[364] The technique of spin trapping (Sec. 5.C.i) has been applied to the detection of transient triplet carbenes: Forrester, A.R.; Sadd, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1273.
[365] Wasserman, E.; Kuck, V.J.; Hutton, R.S.; Anderson, E.D.; Yager, W.A. *J. Chem. Phys.* ***1971***, *54*, 4120; Bernheim, R.A.; Bernard, H.W.; Wang, P.S.; Wood, L.S.; Skell, P.S. *J. Chem. Phys.* ***1971***, *54*, 3223.
[366] Hahn, F.E. *Angew. Chem. Int. Ed.* ***2006****, 45,* 1348. For imidazopyridine carbenes, see Moss, R.A.; Tian, J.; Sauers, R.R.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2007****, 129,* 10019.
[367] Herzberg, G.; Johns, J.W.C. *J. Chem. Phys.* ***1971***, *54*, 2276 and cited references.
[368] Ivey, R.C.; Schulze, P.D.; Leggett, T.L.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3174.
[369] Senthilnathan, V.P.; Platz, M.S. *J. Am. Chem. Soc.* ***1981***, *103*, 5503; Gilbert, B.C.; Griller, D.; Nazran, A.S. *J. Org. Chem.* ***1985***, *50*, 4738.

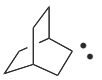
The most common carbenes are $:CH_2$ and $:CCl_2$,[370] but many others have been reported,[371] including heterocyclic carbenes[372] diboron carbenes,[373] **65** (stabilized by the steric constraints of the ring geometry),[374] **66** (an aminocarbene without π conjugation),[375] bicyclo[2.2.2]octylidene, (**67**),[376] alkylidene carbenes (e.g., **68**),[377] conformationally restricted cyclopropylcarbenes, (e.g., **69**),[378] β-silylcarbenes (e.g., **70**),[379] α-keto carbenes,[380] vinyl carbenes,[381] and chiral carbenoids.[382] Fluoro(phenoxy)carbene is stable for several days if it is generated within the cavity of a hemicarcerand (see Sec. 3.C.iii).[383] In the case of **65** (R = Ph),[384] the precursor is a tetraaminoethylene, and when potassium hydride is present to preclude electrophilic catalysis, starting tetraaminoethylenes are recovered unchanged.

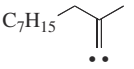


65



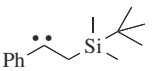
66


67



68


69



70

Flash photolysis of $CHBr_3$ produced the intermediate CBr,[385] which is a *carbyne*.

$$CHBr_3 \xrightarrow[\text{photolysis}]{\text{flash}} \cdot\bar{C}\text{—Br}$$

The intermediates CF and CCl were generated similarly from $CHFBr_2$ and $CHClBr_2$, respectively. Triplet acetylenes have been reported as equivalents for 1,2-bicarbenes.[386]

[370] For reviews of halocarbenes, see Burton, D.J.; Hahnfeld, J.L. *Fluorine Chem. Rev.* ***1977***, *8*, 119; Margrave, J.L.; Sharp, K.G.; Wilson, P.W. *Fort. Chem. Forsch.* ***1972***, *26*, 1, pp. 3–13.

[371] See Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383; Marchand, A.P.; Brockway, N.M. *Chem. Rev.* ***1974***, *74*, 431; Schuster, G.B. *Adv. Phys. Org. Chem.* ***1986***, *22*, 311. For a review of carbenes with neighboring hetero atoms, see Taylor, K.G. *Tetrahedron* ***1982***, *38*, 2751.

[372] Alcarazo, M.; Roseblade, S.J.; Cowley, A.R.; Fernández, R.; Brown, J.M.; Lassaletta, J.M. *J Am. Chem. Soc.* ***2005***, *127,* 3290. See also, Kassaee, M.Z.; Shakib, F.A.; Momeni, M.R.; Ghambarian, M.; Musavi, S.M. *J. Org. Chem.* ***2010***, *75*, 2539.

[373] Krahulic, K.E.; Enright, G.D.; Parvez, M.; Roesler, R. *J. Am. Chem. Soc.* ***2005***, *127,* 4142.

[374] Herrmann, W.A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1290.

[375] Ye, Q.; Komarov, I. V.; Kirby, A. J.; Jones, Jr., M. *J. Org. Chem.* ***2002***, *67*, 9288.

[376] Ye, Q.; Jones Jr., M.; Chen, T.; Shevlin, P.B. *Tetrahedron Lett.* ***2001***, *42*, 6979.

[377] Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 8843. For dimethylvinylidene carbene see Reed, S.C.; Capitosti, G.J.; Zhu, Z.; Modarelli, D.A. *J. Org. Chem.* ***2001***, *66,* 287. For a review of akylidenecarbenes, see Knorr, R. *Chem. Rev.* ***2004***, *104*, 3795.

[378] Fernamberg, K.; Snoonian, J.R.; Platz, M.S. *Tetrahedron Lett.* ***2001***, *42*, 8761.

[379] Creary, X.; Butchko, M.A. *J. Org. Chem.* ***2002***, *67,* 112.

[380] Bonnichon, F.; Richard, C.; Grabner, G. *Chem. Commun.* ***2001***, 73.

[381] Zuev, P. S.; Sheridan, R. S. *J. Am. Chem. Soc.* ***2004***, *126,* 12220.

[382] Topolski, M.; Duraisamy, M.; Rachoń, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1993***, *58*, 546.

[383] Kirmse, W. *Angew. Chem. Int. Ed. 2005, 44,* 2476.

[384] See Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* ***1960***, *72*, 494.

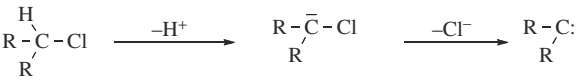
[385] Ruzsicska, B.P.; Jodhan, A.; Choi, H.K.J.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 2489.

[386] Zeidan, T.A.; Kovalenko, S.V.; Manoharan, M.; Clark, R.J.; Ghiviriga, I.; Alabugin, I.V. *J. Am. Chem. Soc.* ***2005***, *127,* 4270.

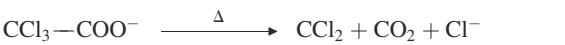
5.D.ii. The Generation and Fate of Carbenes[387]

There are two primary methods to form carbenes, although other pathways are also known.

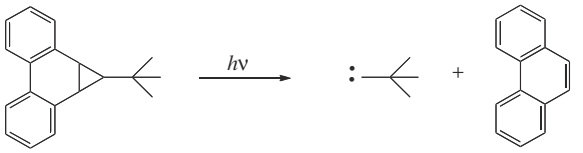
1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:[388]



The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see Reaction **10-3**) and geminal alkyl dihalides with Me_3Sn^-,[389] but many other examples are known, such as

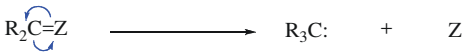


Ref. 390

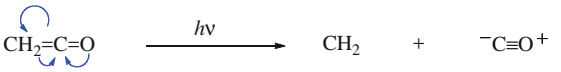


Ref. 391

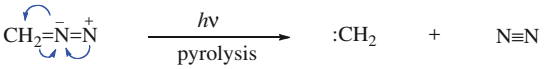
2. Disintegration of compounds containing certain types of double bonds:



The two most important ways of forming:CH_2 are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane.[392]



[387] See Jones, Jr., M. *Acc. Chem. Res.* ***1974***, *7*, 415; Kirmse, W. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, ***1973***, pp. 373–415; Ref. 348; Petrosyan, V.E. ; Niyazymbetov, M.E. *Russ. Chem. Rev.* ***1989***, *58*, 644.

[388] For a review of formation of carbenes in this manner, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1.

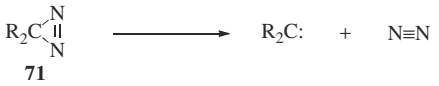
[389] Ashby, E.C.; Deshpande, A.K.; Doctorovich, F. *J. Org. Chem.* ***1993***, *58*, 4205. For a preparation from diclorodiazirine, see Chu, G.; Moss, R.A.; Sauers, R.R. *J. Am. Chem. Soc.* ***2005***, *127,* 14206. Also see Moss, R.A.; Tian, J.; Sauers, R.R.; Ess, D.H.; Houk, K.N.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2007***, *129,* 5167.

[390] Wagner, W.M. *Proc. Chem. Soc.* ***1959***, 229.

[391] Glick, H.C.; Likhotvovik, I.R.; Jones, Jr., M. *Tetrahedron Lett.* ***1995***, *36*, 5715; Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383.

[392] For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 170–184.

Some diazoalkanes decompose to the corresponding carbene.[393] Diazirines[394] (isomeric with diazoalkanes) give carbenes,[395] but arylmethyl radicals have also been generated from diazirines.[396] In a different study, thermolysis of diaryloxydiazirines (**71**) gave the anticipated carbene products, but photolysis gave both carbenes and aryloxy radicals by α-scission.[397]



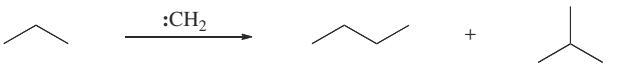
71

Because most carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. The lifetime of formylcarbene was measured to be 0.15–0.73 ns by transient absorption and transient grating spectroscopy in dichloromethane.[398] In many instances, where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound, there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α-Halo organometallic compounds, (R_2CXM) are often called *carbenoids* because they readily give elimination reactions[399] (e.g., see Reaction **12-39**).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter.[400] Solvent effects have been observed in carbene reactions. The selectivity of certain carbenes is influenced by the nature of the solvent.[401] The distribution of rearrangement products (see below) from *tert*-butylcarbene[402] are influenced by changes in solvent.[403] It is known that singlet methylene forms a charge-transfer complex with benzene.[404] Solvent interactions for chlorophenylcarbene and fluorophenylcarbene, however, are weak.[405]

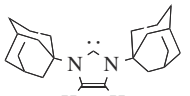
1. Additions to carbon–carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see Reaction **15-65**). Additions of carbenes to other double bonds [e.g., C=N (Reactions **16-46** and **16-48**), and to triple bonds], have also been reported.
2. An unusual reaction of carbenes is that of insertion into C—H bonds (Reaction **12-21**). Thus $:CH_2$ reacts with methane to give ethane and with propane

[393] For example, see Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* ***2006****, 71,* 6975.
[394] See Martinu, T.; Dailey, W.P. *J. Org. Chem.* ***2004****, 69*, 7359.
[395] Liu, M.T.H. *Chemistry of Diazirines*, 2 Vols, CRC Press, Boca Raton, FL, ***1987***. For reviews, see Moss, R.A. *Acc. Chem. Res.* ***2006****, 39,* 267; Liu, M.T.H. *Chem. Soc. Rev.* ***1982***, *11*, 127.
[396] Moss, R.A.; Fu, X. *Org. Lett.* ***2004****, 6*, 3353.
[397] Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R.A.; Turro, N.J. *Org. Lett.* ***2003****, 5,* 5027.
[398] Toscano, J.P.; Platz, M.S.; Nikolaev, V.; Cao, Y.; Zimmt, M.B. *J. Am. Chem. Soc.* ***1996***, *118*, 3527.
[399] For a review, see Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941.
[400] For a discussion of the nucleophilcity of dichlorocarbene, see Moss, R.A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* ***2009****, 11,* 1947.
[401] Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985****, 41,* 4987.
[402] Krogh-Jespersen, K.; Yan, S.; Moss, R.A. *J. Am. Chem. Soc.* ***1999****, 121,* 6269.
[403] Ruck, R. T.; Jones, Jr., M. *Tetrahedron Lett.* ***1998****, 39*, 2277.
[404] Khan, M. I.; Goodman, J. L. *J. Am. Chem. Soc.* ***1995****, 117,* 6635.
[405] Sun, Y.; Tippmann, E. M.; Platz, M. S. *Org. Lett.* ***2003****, 5*, 1305.

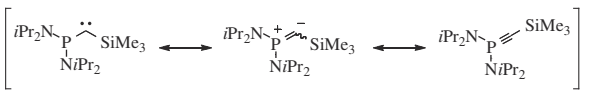


to give *n*-butane and isobutane, as shown. Elimination to give an alkene is a competing side reaction in polar solvents, but this is suppressed in nonpolar solvents.[406] Simple alkyl carbenes, such as this, are not very useful for synthetic purposes, but do illustrate the extreme reactivity of carbene. However, carbenoids generated by rhodium-catalyzed decomposition of diazoalkanes are very useful (see Reaction **12-23**) and have been used in a variety of syntheses. Treatment in the liquid phase of an alkane (e.g., pentane) with carbene formed from the photolysis of diazomethane, gives the three possible products in statistical ratios[407] demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this principle is no longer regarded as general because many exceptions have been found.[408] Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has been proposed on the basis of discrimination between insertion and addition reactions: $CH_2 > HCCOOR > PhCH > BrCH \sim ClCH$.[409] Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, although not insertion into C—C bonds.[410]

Two carbenes that are stable at room temperature have been reported:[411] **72** and **73**. In the absence of oxygen and moisture, **72** exists as stable crystals with a melting point of 240–241 °C.[412] This structure was proved by X-ray crystallography.



72



73

3. It would seem that dimerization to form an alkene should be an important reaction of carbenes, but it is not.

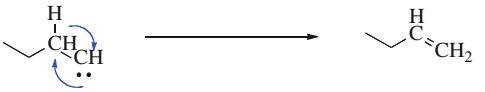
$$R_2C: + R_2C: \longrightarrow R_2C{=}CR_2$$

[406] Ruck, R.T.; Jones, Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.
[407] See Halberstadt, M.L.; McNesby, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 3417.
[408] See Buncel, E.; Wilson, H. *J. Chem. Educ.* ***1987***, *64*, 475; Johnson, C.D. *Tetrahedron* ***1980***, *36*, 3461; *Chem. Rev.* ***1975***, *75*, 755; Giese, B. *Angew. Chem. Int. Ed.* ***1977***, *16*, 125; Pross, A. *Adv. Phys. Org. Chem.* ***1977***, *14*, 69. See also, Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 17; Bordwell, F.G.; Branca, J.C.; Cripe, T.A. *Isr. J. Chem.* ***1985***, *26*, 357; Formosinho, S.J. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 839; Johnson, C.D.; Stratton, B. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1903. For a group of papers on this subject, see *Isr. J. Chem.* ***1985***, *26*, 303.
[409] Closs, G.L.; Coyle, J.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4270.
[410] See Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987; Frey, H.M.; Walsh, R.; Watts, I.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 284.
[411] For a discussion, see Regitz, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 674.
[412] Arduengo, III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1991***, *113*, 361.

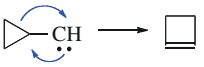
Generally, the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerization has been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes, but come from attack by a carbene on a molecule of a carbene precursor, for example,

$$R_2C: + R_2CN_2 \longrightarrow R_2C{=}CR_2 + N_2$$

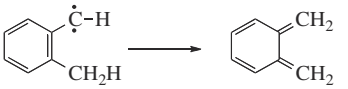
4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.[413] Indeed these rearrangements are generally so rapid[414] that additions to multiple bonds and insertion reactions, which are so common for CH_2, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. A carbene intermediate has been suggested for the isomerization of cyclopropane.[415] Some examples of carbene rearrangement are



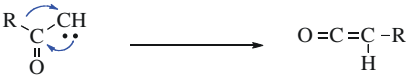
Ref. 416



Ref. 417



Ref. 418



Ref. 419

The rearrangement of acylcarbenes to ketenes is called the *Wolff rearrangement* (Reaction **18-8**). A few rearrangements in which carbenes rearrange to other

[413] See Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001****, 123,* 1658; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry,* Academic Press, NY, ***1980***, pp. 115–163; Wentrup, C. *Adv. Heterocycl. Chem,*. ***1981***, *28*, 231; Jones, W.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 95–160; Schaefer, III, H.F. *Acc. Chem. Res.* ***1979***, *12*, 288; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 457–496.

[414] The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal mol^{-1} (4.5 kJ mol^{-1}), an exceedingly low value: Stevens, I.D.R.; Liu, M.T.H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* ***1989***, *30*, 481. Also see, Pezacki, J. P.; Couture, P.; Dunn, J. A.; Warkentin, J.; Wood, P. D.; Lusztyk, J.; Ford, F.; Platz, M. S. *J. Org. Chem.* ***1999****, 64,* 4456.

[415] Bettinger, H.F.; Rienstra-Kiracofe, J.C.; Hoffman, B.C.; Schaefer, III, H.F.; Baldwin, J.E.; Schleyer, P.v.R. *Chem. Commun.* ***1999***, 1515.

[416] Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6873; Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. *J. Am. Chem. Soc.* ***1989***, *111*, 6874; Ho, G.; Krogh-Jespersen, K.; Moss, R. A.; Shen, S.; Sheridan, R.S.; Subramanian, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6875; LaVilla, J.A.; Goodman, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6877.

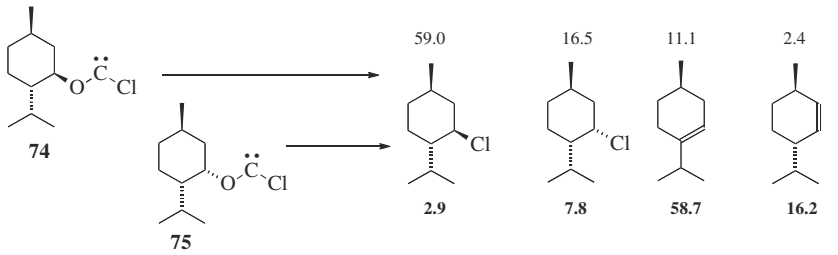
[417] Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* ***1960***, *82*, 1002.

[418] McMahon, R.J.; Chapman, O.L. *J. Am. Chem. Soc.* ***1987***, *109*, 683.

[419] Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500.

carbenes are also known.[420] Of course, the new carbene must stabilize itself in one of the ways mentioned.

5. The fragmentation reactions of alicyclic oxychlorocarbenes (e.g., **74** and **75**)[421] give substitution and elimination products. Menthyloxychlorocarbene (**74**) gave primarily the substitution product, whereas neomenthyloxychlorocarbene (**75**) gave primarily the elimination product, as shown. In this case, the substitution product is likely due to rearrangement of the chlorocarbene.[422] It is known that fragmentation of nortricyclyloxychlorocarbene in pentane occurs by an S_Ni-like process to give nortricyclyl chloride.[423] In more polar solvents, fragmentation leads to nortricyclyl cation–chloride anion pair that gives nortricyclyl chloride and a small amount of *exo*-2-norbornenyl chloride. Fragmentation can also lead to radicals.[424]



6. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, for example,

$$^{\bullet}\dot{C}H_2 + CH_3CH_3 \longrightarrow {}^{\bullet}CH_3 + {}^{\bullet}CH_2CH_3$$

This is not surprising, since triplet carbenes are free radicals. But singlet carbenes[425] can also give this reaction, although in this case only halogen atoms are abstracted, not hydrogen.[426]

5.E. NITRENES

Nitrenes (R—N),[427] are the nitrogen analogues of carbenes, and most of the comments about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary

[420] For a review, see Jones, W.M. *Acc. Chem. Res.* ***1977***, *10*, 353.
[421] Moss, R.A.; Johnson, L.A.; Kacprzynski, M.; Sauers, R.R. *J. Org. Chem.* ***2003***, *68,* 5114.
[422] See Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R.S. *Tetrahedron Lett.* ***1999***, *40*, 17.
[423] Moss, R. A.; Ma, Y.; Sauers, R. R.; Madni, M. *J. Org. Chem.* ***2004***, *69,* 3628.
[424] Mekley, N.; El-Saidi, M.; Warkentin, J. *Can. J. Chem.* ***2000***, *78*, 356.
[425] Vignolle, J.; Catton, X.; Bourissou, D. *Chem. Rev.* ***2009***, *109*, 3333.
[426] Roth, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 1527, 4935, *Acc. Chem. Res.* ***1977***, *10*, 85.
[427] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**; Lwowski, W. *React. Intermed. (Wiley)* ***1985***, *3*, 305; ***1981***, *2*, 315; ***1978***, *1*, 197; Abramovitch, R.A. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 127–192; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* ***1989***, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* ***1987***, *20*, 18 (oxycarbonylnitrenes); Abramovitch, R.A.; Sutherland, R.G. *Fortsch. Chem. Forsch.* ***1970***, *16*, 1 (sulfonyl nitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* ***1972***, *41*, 131 (*N*-nitrenes).

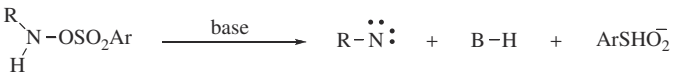
conditions,[428] although *ab initio* calculations show that nitrenes are more stable than carbenes with an enthalpy difference of 25–26 kcal mol^{-1} (104.7–108.8 kJ mol^{-1}).[429]



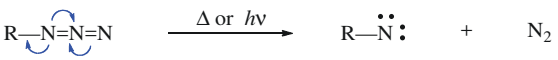
Alkyl nitrenes have been isolated by trapping in matrices at 4 K,[430] while aryl nitrenes, which are less reactive, can be trapped at 77 K.[431] The ground state of NH, and probably of most nitrenes,[432] is a triplet, although nitrenes can be generated in both triplet[433] and singlet states. A quartet ground-state nitreno radical has been reported.[434] In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds in a stereospecific manner and the other not. By analogy with Skell's proposal involving carbenes (Sec. 5.D.i) these are taken to be the singlet and triplet species, respectively.[435]

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination*. An example is



2. *Breakdown of Certain Double-Bond Compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,[436]

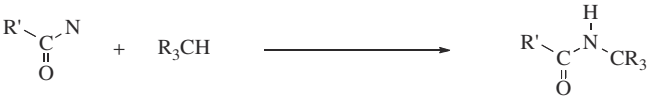


The unsubstituted nitrene (NH) has been generated by photolysis of electric discharge through NH_3, N_2H_4, or HN_3.

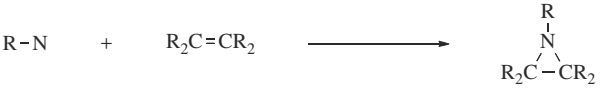
The reactions of nitrenes are also similar to those of carbenes.[437] As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

[428] McClelland, R.A. *Tetrahedron* ***1996***, *52*, 6823.
[429] Kemnitz, C.R.; Karney, W.L.; Borden, W.T. *J. Am. Chem. Soc.* ***1998***, *120*, 3499.
[430] Wasserman, E.; Smolinsky, G.; Yager, W.A. *J. Am. Chem. Soc.* ***1964***, *86*, 3166. See Carrick, P.G.; Brazier, C. R.; Bernath, P.F.; Engelking, P.C. *J. Am. Chem. Soc.* ***1987***, *109*, 5100.
[431] Smolinsky, G.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 3220. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 159–248.
[432] See Sigman, M.E.; Autrey, T.; Schuster, G.B. *J. Am. Chem. Soc.* ***1988***, *110*, 4297.
[433] See Singh, P.N.D.; Mandel, S.M.; Robinson, R.M.; Zhu, Z.; Franz, R.; Ault, B.S.; Gudmundsdottir, A.D. *J. Org. Chem.* ***2003***, *68,* 7951.
[434] Sander, W.; Grote, D.; Kossmann, S.; Neese, F. *J. Am. Chem. Soc.* ***2008, 130,*** 4396.
[435] McConaghy, Jr., J.S.; Lwowski, W. *J. Am. Chem. Soc.* ***1967***, *89*, 2357, 4450; Mishra, A.; Rice, S.N.; Lwowski, W. *J. Org. Chem.* ***1968***, *33*, 481.
[436] See Dyall, L.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 287–320; Dürr, H.; Kober, H. *Top. Curr. Chem.* ***1976***, *66*, 89; L'Abbé, G. *Chem. Rev.* ***1969***, *69*, 345.
[437] See Subbaraj, A.; Subba Rao, O.; Lwowski, W. *J. Org. Chem.* ***1989***, *54*, 3945.

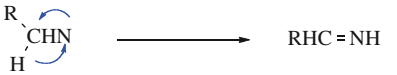
1. *Insertion* (*see Reaction* ***12-13***). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, for example,



2. *Addition to C=C bonds* (*see Reaction* ***15-54***):

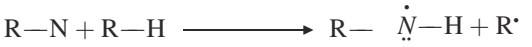


3. *Rearrangements*.[413] Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, for example,



Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all; that is, that migration takes place at the same time the nitrene is formed[438] (see Reaction **18-12**). However, the rearrangement of naphthylnitrenes to novel bond-shift isomers has been reported.[439]

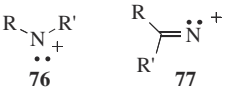
4. *Abstraction*, For example,



5. *Dimerization*. One of the principal reactions of NH is dimerization to diimide (N_2H_2). Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:[440]



It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proven that free nitrenes are actually involved.



76 **77**

At least two types of *nitrenium ions*,[441] the nitrogen analogues of carbocations, can exist as intermediates, although much less work has been done in this area

[438] See Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1537.
[439] Maltsev, A.; Bally, T.; Tsao, M.-L.; Platz, M. S.; Kuhn, A.; Vosswinkel, M.; Wentrup, C. *J. Am. Chem. Soc.* ***2004***, *126,* 237.
[440] See, for example, Leyva, E.; Platz, M.S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1986***, *108*, 3783.
[441] Novak, M.; Rajagopal, S. *Adv. Phys. Org. Chem.* ***2001***, *36,* 167; Falvey, D. E. in Moss, R. A.; Platz, M. S.; Jones, Jr., M. *Reactve Intermediate Chemistry*, Wiley–Interscience, Hoboken, NJ, ***2004***, Vol. 1, pp 593–650.

than on carbocations. In one type (**76**), the nitrogen is bonded to two atoms (R or R′ can be H),[442] and in the other (**77**) to only one atom.[443] When R = H in **76** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.[444]

[442] Winter, A.H.; Falvey, D.E.; Cramer, C.J. *J. Am. Chem. Soc.,* ***2004****, 126*, 9661.

[443] See Abramovitch, R.A.; Jeyaraman, R. in Scriven, E.F.V. *Azides and Nitrenes*, Acaademic Press, NY, ***1984***, pp. 297–357; Gassman, P.G. *Acc. Chem. Res.* ***1970***, *3*, 26; Lansbury, P.T. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 405–419.

[444] Gassman, P.G.; Cryberg, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5176.

CHAPTER 6

Mechanisms and Methods of Determining Them

A mechanism is the actual process by which a reaction takes place: which bonds are broken, in what order, how many steps are involved, the relative rate of each step, and so on. In order to state a mechanism completely, the positions of all atoms should be specified, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely.[1] There is much about the fine details that is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases, there are several proposed mechanisms, each of which completely explains all the data.

6.A. TYPES OF MECHANISM

In most reactions of organic compounds, one or more covalent bonds are broken. Organic mechanisms may be divided into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, although they often do. The important thing is that the electrons are never unpaired. For most reactions, it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book, the substrate is always designated as that molecule that supplies carbon to the new bond. When carbon–carbon bonds are formed via heterolytic reactions, the reagent generally brings a pair of electrons

[1] *Perspectives on Structure and Mechanism in Organic Chemistry*, Carroll, F.A., Wiley, ***2010***; *Arrow-Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms*, Levy, D.E., Wiley–Interscience, ***2008***; *Guidebook to Mechanism in Organic Chemistry*, 6th Edition, Sykes, P., Prentice Hall, **1996**.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. For a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free radical mechanisms*.
3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*[2] (see Reactions **15-58–15-61** and **18-29–18-33**.

Examples of all three types of mechanisms are given in Section 6.B.

6.B. TYPES OF REACTION

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, although in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely for the purpose of classification and comparison. All are discussed in detail in Part II.

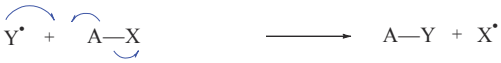
1. *Substitutions*. If heterolytic, these reactions can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).
   a. Nucleophilic substitution (Chaps 10 and 13).



   b. Electrophilic substitution (Chaps 11 and 12).



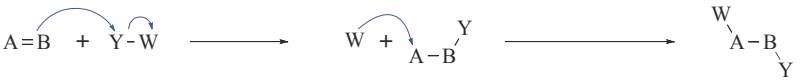
   c. Free radical substitution (Chap 14).



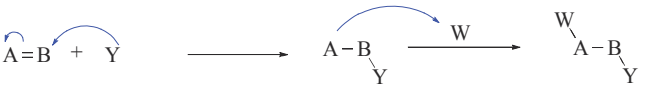
[2] For a classification of pericyclic reactions, see Hendrickson, J.B. *Angew. Chem. Int. Ed.* ***1974***, *13*, 47. Also see, Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***.

In free radical substitution, $Y^{\bullet}$ is usually produced by a previous free radical cleavage, and $X^{\bullet}$ goes on to react further.

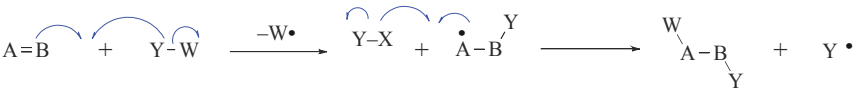
2. *Additions to Double or Triple Bonds (Chaps 15 and 16).* These reactions can take place by all three of the mechanistic possibilities.
   a. Electrophilic addition (heterolytic).



   b. Nucleophilic addition (heterolytic).



   c. Free-radical addition (homolytic).



   d. Simultaneous addition (pericyclic).



The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules, as illustrated by (b). Cleavage of the Y—W bond may occur at the same time that Y is bonding to B, but the cleavage may also occur earlier.

3. β *Elimination (Chap 17).*

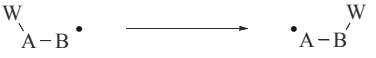


These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown in Section 17.C.i. Free radical β eliminations are extremely rare. In heterolytic eliminations, W and X may or may not leave simultaneously and may or may not combine afterwards.

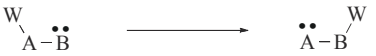
4. *Rearrangement (Chap 18).* Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.
   a. Migration with electron pair (nucleophilic; common).



   b. Migration with one electron (free radical; rare).



c. Migration without electrons (electrophilic; rare).



The generic examples show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all, but rather migration across a π-framework (see Chap 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and Reduction (Chap 19).* Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see Section 19.A.
6. *Combinations of the Above.* Note that arrows are used to show movement of *electrons*. An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, but in these reactions how or in which direction the electrons are moving is usually unknown.

While not mentioned here as a distinct category, it must be said that many reactions, including some examples of 1–6 are actually acid–base reactions. In other cases, an acid–base reaction initiates the process or sometimes ends the process. In 2a, for example, Y = H and this is an acid–base reaction in which the π bond is the base and the proton is the acid. If W = H in 3a, then the elimination process begins with an acid–base reaction in which a base donates two electrons to H (= W). In 2b, if A donates electrons to W and W = H, this is another example of an acid–base reaction. Always be mindful of the acid–base properties of reactions.

Many, if not most of the reactions, noted above are subject to modification of the reactivity by the introduction of π bonds. Most reactions involve the transfer of two electrons to make or break a bond. The presence of two electrons in a π bond allows this two- electron-transfer process to proceed through the intervening atoms. In effect, the reactivity of a given center is extended by the presence of π bonds. This is the concept of *vinylogy*: the extension of points of reactivity by intervening π bonds. In other words, if a system X—C-1—C-2 undergoes a reaction at C-2 with loss of X from C-1, X—C-1—C-2=C-3—C-4 may undergo reaction at C-4. Reaction at C-4 initiates electron transfer via the π bond that is extended to C-1 for loss of X. Several examples of this type of reaction will be presented in later chapters.

6.C. THERMODYNAMIC REQUIREMENTS FOR REACTION

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants (i.e., ΔG must be negative). Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which naturally flows only downhill and never uphill, molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy (H) and entropy (S).

These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain,[3] and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The lower the order in a system, the greater the entropy. The preferred conditions in Nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions, entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain processes entropy is important and can sometimes dominate enthalpy. Several examples will be discussed.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.
2. In a reaction in which the number of product molecules is equal to the number of reactant molecules (e.g., $A + B \rightarrow C + D$), entropy effects are usually small, but if the number of molecules is increased, (e.g., $A \rightarrow B + C$), there is a gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are likely to be thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.
3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy.[4] An example is cleavage of ethane into two methyl radicals. In this case, a bond of $\sim$79 kcal mol^{-1} (330 kJ mol^{-1}) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

[3] For a discussion of the activation strain model of chemical reactivity, see van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.*, ***2010***, *8*, 3118.

[4] For calculations of long-chain alkane energies see Song, J.-W.; Tsuneda, T.; Sato, T.; Hirao, K. *Org. Lett.* ***2010***, *12*, 1440.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (cf. hexane and cyclohexane). Ring opening therefore correlates with a gain in entropy and ring closing a loss.

6.D. KINETIC REQUIREMENTS FOR REACTION

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary*, but not a *sufficient,* condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* ($\Delta G^{\ddagger}$) must be added.[5] This situation is illustrated in Fig. 6.1,[6] which is an energy profile for a one-step reaction without an intermediate. In this type of diagram, the horizontal axis (called the *reaction coordinate*)[7] signifies the progression of the reaction. The parameter $\Delta G_f^{\dagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Fig. 6.1 is reversible, $\Delta G_r^{\dagger}$ must be $> \Delta G_f^{\dagger}$, since it is the sum of ΔG and $\Delta G_f^{\dagger}$.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution, but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.[8]

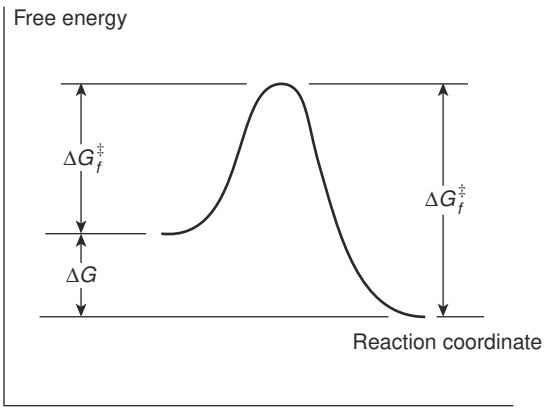


FIG. 6.1. Free energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

[5] To initiate a reaction of a mixture of H_2 and O_2, energy must be added such as by striking a match.

[6] Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in an approximate way, to other reactions.

[7] For a review of reaction coordinates and structure–energy relationships, see Grunwald, E. *Prog. Phys. Org. Chem.* ***1990***, *17*, 55.

[8] For a discussion of transition states, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 540.

In *transition-state theory*,[9] the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, although at first sight is surprising, is not unreasonable since they are all "falling downhill") so that the rate constant (see Sec. 6.J.vi) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, (i.e., on the value of $K^{\ddagger}$). The parameter $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3\,RT \log K^{\ddagger}$$

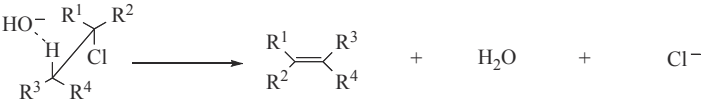
so that a higher value of $\Delta G^{\ddagger}$ is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier.[10] Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion controlled*.[11]

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components

$$\boldsymbol{\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions, bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is $\Delta H^{\ddagger}$. It is true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

Entropy of activation, ($\Delta S^{\ddagger}$), which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple non-cyclic alkyl chloride and hydroxide ion to give an alkene (Reaction **17-13**) takes place only if, in the transition state, the reactants are oriented as shown. This is an acid–base reaction because the proton on the carbon β to the chlorine is polarized δ^{+}, and is a weak acid. Removal of that proton initiates loss of the chlorine atom and formation of the alkene. The electrons in the C—H bond (the acidic proton) must align anti to the leaving groups (Cl) for the reaction to proceed.[12]



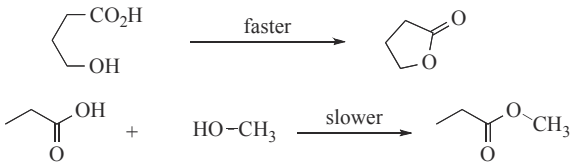
[9] See Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 137–181; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***; pp. 227–378. See Zevatskii, Y.E.; Samoilov, D.V. *Russ. J. Org. Chem.* ***2007***, *43*, 483.

[10] See Donahue, N.M. *Chem. Rev.* ***2003***, *103*, 4593.

[11] For a monograph on diffusion-controlled reactions, see Rice, S.A. *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford, C.H.; Tipper, C.F.H.; Compton, R.G.); Elsevier: NY, ***1985***.

[12] As will be seen in Chapter 17, elimination is also possible with some molecules if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

When the two reacting molecules collide, if the $^{-}$OH should approach the molecule, the chlorine atom, or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space because only one leads to reaction. Thus, a considerable loss in entropy is involved, (i.e., $\Delta S^{\ddagger}$ is negative).



Entropy of activation is also responsible for the difficulty in closing rings[13] larger then six membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a 10-carbon chain. In order for reaction to take place, the groups must encounter each other. But a 10-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[14] This factor is also present, although less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. Although $\Delta H^{\ddagger}$ is about the same, $\Delta S^{\ddagger}$ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable $\Delta S^{\ddagger}$ may not be sufficient to overcome the unfavorable $\Delta H^{\ddagger}$ change. Table 6.1 shows the relative rate constants for the closing of rings of 3–23 members all by the same reaction.[15] Reactions in which the transition state has more disorder than the starting compounds, for example, the pyrolytic conversion of cyclopropane to propene, have positive $\Delta S^{\ddagger}$ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions, there is an energy "well". There are two transition states, each with an energy higher than the intermediate (Fig. 6.2). The deeper the well, the more stable the intermediate. In Fig. 6.2*a*, the second peak is higher than the first. The opposite situation is shown in Fig. 6.2*b*. Note that in reactions in which the second peak is higher than the first, the overall $\Delta G^{\ddagger}$ is less than the sum of the $\Delta G^{\ddagger}$ values for the two steps. Minima in free energy profile diagrams (*intermediates*) correspond to real species that have a finite though usually short existence.

[13] See De Tar, D.F.; Luthra , N.P.*J. Am. Chem. Soc.* ***1980***, *102*, 4505; Mandolini, L. *Bull. Soc. Chim. Fr.* ***1988***, 173. For a related discussion, see Menger, F.M. *Acc. Chem. Res.* ***1985***, *18*, 128.

[14] See Nakagaki. R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* ***1989***, *2*, 187; Mandolini, L. *Adv. Phys. Org. Chem.* ***1986***, *22*, 1; Winnik, M.A. *Chem. Rev.* ***1981***, *81*, 491; Valters, R. *Russ. Chem. Rev.* ***1982***, *51*, 788.

[15] The values for ring sizes 4, 5, and 6 are from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550; the others are from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. See also, Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* ***1981***, *14*, 95. See, however, Benedetti, F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 605.

TABLE 6.1[15] Relative Rate Constants at 50 °C[a]

$Br(CH_2)_{n-2}CO_2^- \longrightarrow (CH_2)_{n-2}\overset{O}{\underset{O}{<}}$ where n = *the ring size*.

Ring Size	Relative Rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

[a]The rate for an eight-membered ring = 1 for the reaction.

Reprinted with permission from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550. Copyright © 1978 American Chemical Society. Reprinted with permission from Galli, C.; Illuminati, G.; Mandolini, L., Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. Copyright © 1977 American Chemical Society.

These may be the carbocations, carbanions, free radicals, and so on., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^{\ddagger}$ is small), but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species, but only to

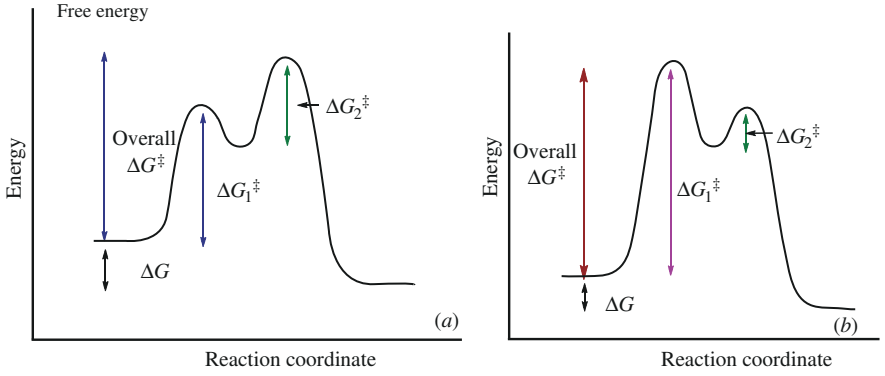
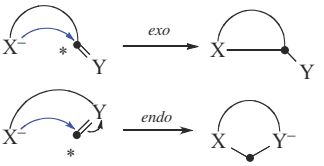


FIG. 6.2. (*a*) Free energy profile for a reaction with an intermediate $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ are the free energy of activation for the first and second stages, respectively. (*b*) Free energy profile for a reaction with an intermediate in which the first peak is higher than the second

transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.[16]

6.E. THE BALDWIN RULES FOR RING CLOSURE[17]

In previous sections, the kinetic and thermodynamic aspects of ring-closure reactions were discussed in a general way. J.E. Baldwin[18] supplied a more specific set of rules for certain closings of three seven-membered rings. These rules distinguish two types of ring closure, called *exo* and *endo*, and three kinds of atoms at the starred positions: *Tet* for sp^3, *Trig* for sp^2, and *Dig* for *sp*. The following are *Baldwin's rules* for closing rings of 3–7 members.



Rule 1. Tetrahedral systems
- a. 3-7-*Exo–Tet* are all favored processes
- b. 5-6-*Endo–Tet* are disfavored

Rule 2. Trigonal systems
- a. 3-7-*Exo–Trig* are favored
- b. 3-5-*Endo–Trig* are disfavored[19]
- c. 6-7-*Endo–Trig* are favored

Rule 3. Digonal systems
- a. 3-4-*Exo–Dig* are disfavored
- b. 5-7-*Exo–Dig* are favored
- c. 3-7-*Endo–Dig* are favored

"Disfavored" does not mean it cannot be done, only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain will enable the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in

[16] See laser femtochemistry: Zewall, A.H.; Bernstein, R.B. *Chem. Eng. News* ***1988***, *66*, No. 45 (Nov. 7), 24–43. For another method, see Collings, B.A.; Polanyi, J.C.; Smith, M.A.; Stolow, A.; Tarr, A.W. *Phys. Rev. Lett.* ***1987***, *59*, 2551.

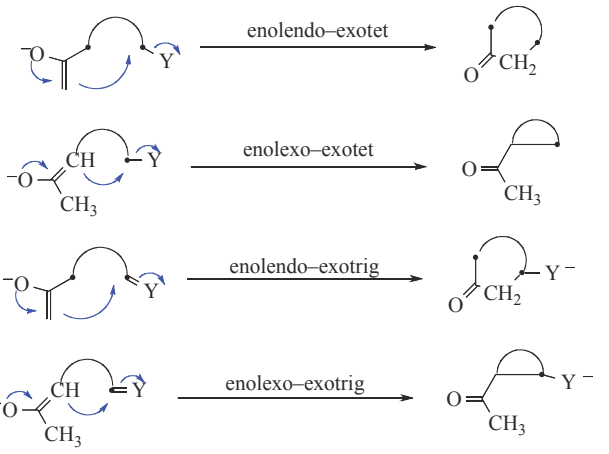
[17] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 564–572.

[18] Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* ***1976***, 734; Baldwin, J.E. in *Further Perspectives in Organic Chemistry (Ciba Foundation Symposium 53)*, Elsevier, Amsterdam, The Netherlands, ***1979***, pp. 85–99. See also, Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.* ***1977***, *42*, 3846; Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939; Fountain, K.R.; Gerhardt , G. *Tetrahedron Lett.* ***1978***, 3985.

[19] For some exceptions to the rule in this case, see Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1778; Torres, L.E.; Larson, G.L. *Tetrahedron Lett.* ***1986***, *27*, 2223.

substantial accord with these rules, and they are important in the formation of five- and six-membered rings.[20]

Although Baldwin's rules can be applied to ketone enolates,[21] additional rules were added to make the terminology more specific.[22] The orientation of the orbital as it approaches the reactive center must be considered for determining the correct angle of approach. Diagrams that illustrate the enolate rules are shown.



The rules are

a. 6–7 enolendo–exo–tet reactions are favored
b. 3–5 enolendo–exo–tet reactions are disfavored
c. 3–7 enolexo–exo–tet reactions are favored
d. 3–7 enolexo–exo–trig reactions are favored
e. 6–7 enolendo–exo–trig reactions are favored
f. 3–5 enolendo–exo–trig reactions are disfavored

6.F. KINETIC AND THERMODYNAMIC CONTROL

$$\mathbf{C} \longleftarrow \mathbf{A} \longrightarrow \mathbf{B}$$

There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products. Starting material **A** may give either **B** or **C**, for example. Figure 6.3 shows a free energy profile for a reaction in which **B** is thermodynamically more stable than **C** ($\Delta G_{\mathbf{B}}$ is $> \Delta G_{\mathbf{C}}$), but **C** is formed faster (lower $\Delta G^{\ddagger}$). If neither reaction is reversible, **C** will be formed in a larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the

[20] Johnson, C.D. *Accts. Chem. Res.* ***1997***, *26*, 476.
[21] Baldwin, J.E.; Kruse, L.I. *J. Chem. Soc. Chem. Commun.* ***1977***, 233.
[22] Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939.

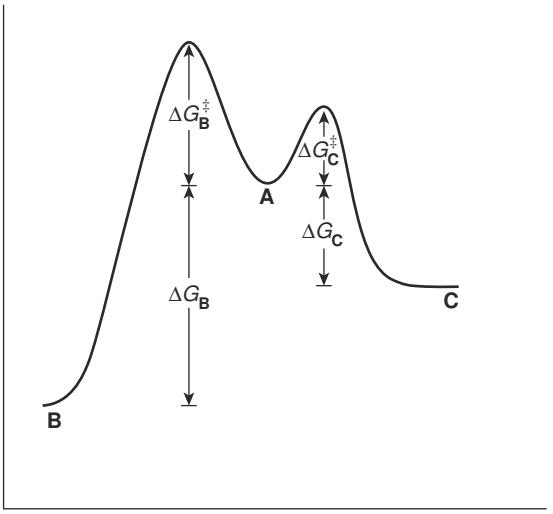


FIG. 6.3. Free energy profile illustrating kinetic versus thermodynamic control of products. The starting compounds (**A**) can react to give either **B** or **C**.

equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be **B**. Under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is *thermodynamically controlled*.[23] Of course, Fig. 6.3 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases, the product of kinetic control is also the product of thermodynamic control.

6.G. THE HAMMOND POSTULATE

Transition states are not detectable and have zero lifetimes, so it is impossible to observe them directly. Information about their geometries must be obtained from inference and modeling. In some cases, the inferences can be very strong. For example, in the S_N2 reaction (Sec. 10.A.i) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, it is not possible to reach such easy conclusions, and conclusions are greatly aided by the *Hammond postulate*,[24] which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer in free energy*. Thus, for an exothermic reaction like that shown in Fig. 6.1, the transition state resembles the reactants more than the products, although not much more because there is a substantial $\Delta G^{\ddagger}$ on both sides.

The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Fig. 6.2*a*, the first transition state lies much closer in energy to the

[23] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 36–89.
[24] Hammond, G.S. *J. Am. Chem. Soc.* ***1955***, *77*, 334. For a discussion, see Farcasiu, D. *J. Chem. Educ.* ***1975***, *52*, 76.

intermediate than to the reactants, and it is possible to predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. More is usually known about the structure of intermediates than of transition states, so a knowledge of intermediates is used to draw conclusions about the transition states (e.g., see Sec. 10.G.i and 15.B.i).

6.H. MICROSCOPIC REVERSIBILITY

In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction $\mathbf{A} \rightarrow \mathbf{B}$ there is an intermediate **C**, then **C** must also be an intermediate in the reaction $\mathbf{B} \rightarrow \mathbf{A}$. This is a useful principle since it enables one to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chap 7).

6.I. MARCUS THEORY

It is often useful to compare the reactivity of one compound with that of similar compounds. The real goal is to find out how a reaction coordinate (and in particular the transition state) changes when one reactant molecule is replaced by a similar molecule. *Marcus theory* is a method for doing this.[25]

In this theory, the activation energy ($\Delta G^{\ddagger}$) is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG°.[26]

This is a kinetic part, called the *intrinsic barrier* $\left(\Delta G^{\ddagger}_{\text{int}}\right)$

2. A thermodynamic part, which arises from the ΔG° for the reaction.

The Marcus equation says that the overall $\Delta G^{\ddagger}$ for a one-step reaction is[27]

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}\Delta G^{\Delta} + \frac{(\Delta G^{\Delta})^2}{16(\Delta G^{\ddagger}_{\text{int}} - \text{w}^{\text{R}})}$$

[25] See Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227; Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95.

[26] The parameter ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

[27] Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87, pp. 98–99.

where the term ΔG^{Δ} stands for

$$\Delta G^{\Delta} = \Delta G^{\circ} - w^{R} + w^{P}$$

w^{R}, a work term, is the free energy required to bring the reactants together and w^{P} is the work required to form the successor configuration from the products.

For a reaction of the type $\mathbf{AX} + \mathbf{B} \rightarrow \mathbf{BX}$, the intrinsic barrier[28] $\Delta G^{\ddagger}_{int}$ is taken to be the average $\Delta G^{\ddagger}$ for the two symmetrical reactions

$$\mathbf{AX} + \mathbf{A} \longrightarrow \mathbf{AX} + \mathbf{A} \qquad \Delta G^{\ddagger}_{\mathbf{A},\mathbf{A}}$$

$$\mathbf{BX} + \mathbf{B} \longrightarrow \mathbf{BX} + \mathbf{B} \qquad \Delta G^{\ddagger}_{\mathbf{B},\mathbf{B}}$$

so that

$$\Delta G^{\ddagger}_{int} + \frac{1}{2}(\Delta G^{\ddagger}_{\mathbf{A},\mathbf{A}} + \Delta G^{\ddagger}_{\mathbf{B},\mathbf{B}})$$

One type of process that can successfully be treated by the Marcus equation is the S_N2 mechanism (Sec. 10.A.i).

$$R{-}X + Y \longrightarrow R{-}Y + X$$

When R is CH_3 the process is called *methyl transfer*.[29] For such reactions, the work terms w^{R} and w^{P} are assumed to be very small compared to ΔG°, and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{int} + \frac{1}{2}\Delta G^{\circ} + \frac{(\Delta G)^2}{16\Delta G^{\ddagger}_{int}}$$

The Marcus equation allows $\Delta G^{\ddagger}$ for $RX + Y \rightarrow RY + X$ to be calculated from the barriers of the two symmetrical reactions $RX + X \rightarrow RX + X$ and $RY + Y \rightarrow RY + Y$. The results of such calculations are generally in agreement with the *Hammond postulate*.

Marcus theory can be applied to any single-step process where something is transferred from one particle to another. It was originally derived for electron transfers,[30] and then extended to transfers of H^+ (see Sec. 8.D), H^-,[31] and $H^{\bullet}$[32], as well as methyl transfers.

[28] See Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 943, *Chem. Soc. Rev.* ***1990***, *19*, 133.
[29] See Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87. See also, Lee, I. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 943; Lewis, E.S.; McLaughlin, M.L.; Douglas, T.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6668; Lewis, E.S. *Bull. Soc. Chim. Fr.* ***1988***, 259.
[30] Marcus, R.A. *J. Phys. Chem.* ***1963***, *67*, 853, *Annu. Rev. Phys. Chem.* ***1964***, *15*, 155; Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer: NY, ***1987***.
[31] Kim, D.; Lee, I.H.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1990***, *112*, 1889 and references cited therein.
[32] See, for example, Dneprovskii, A.S.; Eliseenkov, E.V. *J. Org. Chem. USSR* ***1988***, *24*, 243.

6.J. METHODS OF DETERMINING MECHANISMS[33]

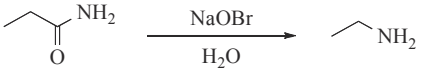
There are a number of commonly used methods for determining mechanisms.[34] In most cases, one method is not sufficient, and the problem is generally approached from several directions.

6.J.i. Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the *von Richter reaction* (Reaction **13-30**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$

that fails to account for the formation of a small amount of ethane cannot be correct (see Reaction **14-1**), and any mechanism proposed for the *Hofmann rearrangement* (Reaction **18-13**):



must account for the fact that the carbonyl carbon is lost as CO_2.

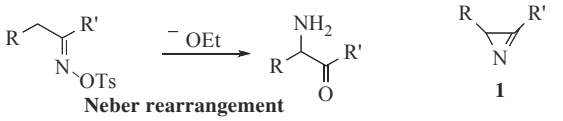
6.J.ii. Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms, and the presence or absence of an intermediate is essential information. There are several methods, none of them foolproof,[35] for attempting to learn whether or not an intermediate is present and, if so, its structure. All methods are experimental, and an intermediate must be detected in one way or another, often by isolation or trapping.

1. *Isolation of an Intermediate*. It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the *Neber rearrangement* (Reaction **18-12**) the intermediate **1** (an azirene)[36] has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions, and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, although it is not conclusive,

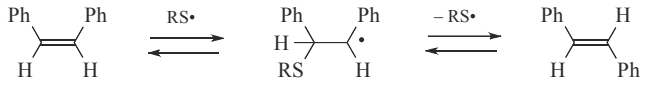
[33] *The Investigation of Organic Reactions and their Mechanisms* Maskill, H. (Ed.), Blackwell, Oxford, ***2006***.
[34] See Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 2 pts., Wiley: NY, ***1986***; Carpenter, B.K. *Determination of Organic Reaction Mechanisms*, Wiley: NY, ***1984***.
[35] For a discussion, see Martin, R.B. *J. Chem. Educ.* ***1985***, *62*, 789.
[36] See Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***1995***, *36*, 4665.

since the compound may arise by an alternate path and by coincidence give the same product.



Neber rearrangement **1**

2. *Detection of an Intermediate*. In many cases an intermediate cannot be isolated, but can be detected by normal IR, ReactIR,[37] NMR, or other spectra.[38] The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see Reaction **11-2**). Free radical and triplet intermediates can often be detected by ESR and by CIDNP (see Chap 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method, a double-bond compound is added to the reaction mixture, and its fate traced.[39] One possible result is cis–trans conversion. For example, *cis*-stilbene is isomerized to the trans isomer in the presence of RS• radicals, by this mechanism:



cis-Stilbene *trans*-Stilbene

Since the trans isomer is more stable than the cis, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

3. *Trapping of an Intermediate*. In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzynes (Sec. 13.A.iii) react with dienes in the *Diels–Alder reaction* (**15-60**). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the *Diels–Alder* adduct indicate that the benzyne was probably present.
4. *Addition of a Suspected Intermediate*. If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The *von Richter reaction* (Reaction **13-30**) provides a good example here too. For many years, it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (Reaction **16-4**). Indeed, *p*-chlorobenzonitrile was shown to

[37] ReactIR uses mid-range IR spectroscopy for the identification and monitoring of critical reaction species and follows the changes in the reaction on a second-by-second basis. For applications, see Stead, D.; Carbone, G.; O'Brien, P.; Campos, K.R.; Coldham, I; Sanderson, A. *J. Am. Chem. Soc.* ***2010***, *132*, 7260; Pippel, D.J.; Weisenburger, G.A.; Faibish, N.C.; Beak, P. *J. Am. Chem. Soc.* ***2001***, *123*, 4919.; Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002***, *124*, 264.

[38] See Parker, V.D. *Adv. Phys. Org. Chem.* ***1983***, *19*, 131; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159.

[39] For a review, see Todres, Z.V. *Tetrahedron* ***1987***, *43*, 3839.

give *p*-chlorobenzoic acid under normal *von Richter* conditions.[40] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[41] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

6.J.iii. The Study of Catalysis[42]

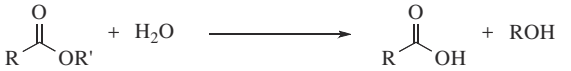
Many organic reactions are slow in the absence of a catalyst. Acid-catalyzed reactions are prevalent for example. Once it is known that a reaction is subject to catalysis, much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, *catalysts perform their actions by providing an alternate pathway for the reaction* in which $\Delta G^{\ddagger}$ is less than it would be without the catalyst. Catalysts do not change ΔG.

6.J.iv. Isotopic Labeling[43]

Molecules that have been isotopically labeled can be used to trace the path of the reaction, which may provide much useful mechanistic information. For example, in the reaction

$$R\overset{*}{C}OO^- + BrCN \longrightarrow R\overset{*}{C}N$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[44] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see Reaction **16-94**). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters



Which bond of the ester is broken, the acyl–O or the alkyl–O bond? The answer is found by the use of $H_2{}^{18}O$. If the acyl–O bond breaks, the labeled oxygen will appear in the acid;

[40] Bunnett, J.F.; Rauhut, M.M.; Knutson, D.; Bussell, G.E. *J. Am. Chem. Soc.* ***1954***, *76*, 5755.
[41] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 944.
[42] See Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***; Coenen, J.W.E. *Recl. Trav. Chim. Pays-Bas*, ***1983***, *102, 57;* and in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol.6 of Weissberger, *A. Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Keeffe, J.R.; Kresge, A.J. pp. 747–790; Haller, G.L.; Delgass, W.N. pp. 951–979.
[43] See Wentrup, C. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger. A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 613–661; Collins, C.J. *Adv. Phys. Org. Chem.* ***1964***, *2*, 3. See also, the series *Isotopes in Organic Chemistry*.
[44] Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.

otherwise it will be in the alcohol (see Reaction **16-59**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case, mass spectrometry is not the only option since IR and ^{1}H and ^{13}C NMR[45] spectra can be used to determine when deuterium has been substituted for hydrogen.

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

6.J.v. Stereochemical Evidence[46]

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism.[47] For example, Walden[48] discovered that (+)-malic acid gives (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$, showing that the mechanisms of these apparently similar conversions could not be the same (see Sec. 10.A.i and 10.D). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with $KMnO_4$ gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see Reaction **15-48**).

6.J.vi. Kinetic Evidence[49]

The rate of a homogeneous reaction[50] is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases, a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (**A**), the *rate law* (the rate of change of concentration of **A** with time t) is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}]$$

[45] For a review, see Hinton, J.; Oka, M.; Fry, A. *Isot. Org. Chem.* ***1977***, *3*, 41.

[46] See Billups, W.E.; Houk, K.N.; Stevens, R.V. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 663–746; Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***; Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***.

[47] Bonnet, L.; Larrégaray, P.; Duguay, B.; Rayez, J.-C.; Che, D.C.; Kasai, T. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 707.

[48] Walden, P. *Ber.* ***1896***, *29*, 136; ***1897***, *30*, 3149; ***1899***, *32*, 1833.

[49] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***; Drenth, W.; Kwart, H. *Kinetics Applied to Organic Reactions*, Marcel Dekker, NY, ***1980***; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 53–100; Gardiner Jr., W.C. *Rates and Mechanisms of Chemical Reactions*, W.A. Benjamin: NY, ***1969***; Leffler, J.E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley, NY, ***1963***; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 555–614.

[50] A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

where k is the *rate constant* for the reaction.[51] There is a minus sign because the concentration of **A** decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of k for a first-order reaction are reciprocal second (s^{-1}). The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}][\mathbf{B}] \quad \text{or} \quad \text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}]^2$$

For a second-order reaction, the units are $L\,mol^{-1}\,s^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to [**A**] and to [**B**] is said to be first order in **A** and in **B**, second order overall. A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2\mathbf{A} + \mathbf{B} \rightarrow \mathbf{C} + \mathbf{D}$ then, on a molar basis, **A** must disappear twice as fast as **B**, so that $-d[\mathbf{A}]/dt$ and $-d[\mathbf{B}]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. The rate law leads to an understanding of the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if it is known how many (and which) molecules take part in the activated complex, a good deal is known about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate), the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in **A** always involves two molecules of **A**; if it is first order in **A** and in **B**, then a molecule of **A** reacts with one of **B**, and so on. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may get lengthy at times.[52] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.[53]

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $\mathbf{A} + 2\mathbf{B} \rightarrow \mathbf{C}$ has the mechanism

$$\mathbf{A} + \mathbf{B} \xrightarrow{\text{slow}} \mathbf{I}$$
$$\mathbf{I} + \mathbf{B} \xrightarrow{\text{fast}} \mathbf{C}$$

[51] Colins, C.C.; Cronin, M.F.; Moynihan, H.A.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 1267.
[52] For a discussion of how order is related to *molecularity* in many complex situations, see Szabó, Z.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol.2, Elsevier, NY, ***1969***, pp. 1–80.
[53] Many chemists prefer to use the term *rate-limiting step or rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions in Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *IUPAC Compendium of Chemical Terminology,* Blackwell Scientific Publications, Oxford, ***1987***, p. 337. For a discussion of rate-determining steps, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 250.

where **I** is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}][\mathbf{B}]$$

2. When the first step is not rate determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give **C**. The rate of disappearance of **A** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1\,[\mathbf{A}][\mathbf{B}] - k_{-1}\,[\mathbf{I}]$$

Both terms must be included because **A** is being formed by the reverse reaction, as well as being used up by the forward reaction. This equation is of very little help as it stands since the concentration of the intermediate cannot be measured. However, the combined rate law for the formation and disappearance of **I** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1\,[\mathbf{A}][\mathbf{B}] - k_{-1}\,[\mathbf{I}] - k_2\,[\mathbf{I}][\mathbf{B}]$$

This equation is of little help unless the assumption is made that *the concentration of I does not change with time*, since it is an intermediate that is used up (going either to $\mathbf{A} + \mathbf{B}$ or to **C**) as fast as it is formed. This assumption, called the assumption of the *steady state*,[54] enables $d[\mathbf{I}]/dt$ to be set equal to zero, and hence to solve for [**I**] in terms of the measurable quantities [**A**] and [**B**]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

Inserting this value for [**I**] into the original rate expression gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

[54] For a discussion, see Raines, R.T.; Hansen, D.E. *J. Chem. Educ.* ***1988***, *65*, 757.

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

this gives

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [**I**] gives

$$k_{-1} \gg k_2[\mathbf{B}]$$

Neglecting $k_2[\mathbf{B}]$ in comparison with k_{-1} gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in **A** and second order in **B**. Incidentally, if the first step is rate determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \qquad \text{and} \qquad \frac{-d[\mathbf{A}]}{dt} = k_1\,[\mathbf{A}][\mathbf{B}]$$

which is the same rate law deduced from the rule that where the first step is rate determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve **A** and **B** in the rate-determining step, although only [**A**] appears in the rate law. This occurs when a large excess of **B** is present, say 100 times the molar quantity of **A**. In this case, the complete reaction of **A** uses up only 1 equiv of **B**, leaving 99 equiv. It is not easy to measure the change in concentration of **B** with time in such a case, and it is seldom attempted, especially when **B** is also the solvent. Since [**B**], for practical purposes, does not change with time, the reaction appears to be first order in **A** although actually both **A** and **B** are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or ^-OH is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.[55] The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are the following:

1. *Periodic or Continuous Spectral Readings.* In many cases, the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that

[55] See Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***. See Batt, L. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 1–111.

the instrument be read, periodically or continuously. Among the methods used are IR and UV spectroscopy, polarimetry, NMR, and ESR.[56]

2. *Quenching and Analyzing*. A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.
3. *Removal of Aliquots at Intervals*. Each aliquot is then analyzed as in method 2.
4. *Measurement of Changes in Total Pressure, for Gas-Phase Reactions.*[57]
5. *Calorimetric Methods*. The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.[58]

A graph is usually obtained that shows the change in concentration with time. Interpretation[59] is required to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, for a concentration at the start $= A_0$, the first-order rate law

$$\frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}] \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]} = k\,dt$$

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln\frac{[\mathbf{A}]}{\mathbf{A}_o} = kt \qquad \text{or} \qquad \ln[\mathbf{A}] = -kt + \ln\mathbf{A}_o$$

Therefore, if a plot of ln [**A**] against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions, it is customary to express the rate not only by the rate constant k, but also by the *half-life*, which is the time required for one-half of any given quantity of a reactant to be used up. Since the half-life $t\frac{1}{2}$ is the time required for [**A**] to reach $\mathbf{A}_o/2$,:

$$\ln\frac{\mathbf{A}_o}{2} = kt_{1/2} + \ln\mathbf{A}_o$$

[56] For a review of ESR to measure kinetics, see Norman, R.O.C. *Chem. Soc. Rev.* ***1979***, *8*, 1.

[57] See le Noble, W.J. *Prog. Phys. Org. Chem.* ***1967***, *5*, 207; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[58] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 133–186; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***, pp. 247–327; Krüger, H. *Chem. Soc. Rev.* ***1982***, *11*, 227; Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***. See also, Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol.24, Elsevier, NY, ***1983***.

[59] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 17–131; Ritchie, C.D. *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, ***1990***, pp. 1–35; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***; Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 343–421; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 12–82; in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Bunnett, J.F. pp. 251–372, Noyes Pub., pp. 373–423, Bernasconi, C.F. pp. 425–485, Wiberg, K.B. pp. 981–1019.

so that

$$t_{1/2} = \frac{\ln\left[\frac{\mathbf{A}_o}{\mathbf{A}_o/2}\right]}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in **A** and first order in **B**, second order overall, integration is complicated, but it can be simplified if equimolar amounts of **A** and **B** are used, so that $\mathbf{A}_o = \mathbf{B}_o$. In this case,

$$\frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}][\mathbf{B}]$$

is equivalent to

$$\frac{-d[\mathbf{A}]}{dt} = k\,[\mathbf{A}]^2 \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]^2} = k\,dt$$

Integrating as before gives

$$\frac{1}{[\mathbf{A}]} - \frac{1}{\mathbf{A}_o} = kt$$

Thus, under equimolar conditions, if a plot of $1/[\mathbf{A}]$ against t is linear, the reaction is second order with a slope of k. It is obvious that the same will hold true for a reaction second order in **A**.[60]

Although many reaction-rate studies do give linear plots, which are easily interpreted, the results in many other studies are not so simple. In some cases, a reaction may be first order at low concentrations but second order at higher concentrations. In other cases, fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetic data are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining sufficiently precise measurements.[61]

Nuclear magnetic resonance spectra can be used to obtain kinetic information in a completely different manner from that mentioned above. This method, which involves the study of NMR line shapes,[62] depends on the fact that NMR spectra have an inherent time factor: If a proton changes its environment less rapidly than $\sim 10^3$ times s^{-1}, an NMR spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the C—N bond of N,N-dimethylacetamide is slower than 10^3 rotations per second, the two N-methyl groups appear as a separate signal with different chemical shifts indicating that they are not equivalent, one being cis to the oxygen and the other trans to the acyl methyl group. However, if the environmental change takes place more rapidly than $\sim 10^3$ times per second, only one signal is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more signals

[60] See Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, p. 361.

[61] See Hammett, L.P. *Physical Organic Chemistry,* 2nd ed., McGraw-Hill, NY, ***1970***, pp. 62–70.

[62] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**; Fraenkel, G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. Techniques of Chemistry), pt. 2, Wiley, NY, **1986**, pp. 547–604; Roberts, J.D. *Pure Appl. Chem.* **1979**, 51, 1037; Binsch, G. *Top. Stereochem.* **1968**, 3, 97.

are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes, but can also be used for other atoms that give NMR and ESR spectra (Sec. 5.C.i).

Several types of mechanistic information can be obtained from kinetic studies.

1. Information can be obtained from the order of a reaction. Which molecules and how many take part in the rate-determining step may be determined. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed in the beginning of this section. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. It is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can relate the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent,[63] the ionic strength, the addition of catalysts, and so on.
3. If the rate is measured at several temperatures, in most cases a plot of ln k against l/T (T stands for absolute temperature) is nearly linear[64] with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A is a constant called the *frequency factor*. This permits the calculation of E_a, which is the *Arrhenius activation energy* of the reaction. Now $\Delta H^{\ddagger}$ can then be obtained by

$$E_a = \Delta H^{\ddagger} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ddagger}$ by the formula[65]

$$\frac{\Delta S^{\ddagger}}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

for energies in calorie units. For joule units, the formula is

$$\frac{\Delta S^{\ddagger}}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains $\Delta G^{\ddagger}$ from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

[63] For a discussion of organic reaction rate acceleration by immediate solvent evaporation, see Orita, A.; Uehara, G.; Miwa, K.; Otera, J. *Chem. Commun.* ***2006***, 4729.

[64] See Blandamer, M.J.; Burgess, J.; Robertson, R.E.; Scott, J.M.W. *Chem. Rev.* ***1982***, *82*, 259.

[65] See Bunnett, J.F. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, p. 287.

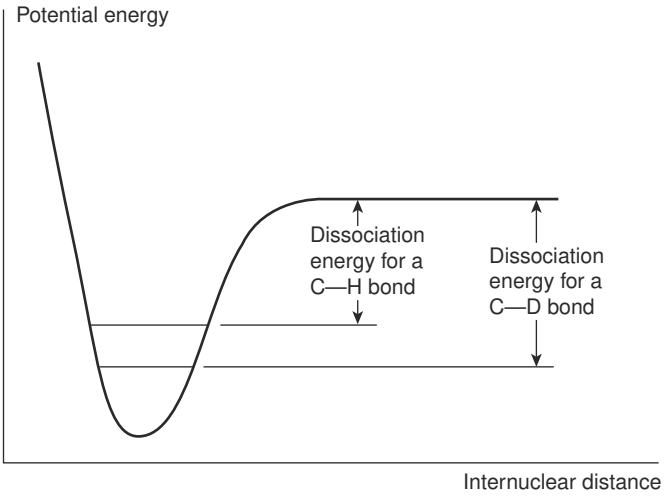


FIG. 6.4. A C—D bond has a lower zero point than a corresponding C—H bond; thus the dissociation energy is higher.

6.J.vii. Isotope Effects

When a hydrogen atom in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*[66] and are expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[67] Therefore, D—C, D—O, D—N bonds, and so on, have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, and so on. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Fig. 6.4). If a H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (Reaction **12-4**) the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior to

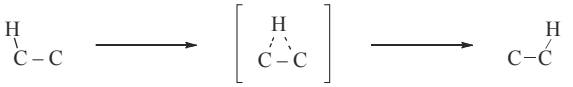
[66] See Melander, L.; Saunders, Jr., W.H. *Reaction Rates of Isotopic Molecules*, Wiley, NY, ***1980***. For reviews, see Isaacs, N.S. *Physical Organic Chemistry*, Longman Scientific and Technical, Essex, ***1987***, pp. 255–281; Lewis, E.S. *Top. Curr. Chem.* ***1978***, *74*, 31; Saunders, Jr., W.H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 565–611; Bell, R.P. *Chem. Soc. Rev.* ***1974***, *3*, 513; Bigeleisen, J.; Lee, M.W.; Mandel, F. *Annu. Rev. Phys. Chem.* ***1973***, *24*, 407; Wolfsberg, M. *Annu. Rev. Phys. Chem.* ***1969***, *20*, 449. Also see Kwart, H. *Acc. Chem. Res.* ***1982***, *15*, 401; Isaacs, E.S. *Isot. Org. Chem.* ***1984***, *6*, 67; Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* ***1989***, *18*, 209. See also, the series *Isotopes in Organic Chemistry*.

[67] The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1m_2/(m_1 + m_2)$.

tautomerization of the acetone:



In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see Reaction **12-3**). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, k_H/k_D was found to be ~ 7.[68] Deuterium isotope effects usually range from 1 (no isotope effect at all) to ~ 7 or 8, although in a few cases, larger[69] or smaller values have been reported.[70] Values of $k_H/k_D < 1$ are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[71] Also, calculations show that isotope effects are at a maximum when the hydrogen atom in the transition state is on the straight line connecting the two atoms between which it is being transferred, and that for sufficiently nonlinear configurations, they decrease to $k_H/k_D = 1$–2.[72] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, (e.g., in a 1,2-migration of a hydrogen)



Transition state

To measure isotope effects, it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high field NMR instrument.[73]

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, ~ 1.02–1.10. For example, k_{12C}/k_{13C} for the reaction of methoxide with benzyl bromide is 1.053.[74] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.[75]



[68] Reitz, O.; Kopp, J. *Z. Phys. Chem. Abt. A* ***1939***, *184*, 429.

[69] For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis, E.S.; Funderburk, L.H. *J. Am. Chem. Soc.* ***1967***, *89*, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: See Lewis, E.S.; Robinson, J.K. *J. Am. Chem. Soc.* ***1968***, *90*, 4337; Kresge, A.J.; Powell, M.F. *J. Am. Chem. Soc.* ***1981***, *103*, 201; Caldin, E.F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* ***1981***, *103*, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see Thibblin, A. *J. Phys. Org. Chem.* ***1988***, *1*, 161; Kresge, A.J.; Powell, M.F. *J. Phys. Org. Chem.* ***1990***, *3*, 55.

[70] See Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[71] Bethell, D.; Hare, G.J.; Kearney, P.A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 684, and references cited therein. See, however, Motell, E.L.; Boone, A.W.; Fink, W.H. *Tetrahedron* ***1978***, *34*, 1619.

[72] More O'Ferrall, R.A. *J. Chem. Soc. B* ***1970***, 785, and references cited therein.

[73] Pascal, R.A.; Baum, M.W.; Wagner, C.K.; Rodgers, L.R.; Huang, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6477.

[74] Stothers, J.B.; Bourns, A.N. *Can. J. Chem.* ***1962***, *40*, 2007. See also, Ando, T.; Yamataka, H.; Tamura, S.; Hanafusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 5493.

[75] For a review of carbon isotope effects, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 237.

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[76] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of 2-bromopropane to 2-propanol,where k_H/k_D was found to be 1.34.[77] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.[78] Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation (Sec. 2.M) involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

$$(CH_3)_2CHBr + H_2O \xrightarrow{k_H} (CH_3)_2CHOH$$
$$(CD_3)_2CHBr + H_2O \xrightarrow{k_D} (CD_3)_2CHOH$$

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group[79] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[80] There is evidence that at least some β isotope effects are steric in origin[81] (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3[82]), but hyperconjugation is the most probable cause in most instances.[83] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as ~ 1.5.[84] Another complicating factor is that they can change with temperature. In one case,[85] k_H/k_D was 1.00 ± 0.01 at 0 °C, 0.90 ± 0.01 at 25 °C, and 1.15 ± 0.09 at 65 °C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state. They are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These so-called *secondary isotope*

[76] See Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275; Sunko, D.E.; Hehre, W.J. *Prog. Phys. Org. Chem.* ***1983***, *14*, 205; Halevi, E.A. *Prog. Phys. Org. Chem.* ***1963***, *1*, 109. See McLennan, D.J. *Isot. Org. Chem.* ***1987***, *7*, 393. See also, Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[77] Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *Can. J. Chem.* ***1960***, *38*, 2171.

[78] Bender, M.L.; Feng, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 6318; Jones, J.M.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 6322.

[79] DeFrees, D.J.; Hehre, W.J.; Sunko, D.E. *J. Am. Chem. Soc.* ***1979***, *101*, 2323. See also, Siehl, H.; Walter, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 76.

[80] Shiner, Jr., V.J.; Kriz, Jr., G.S. *J. Am. Chem. Soc.* ***1964***, *86*, 2643.

[81] Carter, R.E.; Dahlgren, L. *Acta Chem. Scand.* ***1970***, *24*, 633; Leffek, K.T.; Matheson, A.F. *Can. J. Chem.* ***1971***, *49*, 439; Sherrod, S.A.; Boekelheide, V. *J. Am. Chem. Soc.* ***1972***, *94*, 5513.

[82] Halevi, E.A.; Nussim, M.; Ron, M. *J. Chem. Soc.* ***1963***, 866; Halevi, E.A.; Nussim, M. *J. Chem. Soc.* ***1963***, 876.

[83] Sunko, D.E.; Szele, I.; Hehre, W.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5000; Kluger, R.; Brandl, M. *J. Org. Chem.* ***1986***, *51*, 3964.

[84] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174. A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu, K.; Wu, Y.W. *Tetrahedron Lett.* ***1986***, *27*, 3623.

[85] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174.

effects are varied, with values so far reported[86] ranging from 0.87 to 1.26.[87] These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have an isotope effect near unity.[88] Those that do involve carbocations (S_N1 reactions) have higher isotope effects, which depend on the nature of the leaving group.[89] The accepted explanation for a isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[90] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. The α isotope effects on S_N2 reactions can vary with concentration,[91] an effect attributed to a change from a free nucleophile to one that is part of an ion pair[92] (see Sec. 10.G.ii). This illustrates the use of secondary isotope effects as a means of studying transition state structure. The γ secondary isotope effects have also been reported.[93]

Another kind of isotope effect is the *solvent isotope effect*.[94] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent–solute interactions may be different in the deuterated and non-deuterated solvents; this may change the energies of the transition state, and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[95]

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[96]

The methods described in this chapter are not the only means of determining mechanisms. A detailed examination of the literature, coupled with well-planned experiments is the best way to devise an approach to the mechanism of a given reaction.

[86] See Caldwell, R.A.; Misawa, H.; Healy, E.F.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6869.
[87] See Harris, J.M.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 2551.
[88] For reported exceptions, see Tanaka, N.; Kaji, A.; Hayami, J. *Chem. Lett.* ***1972***, 1223; Westaway, K.C. *Tetrahedron Lett.* ***1975***, 4229.
[89] Shiner, Jr., V.J.; Neumann, A.; Fisher, R.D. *J. Am. Chem. Soc.* ***1982***, *104*, 354 and references cited therein.
[90] Streitwieser, Jr., A.; Jagow, R.H.; Fahey, R.C.; Suzuki, S. *J. Am. Chem. Soc.* ***1958***, *80*, 2326.
[91] Westaway, K.C.; Waszczylo, Z.; Smith, P.J.; Rangappa, K.S. *Tetrahedron Lett.* ***1985***, *26*, 25.
[92] Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1988***, *66*, 1263.
[93] Werstiuk, N.H.; Timmins, G.; Cappelli, F.P. *Can. J. Chem.* ***1980***, *58*, 1738.
[94] See Alvarez, F.J.; Schowen, R.L. *Isot. Org. Chem.* ***1987***, *7*, 1; Kresge, A.J.; More O'Ferrall, R.A.; Powell, M.F. *Isot. Org. Chem.* ***1987***, *7*, 177; Schowen, R.L. *Prog. Phys. Org. Chem.* ***1972***, *9*, 275;. See Arnett, E.M.; McKelvey, D.R. in Coetzee, J.F.; Ritchie, C.D. cited above, pp. 343–398.
[95] Bunton, C.A.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1961***, *83*, 42, 3207, 3214; Swain, C.G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3884, 3890. See also, Mitton, C.G.; Gresser, M.; Schowen, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2045.
[96] More O'Ferrall, R.A.; Koeppl, G.W.; Kresge, A.J. *J. Am. Chem. Soc.* ***1971***, *93*, 9.

CHAPTER 7

Irradiation Processes in Organic Chemistry

Most reactions carried out in organic chemistry laboratories take place between molecules, all of which are in their ground electronic states. In a *photochemical reaction*,[1] however, a reacting molecule has been previously promoted to an electronically excited state by absorption of light. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited state for long. The subject of electronic spectra is closely related to photochemistry. A chemical reaction is not the only possible means of relinquishing the extra energy in a photochemical process. In this chapter, electronically excited states and the processes of promotion to these states will be discussed. Reactions of such molecules are called photoreactions. There are enantioselective organocatalytic photoreactions, but they will not be discussed here.[2] Two other methods are available to facilitate chemical reactions: sonochemistry and microwave chemistry. Although the physical processes involved are not the same excitation processes observed in photochemistry, irradiation with ultrasound or with microwaves have a significant influence on chemical reactivity, and both are widely used. For that reason, they are included in this chapter.

7.A. PHOTOCHEMISTRY[3]

7.A.i. Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied. In a photochemical

[1] See Michl, J.; Bonač ić-Koutecky, V. *Electronic Aspects of Organic Photochemistry,* Wiley, NY, ***1990***; Scaiano, J.C. *Handbook of Organic Photochemistry*, 2 vols., CRC Press, Boca Raton, FL, ***1989***; Coxon, J.M.; Halton, B. *Organic Photochemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1987***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, *Introduction to Organic Photochemistry*, Wiley, NY, ***1986***; Horspool, W.M. *Synthetic Organic Photochemistry,* Plenum, NY, ***1984***; Margaretha, P. *Preparative Organic Photochemistry*, *Top. Curr. Chem.* ***1982***, *103*; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***; Rohatgi-Mukherjee. K.K. *Fundamentals of Photochemistry,* Wiley, NY, ***1978***; Barltrop, J.A.; Coyle, J.D. *Principles of Photochemistry*, Wiley, NY, ***1978***; Scaiano, J.; Johnston, L.J. *Org. Photochem.* ***1989***, *10,* 309. For a history of photochemistry, see Roth, H.D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1193; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055. See also, the series, *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States.*

[2] Wessig, P. *Angew. Chem. Int. Ed.* ***2006***, *45,* 2168.

[3] Zimmerman, H.E. *Pure Appl. Chem.* ***2006***, *78,* 2193.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

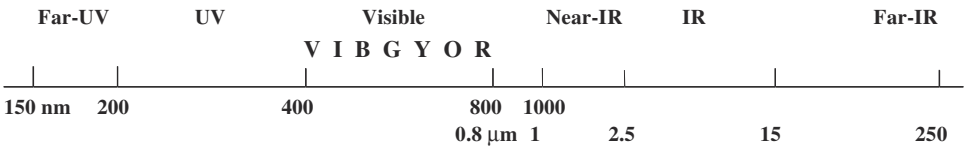


FIG. 7.1. The UV, vis, and IR portions of the electromagnetic spectrum.

process, this energy is in the form of light. Light of any wavelength has an energy value associated with it given by $E = h\nu$, where n is the frequency of the light (n = velocity of light c divided by the wavelength λ), and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed into a sample, molecules will use that energy for electron promotion, and the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, that is, not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the vis, UV, and far-UV regions of the spectrum (Fig. 7.1). Absorption positions are normally expressed in wavelength units, usually nanometers (nm).[4] If a compound absorbs in the visible, it is colored, possessing a color complementary to that absorbed.[5] Thus a compound absorbing in the violet has a yellow color. Organic chemists study the far-UV region less often than the vis or ordinary UV regions because special vacuum instruments are required, owing to the fact that oxygen and nitrogen absorb in these regions.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not only in a given electronic state, but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Fig. 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed

[4] Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.

[5] For monographs, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***; Griffiths, J. *Colour and Constitution of Organic Molecules*, Academic Press, NY, ***1976***. See also, Fabian, J.; Zahradník, R. *Angew. Chem. Int. Ed.* ***1989***, *28*, 677.

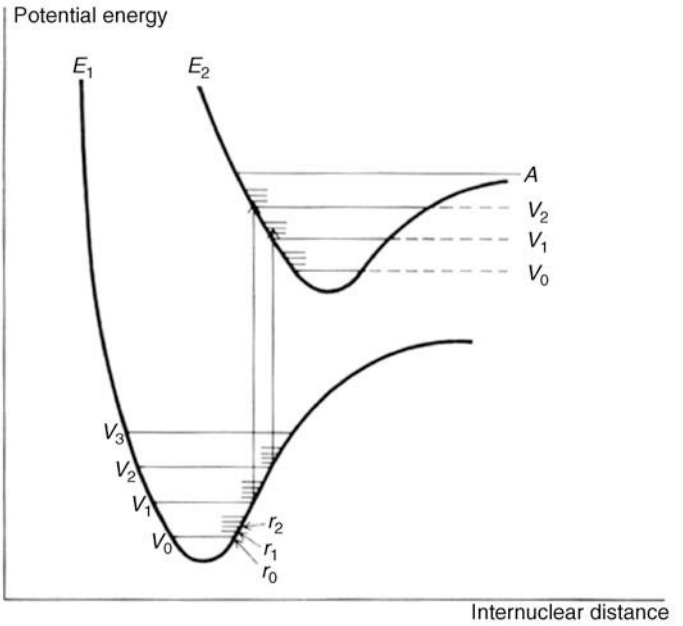


FIG. 7.2. Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked *A*, the molecule may cleave (Sec. 7.A.v).

among the vibrational and rotational states (though the ground vibrational state, V_o, is most heavily populated). This means that not just one wavelength of light will be absorbed, but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms, there are so many possible transitions, and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient*. The extinction coefficient can be expressed by $\varepsilon = E/cl$, where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_o/I$, where I_o is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{max}, meaning that this is the top of the peak. Purely vibrational transitions (e.g., between V_o and V_1 of E_1), which require much less energy, are found in the IR region and are the basis of IR spectra. Purely rotational transitions are found in the far-IR and microwave (beyond the far-IR) regions.

A UV or vis absorption peak is caused by the promotion of an electron in one orbital (usually ground-state) to a higher orbital. Normally, the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group (e.g., the C=C double bond) always causes absorption in the same general area. A group that causes absorption is called a *chromophore*.

7.A.ii. Singlet and Triplet States: "Forbidden" Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin, as demanded by the *Pauli principle*. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an

orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As seen in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*,[6] while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet, which is in accord with *Hund's rule*. Therefore, a different amount of energy, and hence a different wavelength, is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are "forbidden". There are several types of "forbidden" transitions, two of which are more important than the others.

1. *Spin-Forbidden Transitions*. If the spin of an electron changes, transitions are not allowed, because a change from one spin to the opposite involves a change in angular momentum. Such a change would violate the law of conservation of angular momentum. Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.
2. *Symmetry-Forbidden Transitions*. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or $u \rightarrow u$ transition (see Sec. 1.A.) is "forbidden", while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

The word "forbidden" is in quotation marks because these transitions are not actually forbidden, but only highly improbable. In most cases, promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (e.g., iodine) is present in the molecule, in which cases it can be shown from spectra that singlet–triplet promotions are occurring.[7] Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

7.A.iii. Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules, there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no *n* or π electrons, can be excited only in this way.[8]
2. $n \rightarrow \sigma^*$. Alcohols, amines,[9] ethers, and so on can also be excited in this manner.

[6] See Kurreck, H. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1409.
[7] See Koziar, J.C.; Cowan, D.O. *Acc. Chem. Res.* ***1978***, *11*, 334.
[8] An *n* electron is one in an unshared pair.
[9] See Malkin, Yu.N.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1985***, *54*, 1041.

TABLE 7.1 Ultraviolet Absorption[10] of $CH_3-(CH=CH)_n-CH_3$ for Some Values of *n*

n	nm
2	227
3	263
6	352
9	413

3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, and so on.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, and so on can undergo this promotion, as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far-UV) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary UV light. However, the order may sometimes be altered in some solvents.

In 1,3-butadiene (and other compounds with two conjugated double bonds), there are two π and two π^* orbitals (Sec. 2.C). The energy difference between the higher π (χ_2) and the lower π^* (χ_3) orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule*, *the more the absorption is displaced toward higher wavelengths* (see Table 7.1).[10] When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the UV.

As seen above, a *chromophore* is a group that causes a molecule to absorb light. Examples of chromophores in the vis or UV are C=O, N=N,[11] Ph, and NO_2. Some chromophores in the far-UV (beyond 200 nm) are C=C, C≡C, Cl, and OH. An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups (e.g., Cl, OH, and NH_2) are generally regarded as auxochromes since they shift (usually bathochromically) the UV and vis bands of chromophores (e.g., Ph or C=O; see Table 7.2).[12] Since auxochromes are themselves chromophores (to be sure, generally in the far-UV), it is sometimes difficult to decide which group in a molecule is an auxochrome and which is a chromophore. For

[10] Bohlmann, F.; Mannhardt, H. *Chem. Ber.* ***1956***, *89*, 1307.
[11] For a review of the azo group as a chromophore, see Rau, H. *Angew. Chem. Int. Ed.* **1973**, *12*, 224.
[12] These values are from Silverstein, R.M.; Bassler, G.C. Spectrometric Identification of Organic Compounds, 2nd ed., John Wiley, NY, ***1967***, pp. 164–165. Also see Jaffé, H.H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, NY, ***1962***, p. 257.

TABLE 7.2 Some UV Peaks of Substituted Benzenes[a]

	Primary Band		Secondary Band	
	λ_{max} (nm)	ε_{max}	λ_{max} (nm)	ε_{max}
PhH (hexane)[b]	204	7,900	256	200
PhCl	210	7,600	265	240
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	10,000	270	800
$PhNH_2$	230	8600	280	1,430
PhO^-	235	9,400	287	2,600
PhAc	240	13,000	278	1,100
PhCHO	244	15,000	280	1,500
$PhNO_2$	252	10,000	280	1,000

[a]Note how auxochromes shift and usually intensify the peaks. See Ref. 12.

[b]The solvent is in parentheses.

[Reprinted with permission from Silverstein, R.M.; Bassler, G.C. Spectrometric Identification of Organic Compounds, 2nd ed., John Wiley, NY, ***1967***, pp. 164–165, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***1967*** by Wiley–VCH Verlag]

example, in acetophenone (PhCOMe) is the chromophore Ph or C=O? In such cases, the distinction becomes practically meaningless.

7.A.iv. Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that some method of naming excited states is required. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy, or MO theory.[13] One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi, \pi^*)$ state or the π,$\pi*$ singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest-energy excited state is called S_1, the next is S_2, and so on. Triplet states are similarly labeled T_1, T_2, T_3, and so on. In this notation, the ground state is S_o. Other notational systems exist, but this text shall discuss only the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment, and acid or base strength.[14]

[13] See Pitts, Jr., J.N.; Wilkinson, F.; Hammond, G.S. *Adv. Photochem.* ***1963***, *1*, 1; Porter, G.B.; Balzani, V.; Moggi, L. *Adv. Photochem.* ***1974***, *9*, 147; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055.

[14] For reviews of the structures of excited states, see Zink, J.I.; Shin, K.K. *Adv. Photochem.* ***1991***, *16*, 119; Innes, K.K. *Excited States* ***1975***, *2*, 1; Hirakawa, A.Y.; Masamichi, T. *Vib. Spectra Struct.* ***1983***, *12*, 145.

TABLE 7.3 Typical Energies for Some Covalent Single Bonds[a] and the Corresponding Approximate Wavelengths

	E		
Bond	kcal mol^{-1}	kJ mol^{-1}	nm
C—H	95	397	300
C—O	88	368	325
C—C	83	347	345
Cl—Cl	58	243	495
C—O	35	146	820

[Reprinted with permission from Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* ***1960****, 38*, 2367. Copyright © 1960, with permission from Canadian Science Publishing or its Licensors.]

[a]See Table 1.7.

For example, acetylene, which is linear in the ground state, has a trans geometry in the excited state with $\sim sp^2$ carbons in the $^1(\pi,\pi^*)$ state.[15] Similarly, the $^1(\pi,\pi^*)$ and the $^3(\pi,\pi^*)$ states of ethylene have a perpendicular and not a planar geometry,[16] and the $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states of formaldehyde are both pyramidal.[17] Triplet species tend to stabilize themselves by distortion, which relieves interaction between the unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.[18] For example, the S_1 state of 2-naphthol is a much stronger acid ($pK = 3.1$) than the ground state (S_0) of the same molecule ($pK = 9.5$).[19]

7.A.v. Photolytic Cleavage

As stated above, when a molecule absorbs a quantum of light it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of vis and UV light is of the same order of magnitude as that of covalent bonds (Table 7.3), another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line *A* in Fig. 7.2). In such a case, the excited molecule cleaves at its first vibration.
2. Even where the promotion is to a lower vibrational level, one that lies wholly within the E_2 curve (e.g., V_1 or V_2), the molecule may still cleave. As shown in Fig. 7.2, equilibrium distances are greater in excited states than in the ground state. The

[15] Ingold, C.K.; King, G.W. *J. Chem. Soc.* ***1953***, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle, J.D. *Org. Photochem.* ***1985***, *7*, 1.
[16] Merer, A.J.; Mulliken, R.S. *Chem. Rev.* ***1969***, *69*, 639.
[17] Garrison, B.J.; Schaefer III, H.F.; Lester Jr., W.A. *J. Chem. Phys.* ***1974***, *61*, 3039; Streitwieser Jr., A.; Kohler, B. *J. Am. Chem. Soc.* ***1988***, *110*, 3769. For reviews of excited states of formaldehyde, see Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 193, 225; Moule, D.C.; Walsh, A.D. *Chem. Rev.* ***1975***, *75*, 67.
[18] See Ireland, J.F.; Wyatt, P.A.H. *Adv. Phys. Org. Chem.* ***1976***, *12*, 131.
[19] Weller, A. *Z. Phys. Chem. (Frankfurt am Main)* ***1955***, 3, 238, *Discuss. Faraday Soc.* ***1959***, *27*, 28.

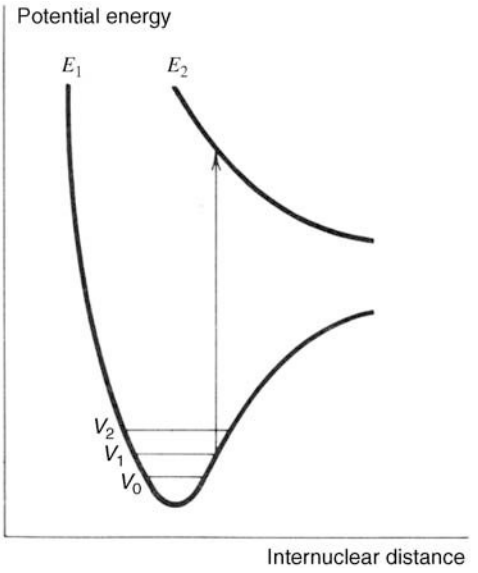


FIG. 7.3. Promotion to a dissociative state results in bond cleavage.

Franck–Condon principle states that promotion of an electron takes place much faster than a single vibration (the promotion takes $\sim 10^{-15}$ s; a vibration $\sim 10^{-12}$ s). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

3. In some cases, the excited state is entirely dissociative (Fig. 7.3); that is, there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma^*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (see Sec. 7.A.vii). Cleavage into two ions, though known, is rare. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chap 5) except that they may be in excited states, and this can cause differences in behavior.[20]

7.A.vi. The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain in the excited state for long. Most promotions are from the S_0 to the S_1 state. As seen previously, promotions from S_o to triplet states are "forbidden". Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state ($\sim 10^{-13}$ to $\sim 10^{-11}$ s). The energy lost when an S_2 or S_3

[20] Lubitz, W.; Lendzian, F.; Bittl, R. *Acc. Chem. Res.* ***2002****, 35*, 313.

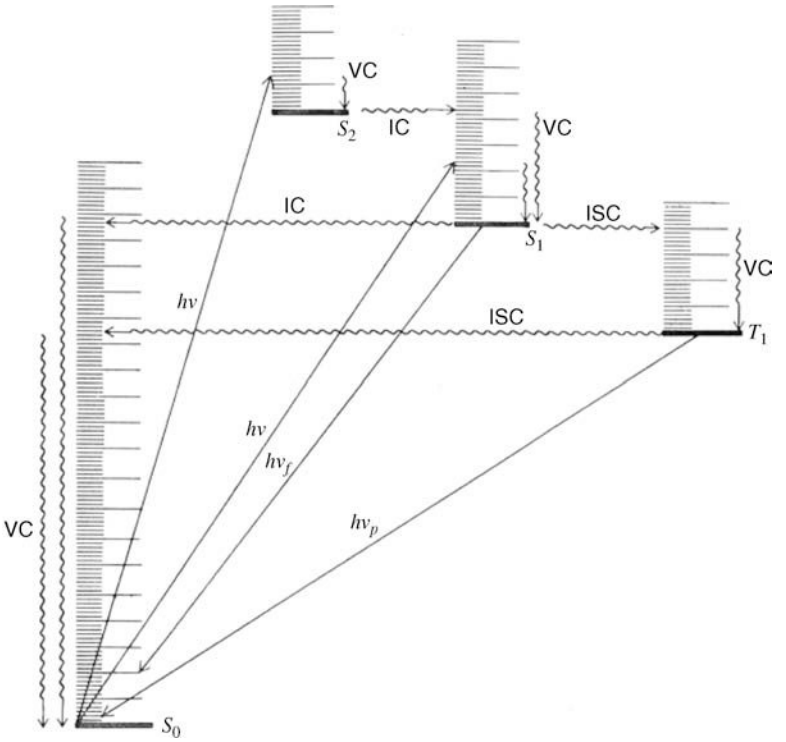


FIG. 7.4. Modified Jablonski diagram showing transitions between the excited and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1, but these also cascade, down to the lowest vibrational level of S_1. Therefore, in most cases, the lowest vibrational level of the S_1 state is the only important excited singlet state.[21] This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified *Jablonski diagram* (Fig. 7.4) and in Table 7.4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment. This process is generally quite slow because the amount of energy is large and is called *internal conversion* (IC, see Fig. 7.4). Because it is slow, most molecules in the S_1 state adopt other pathways.[22]

[21] See Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125.
[22] See Lin, S.H. *Radiationless Transitions*, Academic Press, NY, ***1980***. For reviews, see Kommandeur, J. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 421; Freed, K.F. *Acc. Chem. Res.* ***1978***, *11*, 74.

TABLE 7.4 Physical Processes Undergone by Excited Molecules[a]

$S_o + h\nu \rightarrow S_1^v$	Excitation
$S_1^v \rightsquigarrow S_1 + \Delta$	Vibrational relaxation
$S_1 \rightarrow S_1 + h\nu$	Fluorescence
$S_1 \rightsquigarrow S_o + \Delta$	Internal conversion
$S_1 \rightsquigarrow T_1^v$	Intersystem crossing
$T_1^v \rightsquigarrow T_1 + \Delta$	Vibrational relaxation
$T_1 \rightarrow S_o + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_o + \Delta$	Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_o + A_{(S_1)}$	Singlet–singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_o + A_{(T_1)}$	Triplet–triplet transfer (photosensitization)

[a]The superscript v indicates vibrationally excited state: excited states higher than S_1 or T_1 are omitted.

2. A molecule in the S_1 state can drop to some low vibrational level of the S_o state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} s, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules (e.g., diatomic) and rigid molecules (e.g., aromatic). For most other compounds, fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_0, while excitation is from the lowest vibrational level of S_o to various levels of S_1 (Fig. 7.5). The only peak in common is the one that results from transitions between the lowest vibrational levels of the two states (called the 0–0 peak). In solution, even the 0–0 peak may be noncoincidental because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_o$ transition, although azulene (Sec. 2.I.iii) and its simple derivatives are exceptions,[23] emitting fluorescence from $S_2 \rightarrow S_o$ transitions.

   Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

3. Most molecules (but by no means all) in the S_1 state can undergo an *intersystem crossing* (ISC, see Fig. 7.4) to the lowest triplet state T_1.[24] An important example is benzophenone, of which 100% of the molecules that are excited to the S_1 state cross over to the T_1.[25] Intersystem crossing from singlet to triplet is of course a "forbidden" pathway, since the angular-momentum problem (Sec. 7.A.ii) must

[23] For other exceptions, see Sugihara, Y.; Wakabayashi, S.; Murata, I.; Jinguji, M.; Nakazawa, T.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1985***, *107*, 5894, and references cited therein. See also, Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125, see pp. 126–129.

[24] Also see Li, R.; Lim, E.C. *Chem. Phys.* ***1972***, *57*, 605; Sharf, B.; Silbey, R. *Chem. Phys. Lett.* ***1970***, *5*, 314; Schlag, E.W.; Schneider, S.; Fischer, S.F. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 465, pp. 490. There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta, A. *J. Am. Chem. Soc.* ***1991***, *113*, 7427; Ohsaku, M.; Koga, N.; Morokuma, K. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 71.

[25] Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789.

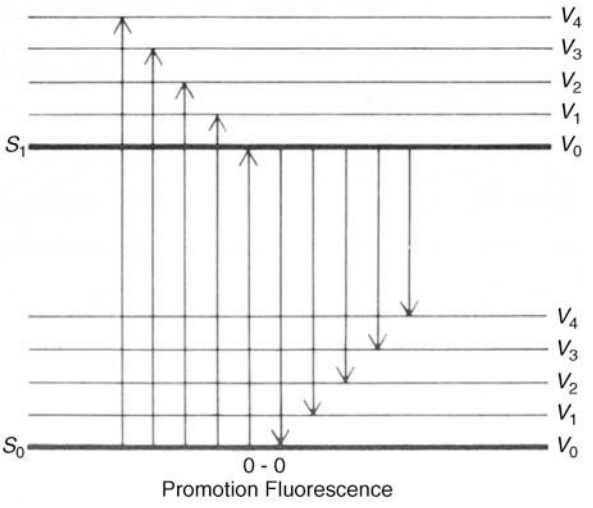


FIG. 7.5. Promotion and fluorescence between S_1 and S_0 states.

be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Fig. 7.4). This cascade is very rapid (10^{-12} s). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.

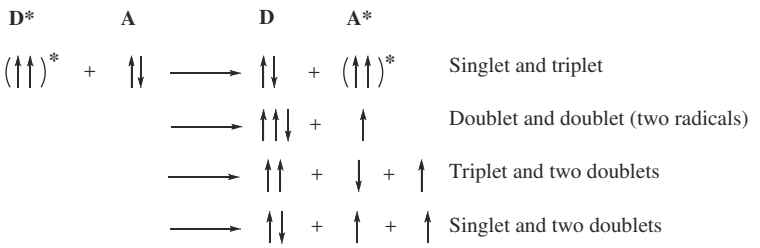
4. A molecule in the T_1 state may return to the S_o state by giving up heat (ISC) or light (this is called *phosphorescence*).[26] Of course, the angular momentum difficulty exists here, so that both ISC and phosphorescence are very slow ($\sim 10^{-3}$–10^{1} s). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence (because of the higher difference in energy between S_1 and S_o than between T_1 and S_o) and is longer-lived (because of the longer lifetime of the T_1 state).
5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.[27] The excited molecule, which we will call D for donor, thus drops to S_o while the other molecule (A for acceptor) becomes excited:

$$D^* + A \longrightarrow A^* + D$$

[26] See Lower, S.K.; El-Sayed, M.A. *Chem. Rev.* ***1966***, *66*, 199. For a review of physical and chemical processes of triplet states see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21.
[27] See Albini, A. *Synthesis*, ***1981***, 249; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1. Ionic liquids may be soluble photosensitizers. See Hubbard, S.C.; Jones, P.B. *Tetrahedron* ***2005***, *61,* 7425.

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light or by transfer from a previously excited molecule.[28] The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:[29]

In all these cases, the products have three electrons spinning "up" and the fourth "down" (as do the starting molecules). However, formation of, say, two triplets ($\uparrow\downarrow + \downarrow\downarrow$) or two singlets ($\uparrow\downarrow + \uparrow\downarrow$), whether ground states or excited, would violate the rule.



In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:

$$D_{T_1} + A_{S_O} \longrightarrow A_{T_1} + D_{S_O} \qquad \text{Triplet–triplet transfer}$$

$$D_{S_1} + A_{S_O} \longrightarrow A_{S_1} + D_{S_O} \qquad \text{Singlet–triplet transfer}$$

Singlet–singlet transfer can take place over relatively long distances (e.g., 40 Å), but triplet transfer normally requires a collision between the molecules.[30] Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet–triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.[31]

In choosing a photosensitizer,[32] one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.[33] For

[28] In certain cases excited states can be produced directly in ordinary reactions. See White, E.H.; Miano, J.D.; Watkins, C.J.; Breaux, E.J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 229.

[29] For another table of this kind, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 89.

[30] See Bennett, R.G.; Schwenker, R.P.; Kellogg, R.E. *J. Chem. Phys.* ***1964***, *41*, 3040; Ermolaev, V.L.; Sveshnikova, E.B. *Opt. Spectrosc. (USSR)* ***1964***, *16*, 320.

[31] SeeKavarno, G.J.; Turro, N.J. *Chem. Rev.* ***1986***, *86*, 401; Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

[32] For a discussion of pyrylogens as an electron-transfer sensitizer, see Clennan, E.L.; Liao, C.; Ayokosok, E. *J. Am. Chem. Soc.* ***2008***, *130,* 7552.

[33] See Engel, P.S.; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 245.

examples of the use of photosensitization to accomplish reactions, see Reactions **15-62** and **15-63**.

6. An excited species can be quenched. Quenching is the deactivation of an excited molecular entity intermolecularly by an external environmental influence (e.g., a quencher), or intramolecularly by a substituent through a nonradiative process.[34] When the external environmental influence (quencher) interferes with the behavior of the excited state after its formation, the process is referred to as dynamic quenching. Common mechanisms include energy transfer, charge transfer, and so on. When the environmental influence inhibits the excited state formation, the process is referred to as static quenching. A quencher is defined as a molecular entity that deactivates (quenches) an excited state of another molecular entity, either by energy transfer, electron transfer, or by a chemical mechanism.[34]

   An example is the rapid triplet quenching of aromatic ketone triplets[35] by amines, which is well known.[36] Alkyl and aryl thiols and thioethers also serve as quenchers in this system.[37] In this latter case, the mechanism involves electron transfer from the sulfur atom to the triplet ketone, and this is supported by theoretical calculations.[38] Aromatic ketone triplets are quenched by phenols, and the photochemical reaction between aromatic ketones and phenols is efficient only in the presence of an acid catalyst.[39] Indirect evidence has been provided for involvement of the hydrogen-bonded triplet exciplex and for the role of electron transfer in this reaction.[40]

7.A.vii. The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of $<10^{-10}$ s and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.[41] Table 7.5[42] lists many of the possible chemical pathways that can be taken by an excited molecule.[43] The first four of these are unimolecular reactions; the others are bimolecular. In

[34] Verhoeven, J.W. *Pure Appl. Chem.* ***1996****, 68,* 2223 (see p. 2268).
[35] See Samanta, S.; Mishra, B.K.; Pace, T.C.S.; Sathyamurthy, N.; Bohne, C.; Moorthy, J.N. *J. Org. Chem.* ***2006****, 71,* 4453.
[36] See Aspari, P.; Ghoneim, N.; Haselbach, E.; von Raumer, M.; Suppan, P.; Vauthey, E. *J. Chem. Soc., Faraday Trans.* ***1996****, 92,* 1689; Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973****, 73*, 141; von Raumer, M.; Suppan, P.; Haselbach, E. *Helv. Chim. Acta* ***1997****, 80,* 719.
[37] Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1982****, 104*, 1679; Bobrowski, K.; Marciniak, B.; Hug, G.L. *J. Photochem. Photobiol. A: Chem.* ***1994****, 81,* 159; Wakasa, M.; Hayashi, H. *J. Phys. Chem.* ***1996****, 100,* 15640.
[38] Marciniak, B.; Bobrowski, K.; Hug, G.L. *J. Phys. Chem.* ***1993****, 97*, 11937.
[39] Becker, H.-D. *J. Org. Chem.* ***1967****, 32*, 2115; 2124; 2140.
[40] Lathioor, E.C.; Leigh, W.J.; St. Pierre, M.J. *J. Am. Chem. Soc.* ***1999****, 121,* 11984.
[41] See Wagner, P.J.; Hammond, G.S.; Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968****, 5,* 21. For other reviews of triplet states, see *Top. Curr. Chem.* ***1975***, Vols. 54 and 55.
[42] Adapted from Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 367.
[43] For a different kind of classification of photochemical reactions, see Dauben, W.G.; Salem, L.; Turro, N.J. *Acc. Chem. Res.* ***1975***, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy, V. *Tetrahedron* ***1986***, *42*, 5753; Ramamurthy, V.; Eaton, D.F. *Acc. Chem. Res.* ***1988***, *21*, 300; Turro, N.J.; Cox, G.S.; Paczkowski, M.A. *Top. Curr. Chem.* ***1985***, *129*, 57.

TABLE 7.5 Primary Photochemical Reactions[a] of an Excited Molecule A—B—C[b]

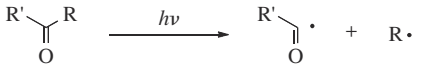
Reactions	Reaction Type	Example Number
$(A—B—C) \rightarrow A—B\bullet + C\bullet$	Simple cleavage into radicals[46]	(1)
$(A—B—C) \rightarrow E + F$	Decomposition into molecules	(2)
$(A—B—C) \rightarrow A—C—B$	Intramolecular rearrangement	(3)
$(A—B—C) \rightarrow A—B—C'$	Photoisomerization	(4)
$(A—B—C) + RH \rightarrow A—B—C—H + R\bullet$	Hydrogen-atom abstraction	(5)
$(A—B—C) \rightarrow (ABD)_2$	Photodimerization	(6)
$(A—B—C) + A \rightarrow ABX + A^*$	Photosensitization	(7)

[a]Examples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule (7).

[b]See Ref. 42.

the case of bimolecular reactions, it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases, the primary products of photochemical reactions are in their ground states, though exceptions are known.[44] Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1)–(6). Other examples are discussed in Part II.[45,46]

Category 1. Simple Cleavage into Radicals.[47] Aldehydes and ketones absorb in the 230–330-nm region. This is assumed to result from an $n \rightarrow \pi*$ singlet–singlet transition. The excited aldehyde or ketone can then cleave.[48]



[44] Turro, N.J.; Lechtken, P.; Lyons, A.; Hautala, R.T.; Carnahan, E.; Katz, T.J. *J. Am. Chem. Soc.* ***1973***, ***95***, 2035.

[45] See Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***; Schönberg, A. *Preparative Organic Photochemistry*, Springer, Berlin, ***1968***.

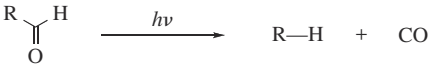
[46] See DeLuca, L.; Giacomelli, G.; Porcu, G.; Taddei, M. *Org. Lett.* ***2001***, *3*, 855.

[47] For reviews, see Jackson, W.M.; Okabe, H. *Adv. Photochem.* ***1986***, *13*, 1; Kresin, V.Z.; Lester, Jr., W.A. *Adv. Photochem.* ***1986***, *13*, 95.

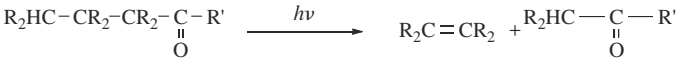
[48] See Formosinho, S.J.; Arnaut, L.G. *Adv. Photochem.* ***1991***, *16*, 67; Newton, R.F. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 39–60; Lee, E.K.C.; Lewis, R.S. *Adv. Photochem.* ***1980***, *12*, 1; Coyle, J.D.; Carless, H.A.J. *Chem. Soc. Rev.* ***1972***, *1*, 465; Bérces, T. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5; Elsevier, NY, ***1972***, pp. 277–380; Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* ***1972***, *5*, 92; Wagner, P.J. *Top. Curr. Chem.* ***1976***, *66*, 1. Also see Weiss, D.S. *Org. Photochem.* ***1981***, *5*, 347; Rubin, M.B. *Top. Curr. Chem.* ***1985***, *129*, 1; ***1969***, *13*, 251; Childs, R.F. *Rev. Chem. Intermed.* ***1980***, *3*, 285. C=S compounds, see Coyle, J.D. *Tetrahedron* ***1985***, *41*, 5393; Ramamurthy, V. *Org. Photochem.* ***1985***, *7*, 231. C=N compounds, see Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical (R′—CO•) can then lose CO to give R′• radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds (R—N=N—R).[49] The latter is an important source of radicals R•, since the other product is the very stable N_2.

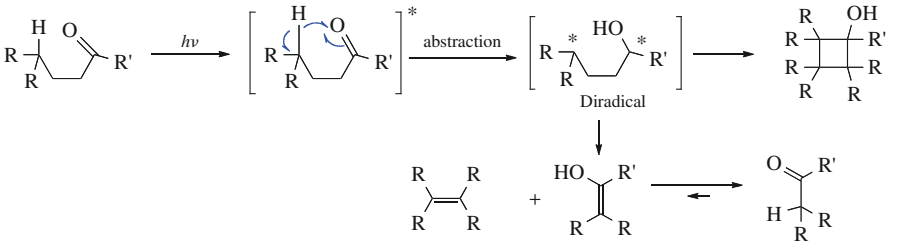
Category 2. Decomposition into Molecules. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with an γ hydrogen can cleave in still another way (a β-elimination, see Chap 17):



This reaction, called *Norrish Type II cleavage*,[50] involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical[51] (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.[52]



Both singlet and triplet n,π^* states undergo the reaction.[53] The intermediate diradical can also cyclize to a cyclobutanol, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.[54] The

[49] See Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Dürr, H.; Ruge, B. *Top. Curr. Chem.* ***1976***, *66*, 53; Drewer, R.J. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 935–1015.

[50] See Wagner, P.J. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 381–444; *Acc. Chem. Res.* ***1971***, *4*, 168. See Niu, Y.; Christophy, E.; Hossenlopp, J.M. *J. Am. Chem. Soc.* ***1996***, *118*, 4188 for a new view of Norrish Type II elimination.

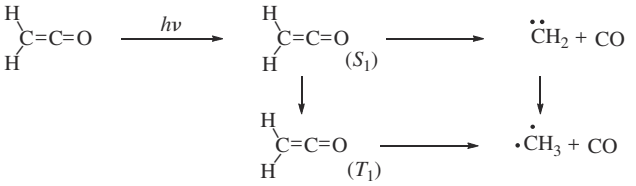
[51] See Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339, pp. 349–373; Scaiano, J.C.; Lissi, E.A.; Encina, M.V. *Rev. Chem. Intermed.* ***1978***, *2*, 139. Also see Wagner, P.J. *Acc. Chem. Res.* ***1989***, *22*, 83.

[52] This mechanism was proposed by Yang, N.C.; Yang, D.H. *J. Am. Chem. Soc.* ***1958***, *80*, 2913. The diradical intermediate has been trapped: Wagner, P.J.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 287; Wagner, P.J.; Kelso, P.A.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7480; Adam, W.; Grabowski, S.; Wilson, R.M. *Chem. Ber.* ***1989***, *122*, 561. See also, Caldwell, R.A.; Dhawan, S.N.; Moore, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 5163.

[53] See Casey, C.P.; Boggs, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6457.

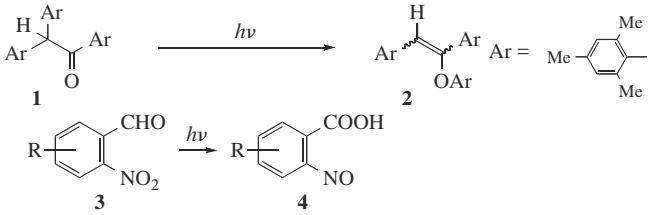
[54] For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens, R.S.; Levi, N. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1; Wiley, NY, ***1979***, pp. 641–753.

photolysis of ketene to CH_2 (Sec. 5.D.ii) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:

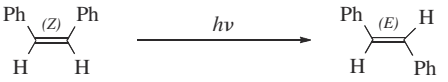


Reactions are known where *both* Norrish Type I and Type II reactions compete, and the substituents on and nature of the substrate will determine which leads to the major product.[55]

Category 3. Intramolecular Rearrangement. Two examples are the rearrangement of the trimesityl compound **1** to the enol ether (**2**),[56] and irradiation of *o*-nitrobenzaldehydes (**3**) to give *o*-nitrosobenzoic acids (**4**).[57]



Category 4. Photoisomerization. The most common reaction in this category is photochemical cis–trans isomerization.[58] For example, *cis*-stilbene can be converted to the trans isomer,[59] and the photoisomerization of *O*-methyl oximes is known.[60]



The isomerization takes place because the excited states, both S_1 and T_1, of many alkenes have a perpendicular instead of a planar geometry (Sec. 7.A.iv), so cis–trans isomerism disappears upon excitation. When the excited molecule drops back to the S_o state, either isomer can be formed. A useful example is the photochemical

[55] See Hwu, J.R.; Chen, B.-L.; Huang, L.W.; Yang, T.-H. *J. Chem. Soc. Chem. Commun.* ***1995***, 299.

[56] Wagner, P.J.; Zhou, B. *J. Am. Chem. Soc.* ***1988***, *110*, 611.

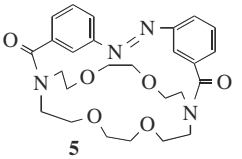
[57] See Morrison, H.A. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 165–213, 185–191; Kaupp, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 243. See also, Yip, R.W.; Sharma, D.K. *Res. Chem. Intermed.* ***1989***, *11*, 109.

[58] See Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557; Schulte-Frohlinde, D.; Görner, H. *Pure Appl. Chem.* ***1979***, *51*, 279; Saltiel, J.; Charlton, J.L. in de Mayo, P. *Rearrangements in Grund and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 25–89; Saltiel, J.; Chang, D.W.L.; Megarity, E.D.; Rousseau, A.D.; Shannon, P.T.; Thomas, B.; Uriarte, A.K. *Pure Appl. Chem.* ***1975***, *41*, 559; Saltiel, J.; D'Agostino, J.; Megarity, E.D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Org. Photochem.* ***1979***, *3*, 1. Also see Leigh, W.J.; Srinivasan, R. *Acc. Chem. Res.* ***1987***, *20*, 107; Steinmetz, M.G. *Org. Photochem.* ***1987***, *8*, 67; Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Johnson, R.P. *Org. Photochem.* ***1985***, *7*, 75.

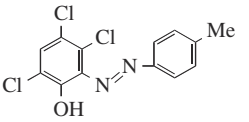
[59] For a review of the photoisomerization of stilbenes, see Waldeck, D.H. *Chem. Rev.* ***1991***, *91*, 415.

[60] Kawamura, Y.; Takayama, R.; Nishiuchi, M.; Tsukayama, M. *Tetrahedron Lett.* ***2000***, *41*, 8101.

conversion of *cis*-cyclooctene to the much less stable trans isomer.[61] Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the N=N bond is anti, preferentially binds NH_4^+, Li^+, and Na^+, but the syn isomer preferentially binds K^+ and Rb^+ (see Sec. 3.C.ii). Thus, ions can be selectively put in or taken out of solution merely by turning a light source on or off.[62]

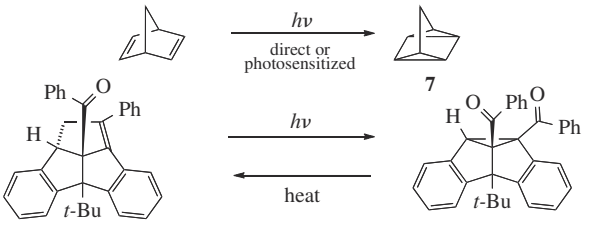


5



6

In another example, the trans azo compound (**6**) is converted to its cis isomer when exposed to light. In this case[63] the cis isomer is a stronger acid than the trans. The trans isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the trans isomer to the cis. The cis isomer, being a stronger acid, donates its proton to the base, converting cis-ArOH to cis-ArO^-. This ion migrates to the dark side, where it rapidly reverts to the trans ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one ^-OH ion in the dark compartment, the process reverses the normal reaction whereby these ions neutralize each other.[64] Thus the energy of light is used to do chemical work.[65] Another example of a category 4 reaction is the conversion of bicyclo[2.2.1]hept-2,5-diene to **7**.[58] The thermal isomerization of dibenzosemibullvalene (**9**) to the corresponding dibenzodihydropentalenofuran (**8**) in quantitative yield was known,[66] but in another example of a category 4 reaction the photochemical isomerization of **8** to **9** has now been reported.[67]



8 **7** **9**

These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed in Reaction **15-63**.

[61] Deyrup, J.A.; Betkouski, M. *J. Org. Chem.* ***1972***, *37*, 3561.

[62] Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1497; Shinkai, S.; Yoshioka, A.; Nakayama, H.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1905. For a review, see Shinkai, S.; Manabe, O. *Top. Curr. Chem.* ***1984***, *121*, 67.

[63] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6177.

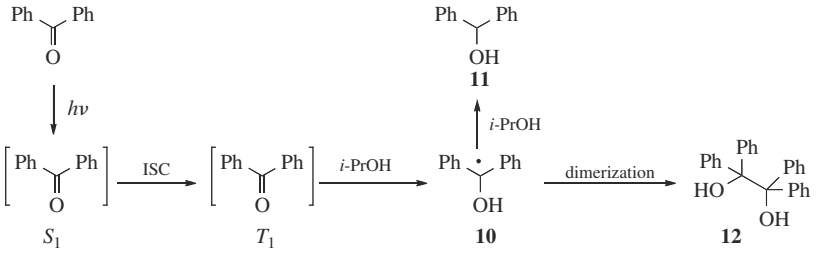
[64] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6178.

[65] See Beer, P.D. *Chem. Soc. Rev.* ***1989***, *18*, 409. For an example not involving a macrocycle, see Feringa, B.L.; Jager, W.F.; de Lange, B.; Meijer, E.W. *J. Am. Chem. Soc.* ***1991***, *113*, 5468.

[66] Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Rath, N.P.; George, M.V. *J. Photochem. Photobiol. A Chem.* ***2000***, *136*, 209.

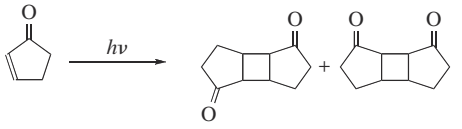
[67] Sajimon, M.C.; Ramaiah, D.; Thomas, K.G.; George, M.V. *J. Org. Chem.* ***2001***, *66*, 3182.

Category 5. Hydrogen-Atom Abstraction. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **10**. Radical **10** then abstracts another hydrogen to give benzhydrol (**11**) or dimerizes to benzpinacol (**12**):



An example of intramolecular abstraction has already been given (see category 2 in this section).

Category 6. Photodimerization. An example is dimerization of cyclopentenone:[68]



See Reaction **15-63** for a discussion of this and similar reactions.

7.A.viii. The Determination of Photochemical Mechanisms[69]

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (1) there are generally many products in a photochemical reaction, as many as 10 or 15; (2) in measuring kinetics, there are more variables, since it is possible to study the effect on the rate of the intensity or the wavelength of light; (3) in the detection of intermediates by spectra the technique of *flash photolysis* can be used, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence), as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.
2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to

[68] Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1*, 50. For a review of the photochemistry of α,β-unsaturated ketones, see Schuster, D.I. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 623–756.
[69] For a review, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 580–670.

the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as:

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: In some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see Sec. 14.A.i for a discussion of chain reactions).

7.B. SONOCHEMISTRY

Sonochemistry (chemical events induced by exposure to ultrasound) occupies an important place in organic chemistry.[70] The chemical effects of high-intensity ultrasound were extensively studied in aqueous solutions for many years,[71] but are now applied to a variety of organic solvents. The origin of sonochemistry is acoustic cavitation: the creation, growth, and implosive collapse of gas vacuoles in solution by the sound field. Acoustic cavitation is the phenomenon by which intense ultrasonic waves induce the formation, oscillation, and implosion of gas bubbles in liquids.[72] Liquids irradiated with high-power ultrasound undergo chemical decomposition and emit light.[73] These phenomena occur near the end of the collapse of bubbles expanded many times their equilibrium sizes. Chemistry (sonochemistry), light emission (sonoluminescence), and cavitation noise often accompany the process of acoustic cavitation.[74]

Sonochemistry generates gas vacuoles *in situ*. The collapse of gas vacuoles generates transient hot spots with local temperatures of several thousand Kelvin, and pressures of hundreds of atmospheres. A sonochemical hot spot forms where the gas- and liquid-phase

[70] Mason, T.J., Ed. *Advances in Sonochemistry*, JAI Press, NY, ***1990–1994***; Vols. 1–3, Price, G.J., Ed. *Current Trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, UK, ***1992***; Suslick, K.S. *Science* ***1990***, *247,* 1439; Suslick, K.S. *Ultrasound: Its Chemical, Physical, and Biological Effects*, VCH, NY, ***1988***; Young, F.R. *Cavitation*, McGraw-Hill, NY, ***1989***; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, Oxford, UK, ***1995***; Anbar, M. *Science* ***1968***, *161,* 1343. For a discussion of ultrasound in the chemistry of heterocycles, see Cella, R.; Stefani, H.A. *Tetrahedron* ***2009***, *65,* 2619.

[71] Apfel, R.E., in Edmonds, P. *Methods in Experimental Physics*, Academic Press, New York, ***1981***; Vol. 19; Makino, K.; Mossoba, M.M.; Riesz, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3537.

[72] Stottlemeyer, T.R.; Apfel, R.E. *J. Acoust. Soc. Am.* ***1997***, *102*, 1413.

[73] Suslick, K.S.; Crum, L.A. In *Sonochemistry and Sonoluminescence, Handbook of Acoustics*, Crocker, M.J., Ed., Wiley, NY, ***1998***; Chapter 23; Leighton, T.G. *The Acoustic Bubble*, Academic Press, London, ***1994***; Chapter 4; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, ***1995***, Chapters 1–4; Hua, I.; Hoffmann, M.R. *Environ. Sci. Technol.* ***1997***, *31*, 2237.

[74] Suslick, K.S.; Didenko, Y.T.; Fang, M.M.; Hyeon, T.; Kolbeck, K.J.; McNamara, III, W.B.; Mdleleni, M.M.; Wong, M. *Philos. Trans. R. Soc. London A* ***1999***, *357,* 335. For problems of sonochemistry and cavitation, see Margulis, M.A. *Ultrasonics Sonochemistry,* ***1994***, *1,* S87.

reaction zones have effective temperatures of 5200 and 1900 K, respectively.[75] The high temperatures and pressures that are achieved in the bubbles during the quasiadiabatic collapse[76] lead to the generation of chemistry and to the emission of light, most probably coming from molecular excited states and molecular recombination. Note that work has been done that shows the commonly held view that bubbles are filled with saturated gas is inconsistent with a realistic estimate of condensation rates.[77] The alternative view of extensive solvent vapor supersaturation in bubbles uniformly heated to a few thousand kelvin, depending on the conditions, is in accord with sonochemical rates and products.[78]

There is a correlation between sonochemical and sonoluminescence measurements, which is usually not observed. Sonoluminescence is the consequence that both the sonochemical production (under air) of oxidizing species, and the emission of light reflect the variations of the primary sonochemical acts, which are themselves due to variations of the number of "active" bubbles.[79] Pulsed ultrasound in the high-frequency range (>1 MHz) is extensively used in medical diagnosis, and the effects of pulsed ultrasound in the 20-kHz range using an immersed titanium horn has been reported.[80]

The chemical effects of ultrasound have been studied for >50 years,[81] and applied to colloid chemistry in the 1940s.[82] Modern interest in the chemical uses of ultrasound involves chemistry in both homogeneous[83] and heterogeneous[84] systems. Organic solvents (e.g., alkanes) support acoustic cavitation and the associated sonochemistry. This leads to carbon–carbon bond cleavage and radical rearrangements, with the peak temperatures reached in such cavities controlled by the vapor pressure of the solvent.[85]

It is often difficult to compare the sonochemical results reported from different laboratories (the reproducibility problem in sonochemistry).[86] The sonochemical power irradiated into the reaction system can be different for different instruments. Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction,[86] the most common being calorimetry. This experiment involves measurement of the initial rate of a temperature rise produced when a system is irradiated by power ultrasound. It has

[75] Suslick, K.S.; Hammerton, D.A.; Cline, Jr., R.E. *J. Am. Chem. Soc.* ***1986****, 108,* 5641.
[76] Didenko, Y.T.; McNamara, III, W.B.; Suslick, K.S. *J. Am. Chem. Soc.* ***1999****, 121*, 5817.
[77] Colussi, A. J.; Hoffmann, M.R. *J. Phys. Chem. A.* ***1999****, 103,* 11336.
[78] Colussi, A.J.; Weavers, L.K.; Hoffmann, M.R. *J. Phys. Chem. A* ***1998****, 102,* 6927.
[79] Segebarth, N.; Eulaerts, O.; Reisse, J.; Crum, L.A.; Matula, T.J. *J. Phys. Chem. B.* ***2002****, 106*, 9181.
[80] Dekerckheer, C.; Bartik, K.; Lecomte, J.-P.; Reisse, J. *J. Phys. Chem. A.* ***1998****, 102*, 9177.
[81] Elpiner, I. E. *Ultrasound: Physical, Chemical, and Biological Effects*, Consultants Bureau, NY, ***1964***.
[82] Sollner, K. *Chem. Rev.* ***1944****, 34,* 371.
[83] Suslick, K.S.; Schubert, P.F.; Goodale, J.W. *J. Am. Chem. Soc.* ***1981*** *,103*, 7342; Sehgal, C.; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1982****, 86,* 2982; Sehgal, C.M.; Wang, S.Y. *J. Am. Chem. Soc.* ***1981****, 103*, 6606.
[84] Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982****, 47*, 5030; Boudjouk, P.; Han, B.-H. *Tetrahedron Lett*. ***1981****, 22,* 3813; Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982****, 47,* 751; Boudjouk, P.; Han, B.-H.; Anderson, K.R. *J. Am. Chem. Soc.* ***1982****, 104,* 4992; Boudjouk, P.; Han, B.-H. *J. Catal.* ***1983****, 79,* 489; Racher, S.; Klein, P. *J. Org. Chem.* ***1981****, 46*, 3558; Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982****, 47,* 1587; Kegelaers, Y.; Eulaerts, O.; Reisse, J.; Segebarth, N. *Eur. J. Org. Chem.* ***2001***, 3683.
[85] Suslick, K.S.; Gawienowski, J.J.; Schubert, P.F.; Wang H.H. *J. Phys. Chem.* ***1983****, 87*, 2299.
[86] Mason, T.J. *Practical Sonochemistry: User's Guide to Applications in Chemistry and Chemical Engineering*, Ellis Horwood, West Sussex, ***1991***, pp. 43–46; Broeckaert, L.; Caulier, T.; Fabre, O.; Maerschalk, C.; Reisse, J.; Vandercammen, J.; Yang, D.H.; Lepoint, T.; Mullie, F. *Current Trends in Sonochemistry,* Price, G.J., Ed., Royal Society of Chemistry, Cambridge, ***1992***, p. 8; Mason, T.J.; Lorimer, J.P.; Bates, D.M.; Zhao, Y. *Ultrasonics Sonochemistry* ***1994****, 1,* S91; Mason, T.J.; Lorimer, J.P.; Bates, D.M. *Ultrasonics* ***1992****, 30,* 40.

been shown that calorimetric methods combined with the Weissler reaction can be used to standardize the ultrasonic power of individual ultrasonic devices.[87]

Sonochemistry has been used to facilitate or assist many organic reactions,[88] and there are other applications.[89] The scope of reactions studied is beyond this work, but some representative examples will be listed. Ultrasound has been used to promote lithiation of organic compounds,[90] for the generation of carbenes,[91] and reactions of metal carbonyls where sonochemical ligand dissociation has been observed, which often produces multiple CO substitution.[92] The influence of ultrasound on phase-transfer catalyzed thioether synthesis has been studied.[93]

Sonochemistry has been applied to acceleration of the *Reformatsky reaction*,[94] *Diels–Alder reactions*,[95] the arylation of active methylene compounds[96] nucleophilic aromatic substitution of haloarenes,[97] and to hydrostannation and tin hydride reduction.[98] Other sonochemical applications involve the reaction of benzyl chloride and nitrobenzene,[99] an $S_{RN}1$ reaction in liquid ammonia at room temperature,[100] and *Knoevenagel condensation* of aromatic aldehydes.[101] Iodination of aliphatic hydrocarbons can be accelerated,[102] and oxyallyl cations have been prepared from α,α'-diiodoketones using sonochemistry.[103] Sonochemistry has been applied to the preparation of carbohydrate compounds.[104] When sonochemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

7.C. MICROWAVE CHEMISTRY

In 1986, independent work by Gedye et al.,[105] as well as Majetich and co-workers[106] reported the use of microwave irradiation for organic reactions. Gedye described four different types of reactions, including the hydrolysis of benzamide to benzoic acid under acidic conditions, and all reactions showed significant rate enhancements when

[87] Kimura, T.; Sakamoto, T.; Leveque, J.-M.; Sohmiya, H.; Fujita, M.; Ikeda, S.; Ando, T. *Ultrasonics Sonochemistry* ***1996****, 3*, S157.
[88] *Synthetic Organic Sonochemistry* Luche, J.-L. (Universite de Savoie, France), Plenum Press, NY. ***1998***; Luche, J.-L. *Ultrasonics Sonochemistry,* ***1996****, 3,* S215.
[89] Adewuyi, Y.G. *Ind. Eng. Chem. Res.* ***2001****, 40,* 4681.
[90] Boudjouk, P.; Sooriyakumaran, R.; Han, B.H. *J. Org. Chem.* ***1986****, 51,* 2818, and Ref. 1 therein.
[91] Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982****, 47,* 1587.
[92] Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* ***1983****, 105*, 5781.
[93] Wang, M.-L.; Rajendran, V. *J. Mol. Catalysis A: Chemical* ***2005****, 244,* 237.
[94] Han, B.H.; Boudjouk, P. *J. Org. Chem.* ***1982****, 47*, 5030.
[95] Nebois, P.; Bouaziz, Z.; Fillion, H.; Moeini, L.; Piquer, Ma.J.A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericàs, M.A. *Ultrasonics Sonochemistry* ***1996****, 3,* 7.
[96] Meč iarová, M.; Kiripolsky, M.; Toma, Š. *Ultrasonics Sonochemistry* ***2005****, 12,* 401.
[97] Meč iarová, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochemistry* ***2003****, 10,* 265.
[98] Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* ***1989****, 111,* 6849.
[99] Vinatoru, M.; Stavrescua, R.; Milcoveanu, A.B.; Toma, M.; Mason, T.J. *Ultrasonics Sonochemistry* ***2002****, 9,* 245.
[100] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994****, 35,* 677.
[101] McNulty, J.; Steere, J.A.; Wolf, S. *Tetrahedron Lett.* ***1998****, 39,* 8013.
[102] Kimura, T.; Fujita, M.; Sohmiya, H.; Ando, T. *Ultrasonics Sonochemistry* ***2002****, 9,* 205.
[103] Montaña, A.M.; Grima, P.M. *Tetrahedron Lett.* ***2001****, 42,* 7809.
[104] Kardos, N.; Luche, J.-L. *Carbohydrate Res.* ***2001****, 332,* 115.
[105] Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* ***1987****, 66*, 17.
[106] Giguere, R.J.; Bray, T.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* ***1986****, 27,* 4945.

compared to the same reactions done at reflux conditions.[107] Majetich, Giguere and co-workers[106] reported rate enhancements for microwave-promoted *Diels–Alder*, *Claisen*, and ene reactions. Many publications[108] have appeared that describe chemical synthesis promoted by microwave irradiation, including many review articles[109] and books.[110]

Microwaves are electromagnetic waves (see Sec. 7.A.i) and there are electric and magnetic field components. Charged particles start to migrate or rotate as the electric field is applied,[111] which leads to further polarization of polar particles. Because the concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction (2.4×10^9 s^{-1}), warming occurs.[111] In general, the most common frequencies used for microwave dielectric heating[112] are 918 MHz and 2.45 GHz[113] (wavelengths of 33.3 and 12.2 cm, respectively), which are in the region between the IR and radiowave wavelengths in the electromagnetic spectrum. For chemical reactions done with microwave irradiation, rapid heating is usually observed,[114] and if a solvent is used superheating of that solvent was always observed.[112] Agitation is usually important.[115] In the early days of microwave chemistry, reactions were often done in open vessels, but also in sealed Teflon or glass vessels using unmodified domestic household ovens.[116] Dielectric heating is direct so if the reaction matrix has a sufficiently large dielectric loss tangent, and contains molecules possessing a dipole moment, a solvent is not required. The use of dry-reaction microwave chemistry is increasingly popular.[117]

Microwave dielectric heating was initially categorized by thermal effects and nonthermal effects.[118] "Thermal effects are those which are caused by the different temperature regime which can be created due to microwave dielectric heating. Nonthermal effects are effects,[119] which are caused by effects specifically inherent to the microwaves and are not caused by

[107] Taken from Horeis, G.; Pichler, S.; Stadler, A.; Gössler, W.; Kappe, C.O. *Microwave-Assisted Organic Synthesis - Back to the Roots*, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), ***2001***. (available at http://www.mdpi.org/ecsoc-5.htm).

[108] Kappe, C. O. *Angew. Chem. Int. Ed.* ***2004****, 43,* 6250.

[109] Majetich, G.; Karen, W. in Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, Washington, DC, ***1997***, p. 772; Bose, A.K.; Manhas, M.S.; Banik, B.K.; Robb, E.W. *Res. Chem. Intermed.* ***1994****, 20,* 1; Majetich, G.; Hicks, R. *Res. Chem. Intermed.* ***1994****, 20,* 61; Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.* ***1995****, 48,* 1665; Caddick, S. *Tetrahedron* ***1995****, 51,* 10403; Mingos, D M.P. *Res. Chem. Intermed.* ***1994****, 20,* 85; Berlan, J. *Rad. Phys. Chem.* ***1995****, 45*, 581; Fini, A.; Breccia, A. *Pure Appl. Chem.* ***1999****, 71,* 573.

[110] Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications, American Chemical Society*, ***1997***; Loupy, A. *Microwaves in Organic Synthesis,* Wiley-VCH, Weinheim, ***2002***; Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light,* CEM Publishing, Matthews, NC, ***2002***; Lidström, P., Tierney, J.P. *Microwave-Assisted Organic Synthesis, Blackwell Scientific,* ***2005***; Kappe, C.O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry,* Wiley–VCH, Weinheim, ***2005***.

[111] Galema, S.A. *Chem. Soc. Rev.* ***1997****, 26,* 233.

[112] Gabriel, C.; Gabriel, S.; Grant, E.H.; Halstead, B.S.J.; Mingos, D.M.P. *Chem. Soc. Rev.* ***1998****, 27,* 213.

[113] This frequencey is usually applied in domestic microwave ovens.

[114] See Hoogenboom, R.; Wilms, T.F.A.; Erdmenger, T.; Schubert, U.S. *Austr. J. Chem.* ***2009****, 62*, 236.

[115] Moseley, J.D.; Lenden, P.; Thomson, A.D.; Gilday, J.P. *Tetrahedron Lett.* ***2007****, 48,* 6084.

[116] Caddick, S. *Tetrahedron* ***1995****, 51,* 10403.

[117] Varma, R. S. *Green Chem.* ***1999***, 43; Kidawi, M. *Pure Appl. Chem.* ***2001****, 73,* 147; Varma, R. S. *Pure Appl. Chem.* ***2001****, 73,* 193.

[118] Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* ***1997****, 4,* 373. Also see Schmink, J.R.; Leadbeater, N.E. *Org. Biomol. Chem.,* ***2009****, 7,* 3842.

[119] See Kuhnert, N. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1863.

different temperature regimes."[111] Some claimed special effects[120] in microwave chemistry, such as lowering of Gibbs energy of activation, but later study under careful temperature control indicated no special rate effects.[121] When conventional microwave ovens were used, temperature control was difficult, particularly when reactions are carried out in closed reaction vessels. The main contributing factor to any rate acceleration caused by microwave dielectric heating seems to be due to a thermal effect. The thermal effect may be due to a faster initial heating rate or to the occurrence of local regions with higher temperatures.[111]

Conventional microwave ovens are used less often for microwave chemistry today. Microwave reactors for chemical synthesis are commercially available and widely used in academia and in industry. These instruments have built-in magnetic stirring, direct temperature control of the reaction mixture, shielded thermocouples or IR sensors, and the ability to control temperature and pressure by regulating microwave output power.

The applications of microwave chemistry to organic chemistry are literally too numerous to mention. A few representative examples will be given to illustrate the scope and utility. The combined use of microwaves and ultrasound is important in process chemistry and organic synthesis.[122] Microwave chemistry is widely used in synthesis,[123] including organocatalyzed asymmetric reactions.[124] Examples include the *Heck reaction* (Reaction **13-10**),[125] the *Suzuki reaction* (Reaction **13-12**),[126] the *Sonogashira reaction* (Reaction **13-13**),[127] *Ullman-type couplings* (Reaction **13-3**),[128] cycloaddition reactions (Reactions **15-58**–**15-66**),[129] dihydroxylation (Reaction **15-48**),[130] and the *Mitsunobu reaction* (Reaction **10-23**).[131] There are a multitude of other reactions types from earlier literature that can be found in the cited review articles. When microwave chemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

[120] Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* ***1992****, 57,* 7099 and references therein.

[121] Raner, K.D.; Strauss, C.R.; Vyskoc, F.; Mokbel, L. J. *Org. Chem.* ***1993****, 58,* 950, and references cited therein.

[122] Cravotto, G.; Cintas, P. *Chemistry: European J.* ***2007****, 13,* 1902.

[123] See Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002****, 35,* 717; Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* ***2004****, 6*, 128; Roberts, B.A.; Strauss, C.R. *Acc. Chem. Res.* ***2005****, 38*, 653; Kuznetsov, D.V.; Raev, V.A.; Kuranov, G.L.; Arapov, O.V.; Kostikov, R.R. *Russ. J. Org. Chem.* ***2005****, 41*, 1719. For a discussion of microwave-assisted organic synthesis in near critical water, see Kremsner, J.M.; Kappe, C.O. *Eur. J. Org. Chem.* ***2005***, 3672.

[124] Mossé, S.; Alexakis, A. *Org. Lett.* ***2006****, 8,* 3577.

[125] Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002****, 35,* 717; Olofsson, K.; Larhed, M. in Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, ***2004***, Chap. 2., Andappan, M.M.S.; Nilsson, P.; Larhed, M. *Mol. Diversity* ***2003****, 7,* 97.

[126] Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M. *J. Comb. Chem.* ***2003****, 5,* 456; Miller, S.P.; Morgan, J.B.; Nepveux, F.J.; Morken, J.P. *Org. Lett.* ***2004****, 6,* 131; Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003****, 7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004****, 62,* 851; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003****, 68,* 888; Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* ***2003****, 5,* 615; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003****, 68,* 5660.

[127] Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003****, 7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004****, 62,* 851; Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003****, 5,* 3919; Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* ***2003***, 4713.

[128] Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* ***2003****, 44*, 4217; Lange, J.H.M.; Hofmeyer, L.J.F.; Hout, F.A.S.; Osnabrug, S.J.M.; Verveer, P.C.; Kruse, C.G.; Feenstra, R.W. *Tetrahedron Lett.* ***2002****, 43,* 1101.

[129] See Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* ***2002****, 67*, 7904 ; Pinto, D.C.G.A.; Silva, A.M.S.; Almeida, L.M.P.M.; Carrillo, J.R.; D'az-Ortiz, A.; de la Hoz, A.; Cavaleiro, J.A.S. *Synlett* ***2003***, 1415.

[130] Dupau, P.; Epple, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* ***2002****, 344,* 421.

[131] Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004****, 126,* 706.

CHAPTER 8

Acids and Bases

Two acid–base theories are used in organic chemistry today: the Brønsted theory and the Lewis theory.[1] These theories are quite compatible and are used for different purposes.[2] However, the Lewis-based idea of electron-donating species (bases) and electron-accepting species (acids) is often the more useful for organic chemistry. Remember also that most organic reactions are not done in an aqueous medium, and focus on electron transfer rather than proton transfer is far more useful.

8.A. BRØNSTED THEORY

According to this theory, an acid is defined as a *proton donor*[3] and a base as a *proton acceptor*. However, a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital. By this definition, an acid–base reaction is the transfer of a proton from an acid to a base. However, protons do not exist free in solution, but must be attached to an electron pair. In fact, the acid does not "give up" a proton, but rather the base donates electrons to the proton, "pulling it away" to form the conjugate acid. After removal of the proton, the species remaining (the *conjugate base*) still retains the electron pair to which the proton was formerly attached. The conjugate base, in theory at least, can reacquire a proton and is therefore a base. All acids will generate a conjugate base upon reaction with a suitable base, and all bases will generate a *conjugate acid* by reaction with a suitable acid. All acid–base reactions fit the equation

$$\underset{\text{Acid}_1}{\text{A—H}} + \underset{\text{Base}_2}{\text{B}} \rightleftharpoons \underset{\text{Base}_1}{\text{A}} + \underset{\text{Acid}_2}{\text{B—H}}$$

[1] For monographs on acids and bases, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***; Finston, H.L.; Rychtman, A.C. *A New View of Current Acid–Base Theories*, Wiley, NY, ***1982***.

[2] For discussion of the historical development of acid–base theory, see Bell, R.P. *Q. Rev. Chem. Soc.* ***1947***, *1*, 113; Bell, R.P. *The Proton in Chemistry*, 1st ed., Cornell University Press, Ithaca, NY, ***1959***, pp. 7–17.

[3] According to IUPAC terminology (Bunnett, J.F.; Jones, R.A.Y. *Pure Appl. Chem.* ***1988***, *60*, 1115), an acid is a *hydron* donor. The IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element, which contains ∼0.015% deuterium, be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

8.A.i Brønsted Acids

According to the Brønsted definition, *acid strength* may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. All acid–base reactions are reversible, and both an acid and a conjugate acid are present in the equilibrium mixture. In one sense, acid–base reactions occur because the acid and the conjugate acid are not of equal strength (i.e., the equilibrium can be shifted to one side or the other). If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the conjugate acid in this reaction would be acetic acid. Since HCl is a stronger acid than acetic acid (see Table 8.1), the equilibrium lies well to the right. As the reaction is written, if the equilibrium lies to the right (higher concentration of acetic acid and a lower concentration of HCl), HCl is the stronger acid. Likewise, acetate is taken to be a stronger base than the chloride ion. If this is a correct statement, treatment of acetic acid with chloride ion should give essentially no reaction, since the weaker acid already has the proton. This is found to be correct.

$$HCl + CH_3COO^- \rightleftharpoons CH_3COOH + Cl^-$$

For a comparison of two different acids, the position of the equilibrium in reaction with a common base allows the relative strengths of acids to be determined.[4] Likewise, the strength of two different bases will be determined by comparing the equilibrium established when they react with a common acid. By definition, the acid and base are always drawn on the left side of the equation, and the conjugate acid and conjugate base are assumed to be on the right side of the equation.

Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides. This finding really means that the concentration of acid and base at equilibrium will be close to that of the concentration of the conjugate acid and conjugate base. However, the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). If the concentration of acid and base is higher, the reaction of conjugate acid and conjugate base is more facile, and the compound labeled as the acid is considered to be a weaker acid. If the concentration of the conjugate acid and conjugate base is higher, the reaction of the acid and base is more facile, and the compound labeled as the acid is a stronger acid.

Using these protocols as the definition of acid strength, it is possible to construct a table in which acids are listed in order of acid strength[5] (Table 8.1).[6] The conjugate base is shown next to each acid in Table 8.1. Using the axiom that a strong acid generates a weak conjugate base and a weak acid will generate a strong conjugate base, it is clear that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength. The pK_a values[7] in Table 8.1 are most accurate in the middle of the table.[8–67]

[4] Although equilibrium is reached in most acid–base reactions extremely rapidly (see Sec. 8.B), some are slow (especially those in which the proton is lost from a carbon) and in these cases time must be allowed for the system to come to equilibrium.

[5] For a review of stronger Bronsted acids, see Akiyama, T. *Chem. Rev.* ***2007***, *107*, 5744.

[6] Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity (see Sec. 8.B).

[7] For a first principles calculation of p*K* values in nonaqueous solution, see Ding, F.; Smith, J.M.; Wang, H. *J. Org. Chem.* ***2009***, *74,* 2679.

TABLE 8.1 The pK_a Values for Many Types of Acids[a]

Acid	Base	Approximate pK_a (relative to water)[b]	References
$HF—SbF_5$	SbF_6^-		8
$FSO_3H—SbF_5—SO_3$			66
$FSO_3H—SbF_5$			66,8
FSO_3H	FSO_3^-		66
RNO_2H^+	RNO_2	−12	9
$ArNO_2H^+$	$ArNO_2$	−11	9
$HClO_4$	ClO_4^-	−10	10
HI	I^-	−10	10
$RCNH^+$	RCN	−10	11
$R—C(=^+OH)—H$	$R—C(=O)—H$	−10	12
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	10
$Ar—C(=^+OH)—OR$[c]	$Ar—C(=O)—OR$	−7.4	9
HCl	Cl^-	−7	10
RSH_2^+	RSH	−7	9
$Ar—C(=^+OH)—OH$[c]	$Ar—C(=O)—OH$	−7	14
$Ar—C(=^+OH)—H$	$Ar—C(=O)—H$	−7	15
$R—C(=^+OH)—R$	$R—C(=O)—R$	−7	67,11,16

[8] Gold,V.; Laali, K.; Morris, K.P.; Zdunek, L.Z. *J. Chem. Soc. Chem. Commun.* ***1981***, 769; Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* ***1981***, *5*, 45.

[9] Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223, pp. 324–325.

[10] Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.

[11] Deno, N.C.; Gaugler, R.W.; Wisotsky, M.J. *J. Org. Chem.* ***1966***, *31*, 1967.

[12] Levy, G.C.; Cargioli, J.D.; Racela, W. *J. Am. Chem. Soc.* ***1970***, *92*, 6238. See, however, Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1010.

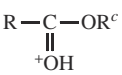
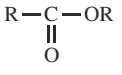
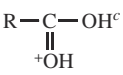
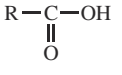
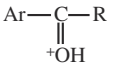
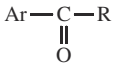
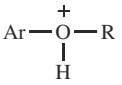
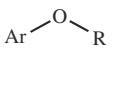
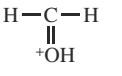
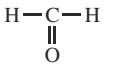
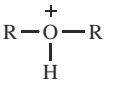
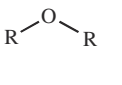
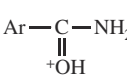
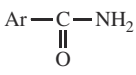
[13] Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. See Smith, C.R.; Yates, K. *Can. J. Chem.* ***1972***, *50*, 771; Benedetti, E.; Di Blasio, B.; Baine, P. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 500; Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 188–197. It has been shown that some amides protonate at nitrogen: see Perrin, C.L. *Acc. Chem. Res.* ***1989***, *22*, 268. For a review of alternative proton sites, see Liler, M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 267.

[14] Stewart, R.; Granger, M.R. *Can. J. Chem.* ***1961***, *39*, 2508.

[15] Yates, K.; Stewart, R. *Can. J. Chem.* ***1959***, *37*, 664; Stewart, R.; Yates, K. *J. Am. Chem. Soc.* ***1958***, *80*, 6355.

[16] Lee, D.G. *Can. J. Chem.* ***1970***, *48*, 1919.

TABLE 8.1 (***Continued***)

Acid	Base	Approximate pK_a (relative to water)[b]	References
$ArSO_3H$	$ArSO_3^-$	−6.5	17
		−6.5	9
$ArOH_2^+$	ArOH	−6.4	18
		−6	9
		−6	15,19
		−6	18,20
$CH(CN)_3$	$^-C(CN)_3$	−5	21
Ar_3NH^+	Ar_3N	−5	22
		−4	23
		−3.5	11,20,24
$R_3COH_2^+$	R_3COH	−2	24
$R_2CHOH_2^+$	R_2CHOH	−2	24,25
$RCH_2OH_2^+$	RCH_2OH	−2	11,24,25
H_3O^+	H_2O	**−1.74**	26
		−1.5	27
HNO_3	NO_3^-	−1.4	10

(*continued*)

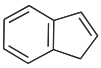
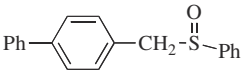
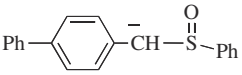
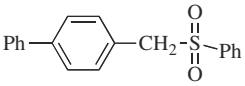
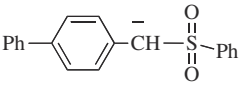
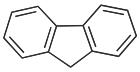
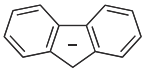
[17] Cerfontain, H.; Koeberg-Telder, A.; Kruk, C. *Tetrahedron Lett.* ***1975***, 3639.
[18] Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 5660; Koeberg-Telder, A.; Lambrechts, H.J.A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 293.
[19] Fischer, A.; Grigor, B.A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* ***1961***, *83*, 4208.
[20] Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 4999.
[21] Boyd, R.H. *J. Phys. Chem.* ***1963***, *67*, 737.
[22] Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.
[23] McTigue. P.T.; Sime, J.M. *Aust. J. Chem.* ***1963***, *16*, 592.
[24] Deno, N.C.; Turner, J.O. *J. Org. Chem.* ***1966***, *31*, 1969.
[25] Chandler, W.D.; Lee, D.G. *Can. J. Chem.* ***1990***, *68*, 1757.
[26] For a discussion, see Campbell, M.L.; Waite, B.A. *J. Chem. Educ.* ***1990***, *67*, 386.
[27] Grant, H.M.; McTigue, P.; Ward, D.G. *Aust. J. Chem.* ***1983***, *36*, 2211.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)[b]	References
$RC(=NH_2^+)OH$[c]	$RC(=O)NH_2$	−0.5	27
$Ar_2NH_2^+$	Ar_2NH	1	22
HSO_4^-	SO_4^{2-}	**1.99**	28
HF	F^-	**3.17**	28
HONO	NO_2^-	**3.29**	28
$ArNH_3^+$	$ArNH_2$	3–5	29
$ArNR_2H^+$	$ArNR_2$	3–5	29
RCOOH	$RCOO^-$	4–5	29
$HCOCH_2CHO$	$HO\bar{C}HCHO$	5	30
H_2CO_3[d]	HCO_3^-	**6.35**	28
H_2S	HS^-	**7.00**	28
ArSH	ArS^-	6–8	32
$CH_3COCH_2COCH_3$[e]	$CH_3CO\bar{C}HCOCH_3$	9	30
HCN	CN^-	9.2	34
NH_4^+	NH_3	**9.24**	28
ArOH	ArO^-	8–11	35
RCH_2NO_2	$R\bar{C}HNO_2$	10	36
R_3NH^+	R_3N	10–11	29
RNH_3^+	RNH_2	10–11	29
HCO_3^-	CO_3^{2-}	**10.33**	28
RSH	RS^-	10–11	32
$R_2NH_2^+$	R_2NH	11	29
$N{\equiv}CCH_2C{\equiv}N$	$N{\equiv}C\bar{C}HC{\equiv}N$	11	30,37
CH_3COCH_2COOR	$CH_3CO\bar{C}HCOOR$	11	30
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2\bar{C}HSO_2CH_3$	12.5	38
$EtOOCCH_2COOEt$	$EtOOC\bar{C}HCOOEt$	13	30
CH_3OH	CH_3O^-	15.2	39,40
H_2O	OH^-	**15.74**	41

[28] Bruckenstein, S.; Kolthoff, I.M. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, ***1959***, pp. 432–433.
[29] Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***, pp. 567–662.
[30] Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.
[31] This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 in Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.
[32] Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 396–410.
[33] See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11705.
[34] Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford, NY, ***1982***.
[35] Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, p. 374.
[36] Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94.
[37] Bowden, K.; Stewart, R. *Tetrahedron* ***1965***, *21*, 261.
[38] Hine, J.; Philips, J.C.; Maxwel, J.I. *J. Org. Chem.* ***1970***, *35*, 3943. See also, Ang, K.P.; Lee, T.W.S. *Aust. J. Chem.* ***1977***, *30*, 521.
[39] Reeve, W.; Erikson, C.M.; Aluotto, P.F. *Can. J. Chem.* ***1979***, *57*, 2747.
[40] See also, Olmstead, W.N.; Margolin, Z.; Bordwell, F.G. *J. Org. Chem.* ***1980***, *45*, 3295.
[41] Harned, H.S.; Robinson, R.A. *Trans. Faraday Soc.* ***1940***, *36*, 973.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)[b]	References
		16	42
RCH_2OH	RCH_2O^-	16	39
RCH_2CHO	$R\bar{C}HCHO$	16	43
R_2CHOH	R_2CHO^-	16.5	39
R_3COH	R_3CO^-	17	39
$RCONH_2$	$RCONH^-$	17	44
$RCOCH_2R$	$RCO\bar{C}HR$	19–20[f]	46
		20	47,48
		20.08[a]	49
		18.91[a]	49
		23	47,48
$ROOCCH_2R$	$ROOC\bar{C}HR$	24.5	30
$RCH_2C{\equiv}N$	$RC^-HC{\equiv}N$	25	30,50
$HC{\equiv}CH$	$HC{\equiv}CC^-$	25	51
Ph_2NH	PH_2N^-	24.95[g]	45
$EtOCOCH_3$	$EtOCOCH_2^-$	25.6	52
$PhNH_2$	$PhNH^-$	30.6[g]	45
Ar_3CH	Ar_3C^-	31.5	47,53
Ar_2CH_2	Ar_2CH^-	33.5	47,48

(*continued*)

[42] Streitwieser, Jr., A.; Nebenzahl, L. *J. Am. Chem. Soc.* ***1976***, *98*, 2188.
[43] Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 2470.
[44] Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 238–240.
[45] The pK_a of acetone in DMSO is reported to be 26.5. See Bordwell, F.G.; Zhang, X.-M. *Accts. Chem. Res.* ***1997***, *26*, 510.
[46] Guthrie, J.P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* ***1984***, *106*, 1351; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 460.
[47] Streitwieser, Jr., A.; Ciuffarin, E.; Hammons, J.H. *J. Am. Chem. Soc.* ***1967***, *89*, 63.
[48] Streitwieser, Jr., A.; Hollyhead, W.B.; Pudjaatmaka, H.; Owens, P.H.; Kruger, T.L.; Rubenstein, P.A.; MacQuarrie, R.A.; Brokaw, M.L.; Chu, W.K.C.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5088.
[49] Streitwieser, A.; Wang, G.P.; Bors, D.A. *Tetrahedron* ***1997***, *53*, 10103.
[50] For a review of the acidity of cyano compounds, see Hibbert, F. in Patai, S.; Rappoport, Z. *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley, NY, ***1983***, pp. 699–736.
[51] Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, p. 19. See also, Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.
[52] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3129.
[53] Streitwieser, Jr., A.; Hollyhead, W.B.; Sonnichsen, G.; Pudjaatmaka, H.; Chang, C.J.; Kruger, T.L. *J. Am. Chem. Soc.* ***1971***, *93*, 5096.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)[b]	References
H_2	H^-	35	54
NH_3	NH_2^-	38	55
$PhCH_3$	$PhCH_2^-$	40	56
$CH_2{=}CHCH_3$	$\left[H_2C{=}\overset{H}{\overset{\vert}{C}}{-}CH_2\right]^-$	43	57
PhH	Ph^-	43	58
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	59
cyclo-C_3H_6	*cyclo*-$C_3H_5^-$	46	60
CH_4[h]	CH_3^-	48	62
C_2H_6	$C_2H_5^-$	50	63
$(CH_3)_2CH_2$[h]	$(CH_3)_2CH^-$	51	63
$(CH_3)_3CH$[h]	$(CH_3)_3C^-$		64

[a]The pK_a in THF.

[b]The values in boldface are exact values; the others are approximate, especially >18 and < −2.[65]

[c]See Ref. 13.

[d]See Ref. 31.

[e]See Ref. 33.

[f]See Ref. 45.

[g]The pK_a in DMSO.

[h]See Ref. 61.

[54] Buncel, E.; Menon, B. *J. Am. Chem. Soc.* ***1977***, *99*, 4457.
[55] Buncel, E.; Menon, B. *J. Organomet. Chem.* ***1977***, *141*, 1.
[56] Albrech, H.; Schneider, G. *Tetrahedron* ***1986***, *42*, 4729.
[57] Boerth, D.W.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1981***, *103*, 6443.
[58] Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936.
[59] Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.
[60] This value is calculated from results given in Streitwieser, Jr., A.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste, M.A.; Coxon, J.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 255–305.
[61] See Daasbjerg, K. *Acta Chem. Scand. B* ***1995***, *49*, 878 for pK_a values of various hydrocarbons in DMF.
[62] This value is calculated from results given in Streitwieser, Jr., A.; Taylor, D.R. *J. Chem. Soc. D* ***1970***, 1248.
[63] These values are based on those given in Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94, but are corrected to the newer scale of Streitwieser, A.; Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936; Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.
[64] Breslow, R. and co-workers report a value of 71 (Breslow, R.; Grant, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 7745), but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is 53. See also, Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 5741.
[65] This table gives average values for functional groups. See Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***; Serjeant, E.P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution,* Pergamon, Elmsford NY, ***1979***; Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, ***1961***. The index in the 1979 volume covers both volumes. Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* ***1960***, *1*, 190; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223; Perrin, D.D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, ***1965***, and Supplement, 1972; Collumeau, A. *Bull. Soc. Chim. Fr.* ***1968***, 5087; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 456; Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford NY, ***1982***; *Pure Appl. Chem.* ***1969***, *20*, 133.
[66] Gillespie, R.J. *Acc. Chem. Res.* ***1968***, *1*, 202.
[67] For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* ***1987***, 563; Toullec, J. *Tetrahedron Lett.* ***1988***, *29*, 5541.

The pK_a values are much harder to measure[68] for very strong and very weak acids, and these values must be regarded as approximate. If one did not have the pK_a values available, it can be determined experimentally that $HClO_4$ is a stronger acid than H_2SO_4. A mixture of $HClO_4$ and H_2SO_4 in 4-methyl-2-pentanone can be titrated to an $HClO_4$ end point without interference by H_2SO_4.[69] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of −10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$ and $RSH_2{}^+$ must also be regarded as highly speculative.[70] A wide variety of pK_a values have been reported for the conjugate acids of even such simple bases as acetone[67] (−0.24 to −7.2), diethyl ether (−0.30 to −6.2), ethanol (−0.33 to −4.8), methanol (−0.34 to −4.9), and 2-propanol (−0.35 to −5.2), depending on the method used to measure them.[71] Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

A crystallographic scale of acidity has been developed, including the acidity of C—H compounds. Measuring the mean C—H···O distances in crystal structures correlated well with conventional p$K_{a(\mathrm{DMSO})}$ values,[72] where DMSO is dimethyl sulfoxide. An *ab initio* study was able to correlate ring strain in strained hydrocarbons with hydrogen-bond acidity.[73] The kinetic acidity of aliphatic hydrocarbons has been determined.[74]

The bottom portion of Table 8.1 consists of very weak acids (pK_a above that of water ≈15.8).[75] In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. The pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.[76] The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see Sec. 5.B.i).

The extremely strong acids at the top of the table are known as *superacids* (see Sec. 5.A. ii).[77] The actual species present in the $FSO_3H—SbF_5$ mixture are probably $H[SbF_5(SO_3F)]$

[68] For a review of methods of determining pK_a values, see Cookson, R.F. *Chem. Rev.* ***1974***, *74*, 5.

[69] Kolthoff, I.M.; Bruckenstein, S. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, ***1959***, pp. 475–542, p. 479.

[70] For reviews of organic compounds protonated at O, N, or S, see Olah, G.A.; White, A.M.; O'Brien, D.H. *Chem. Rev.* ***1970***, *70*, 561; Olah, G.A.; White, A.M.; O'Brien, D.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1973***, pp. 1697–1781.

[71] Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***. For discussion of the basicity of such compounds, see Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 118–139.

[72] Pedireddi, V.R.; Desiraju, G.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 988.

[73] Alkorta, I.; Campillo, N.; Rozas, I.; Elguero, J. *J. Org. Chem.* ***1998***, *63*, 7759.

[74] Streitwieser, A.; Keevil, T.A.; Taylor, D.R.; Dart, E.C. *J. Am. Chem. Soc.* ***2005***, *127,* 9290.

[75] See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, NY, ***1978***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 1–45; Streitwieser, Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41; Wiberg, K.B. *J. Org. Chem.* ***2002***, *67*, 1613.

[76] See Jones, J.R. *Q. Rev. Chem. Soc.* ***1971***, *25*, 365; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116; Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Chapter 1, Pergamon, NY, ***1978*** (an earlier version of this chapter appeared in *Russ. Chem. Rev.* ***1974***, *43*, 17); Gau, G.; Assadourian, L.; Veracini, S. *Prog. Phys. Org. Chem.* ***1987***, *16*, 237; in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, the reviews by Pellerite, M.J.; Brauman, J.I. pp. 55–96 (gas-phase acidities); and Streitwieser, Jr., A.; Juaristi, E.; Nebenzahl, L. pp. 323–381.

[77] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, ***1985***; Gillespie, R.J.; Peel, T.E. *Adv. Phys. Org. Chem.* ***1971***, *9*, 1; Arata, K. *Adv. Catal.* ***1990***, *37*, 165. For a review of methods of measuring superacidity, see Jost, R.; Sommer, J. *Rev. Chem. Intermed.* ***1988***, *9*, 171.

and $H[SbF_2(SO_3F)_4]$.[66] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[66] There is a study of electrophilic intermediates that are generated in superacids[78] (also see Chapter 10).

By the use of tables (e.g., Table 8.1), it is possible to determine whether a given acid will react with a given base to give reasonable concentrations of the conjugate acid and base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it*.[79] The greater the separation in the table, the better the reaction. It must be emphasized that the order of acid strength in Table 8.1 separation applies when a given acid and base react without a solvent or, when possible, in water. In other solvents, the order may be greatly different (see Sec. 8.G). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.[80] For example, in the gas phase, toluene is a stronger acid than water and *tert*-butoxide ion is a weaker base than methoxide ion[81] (see also Sec. 8.G). It is also possible for the acidity order to change with temperature. For example, $>50\,^{\circ}C$ the order of base strength is $BuOH > H_2O > Bu_2O$; from 1 to $50\,^{\circ}C$ the order is $BuOH > Bu_2O > H_2O$; while $<1\,^{\circ}C$ the order becomes $Bu_2O > BuOH > H_2O$.[82]

8.A.ii. Brønsted Bases

Basicity may be measured by a parameter known as proton affinity of an anion. The dissociation of a hydrogen ion for a molecule in the gas phase is called the *proton affinity* of the conjugate base.[83] A hydrogen-bond basicity scale has been developed that can be used to determine the relative basicity of molecules. Table 8.2 gives the pK_{HB} values for several common heteroatom-containing molecules.[84] This is obtained from the protonated form (conjugated acid) of the base in question. The larger the number, the more basic is that compound. The basicity of aliphatic amines has been calculated,[85] the ion-pair basicity of amines in THF[86] and in water[87] has been determined, and the basicity of pyridine was examined.[88] There are secondary deuterium isotope effects for measuring the basicity of secondary amines, and deuteration was found to increase the basicity.[89] Weaker bases have

[78] Prakash, G.K.S. *J. Org. Chem.* ***2006***, *71,* 3661.

[79] These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within ~2 pK units).

[80] See Gal, J.; Maria, P. *Prog. Phys. Org. Chem.* ***1990***, *17*, 159.

[81] Bohme, D.K.; Lee-Ruff, E.; Young, L.B. *J. Am. Chem. Soc.* ***1972***, *94*, 4608, 5153.

[82] Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. For other examples, see Calder, G.V.; Barton, T.J. *J. Chem. Educ.* ***1971***, *48*, 338; Hambly, A.N. *Rev. Pure Appl. Chem.* ***1965***, *15*, 87, p. 88.

[83] Tal'Rose, V.L.; Frankevitch, E.L. *J. Am. Chem. Soc.* ***1958***, *80,* 2344; DeKock, R.L. *J. Am. Chem. Soc.* ***1975***, *97,* 5592; McDaniel, D.H.; Coffman, N.B.; Strong, J.M. *J. Am. Chem. Soc.* ***1970***, *92,* 6697. For a computational study of the proton affinities of ketones, vicinal diketones and α-keto esters, see Taskinen, A.; Nieminen, V.; Toukoniitty, E.; Murzin, D.Yu.; Hotokka, M. *Tetrahedron* ***2005***, *61,* 8109.

[84] For measnurement of amine basicity via ion pair statibity in ionic liquids (Sec. 9.D.iii), see D'Anna, F.; Renato Noto, R. *Tetrahedron* ***2007***, *63,* 11681.

[85] Caskey, D.C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* ***2002***, *67,* 5098.

[86] Streitwieser, A.; Kim, H.-J. *J. Am. Chem. Soc.* ***2000***, *122*, 11783; Garrido, G.; Koort, E.; Ràfols, C.; Bosch, E.; Rodima, T.; Leito, I.; Rosés, M. *J. Org. Chem.* ***2006***, *71,* 9062.

[87] Canle, L.M.; Demirtas, I.; Freire, A.; Maskill, H.; Mishima, M. *Eur. J. Org. Chem.* ***2004***, 5031.

[88] Chmurzynski, L. *J. Heterocyclic Chem.* ***2000***, *37*, 71.

[89] Perrin, C.L.; Ohta, B.K.; Kuperman, J.; Liberman, J.; Erdélyi, M. *J. Am. Chem. Soc.* ***2005***, *127,* 9641.

TABLE 8.2 The pK_{HB} Values for Many Types of Bases

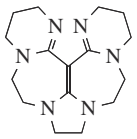
Base	Approximate pK_{HB}	Reference
N-Methyl-2-piperidone	2.60	90
$Et_2NCONEt_2$	2.43	90
N-Methyl-2-pyrrolidinone	2.38	90
$PhCONMe_2$	2.23	90
$HCONMe_2$	2.10	90
PhCONHMe	2.03	90
18-crown-6	1.98	91
HCONHMe	1.96	90
Aniline	4.60	92
N-methylaniline	4.85	92
$PhNHNH_2$	5.27	92
$Ph(Me)NNH_2$	4.99	92
15-crown-5	1.82	91
12-crown-4	1.73	91
$PhOCONMe_2$	1.70	90
$Et_2N—CN$	1.63	93
$Me_2N—CN$	1.56	93
δ-Valerolactone	1.43	94
Oxetane	1.36	91
γ-Butyrolactone	1.32	94
THF	1.28	91
Cyclopentanone	1.27	95
t-BuOMe	1.19	91
Acetone	1.18	95
MeCOOEt	1.07	95
1,4-Dioxane	1.03	91
Et_2O	1.01	91
1,3-Dioxane	0.93	91
1-Methyloxirane	0.97	91
PhCOOMe	0.89	94
MeOCOOMe	0.82	94
PhCHO	0.78	95
Bu_2O	0.75	91
HCOOEt	0.66	94
MeCHO	0.65	95
Me_2NO_2	0.41	96
$MeNO_2$	0.27	96
$PhNO_2$	0.30	96
Furan	−0.40	91

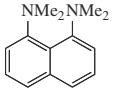
[90] Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 2091.
[91] Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* ***1998***, 925.
[92] Korzhenevskaya, N.G.; Rybachenko, V.I.; Kovalenko, V.V.; Lyashchuk, S.N.; Red'ko, A.N. *Russ. J. Org. Chem.* ***2007*** *, 43,* 1475.
[93] Berthelot, M.; Helbert, M.; Laurence, C.; LeQuestel, J.-Y.; Anvia, F.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 625.
[94] Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 485.
[95] Besseau, F.; Luçon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 101.
[96] Laurence, C.; Berthelot, M.; Luçon, M.; Morris, D.G. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 491.

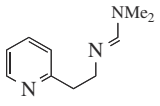
also been examined, and the basicity of carbonyl compounds in carbon tetrachloride has been determined.[97] Alkenes are weak bases[98] that react with strong acids (e.g., HCl or HBr, Reaction **15-02**). Note that extremely twisted amides (Sec. 4.Q.ii) exhibit high basicity.[99]

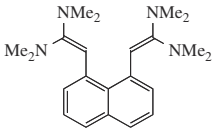
A class of organic compounds termed *superbases* has been developed.[100] Vinamidine type or *Schwesinger proton sponges* (see Sec. 8.F), **1**,[101] are dubbed superbases and are probably the most powerful organic neutral bases known. The pK_a (pK_{BH^+}) in MeCN was measure as 31.94. It has been shown that the pK_a values of strong neutral organic (super) bases in acetonitrile are well described by the density functional theory.[102] The fundamental type of proton sponge is 1,8-bis(dimethylamino)naphthalene (**2**, see Sec. 8.F), with a pK_{BH^+} of 18.18.[103] Other superbase-type compounds include amidinazines [e.g., N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)-formamidine (**3**)], pK_{BH^+} in DMSO = 25.1,[104] 1,8-bis (tetramethylguanidino)naphthalene, (**4**),[105] and quinolino[7,8-*h*]quinolines (e.g., **5**) with a pK_{BH^+} = 12.8.[106]

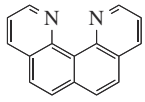
It is important to note that organometallic compounds, such as *Grignard reagents* (RMgX) and organolithium reagents (RLi),[107] are powerful bases. The conjugate bases of both of these bases are alkanes, (R—H), which are very weak acids indeed (see Table 8.1).


1


2


3


4


5

[97] Carrasco, N.; González-Nilo, F.; Rezende, M.C. *Tetrahedron* ***2002***, *58,* 5141.
[98] A new scale of π-basicity is proposed. See Stoyanov, E.S.; Stoyanova, I.V.; Reed, C.A. *Chemistry: European J.* ***2008***, *14,* 7880.
[99] Ly, T.; Krout, M.; Pham, D.K.; Tani, K.; Stoltz, B.M.; Julian, R.R. *J. Am. Chem. Soc.* ***2007***, *129*, 1864.
[100] For calculated basicities of super bases see Glasovac, Z.; Eckert-Maksić, M.; Maksić, Z.B. *New J. Chem.,* ***2009***, *33,* 588.
[101] Schwesinger, R.; Mißfeldt, M.; Peters, K.; von Schnering, H.G. *Angew. Chem. Int. Ed.* ***1987***, *26,* 1165; Schwesinger, R.; Schlemper, H.; Hasenfratz, Ch.; Willaredt, J.; Dimbacher, T.; Breuer, Th.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H.W.; Bordwell, F.G.; Satish, A.V.; Ji, G.Z.; Peters, E.-M.; Peters, K.; von Schnering, H.G. *Liebigs Ann.* ***1996***, 1055.
[102] Kovačević, B.; Maksić, Z.B. *Org. Lett.* ***2001***, *3,* 1523.
[103] Alder, R.W.; Bowman, P.S.; Steele, W.R.S.; Winterman, D.R. *Chem. Commun.* ***1968***, 723 ; Alder, R.W. *Chem. Rev.* ***1989***, *89,* 1215.
[104] Raczynska, E.D.; Darowska, M.; Dabkowska, I.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Poliart, C.D. *J. Org. Chem.* ***2004***, *69,* 4023.
[105] Raab, V.; Kipke, J.; Gschwind, R.M.; Sundermeyer, J. *Chem. Eur. J.* ***2002***, *8*, 1682.
[106] Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28,* 84.
[107] Gorecka-Kobylinska, J.; Schlosser, M. *J. Org. Chem.* ***2009***, *74*, 222.

8.B. THE MECHANISM OF PROTON-TRANSFER REACTIONS

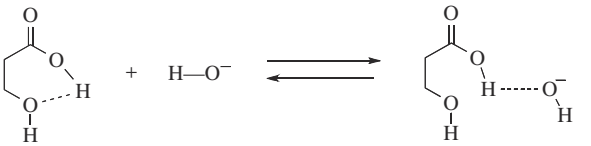
Proton transfers between a base and an oxygen or nitrogen acid are usually extremely fast.[108] Such reactions are generally diffusion controlled in the thermodynamically favored direction.[109] In fact, a *normal acid* is defined[110] as one whose proton-transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a pK value very close (differs by less than ~ 2 pK units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:

1. HA + | B ⇌ AH••|••B
2. AH•••|•B ⇌ A•|••••HB
3. A|••••HB ⇌ A| + HB

The actual proton transfer takes place in the second step the first step is formation of a hydrogen-bonded complex. The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.[111] In a case such as 3-hydroxypropanoic acid, the $^-$OH ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between $^-$OH ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions, the $^-$OH ions will come away "empty-handed", resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium. Other systems are capable of hydrogen bonding (e.g., 1,2-diols). In the case of cyclohexane-1,2-diols, hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry all play a role in determining the acidity.[112] The presence of halogen atoms (e.g., chlorine) can lead to hydrogen-bonding effects.[113] Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown in Sec. 4.L). See also the proton sponges mentioned in Section 8.F. Proton transfers between an acidic and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases, participation of solvent molecules may be necessary.

3-Hydroxypropanoic acid + H—O$^-$ ⇌



[108] For reviews of such proton transfers, see Hibbert, F. *Adv. Phys. Org. Chem.* ***1986***, *22*, 113; Crooks, J.E. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8; Elsevier, NY, ***1977***, pp. 197–250. See Bernasconi, C.F.; Fairchild, D.E.; Montañez, R.L.; Aleshi, P.; Zheng, H.; Lorance, E. *J. Org. Chem.* ***2005***, *70,* 7721.
[109] See Eigen, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 1.
[110] See, for example, Hojatti, M.; Kresge, A.J.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 4023.
[111] See Ritchie, C.D.; Lu, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8542.
[112] Chen, X.; Walthall, D.A.; Brauman, J.I. *J. Am. Chem. Soc.* ***2004***, *126*, 12614.
[113] Abraham, M. H.; Enomoto, K.; Clarke, E. D.; Sexton, G. *J. Org. Chem.* ***2002***, *67*, 4782.

Proton transfers to or from a carbon atom[114] in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,[115] not all of them applying in every case.

1. Hydrogen bonding is very weak or altogether absent for carbon (Chap 3).
2. Loss of a proton from many carbon acids leads to carbanions that are stabilized by resonance. Calculations show that carbon acidity is influenced by coordination based on electrophile coordination geometry.[116] Structural reorganization (movement of atoms to different positions within the molecule) may accompany this process. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these[117] behave kinetically as normal acids.[118] It has been reported that carborane acids [e.g., $H(CHB_{11}H_5Cl_6)$] are the strongest isolable (Lewis-free) Brønsted acids known.[119]
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.[120]

In connection with factors 2 and 3, it has been proposed[115] that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the *Principle of Imperfect Synchronization*.

Mechanisms of proton transfer have been studied for many compounds, including the reactions of acids with lactams,[121] amides with various bases,[122] and amines with alkoxide bases.[123]

8.C. MEASUREMENTS OF SOLVENT ACIDITY[124]

When a solute is added to an acidic solvent it may become protonated by the solvent. This effect can lead to an enhancement of acidity, as in the effect of using formic acid rather than methanol.[125] An acidity scale has been reported for ionic liquids[126] (see Sec. 9.D.iii for a discussion of ionic liquids), and the Lewis acidity of ionic liquids has been established

[114] See Hibbert, F. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 97–196; Kreevoy, M.M. *Isot. Org. Chem.* ***1976***, *2*, 1; Leffek, K.T. *Isot. Org. Chem.* ***1976***, *2*, 89.
[115] See Bernasconi, C.F. *Tetrahedron* ***1985***, *41*, 3219.
[116] Houk, R.J.T.; Anslyn, E.V.; Stanton, J.F. *Org. Lett.* ***2006***, *8,* 3461.
[117] Kresge, A.J.; Powell, M.F. *J. Org. Chem.* ***1986***, *51*, 822; Formosinho, S.J.; Gal, V.M.S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1655.
[118] Not all 1-alkynes behave as normal acids; see Aroella, T.; Arrowsmith, C.H.; Hojatti, M.; Kresge, A.J.; Powell, M.F.; Tang, Y.S.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 7198.
[119] Juhasz, M.; Hoffmann, S.; Stoyanov, E.; Kim, K.-C.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43,* 5352.
[120] See Kurz, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 8631.
[121] Wang, W.; Cheng, P.; Huang, C.; Jong, Y. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 562.
[122] Wang, W.-h.; Cheng, C.-c. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1054.
[123] Lambert, C.; Hampel, F.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1992***, *31*, 1209.
[124] For fuller treatments, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 263–313; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 83–93; Arnett, E.M.; Scorrano, G. *Adv. Phys. Org. Chem.* ***1976***, *13*, 83.
[125] Holt, J.; Karty, J.M. *J. Am. Chem. Soc.* ***2003***, *125*, 2797.
[126] Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. J. *Am. Chem. Soc.* ***2003***, *125,* 5264.

using IR.[127] If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed that works in concentrated solutions and applies to mixed solvents as well. The *Hammett acidity function*[128] is a measurement that is used for acidic solvents of high dielectric constant.[129] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \mathrm{p}K_{\mathrm{BH_w^+}} - \log \frac{[\mathrm{BH^+}]}{[\mathrm{B}]}$$

H_0 is measured by using "indicators" that are weak bases (B) and so are partly converted, in these acidic solvents, to the conjugate acids BH^+. Typical indicators are *o*-nitroanilinium ion, with a pK in water of -0.29, and 2,4-dinitroanilinium ion, with a pK in water of -4.53. For a given solvent, $[BH^+]/[B]$ is measured for one indicator, usually by spectrophotometric means and with the known pK in water ($\mathrm{p}K_{\mathrm{BH_w^+}}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, pK_a values in it can be calculated for any other acid–base pair.

The symbol H_0 is defined as

$$h_0 = \frac{a_{\mathrm{H^+}} f_{\mathrm{I}}}{f_{\mathrm{HI^+}}}$$

where a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,[130] respectively. The parameter H_0 is related to H_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH and H_0 to $[H^+]$, and indeed in dilute aq solution $H_0 = \mathrm{pH}$.

The parameter H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids (nitric, sulfuric, perchloric, etc.). It is apparent that the H_0 treatment is valid only when f_I/f_{HI^+} is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.[131] Other acidity scales[132] have been set up,

[127] Yang, Y.-l.; Kou, Y. *Chem. Commun.* ***2004***, 226.
[128] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1932***, *54*, 2721.
[129] See Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***; Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225; Boyd R.H. in Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 97–218.
[130] See Yates, K.; McClelland, R.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 323.
[131] See Kreevoy, M.M.; Baughman, E.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8178; García, B.; Leal, J.M.; Herrero, L.A.; Palacios, J.C. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1759; Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.
[132] For lengthy tables of many acidity scales, with references, see Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225. For an equation that is said to combine the vast majority of acidity functions, see Zalewski, R.I.; Sarkice, A.Y.; Geltz, Z. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1059.

including a scale for C—H acids,[133] among them H_- for bases with a charge of -1, H_R for aryl carbinols,[134] H_C for bases that protonate on carbon,[135] and H_A for unsubstituted amides.[136] It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.[137]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.[138] The H_- function, which is used for highly acidic solutions when the base has a charge of -1, can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid (BH).[139] When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett et al.,[140] who derived the equation

$$\log \frac{[SH^+]}{[S]} + H_0 = \phi(H_0 + \log [H^+]) + pK_{SH^+}$$

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of log $([SH^+]/[S]) + H_0$ against $H_0 + \log [H^+]$ is the parameter ϕ, while the intercept is the pK_a of the lyonium ion (SH^+, referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium

$$S + H^+ \rightleftharpoons SH^+$$

to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[SH^+]/[S]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The *Bunnett–Olsen equation* given above is a linear free–energy relationship (see Sec. 9.C) that pertains to acid–base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\Psi + H_0 = \Phi(H_0 + \log [H^+]) + \log k_2^o$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2^o is the second-order rate constant at infinite dilution in water. In this case, ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The *Bunnett–Olsen treatment* has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation

[133] See Vianello, R.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2004***, 5003.
[134] Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.
[135] Reagan, M.T. *J. Am. Chem. Soc.* ***1969***, *91*, 5506.
[136] Edward, J.T.; Wong, S.C. *Can. J. Chem.* ***1977***, *55*, 2492; Liler, M.; Marković, D. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 551.
[137] Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, p. 278; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, p. 21.
[138] For another approach to solvent basicity scales, see Catalán, J.; Gómez, J.; Couto, A.; Laynez, J. *J. Am. Chem. Soc.* ***1990***, *112*, 1678.
[139] See Rochester, C.H. *Q. Rev. Chem. Soc.* ***1966***, *20*, 511; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, pp. 234–264; Bowden, K. *Chem. Rev.* ***1966***, *66*, 119.
[140] Bunnett, J.F.; McDonald, R.L.; Olsen, F.P. *J. Am. Chem. Soc.* ***1974***, *96*, 2855.

was found between reaction rates and either H_- or stoichiometric base concentration, but where the rates were successfully correlated by a linear free energy equation similar to those given above.[141]

A treatment partially based on the *Bunnett–Olsen treatment* is that of Bagno et al.,[142] which formulates medium effects (changes in acidity of solvent) on acid–base equilibria. An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free energy equation

$$\log \frac{K'}{K'_0} = m^* \log \frac{K}{K_0}$$

where the K values are the equilibrium constants for the following: K for the reaction under study in any particular medium; K' for the reference reaction in the same medium; K_0 for the reaction under study in a reference solvent; K'_0 for the reference reaction in the same reference solvent; and m^* is the slope of the relationship [corresponding to $(1 - \phi)$ of the *Bunnett–Olsen treatment*]. This equation has been shown to apply to many acid–base reactions.

Another type of classification system was devised by Bunnett[143] for reactions occurring in moderately concentrated acid solutions. Log $k_\psi + H_0$ is plotted against log a_{H_2O}, where K_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; where w is between 3.3 and 7, water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

A new acidity scale has been developed based on calorimetric measurement of *N*-methylimidazole and *N*-methylpyrrole in bulk solvents.[144] A revised version of this method was shown to give better results in some cases.[145] Another scale of solvent acidities was developed based on the hydrogen-bond donor acidities in aq DMSO.[146] Note that bond energies, acidities, and electron affinities are related in a thermodynamic cycle, and Fattahi and Kass[147] show that by measuring two of these quantities the third can be found.

8.D. ACID AND BASE CATALYSIS[148]

Many reactions are catalyzed by acids or bases. Some are catalyzed by both acids and bases. In such cases, the catalyst is involved in a fundamental way in the mechanism. The

[141] More O'Ferrall, R.A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 976.
[142] Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313. See also, Cox, R.A. *Acc. Chem. Res.* ***1987***, *20*, 27.
[143] Bunnett, J.F. *J. Am. Chem. Soc.* ***1961***, *83*, 4956, 4968, 4973, 4978.
[144] Catalán, J.; Couto, A.; Gomez, J.; Saiz, J.L.; Laynez, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1181.
[145] Abraham, M.H.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 305.
[146] Liu, P.C.; Hoz, S.; Buncel, E. *Gazz. Chim. Ital.* ***1996***, *126*, 31. See also, Abraham, M.H.; Zhao, Y.J. *J. Org. Chem.* ***2004***, *69*, 4677.
[147] Fattahi, A.; Kass, S.R. *J. Org. Chem.* ***2004***, *69,* 9176.
[148] See Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985,*** pp. 251–305; Willi, A.V. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 1–95; Jones, R.A. Y. *Physical and Mechanistic Organic Chemistry,* 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 72–82; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins,* Wiley, NY, ***1971***, pp. 19–144.

first step of such a reaction is nearly always a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent (S) is proportional to its conjugate acid [SH^+], the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion (SH^+). The acid that is put into the solvent may be stronger or weaker than SH^+, but the rate is proportional only to the [SH^+] that is actually present in the solution derived from the equilbrium

$$S + HA \rightleftharpoons SH^+ + A^-$$

The identity of HA is important only to the extent that it determines the position of equilibrium, and hence the [SH^+]. Most measurements have been made in water, where SH^+ is H_3O^+.

In *general acid catalysis*, the rate is increased not only by an increase in [SH^+], but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when [SH^+] is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in [H_3O^+]. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*[149]

$$\log k = \alpha \log K_\alpha + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_α. According to this equation, when $\log k$ is plotted against $\log K_\alpha$ for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope and intercept C. Straight lines are obtained in many cases, but not always. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols[150] and carboxylic acids. The Brønsted equation is another linear free energy relationship (see Sec. 9.C).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \log K_b + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_a. In Chapter 6, the *Marcus equation* was seen to relate a rate term (in that case $\Delta G^\ddagger$) to an equilibrium term (ΔG°). When the Marcus treatment is applied to proton transfers[151] between a carbon and an oxygen (or a nitrogen), the simplified[152] equation (Sec. 6.I)

$$\Delta G^\ddagger = \Delta G^\ddagger_{int} + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{16\Delta G^\ddagger_{int}}$$

[149] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 167–179; Bell, R.P. in Chapman, N. B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum Press, ***1978***, pp. 55–84; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[150] See Silva, P.J. *J. Org. Chem.* ***2009***, *74*, 914.

[151] See Marcus, R.A. *J. Phys. Chem.* ***1968***, *72*, 891; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[152] Omitting the work terms.

where

$$\Delta G^{\ddagger}_{\text{int}} = \frac{1}{2}\left(\Delta G^{\ddagger}_{\text{O,O}} + \Delta G^{\ddagger}_{\text{C,C}}\right)$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G^{\ddagger}_{(\text{O,O})}$ is much smaller than $\Delta G^{\ddagger}_{(\text{C,C})}$ and one can write[153]

$$\Delta G^{\ddagger} = \frac{1}{2}\Delta G^{\ddagger}_{\text{C,C}} + \frac{1}{2}\Delta G^{\circ} + \frac{(\Delta G^{\circ})^2}{8\Delta G^{\ddagger}_{\text{C,C}}}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then $\Delta G^{\ddagger}$ is dependent only on ΔG°. Differentiation of this equation yields the Brønsted α:

$$\frac{d\Delta G^{\ddagger}}{d\Delta G^{\circ}} = \alpha = \frac{1}{2}\left(1 + \frac{\Delta G^{\circ}}{2\Delta G^{\ddagger}_{\text{C,C}}}\right)$$

The *Brønsted law* is therefore a special case of the *Marcus equation*.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write

$$\text{Step 1} \quad A + SH^{+} \rightleftharpoons AH^{+}$$

$$\text{Step 2} \quad AH^{+} \longrightarrow \text{Products}$$

If the reaction is catalyzed only by the specific acid SH^{+}, it means that step 1 is rapid and step 2 is rate controlling. This means that an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^{+} (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids that may be present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex (A···HB), since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.[154] Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases, values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; that is, the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; that is, in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,[155] and their theoretical basis has been challenged.[156] In general, the proton in the transition state lies closer to the weaker base.

[153] Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227, p. 244.

[154] See Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; Stewart, R.; Srinivasan, R. *Acc. Chem. Res.* ***1978***, *11*, 271; Guthrie, J.P. *J. Am. Chem. Soc.* ***1980***, *102*, 5286.

[155] See Agmon, N. *J. Am. Chem. Soc.* ***1980***, *102*, 2164; Murray, C.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7561.

[156] Pross, A.; Shaik, S.S. *New J. Chem.* ***1989***, *13*, 427; Lewis, E.S. *J. Phys. Org. Chem.* ***1990***, *3*, 1.

8.E. LEWIS ACIDS AND BASES

At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. However, a *Lewis base* donates electrons to an atom other than H or C.[157] A *Lewis acid* is any species with a vacant orbital.[158] In a Lewis acid–base reaction, the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation

$$A + :B \longrightarrow A{-}B$$

in which charges are not shown, since they may differ. A specific example is

$$BF_3 + :NH_3 \longrightarrow F_3\bar{B} \longrightarrow \overset{+}{N}H_3$$

In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. Lewis acids $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for 10 or 12. Other Lewis acids are simple cations, like Ag^+. The simple reaction $A + \bar{B} \longrightarrow A - B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types shown here, which are very common in organic chemistry, are also Lewis acid–base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid–base reactions. An *ab initio* analysis of the factors that determine Lewis versus Lowry–Brønsted acidity–basicity is available.[159]

$$\begin{aligned} A^1 + A^2{-}B &\longrightarrow A^1{-}B + A^2 \\ B^1 + A{-}B^2 &\longrightarrow A{-}B^1 + B^2 \\ A^1{-}B^1 + A^2{-}B^2 &\longrightarrow A^1{-}B^2 + A^2{-}B^1 \end{aligned}$$

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher than normal valence, the resulting salt is called an *ate complex*.[160] Examples are

$$\begin{aligned} Me_3B + LiMe &\longrightarrow Me_4B^-\ Li^+ \quad \text{Ate complex} \\ Ph_5Sb + LiPh &\longrightarrow Ph_6Sb^-\ Li^+ \quad \text{Ate complex} \end{aligned}$$

[157] Lewis bases are useful catalysts in organic synthesis. See Denmark, S.E.; Beutner, G.L. *Angew. Chem. Int. Ed.* ***2008***, *47,* 1560.

[158] For a monograph on Lewis acid–base theory, see Jensen, W.B. *The Lewis Acid–Base Concept*, Wiley, NY, ***1980***. For a discussion of the definitions of Lewis acid and base, see Jensen, W.B. *Chem. Rev.* ***1978***, *78*, 1.

[159] Rauk, A.; Hunt, I.R.; Keay, B.A. *J. Org. Chem.* ***1994***, *59*, 6808.

[160] For a review of ate complexes, see Wittig, G. *Q. Rev. Chem. Soc.* ***1966***, *20*, 191.

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, for example,

$$Me_3N + MeI \longrightarrow Me_4N^+ \quad I^- \qquad \text{onium salt}$$

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.[161] A simple table of Lewis acidities based on some quantitative measurement (e.g., that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base and any solvent that can function as a base. For example, lithium perchlorate functions as a weak Lewis acid in ether.[162] Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

8.E.i Hard–Soft Acids–Bases

The facility with which an acid–base reaction takes place depends, of course, on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness*[163] or *softness* of the acid or base.[164] Hard and soft acids and bases have these characteristics:

Soft Bases. The donor atoms are of low electronegativity and high polarizability, and are easy to oxidize. They hold their valence electrons loosely.

Hard Bases. The donor atoms are of high electronegativity and low polarizability, and are hard to oxidize. They hold their valence electrons tightly.

Soft Acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard Acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.3.[165] The treatment has also been made quantitative,[166] with the following operational

[161] See Satchell, D.P.N.; Satchell, R.S. *Q. Rev. Chem. Soc.* ***1971***, *25*, 171; *Chem. Rev.* ***1969***, *69*, 251. See also, Sandström, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* ***1990***, *44*, 653; Laszlo, P.; Teston-Henry, M. *Tetrahedron Lett.* ***1991***, *32*, 3837.

[162] Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R.M.; Kabalka, G.W. *J. Org. Chem.* ***1999***, *64,* 2202.

[163] See Ayers, P.W.; Parr, R.G. *J. Am. Chem. Soc.* ***2000***, *122*, 2010.

[164] Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1827. For a monograph on the concept, see Ho, T. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, NY, ***1977;*** Pearson, R.G. *J. Chem. Educ.* ***1987***, *64*, 561; Ho, T. *Tetrahedron* ***1985***, *41*, 1; Pearson, R.G. in Chapman, N.B.; Shorter, J. *Advances in Linear Free-Energy Relationships*, Plenum Press, NY, ***1972***, pp. 281–319. For a collection of papers, see Pearson, R.G. *Hard and Soft Acids and Bases*, Dowden, Hutchinson, and Ross, Stroudsberg, PA, ***1973***.

[165] Taken from Pearson, R.G. *J. Chem. Ed.* ***1968***, *45,* 581, 643.

[166] Pearson, R.G. *Inorg. Chem.* ***1988***, *27*, 734; *J. Org. Chem.* ***1989***, *54*, 1423. See also, Orsky, A.R.; Whitehead M. A. *Can. J. Chem.* ***1987***, *65*, 1970.

TABLE 8.3 Hard and Soft Acids and Bases[a]

Hard Bases	Soft Bases	Borderline Cases
H_2O, OH^-, F^-	R_2S, RSH, RS^-,	$ArNH_2$, C_5H_5N
AcO^-, SO_4^{2-}, Cl^-	I^-, R_3P, $(RO)_3P$,	N_3^-, Br
CO_3^{2-}, NO_3^-, ROH	CN^-, RCN, CO,	NO_2^-
RO^-, R_2O, NH_3	C_2H_4, C_6H_6	
RNH_2	H^-, R^-	
Hard Acids	**Soft Acids**	**Borderline Cases**
H^+, Li^+, Na^+	Cu^+, Ag^+, Pd^{2+}	Fe^{2+}, Co^{2+}, Cu^{2+}
K^+, Mg^{2+}, Ca^{2+}	Pt^{2+}, Hg^{2+}, BH_3	Zn^{2+}, Sn^{2+}, Sb^{3+}
Al^{3+}, Cr^{2+}, Fe^{3+}	$GaCl_3$, I_2, Br_2	Bi^{3+}, BMe_3, SO_2
BF_3, $B(OR)_3$, $AlMe_3$	CH_2, Carbenes	R_3C^+, NO^+, GaH_3
$AlCl_3$, AlH_3, SO_3		$C_6H_5^+$
RCO^+	CO_2	
HX (hydrogen-bonding molecules)		

Reprinted with permission Pearson, R.G. *J. Chem. Ed.* ***1968***, *45*, 581, 643. Copyright © 1968 American Chemical Society.

[a]See Ref. 165.

definition:

$$\eta = \frac{I - A}{2}$$

In this equation, η, the *absolute hardness*, is half the difference between I, the ionization potential, and A, the electron affinity.[167] The softness (σ), is the reciprocal of η. Values of η for some molecules and ions are given in Table 8.4.[168] Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion X^- is the same as that for the radical $X^{\bullet}$.[169] Other methods are also needed to apply the treatment to polyatomic cations.[169]

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases [the HSAB (hard–soft acid–base) principle].*[170] The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to form ionic bonds.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (see above). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag^+, Pt^{2+}, and Hg^{2+} complexes are common, but complexes of Na^+, Mg^{2+}, or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which

[167] See Sauers, R.R. *Tetrahedron* ***1999***, *55,* 10013.

[168] Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* ***1983***, *105*, 7512. Note that there is not always a strict correlation between the values in Table 8.4 and the categories of Table 8.3.

[169] Pearson, R.G. *J. Am. Chem. Soc.* ***1988***, *110*, 7684.

[170] For proofs of this principle, see Chattaraj, P.K.; Lee, H.; Parr, R.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1855.

TABLE 8.4 Some Absolute Hardness Values in Electron Volts[a]

Cations		Molecules		Anions[b]	
Ion	η	Compound	η	Ion	η
H^+	∞	HF	11.0	F^-	7.0
Al^{3+}	45.8	CH_4	10.3	H^-	6.4
Li^+	35.1	BF_3	9.7	OH^-	5.7
Mg^{2+}	32.6	H_2O	9.5	NH_2^-	5.3
Na^+	21.1	NH_3	8.2	CN^-	5.1
Ca^{2+}	19.5	HCN	8.0	CH_3^-	4.9
K^+	13.6	$(CH_3)_2O$	8.0	Cl^-	4.7
Zn^{2+}	10.9	CO	7.9	$CH_3CH_2^-$	4.4
Cr^{3+}	9.1	C_2H_2	7.0	Br^-	4.2
Cu^{2+}	8.3	$(CH_3)_3N$	6.3	$C_6H_5^-$	4.1
Pt^{2+}	8.0	H_2S	6.2	SH^-	4.1
Sn^{2+}	7.9	C_2H_4	6.2	$(CH_3)_2CH^-$	4.0
Hg^{2+}	7.7	$(CH_3)_2S$	6.0	I^-	3.7
Fe^{2+}	7.2	$(CH_3)_3P$	5.9	$(CH_3)_3C^-$	3.6
Pd^{2+}	6.8	CH_3COCH_3	5.6		
Cu^+	6.3	C_6H_6	5.3		
		HI	5.3		
		C_5H_5N	5.0		
		C_6H_5OH	4.8		
		CH_2[c]	4.7		
		C_6H_5SH	4.6		
		Cl_2	4.6		
		$C_6H_5NH_2$	4.4		
		Br_2	4.0		
		I_2	3.4		

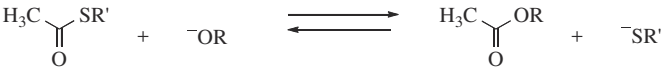
Reprinted with permission from Parr, R.G.; Pearson, R.G.; *J. Chem. Ed.* ***1983***, *105*, 7512. Copyright © 1983 American Chemical Society.

[a]See Ref. 168.

[b]The same as for the corresponding radical.

[c]For singlet state.

softens it) or attached to other soft ligands. Another application is the reaction:



The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base (RO^-) than for the soft base (RS^-). Indeed, thiol esters are easily cleaved by RO^- or hydrolyzed by dilute base (^-OH is also a hard base).[171] Another application of the rule is discussed in Section 10.G.ii.[172] The

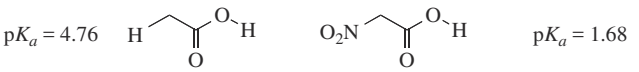
[171] Wolman, Y. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, p. 677; Maskill, H. *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford ***1985***, p. 159.
[172] See also, Bochkov, A.F. *J. Org. Chem. USSR* ***1986***, *22*, 1830, 1837.

HSAB principles have been applied to analyze the reactivity of ketone and ester enolate anions,[173] and in analyzing catalyst selectivity in synthesis.[174]

8.F. THE EFFECTS OF STRUCTURE ON THE STRENGTHS OF ACIDS AND BASES[175]

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.[176] Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. *Field Effects*. These effects were discussed in Section 1.I. In general, changes in substituents can have an effect on acidity. As an example of the influence of field effects on acidity, compare the acidity of acetic acid and 2-nitroacetic acid:



The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO^- group in the anion of 2-nitroacetic acid (compared with the anion of acetic acid). As the pK_a values indicate, 2-nitroacetic acid is $\sim$1000 times stronger than acetic acid.[177] Any effect that results in electron withdrawal from a negatively charged center ($-I$ effect) is a stabilizing effect because it spreads the charge. Thus, $-I$ groups increase the acidity of uncharged acids (e.g., acetic) because they spread the negative charge of the anion. However, $-I$ groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of $+1$ (and its conjugate base is therefore uncharged), a $-I$ group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general, *groups that withdraw electrons by the field effect increase acidity and decrease basicity*, *while electron-donating groups act in the opposite direction*. Another example is the molecule $(C_6F_5)_3CH$, which has three strongly electron-withdrawing C_6F_5 groups and a pK_a of 16,[178] compared with

[173] Méndez, F.; Gázguez, J.L. *J. Am. Chem. Soc.* ***1994***, *116*, 9298.
[174] Woodward, S. *Tetrahedron* ***2002***, *58,* 1017.
[175] See Hine, J. *Structural Effects on Equilibria in Organic Chemistry*, Wiley, NY, ***1975***; Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247; Petrov, E.S. *Russ. Chem. Rev.* ***1983***, *52*, 1144 (NH acids); Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell Univ. Press, Ithaca, NY, ***1973***, pp. 86–110. For a monograph on methods of estimating *pK* values by analogy, extrapolation, and so on, see Perrin, D.D.; Dempsey, B.; Serjeant, E.P. *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, NY, ***1981***.
[176] The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft, R.W.; Koppel, I.A.; Topsom, R.D.; Anvia, F. *J. Am. Chem. Soc.* ***1990***, *112*, 2047.
[177] For a review of the enhancement of acidity by NO_2, see Lewis, E.S. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 715–729.
[178] Filler, R.; Wang, C. *Chem. Commun.* ***1968***, 287.

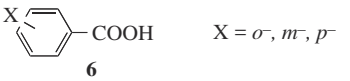
TABLE 8.5 The pK Values for Some Acids[a]

Acid	pK	Acid	pK
HCOOH	3.77	$ClCH_2COOH$	2.86
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3COOH	0.65
$CH_3(CH_2)_nCOOH$	4.82–4.95		
($n = 2$–7)		O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3N^+CH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
		$PhCH_2COOH$	4.31
FCH_2COOH	2.66		
$ClCH_2COOH$	2.86	$^-OOCCH_2COOH$	5.69
$BrCH_2COOH$	2.86		
ICH_2COOH	3.12	$^-O_3SCH_2COOH$	4.05
		$HOCH_2COOH$	3.83
$ClCH_2CH_2CH_2COOH$	4.52	$H_2C{=}CHCH_2COOH$	4.35
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.84		

[Reprinted with permission from Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***, pp. 567–662, Copyright © 1955, with permission from Elsevier Science.]

[a]See Ref. 47.

Ph_3CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of $\sim 10^{15}$. Table 8.5 shows pK_a values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids, the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see Sec. 8.G).[179] The influence of various substituents on the acidity of acetic acid has been calculated,[180] Substituent effects for weak acids (e.g., phenols and benzyl alcohols) have been discussed.[181]

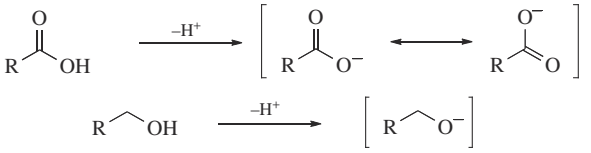


6 X = *o*–, *m*–, *p*–

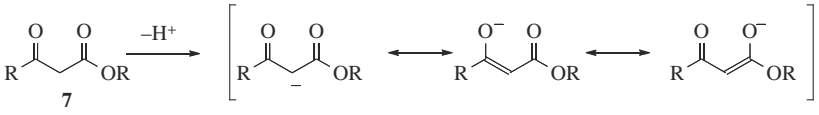
Field effects are important in benzoic acid derivatives, and the pK_a of the acid will vary with the nature and placement of the "X" group in **6**.[182] The pK_a of 3-OMe (**6**) is 5.55, but 4-OMe (**6**) is 6.02 in 50% aq methanol,[183] compared with a pK_a of 5.67 when X = H. When X = 4-NO_2, the pK_a is 4.76 and 4-Br is 5.36.[172] The pK_a of 2,6-diphenylbenzoic acid is 6.39.[184]

[179] See Edward, J.T. *J. Chem. Educ.* ***1982***, *59*, 354; Schwartz, L.M. *J. Chem. Educ.* ***1981***, *58*, 778.
[180] Headley, A.D.; McMurry, M.E.; Starnes, S.D. *J. Org. Chem.* ***1994***, *59*, 1863.
[181] Wiberg, K.B. *J. Org. Chem.* ***2003***, *68*, 875.
[182] For calculated gas-phase acidities of substituted benzoic acids see Wiberg, K.B. *J. Org. Chem.* ***2002***, *67,* 4787. Also see Gupta, K.; Giri, S.; Chattaraj, P.K. *New J. Chem.* ***2008***, *32,* 1945.
[183] DeMaria, P.; Fontana, A.; Spinelli, D.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 649.
[184] Chen, C.-T.; Siegel, J.S. *J. Am. Chem. Soc.* ***1994***, *116*, 5959. See also, Sotomatsu, T.; Shigemura, M.; Murata, Y.; Fujita, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3157.

2. *Resonance Effects*. Resonance that stabilizes a base, but not its conjugate acid, results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids[185] compared with primary alcohols.



The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).[186] Note that the $RCOO^-$ is stabilized not only by the fact that there are 2 equiv canonical forms, but also by the fact that the negative charge is spread over both oxygen atoms, and is therefore less concentrated than in RCH_2O^-. The same effect is found in other compounds containing a C=O or C≡N group. Thus amides ($RCONH_2$) are more acidic than amines (RCH_2NH_2); esters (RCH_2COOR') more than ethers (RCH_2CH_2OR'); and ketones (RCH_2COR') more than alkanes (RCH_2CH_2R') (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading of charge); for example, β-keto esters (see **7**) are more acidic than simple ketones or carboxylic esters (Table 8.1). Compounds such as (**7**) are generically referred to as *active methylene compounds* ($X—CH_2—X$), where X is an electron-withdrawing groups (a carbonyl, cyano, sulfonyl, etc.).[187] The influence of substituents in the α-position of substituted ethyl acetate derivatives has been studied.[188] Extreme examples of this effect are found in the molecules tricyanomethane [$(NC)_3CH$], with a pK_a of −5 (Table 8.1), and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene $(NC)_2C{=}C[CH(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.



7

Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact that can be accounted for by the $-I$ effect of the nitro group. But *p*-nitroaniline is weaker still, though the $-I$ effect should be less because of the greater distance. This result is obtained by taking the canonical form **A** into account. Because **A** contributes to the resonance hybrid,[189] the electron density of

[185] See Exner, O.; Čársky, P. *J. Am. Chem. Soc.* ***2001***, *123,* 9564. See also, Liptak, M.D.; Shields, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 7314.

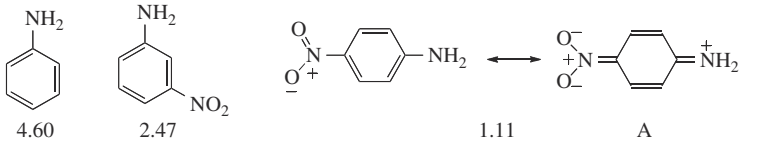
[186] It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the ". . . higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule . . .": Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812. For contrary views, see Exner, O. *J. Org. Chem.* ***1988***, *53*, 1810; Perrin, D.D. *J. Am. Chem. Soc.* ***1991***, *113*, 2865. See also, Godfrey, M. *Tetrahedron Lett.* ***1990***, *31*, 5181.

[187] Copper complexes of active methylene compounds show large pK_a shifts. See Zhong, Z.; Postnikova, B.J.; Hanes, R.E.; Lynch, V.M.; Anslyn, E.V. *Chemistry: European J.* ***2005***, *11,* 2385.

[188] Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* ***2003***, *68,* 6566.

[189] See, however, Krygowski, T.M.; Maurin, J. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 695.

the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form (e.g, **A**) is impossible. Note that the pK_a values reported are those of the conjugate acid, the ammonium ion.[190] The basicity is lower in the para compound for two reasons, both caused by the same effect: (1) the unshared pair is less available for attack by a proton, and (2) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.[191]



4.60 2.47 1.11 A

In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic Table Correlations*. When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:
   a. Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $CH_4 < NH_3 < H_2O <$ HF, and basicity decreases in the order $^-CH_3 > ^-NH_2 > ^-OH > F^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $RCOOH \gg RCONH_2 \gg RCOCH_3$.
   b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $HF < HCl < HBr < HI$ and $H_2O < H_2S$, and basicity decreases in the order $NH_3 > PH_3 > AsH_3$. This behavior is related to the size of the species involved. Thus, for example, F^-, which is much smaller than I^-, attracts a proton much more readily because its negative charge occupies a smaller volume, and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see Sec. 8.E). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $H_2O < H_2S < H_2Se$, the acidity order for the positively charged ions is $H_3O^+ > H_3S^+ > H_3Se^+$.[192]

Lewis acidity is also affected by periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n[161]:

   c. Acids that require only one electron pair to complete an outer shell are stronger than those that require two. Thus $GaCl_3$ is stronger than $ZnCl_2$. This results from the relatively smaller energy gain in adding an electron pair that does not

[190] Smith, J.W. in Patai, S. *The Chemistry of the Amino Group;* Wiley, NY, ***1968***, pp. 161–204.
[191] Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldus, S.; Shields, G.C. *J. Am. Chem. Soc.* ***2002***, *124,* 6421.
[192] Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247, see Sec. 5.B.i.

complete an outer shell and from the buildup of negative charge if two pairs come in.

d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than $AlCl_3$.[193]

4. *Statistical Effects.* In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are 2 equiv ionizable hydrogens, while the second constant is only one-half as large as expected because the conjugate base can accept a proton at 2 equiv sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with 2 equiv basic groups.[194]

5. *Hydrogen Bonding.* Internal hydrogen bonding can greatly influence acid or base strength. For example, the p*K* for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the $^{-}$OH and COO^{-} groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

6. *Steric Effects.* The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 8.6 shows the order of base strength of simple amines when compared against acids of various size.[195] It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

   Steric effects can indirectly affect acidity or basicity by affecting the resonance (Sec. 2.F). For example, *o-tert*-butylbenzoic acid is ~ 10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *tert*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron donating or electron withdrawing.

   Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**8**) is an extremely strong base for a tertiary amine (pK_a of the conjugate acid = 16.3; cf. *N,N*-dimethylaniline, pK_a = 5.1), but proton transfers to and from the nitrogen are exceptionally slow; slow enough to be

[193] Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^{-} and I^{-} give up the proton.

[194] The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, L. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 211–293.

[195] Brown, H.C. *J. Am. Chem. Soc.* ***1945***, *67*, 378, 1452, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 53–64. See also, Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. *J. Am. Chem. Soc.* ***1978***, *100*, 3343.

TABLE 8.6 Bases Listed in Increasing Order of Base Strength when Compared with Certain Reference Acids

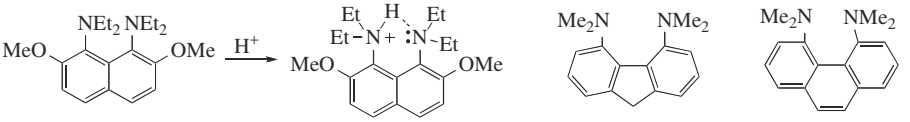
	Reference Acid			
Increasing Order of Base Strength[a]	H^+ or BMe_3	BMe_3	$B(CMe_3)_3$	
↓	NH_3	Et_3N	Me_3N	Et_3N
	Me_3N	NH_3	Me_2NH	Et_2NH
	$MeNH_2$	Et_2NH	NH_3	$EtNH_2$
	Me_2NH	$EtNH_2$	$MeNH_2$	NH_3

[a]The order of basicity (when the reference acids were boranes) was determined by the measurement of dissociation pressures.

Adapted material from *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 53–64, Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.

Reprinted with permission Brown, H.C. *J. Am. Chem. Soc.* ***1945***, *67*, 378, 1452. Copyright © 1945 American Chemical Socity.

followed by a UV spectrophotometer.[196] Compound **8** is severely strained because the two nitrogen lone pairs are forced to be near each other.[197] Protonation relieves the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen

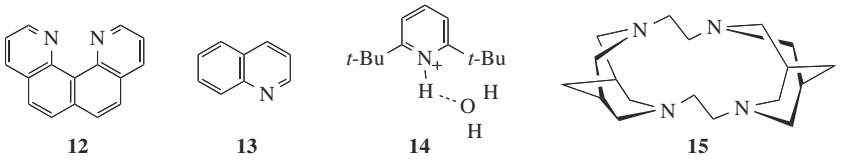


8 **9** **10** **11**

bond to the other lone pair (shown in **9**). The same effects are found in 4,5-bis (dimethylamino)fluorene (**10**)[198] and 4,5-bis(dimethylamino)phenanthrene (**11**).[199] Compounds (e.g., **8**, **10**, and **11**), are known as *proton sponges*.[200] The basicity of a proton sponge has been calculated as the sum of the proton affinity[152] of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation.[201] Another type of proton sponge is quino[7,8-*h*]quinoline (**12**).[202] Protonation of this compound also gives a stable mono protonated ion similar to **9**, but the steric hindrance found in **8**, **10**, and **11** is absent. Therefore, **12** is a much stronger base than quinoline (**13**) (pK_a values of the conjugate acids are 12.8 for **12** and 4.9 for **13**), but proton transfers are not abnormally slow. A cyclam-like macrocyclic tetramine (**15**) was prepared by a coupling reaction of bispidine, and was shown to be a new class of

[196] Hibbert, F.; Simpson, G.R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 243, 613.
[197] For a review of the effect of strain on amine basicities, see Alder, R.W. *Chem. Rev.* ***1989***, *89*, 1215.
[198] Staab, H.A.; Saupe, T.; Krieger, C. *Angew. Chem. Int. Ed.* ***1983***, *22*, 731.
[199] Saupe, T.; Krieger, C.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 451.
[200] For a review, see Staab, H.A.; Saupe, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 865.
[201] Howard, S.T. *J. Am. Chem. Soc.* ***2000***, *122*, 8238.
[202] Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28*, 84. See also, Staab, H. A.; Zirnstein, M.A.; Krieger, C. *Angew. Chem. Int. Ed.* ***1989***, *28*, 86.

proton sponge.[203]

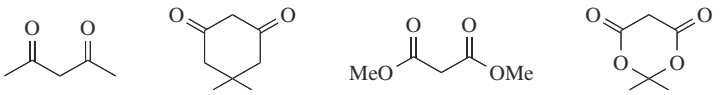


12 **13** **14** **15**

Chiral Lewis acids are known. Indeed, an air stable and storable chiral Lewis acid catalyst has been prepared, a chiral zirconium catalyst combined with molecular sieves powder.[204] Association of a bulky silicon group with the bis (trifluoromethanesulfonyl)imide (known as triflimide) anion leads to enhancement of the electrophilic character of R_3SiNTf_2. The presence of a chiral substituent derived from (−)-myrtenal on the silicon atom led to a chiral silicon Lewis acid.[205]

Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*tert*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.[206] The reason is that the conjugate acid **14** is less stable than the conjugate acids of nonsterically hindered pyridines. In all cases, the conjugate acids are hydrogen bonded to a water molecule, but in the case of **14** the bulky *tert*-butyl groups restrict rotations in the water molecule, lowering the entropy.[207]

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for compounds **16**–**19**.[208]

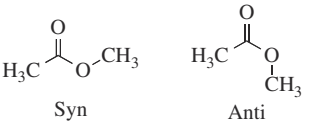


	16	**17**	**18**	**19**
pK_a	13.3	11.2	15.9	7.3

Since ketones are stronger acids than carboxylic esters (Table 8.1), it is not surprising that **16** is a stronger acid than **18**.[209] A comparison of **16** with cyclic diketone **17** shows an increase in acidity of only 2.1 p*K* units, while a comparison of **18** with cyclic diester **19** shows an increase of 8.6 units. Indeed, **19** (called *Meldrum's acid*) is an unusually strong acid for a 1,3-diester. In order to account for this very large effect of a ring, MO calculations were carried out for two conformations of methyl acetate and of its enolate ion.[210] Loss of a proton is easier by ∼5 kcal mol^{-1} (21 kJ mol^{-1}) for the syn than for the anti conformer of the ester.

[203] Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* ***2001***, *42,* 3097.
[204] Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* ***2002***, *4,* 3395.
[205] Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett* ***2000***, *41,* 9651
[206] Brown, H.C.; Kanner, B. *J. Am. Chem. Soc.* ***1953***, *75*, 3865; ***1966***, *88*, 986.
[207] Meot-Ner, M.; Smith, S.C. *J. Am. Chem. Soc.* ***1991***, *113*, 862, and references cited therein. See also, Benoit, R.L.; Fréchette, M.; Lefebvre, D. *Can. J. Chem.* ***1988***, *66*, 1159.
[208] Arnett, E.M.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* ***1987***, *109*, 809.
[209] For a discussion of why esters and amides are weaker acids than ketones, see Fersner, A.; Karty, J.M.; Mo, Y. *J. Org. Chem.* ***2009***, *74,* 7245.
[210] Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 1870; Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1872.

In an acyclic molecule like **18**, the preferred conformations are anti, but in *Meldrum's acid* (**19**) the conformation on both sides is constrained to be syn.



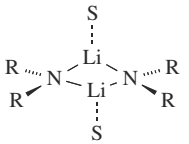
Facial differences in proton reactivity can lead to enantioselective deprotonation. Enantioselective deprotonation is also achieved by using a chiral base and/or a chiral complexing agent. Enantioselective deprotonation in cyclic ketones,[211] and with heterodimer bases has been studied.[212] When a Lewis acid coordinates to a base, the resulting complex can have conformational properties that influence reactivity. Coordination of $SnCl_4$ with aldehydes and esters, for example, leads to a complex where the conformation is determined by interactions of the $C{=}O\cdots SnCl_4$ unit with substituents attached to the carbonyl.[213]

7. *Hybridization*. An *s* orbital has a lower energy than a *p* orbital. Therefore, the more *s* character a hybrid orbital contains, the lower the energy of that orbital. It follows that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* vs sp^2 vs sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygen atoms, where the unshared pair is sp^3, are more strongly basic than carbonyl oxygen atoms, where the unshared pair is sp^2 (Table 8.1).

An understanding of the reactivity of bases arises from the study of their structures in solution and in the crystalline state. Due to the importance of dialkylamide bases, there is a significant body of work, led by independent work by Williard and by Collum, that has attempted to understand the structures of these reactive molecules. It is clear that the dialkylamide bases are aggregates. Note that the simplest member of the amide base family, lithium amide ($LiNH_2$), was shown to be monomeric and unsolvated, as determined using a combination of gas-phase synthesis and millimeter/submillimeter-wave spectroscopy.[214] Both monomeric $LiNH_2$ and $LiNMe_2$ are planar.[215] Lithium diisopropylamide ($LiNiPr_2$, LDA) was isolated from a THF solution and X-ray crystallography revealed a dimeric structure (**20**; R = *i*Pr, S = THF) in the solid state.[216] Lithium diisopropylamide was also shown to be a dimer in solutions of THF[217] and/or HMPA (see **20**, R = *i*Pr and S = THF, HMPA).[218] In the presence of HMPA, many derivatives of **20** tend to be mixed aggregates.[219] Extremely hindered $LiNR_2$ (R = 2-adamantyl) are

[211] Majewski, M.; Wang, F. *Tetrahedron* ***2002***, *58*, 4567.
[212] Amedjkouh, M. *Tetrahedron Asymm.* ***2004***, *15*, 577.
[213] Gung, B.W.; Yanik, M.M. *J. Org. Chem.* ***1996***, *61*, 947.
[214] Grotjahn, D.B.; Sheridan, P.M.; Al Jihad, I.; Ziurys, L.M. *J. Am. Chem. Soc.* ***2001***, *123,* 5489.
[215] Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* ***2001***, *66,* 6476.
[216] Williard, P.G.; Salvino, J.M. *J. Org. Chem.* ***1993***, *58*, 1. For a study of the oligomer structure of LDA at low ligand concentrations, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 199.
[217] Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* ***1992***, *33*, 3769.
[218] Aubrecht, K.B.; Collum, D.B. *J. Org. Chem.* ***1996***, *61*, 8674.
[219] Romesberg, F.E.; Collum, D.B. *J. Am.Chem. Soc.* ***1994***, *116*, 9198, 9187. For a study of other mixed aggregates, see Thomas, R.D.; Huang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 11239.

monomeric under all conditions.[220] In hydrocarbon solvents, lithium tetramethylpiperidide [LTMP, RR′NLi, where RR′ = —$CMe_2(CH_2)_3C(Me_2)$—] forms cyclic trimers and tetramers, with the tetrameric species predominating.[221] In THF, lithium hexamethyldisilazide [LHMDS, $(Me_3Si)_2NLi$] forms a five-coordinate tetrasolvate $[(Me_3Si)_2NLi(thf)_4]$,[222] but in ether there is an equilibrium mixture of monomer and dimer.[223] A review is available that discusses the solution structures of amide bases $LiNR_2$.[224] Chiral lithium amide bases are known and they show similar behavior in solution.[225] Chelation effects are common in enantioenriched amide bases, which also form aggregates.[226] The aggregation state of lithium phenylacetonitrile has been studied.[227] Dianion aggregates can be generated, and in the case of the lithiation reaction of *N*-silyl allylamine, X-ray structure determination showed the presence of three uniquely different aggregates.[228] A mixed aggregate is formed when the lithium enolate of a ketone is mixed with a lithium amide.[229]



S = solvent

20

Similar information is available for other bases. Lithium phenoxide (LiOPh) is a tetramer in THF.[230] Lithium 3,5-dimethylphenoxide is a tetramer in ether, but addition of HMPA leads to dissociation to a monomer.[231]

Enolate anions are nucleophiles in reactions with alkyl halides (Reaction **10-68**), with aldehydes and ketones (Reactions **16-34** and **16-36**) and with acid derivatives (Reaction **16-85**). Enolate anions are also bases, reacting with water, alcohols and other protic solvents, and even the carbonyl precursor to the enolate anion. Enolate anions exist as aggregates, and the effect of solvent on aggregation and reactivity of lithium enolate anions has been studied.[232] Alkyl substitution has a significant influence on the energetics of enolate anions.[233]

[220] Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* ***1993***, *34*, 5213.
[221] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 7949.
[222] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1995***, *117*, 9863. See also, Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1996***, *118*, 2217, 3529. See Romesberg, F.E.; Bernstein, M.P.; Gilchrist, J.H.; Harrison, A.T.; Fuller, D. J.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 3475 for the structure in HMPA.
[223] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 6009.
[224] Collum, D.B. *Acc. Chem. Res.* ***1993***, *26*, 227. For NMR studies of $LiNEt_2$ and ring laddering see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1999***, *121*, 10198.
[225] Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* ***1995***, *60*, 7660. See O'Brien, P. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1439; Sott, R.; Grandander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron Asymm.* ***2004***, *15*, 267.
[226] Arvidsson, P.I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* ***1999***, *121,* 183.
[227] Carlier, P.R.; Madura, J.D. *J. Org. Chem.* ***2002***, *67*, 3832.
[228] Williard, P. G.; Jacobson, M. A. *Org. Lett.* ***2000***, *2,* 2753. For the structure and bonding of dilithiodiamines see Pratt, L.M.; Mu, R. *J. Org. Chem.* ***2004***, *69*, 7519.
[229] Sun, C.; Williard, P.G. *J. Am. Chem. Soc.* ***2000***, *122* , 7829. See also, Pratt, L.M.; Streitwieser, A. *J. Org. Chem.* ***2003***, *68*, 2830.
[230] Jackman, L.M.; Çizmeciyan, D.; Williard, P.G.; Nichols, M.A. *J. Am. Chem. Soc.* ***1993***, *115*, 6262.
[231] Jackman, L.M.; Chen, X. *J. Am. Chem. Soc.* ***1992***, *114*, 403.
[232] Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. *Org. Lett.* ***2000***, *2*, 3839.
[233] Alconcel, L.S.; Deyerl, H.-J.; Continetti, R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 12675.

8.G. THE EFFECTS OF THE MEDIUM ON ACID AND BASE STRENGTH

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the reaction conditions are changed. The effect of temperature (Sec. 8.A) has already been mentioned. More important is the effect of the solvent, which can exert considerable influence on acid and base strengths by differential solvation.[234] If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, Table 8.6 shows that in reactions with a proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.[235] These results are easily explainable if one assumes that methyl groups are electron donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.[236] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[237] It has been estimated that this effect contributes $\sim$11 pK units to the base strength of ammonia.[238] When methyl groups replace hydrogen, this difference in hydration decreases[239] until, for trimethylamine, it contributes only $\sim$6 pK units to the base strength.[195] Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. Taken together, the strongest base is dimethylamine and the weakest is ammonia in solution. If alkyl groups are electron donating, one would expect that in the gas phase,[240] where the solvation effect does not exist, the basicity order of amines toward the proton should be $R_3N > R_2NH > RNH_2 > NH_3$, and this has indeed been confirmed, for R = Me, as well as R = Et and Pr.[241] Aniline too, in the gas phase, is a stronger base than NH_3,[242] so

[234] See Epshtein, L.M.; Iogansen, A.V. *Russ. Chem. Rev.* ***1990***, *59*, 134; Dyumaev, K.M.; Korolev, B.A. *Russ. Chem. Rev.* ***1980***, *49*, 1021; Taft, R.W.; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 463; Heemstra, J.M.; Moore, J. S. *Tetrahedron* ***2004***, *60,* 7287.

[235] See Smith, J.W. in Patai, S. *The Chemistry of the Amino Group,* Wiley, NY, ***1968***, pp. 161–204.

[236] Aue, D.H.; Webb, H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318; Mucci, A.; Domain, R.; Benoit, R.L. *Can. J. Chem.* ***1980***, *58*, 953. See also, Drago, R.S.; Cundari, T.R.; Ferris, D.C. *J. Org. Chem.* ***1989***, *54*, 1042.

[237] For discussions of the solvation of ammonia and amines, see Jones, III, F.M.; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 263; Grunwald, E.; Ralph, E.K. *Acc. Chem. Res.* ***1971***, *4*, 107.

[238] Condon, F.E. *J. Am. Chem. Soc.* ***1965***, *87*, 4481, 4485.

[239] For two reasons: (1) the alkyl groups are poorly solvated by the water molecules, and (2) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau, Y.K.; Kebarle, P. *Can. J. Chem.* ***1981***, *59*, 151.

[240] See Liebman, J.F. *Mol. Struct. Energ.* ***1987***, *4*, 49; Dixon, D.A.; Lias, S.G. *Mol. Struct. Energ.* ***1987***, *2*, 269; Bohme, D.K. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 731–762; Arnett, E.M. *Acc. Chem. Res.* ***1973***, *6*, 404. See Lias, S.G.; Liebman, J.F.; Levin, R.D. *J. Phys. Chem. Ref. Data*, ***1984***, *13*, 695. See also, the tables of gas-phase acidities and basicities in the following articles, and their cited references: Meot-Ner, M.; Kafafi, S.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6297; Headley, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2347; Fujio, M.; McIver, Jr., R.T.; Taft, R.W. *J. Am. Chem. Soc.* ***1981***, *103*, 4017; Lau, Y.K.; Nishizawa, K.; Tse, A.; Brown, R.S.; Kebarle, P. *J. Am. Chem. Soc.* ***1981***, *103*, 6291.

[241] Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Aue, D.H.; Webb H.M.; Bowers, M. T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318.

[242] Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1983***, *61*, 97.

its much lower basicity in aqueous solution (pK_a of $PhNH_3^+$ 4.60 compared with 9.24 for aq NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine[243] and pyrrole[244] are both much less basic than NH_3 in aqueous solution (pyrrole[245] is neutral in aqueous solution), but *more* basic in the gas phase. Care must be taken in attributing relative acidities or basicities to any particular effect. Solvent has a significant influence on the *Hammett reaction constant* (Sec. 11.D), which influences the acidity of substituted benzoic acids.[246]

In the case of Lewis acids, protic solvents (e.g., water or alcohol) can strongly influence their reactivity, cause it to react via an alternative path to the one desired, or even cause decomposition. Rare earth metal triflates have been used to develop water tolerant Lewis acids that can be used in many organic reactions.[247]

For simple alcohols, the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution, the acidity is in the order $H_2O > MeCH_2OH > Me_2CHOH > Me_3COH$, but in the gas phase the order is precisely the opposite.[248] Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH, we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O. This result demonstrates that simple alkyl groups cannot be simply regarded as electron donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O, yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids (e.g., propanoic) are stronger than acetic acid in the gas phase,[249] although weaker in aqueous solution (Table 8.5). The evidence in these and other cases[250] is that alkyl groups can be electron donating when connected to unsaturated systems, but may have either no effect or may actually be electron withdrawing in other systems. It appears that the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is due to the effect of alkyl groups, because of their polarizability, which can spread both positive and negative charges.[251] It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.[252] Polarizability effects on anionic centers

[243] Taft, R.W.; Taagepera, M.; Summerhays, K.D.; Mitsky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3811.
[244] Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1973***, *95*, 3504.
[245] See Catalan, J.; Abboud, J.L.M.; Elguero, J. *Adv. Heterocycl. Chem.* ***1987***, *41*, 187.
[246] Bartnicka, H.; Bojanowska, I.; Kalinowski, M.K. *Aust. J. Chem.* ***1993***, *46*, 31.
[247] Kobayashi, S. *Synlett*, ***1994***, 689.
[248] Arnett, E.M.; Small, L.E.; McIver, Jr., R.T.; Miller, J.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5638; Blair, L.K.; Isolani, P.C.; Riveros, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 1057; McIver, Jr., R.T.; Scott, J.A.; Riveros, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 2706. Also see Bartmess, J.E.; McIver, Jr., R.T. *J. Am. Chem. Soc.* ***1977***, *99*, 4163.
[249] See Caldwell, G.; Renneboog, R.; Kebarle, P. *Can. J. Chem.* ***1989***, *67*, 611.
[250] Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4315; Laurie, V.W.; Muenter, J.S. *J. Am. Chem. Soc.* ***1966***, *88*, 2883.
[251] Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 3914; Huheey, J.E. *J. Org. Chem.* ***1971***, *36*, 204; Radom, L. *Aust. J. Chem.* ***1975***, *28*, 1; Aitken, E.J.; Bahl, M.K.; Bomben, K.D.; Gimzewski, J.K.; Nolan, G.S.; Thomas, T.D. *J. Am. Chem. Soc.* ***1980***, *102*, 4873.
[252] Taft, R.W.; Taagepera, M.; Abboud, J.M.; Wolf, J.F.; DeFrees, D.J.; Hehre, W.J.; Bartmess, J.E.; McIver, Jr., R. T. *J. Am. Chem. Soc.* ***1978***, *100*, 7765. For a scale of polarizability parameters, see Hehre, W.J.; Pau, C.; Headley, A.D.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* ***1986***, *108*, 1711.

TABLE 8.7 Thermodynamic Values for the Ionizations of Acetic and Chloroacetic Acids in H_2O at 25°C[a]

		ΔG		ΔH		$T\Delta S$	
Acid	pK_a	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}
CH_3COOH	4.76	+6.5	+27	−0.1	−0.4	−6.6	−28
$ClCH_2COOH$	2.86	+3.9	+16	−1.1	−4.6	−5.0	−21
Cl_3CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

Reproduced from Bolton, P.D.; Hepler, L.D. *Q. Rev. Chem. Soc.* ***1971,*** *25*, 521 with permission from the Royal Society of Chemistry.

[a]See Ref. 256.

are a major factor in gas-phase acid–base reactions.[253] It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.[254]

The effect on the orientation of solvent molecules when an acid or base is converted to its conjugate is an important aspect of solvent effects. For example, consider an acid (RCOOH) converted to $RCOO^-$ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This leads to a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free energy change ΔG than does the enthalpy ΔH.[255] Two examples are shown in Table 8.7 .[256] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing groups increase acidity by stabilizing $RCOO^-$ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO^- group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

A change from a protic to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[257] The effect can be extreme: In DMF, picric acid is stronger than HBr,[258] though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by DMF than the smaller

[253] Bartmess, J.E.; Scott, J.A.; McIver, Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6056.
[254] Bohme, D.K.; Rakshit, A.B.; Mackay, G.I. *J. Am. Chem. Soc.* ***1982***, *104*, 1100.
[255] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. See also, Wilson, B.; Georgiadis, R.; Bartmess, J.E. *J. Am. Chem. Soc.* ***1991***, *113*, 1762.
[256] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; p. 529.
[257] For a review, see Parker, A.J. *Q. Rev. Chem. Soc.* ***1962***, *16*, 163.
[258] Sears, P.G.; Wolford, R.K.; Dawson, L.R. *J. Electrochem. Soc.* ***1956***, *103*, 633.

ion Br^-.[259] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas phase, the effects discussed in Section 8.F, especially resonance and field effects, operate unhindered by solvent molecules. Electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why pK values in Table 8.5 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.[179]

[259] Miller, J.; Parker, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 117.

CHAPTER 9

Effects of Structure and Medium on Reactivity

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH, where R is a generic alkyl group, which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group usually give more or less the same reactions, the custom is useful, and the practice is used in this text. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. In other words, a reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.[1] In most cases, two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

9.A. RESONANCE AND FIELD EFFECTS

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.[2] Field effects were discussed in Section 1.I. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, in Section 2.F it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; that is, the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron donating by the

[1] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***. For a general theoretical approach to organic reactivity, see Pross, A. *Adv. Phys. Org. Chem.* ***1985***, *21*, 99.
[2] See Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 125, *Mol. Struct. Energ.* ***1987***, *4*, 235.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

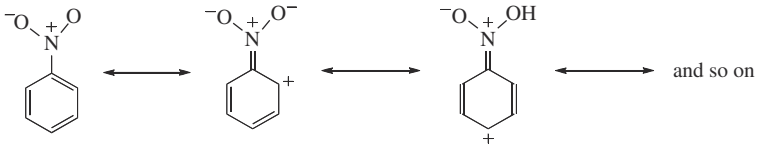
TABLE 9.1 Some Groups with $+M$ and $-M$ Effects, Not Listed in Order of Strength of Effect[a]

$+M$		$-M$	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F	CONHR	Ar
OR	R	$CONR_2$	
OH	Ar		
OCOR			

[a]Argon (Ar) appears in both lists because it is capable of both kinds of effect.

resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation (see Sec. 2.M).

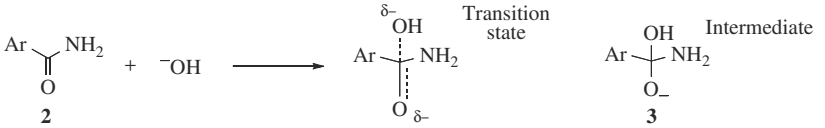
On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases, canonical forms can be drawn in which electrons are delocalized from the unsaturated system into the group, as in nitrobenzene (**1**). Table 9.1 contains a list of some $+M$ and $-M$ groups.



1

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we will use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see Sec. 1.I, 2.F). Complicating the study of these effects on the reactivity of compounds is the fact that a given group may have an effect in the transition state that is considerably more or less than it has in the molecule that does not react.



2 **3**

In the alkaline hydrolysis of aromatic amides (Reaction **16-60**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon. The conversion of **2** to **3**

TABLE 9.2 Relative Rates of Reaction of RBr with Ethanol[a]

R	Relative Rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

Reproduced from Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107 with permission from the Royal Society of Chemistry.

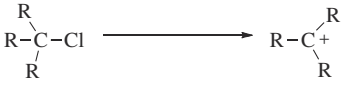
[a]See Ref. 3.

illustrates the nature of electrical effects (resonance and field) on reactivity. In the transition state, which has a structure somewhere between that of the starting amide (**2**) and the intermediate (**3**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **2**. Since G is lowered for the transition state, but not substantially for **2**, $\Delta G^{\ddagger}$ is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

9.B. STERIC EFFECTS

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases, it can often be shown that steric effects have a significant influence on the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see Sec. 10.A.i).[3] All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing b branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see Sec. 10.A.i). The great decrease in rate can be attributed to *steric hindrance* in the transition state of the reaction, which makes attack of the nucleophile more difficult. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 positions. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see Sec. 10.A.ii), the first step, which is rate determining, involves ionization of the alkyl chloride to a carbocation:



[3] Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107.

TABLE 9.3 Rates of Hydrolysis of Tertiary Alkyl Chlorides at 25 °C in 80% Aqueous Ethanol[a]

Halide	Rate	Halide	Rate
Me_3Cl	0.033	Et_3CCl	0.099
Me_2EtCCl	0.055	$Me_3(i\text{Pr})CCl$	0.029
$MeEt_2CCl$	0.086	$Me(i\text{Pr})_2CCl$	0.45

Reproduced with permission Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845. Copyright © 1949 American Chemical Society.

[a]See Ref. 6.

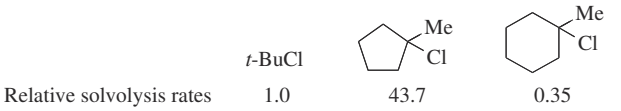
The central carbon in the alkyl chloride is sp^3 hybridized, with angles of ~109.5°, but when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see Sec. 4.Q.iv). This type of strain is called *B strain*[4] (for back strain), and can be relieved by ionization to the carbocation.[5]

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.[6] Substitution of ethyl groups for the methyl groups of *tert*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The increase is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased 10-fold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases the rate of solvolysis is found with the highly crowded molecules tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *tert*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.[7]

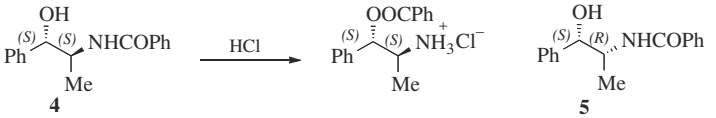
Another type of strain, which can affect rates of cyclic compounds, is called *I strain* (internal strain).[8] This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from ~109.5° to ~120°. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (Sec. 4.Q.iv); thus this compound undergoes solvolysis in 80% ethanol at 25 °C, 43.7 times faster than the reference compound *tert*-butyl chloride.[9] In the corresponding cyclohexyl compound, this factor is absent because the substrate does not have eclipsing strain (Sec. 4.Q.iv), and this compound undergoes the reaction at about one-third the rate of *tert*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of

[4] Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 114–121.
[5] See Stirling, C.J.M. *Tetrahedron* ***1985***, *41*, 1613; *Pure Appl. Chem.* ***1984***, *56*, 1781.
[6] Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845.
[7] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.
[8] See Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 105–107, 126–128.
[9] Brown, H.C.; Borkowski, M. *J. Am. Chem. Soc.* ***1952***, *74*, 1894. See also, Brown, H.C.; Ravindranathan, M.; Peters, E.N.; Rao, C.G.; Rho, M.M. *J. Am. Chem. Soc.* ***1977***, *99*, 5373.

7–11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.[10] *I*-Strain has been shown to be a factor in other reactions as well.[11]

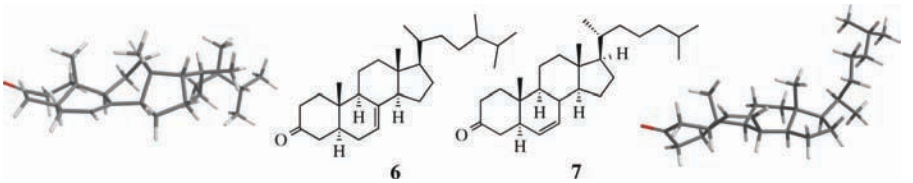


Conformational effects on reactivity can be considered under the heading of steric effects,[12] but in these cases the effect of a group X and that of another group X′ upon reactivity at a site Y are not considered. But the effect of the conformation of the molecule must be considered. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of *N*-benzoylnorephedrine. The two diastereomers of this compound (**4** and **5**) behave very differently when treated with alcoholic HCl. In one of the isomers, nitrogen-to-oxygen migration takes place, while the other does not react at all.[13] In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **4** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **5** has the nitrogen *gauche* to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see Sec. 15.A.i) and E2 elimination reactions (see Sec. 17.A.i.). Also, many examples are known where axial and equatorial groups behave differently.[14]



4 **5**

In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**6**) and cholest-6-en-3-one (**7**), where **7** condenses with benzaldehyde 15 times faster than **6**.[15] The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate). Molecular models of **6** and **7** are provided for illustration.



6 **7**

[10] See Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* ***1980***, *102*, 1424.
[11] Sands, R.D. *J. Org. Chem.* ***1994***, *59*, 468.
[12] See Green, B.S.; Arad-Yellin, R.; Cohen, M.D. *Top. Stereochem.* ***1986***, *16*, 131; Öki, M. *Acc. Chem. Res.* ***1984***, *17*, 154; Seeman, J.I. *Chem. Rev.* ***1983***, *83*, 83. See also, Öki, M.; Tsukahara, J.; Moriyama, K.; Nakamura, N. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 223, and other papers in this series.
[13] Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi , G. *J. Org. Chem.* ***1949***, *14*, 337.
[14] See Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 219–234.
[15] Barton, D.H.R.; McCapra, F.; May, P.J.; Thudium, F. *J. Chem. Soc.* ***1960***, 1297.

9.C. QUANTITATIVE TREATMENTS OF THE EFFECT OF STRUCTURE ON REACTIVITY[16]

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G is a skeleton group to which X and Y are attached. In such a molecule, changing X from H to CH_3 results in a rate increase by a factor, of say, 10. What part of the increase is due to each of the effects previously mentioned? The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is difficult because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[17] For the cases of *m*- and *p*-XC_6H_4Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma \rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC_6H_4COOH in water at 25°C. The values of σ_m and σ_p were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the s values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value calculated and the known s values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups. It correlates an enormous amount of data quite well. Jaffé's review article[17] listed ρ values for 204 reactions,[18] many of which have different ρ values for different conditions. Among them are reactions as disparate as the following reactions.

Rate constants for the following:

$$\begin{aligned}
&ArCOOMe + OH^- \longrightarrow ArCOO^- \\
&ArCH_2Cl + I^- \longrightarrow ArCH_2I \\
&ArNH_2 + PhCOCl \longrightarrow ArNHCOPh \\
&ArH + NO_2{}^+ \longrightarrow ArNO_2 \\
&ArCO_2OCMe_3 \longrightarrow \text{Decomposition (a free radical process)}
\end{aligned}$$

[16] See Exner, O. *Correlation Analysis of Chemical Data*, Plenum, NY, ***1988***; Johnson, C.D. *The Hammett Equation*, Cambridge University Press, Cambridge, ***1973***; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***; Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***. Also see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 311–383; Lewis, E.S. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions* (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 4th ed., Wiley, NY, ***1986***, pp. 871–901; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 38–68; Hine, J. *Structural Effects in Organic Chemistry*, Wiley, NY, ***1975***, pp. 55–102. For a historical perspective, see Grunwald, E. *CHEMTECH* ***1984***, 698.

[17] For a review, see Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191.

[18] Additional ρ values are given in Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 and van Bekkum, H.; Verkade, P.E.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1959***, *78*, 821.

Equilibrium constants for

$$ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+$$

$$ArCHO + HCN \rightleftharpoons ArCH(CN)OH$$

The *Hammett equation* also has been shown to apply to many physical measurements, including IR frequencies and NMR chemical shifts.[19] The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (i.e., the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H.C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ, σ^+, and σ^- values for some common X groups.[20] As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. The values of σ_m^- are not shown in the table, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group.[21] The constant ρ measures the susceptibility of the reaction to electrical effects.[22] Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:[23]

TABLE 9.4 The σ, σ^+, and σ^- Values for Some Common Groups[a]

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O^-	−0.81[b]	−0.47[b]	−4.27[c]	−1.15[c]	
NMe_2	−0.63	10.10	−1.7		
NH_2	−0.57	−0.09	−1.3	−0.16	
OH	−0.38[d]	0.13[d]	−0.92[e]		
OMe	−0.28[d]	0.10	−0.78	0.05	
CMe_3	−0.15	−0.09	−0.26	−0.06	
Me	−0.14	−0.06	−0.31	−0.10[f]	
H	0	0	0	0	0
Ph	0.05[g]	0.05	−0.18	0[g]	
COO^-	0.11[b]	0.02[b]	−0.41[c]	−0.10[c]	

(*continued*)

[19] For a review of *Hammett* treatment of NMR chemical shifts, see Ewing, D.F. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 357–396.

[20] Unless otherwise noted, σ values are from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 439–540, and σ^+ values from Okamoto, Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* ***1958***, *80*, 4969; Brown, H.C.; Okamoto, Y. *J. Am. Chem. Soc.* ***1958***, *80*, 4979. σ^- values, except as noted, are from Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165; Egorochkin, A.N.; Razuvaev, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 846. For values for heteroaromatic groups, see Mamaev, V.P.; Shkurko, O.P.; Baram, S.G. *Adv. Heterocycl. Chem.* ***1987***, *42*, 1.

[21] See Dubois, J.E.; Ruasse, M.; Argile, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4840; Ruasse, M.; Argile, A.; Dubois, J.E. *J. Am. Chem. Soc.* ***1984***, *106*, 4846; Lee, I.; Shim, C.S.; Chung, S.Y.; Kim, H.Y.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1919.

[22] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[23] Binev, I.G.; Kuzmanova, R.B.; Kaneti, J.; Juchnovski, I.N. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1533.

TABLE 9.4 (*Continued*)

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
F	0.15	0.34	−0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28[g]	0.34	0.14	0.36	
N=NPh[h]	0.34	0.28	0.17		
COOH[i]	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF_3	0.53	0.46		0.57[f]	
NH_3^+	0.60[c]	0.86[d]			
CN[j]	0.70	0.62	0.66	0.56	1.00
SO_2Me	0.73	0.64			
NO_2	0.81	0.71	0.79	0.73[f]	1.27
NMe_3^+	0.82[k]	0.88[k]	0.41	0.36	
N_2^+	1.93[l]	1.65[l]	1.88[l]		3[m]

[a]See Ref. 20.

[b]See Ref. 24.

[c]See Ref. 25.

[d]See Ref. 26.

[e]See Ref. 27.

[f]See Ref. 28.

[g]See Ref. 29.

[h]See Ref. 30.

[i]See Ref. 31.

[j]See Ref. 32.

[k]See Ref. 33.

[l]See Ref. 34.

[m]See Ref. 35.

Reprinted with permission from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advance*, Plenum, NY, ***1978***, pp. 439–540, Copyright © 1978 with permission from Sprngr Science + Business Media B.V. Reprinted with permission Okamoto, Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* ***1958***, *80*, 4969. Copyright © 1958 American Chemical Society. Reprinted with permission Brown, H.C.; Okamoto, Y. *J. Am. Chem. Soc.* ***1958***, *80*, 4969. Copyright © 1958 American Chemical Society. Reprinted with permission Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191. Copyright © 1953 American Chemical Society.

[24] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge Univ. Press, Cambridge, ***1984***, p. 42.

[25] See Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[26] Matsui, T.; Ko, H.C.; Hepler, L.G. *Can. J. Chem.* ***1974***, *52*, 2906.

[27] de la Mare, P.B.D.; Newman, P.A. *Tetrahedron Lett.* ***1982***, *23*, 1305 give this value as –1.6.

[28] Amin, H.B.; Taylor, R. *Tetrahedron Lett.* ***1978***, 267.

[29] Sjöström, M.; Wold, S. *Chem. Scr.* ***1976***, *9*, 200.

[30] Byrne, C.J.; Happer, D.A.R.; Hartshorn, M.P.; Powell, H.K.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1649.

[31] For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, M. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 239–298.

[32] For a review of directing and activating effects of C≡N and C≡C groups, see Charton, M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 269–323.

[33] McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* ***1958***, *23*, 420.

[34] Ustynyuk, Yu.A.; Subbotin, O.A.; Buchneva, L.M.; Gruzdneva, V.N.; Kazitsyna, L.A. *Doklad. Chem.* ***1976***, *227*, 175.

[35] Lewis, E.S.; Johnson, M.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2070.

$XC_6H_4—COOH$	1.00	$XC_6H_4—CH=CH—COOH$	0.47
$XC_6H_4—CH_2—COOH$	0.49	$XC_6H_4—CH_2CH_2—COOH$	0.21

This example shows that the insertion of a CH_2 or a CH=CH group diminishes electrical effects to about the same extent, while a CH_2CH_2 group diminishes them much more. A $\rho > 1$ would mean that the reaction is more sensitive to electrical effects than is the ionization of XC_6H_4COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values are sometimes additive and sometimes not,[36] for other ring systems, (e.g., naphthalene)[37] and heterocyclic rings,[38] and for ethylenic and acetylenic systems.[39]

The *Hammett equation* is a *linear free energy relationship* (LFER*)*. This relationship can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^{\ddagger}$ instead of ΔG). For each reaction, where X is any group,

For the unsubstituted case,

$$\Delta G = -RT \ln K$$
$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma \rho$$

so that

$$\frac{-\Delta G}{2.3\,RT} = \frac{\Delta G_o}{2.3\,RT} = \sigma \rho$$

and

$$-\Delta G = \sigma\rho\, 2.3\,RT - \Delta G_0$$

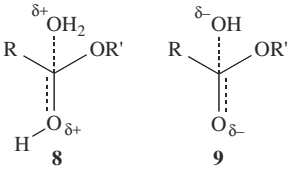
For a given reaction under a given set of conditions, σ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

The Hammett equation is not the only LFER.[40] Some, like the Hammett equation, correlate structural changes in reactants, but the *Grunwald–Winstein relationship*

[36] Stone, R.M.; Pearson, D.E. *J. Org. Chem.* ***1961***, *26*, 257.
[37] Berliner, E.; Winikov, E.H. *J. Am. Chem. Soc.* ***1959***, *81*, 1630; See also, Well, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys.Org. Chem.* ***1968****, 6*, 147.
[38] See Charton, M. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 175–268; Tomasik, P.; Johnson, C.D. *Adv. Heterocycl. Chem.* ***1976***, *20*, 1.
[39] See Ford, G.P.; Katritzky, A.R.; Topsom, R.D. in *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ,***1978***, pp. 269–311; Charton, M. *Prog. Phys. Org. Chem.* ***1973***, *10*, 81.
[40] See Exner, O. *Prog. Phys. Org. Chem.* ***1990***, *18*, 129.

(see Sec. 10.G.iv) correlates changes in solvent and the *Brønsted relation* (see Sec. 8.D) relates acidity to catalysis. The *Taft equation* is a structure–reactivity equation that correlates only field effects.[41]

Taft, following Ingold,[42] assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, Reaction **16-59**). Rate differences would therefore be caused only by the field effects of R and R′



8 **9**

in RCOOR′. This system is presumably good to use for this purpose because the transition state for acid-catalyzed hydrolysis (**8**) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (**9**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR',[43] where R′ is held constant.[38] From these rate constants, a value σ_I could be determined by the equation[44]

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

In this equation, $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. The substituent constant σ_I is for a group X, substituted at a saturated carbon, which reflects only field effects.[45] Once a set of σ_I values was obtained, it was found that the equation

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

[41] For reviews of the separation of resonance and field effects, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Shorter, J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 433; *Chem. Ber.* ***1969***, *5*, 269. For a review of field and inductive effects, see Reynolds, W.F. *Prog. Phys. Org. Chem.* ***1983***, *14*, 165. For a review of field effects on reactivity, see Grob, C.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 569.

[42] Ingold, C.K. *J. Chem. Soc.* ***1930***, 1032.

[43] Also see Draffehn, J.; Ponsold, K. *J. Prakt. Chem.* ***1978***, *320*, 249.

[44] The symbol σ_F is also used in the literature; sometimes in place of σ_I, and sometimes to indicate only the field (not the inductive) portion of the total effect (Sec. 1.G).

[45] There is another set of values (called σ^* values) that are also used to correlate field effects. These are related to σ_I values by $\sigma_{I(X)} = 0.45\sigma$. Only σ_I, and not σ^* values are discussed.

TABLE 9.5 The σ_I and σ_R^o Values for Some Groups[a]

Group (R)	σ_I	σ_R^o	Group (R)	σ_I	σ_R^o
CMe_3	−0.07	−0.17	OMe	0.27	−0.42
Me	−0.05	−0.13	OH	0.27	−0.44
H	0	0	I	0.39	−0.12
$PhCH_2$	0.04		CF_3	0.42	0.08
NMe_3[b]	0.06	−0.55	Br	0.44	−0.16
Ph	0.10	−0.10	Cl	0.46	−0.18
CH_3COCH_2	0.10		F	0.50	−0.31
NH_2	0.12	−0.50	CN	0.56	0.08
CH_3CO	0.20	0.16	SO_2Me	0.60	0.12
COOEt	0.20	0.16	NO_2	0.65	0.15
NHAc	0.26	−0.22	NMe_3[49]	0.86	

Reprinted with permission Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 476. Copyright © 1979 American Chemical Society.

[a]See Ref. 47.

[b]See Ref. 48.

holds for a number of reactions, among them:[46]

$$RCH_2OH \longrightarrow RCH_2O^-$$
$$RCH_2Br + PhS^- \longrightarrow RCH_2SPh + Br^-$$
$$o\text{-Substituted-}ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$$

As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups, the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.[47] The σ_I values are about what is expected for pure field-effect values (see Sec. 1.I) and are additive, as field effects (but not resonance or

[46] Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 196.

[47] These values are from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766, but the values for NHAc, OH, and I are from Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1968***, *6*, 147, the values for Ph and NMe_3^+ are from Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R. *J. Am.Chem. Soc.* ***1959***, *81*, 5352; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *8*, 287, and the value for CMe_3 is from Seth-Paul, W.A.; de Meyer-van Duyse, A.; Tollenaere, J.P. *J. Mol. Struct.* ***1973***, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in ref. 45. Also see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Taylor, P.J.; Wait, A.R. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1765.

[48] For σ_R^o values for some other NR_2 groups, see Korzhenevskaya, N.G.; Titov, E.V.; Chotii, K.Yu.; Chekhuta, V.G. *J. Org. Chem. USSR* ***1987***, *28*, 1109.

[49] It has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott, S.; Reynolds, J.D.; Topsom, R. D. *J. Org. Chem.* ***1985***, *50*, 741.

steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (cf. the values of R in Table 9.5 for R = Ph and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This result is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.[50] The resonance contribution σ_R[51] is defined as:

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant, but depends on the nature of the reaction.[52] In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome[53] the problem of varying σ_R values by using a special set of σ_R values, called σ_R^o,[54] that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R^o scales have been reported; the most satisfactory values are obtained from ^{13}C chemical shifts of substituted benzenes.[55] Table 9.5 lists some values of σ_R^o, most of which were obtained in this way.[56]

An equation, for example,

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^o$$

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.[57]

The only groups in Table 9.5 with negative values of σ_I are the alkyl groups methyl and *tert*-butyl. There has been some controversy on this point.[58] One opinion is that σ_I values decrease in the series methyl, ethyl, isopropyl, *tert*-butyl (respectively, -0.046, -0.057, -0.065, -0.074).[59] Other evidence, however, has led to the belief that all alkyl groups have

[50] Taft, R.W. *J. Phys. Chem.* ***1960***, *64*, 1805; Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1958***, *80*, 2436; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *9*, 287, see pp. 290–293.

[51] Ehrenson, S.; Brownlee, R.T.C.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1973***, *10*, 1. See also, Taft, R.W.; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 1; Charton, M. *Prog. Phys. Org. Chem.* ***1987***, *16*, 287.

[52] Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5343; Reynolds, W.F.; Dais, P.; MacIntyre, D.W.; Topsom, R.D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R.W. *J. Am. Chem. Soc.* ***1983***, *105*, 378.

[53] Also see Happer, D.A.R.; Wright, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 694.

[54] Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R.E. *J. Am. Chem. Soc.* ***1959***, *81*, 5352.

[55] Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766. See also, Marriott, S.; Topsom, R.D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1045.

[56] For a set of σ_R values for use in XY^+ systems, see Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271.

[57] See de Ligny, C.L.; van Houwelingen, H.C. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 559.

[58] See Shorter, J. in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 98–103.

[59] See Screttas, C.G. *J. Org. Chem.* ***1979***, *44*, 3332; Hanson, P. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 101.

TABLE 9.6 The *F* and *R* Values for Some Groups[a]

Group	*F*	*R*	Group	*F*	*R*
COO^-	−0.27	0.40	OMe	0.54	−1.68
Me_3C	−0.11	−0.29	CF_3	0.64	0.76
Et	−0.02	−0.44	I	0.65	−0.12
Me	−0.01	−0.41	Br	0.72	−0.18
H	0	0	Cl	0.72	−0.24
Ph	0.25	−0.37	F	0.74	−0.60
NH_2	0.38	−2.52	NHCOMe	0.77	−1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	−1.89	NMe_3^+	1.54	
COOEt	0.47	0.67	N_2^+	2.36	2.81
COMe	0.50	0.90			

Reprinted with permission Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Copyright © 1983 American Chemical Society.

[a]See Ref. 63.

approximately the same field effect and that the σ_I values are invalid as a measure of the intrinsic field effects of alkyl groups.[60]

Another attempt to divide σ values into resonance and field contributions[61] is that of Swain and Lupton, who show that the large number of sets of σ values (σ_m, σ_p, σ_{p-}, σ_{p+}, σ_I, σ_R^0, etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values *F* (which expresses the field-effect contribution) and *R* (the resonance contribution) satisfactorily express 43 sets of values.[62] Each set is expressed as:

$$\sigma = f_F + r_R$$

where *f* and *r* are weighting factors. Some *F* and *R* values for common groups are given in Table 9.6.[63] From the calculated values of *f* and *r*, Swain and Lupton[63] calculated that the importance of resonance, *%R*, is 20% for σ_m, 38% for σ_p, and 62% for σ_p^+.[64] This is another dual substituent parameter approach.

Taft and co-workers[63] were also able to isolate steric effects.[65] For the acid-catalyzed hydrolysis of esters in aqueous acetone, long (k/k_0) was shown to be insensitive to polar effects.[66] In cases where resonance interaction was absent, this value was proportional only

[60] See DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[61] See Shorter, J. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 119–173, pp. 126–144; Afanas'ev, I.B. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1589; Ponec, R. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 1564.

[62] Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492 and references cited therin.

[63] From Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165.

[64] The Swain-Lupton treatment has been criticized by Reynolds, W.F.; Topsom, R.D. *J. Org. Chem.* ***1984***, *49*, 1989; Hoefnagel, A.J.; Oosterbeek, W.; Wepster, B.M. *J. Org. Chem.* ***1984***, *49*, 1993; Charton, M. *J. Org. Chem.* ***1984***, *49*, 1997. For a reply, see Swain, C.G. *J. Org. Chem.* ***1984***, *49*, 2005. See Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Nakazumi, H.; Kitao, T.; Zollinger, H. *J. Org. Chem.* ***1987***, *52*, 2825.

[65] See Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91.

[66] Also see De Tar, D.F.; Delahunty, C. *J. Am. Chem. Soc.* ***1983***, *105*, 2734.

TABLE 9.7 The E_s, υ, and V^a Values for Some Groups[a]

Group	E_s	υ	$V^a \times 10^2$	Group	E_s	υ	$V^a \times 10^2$
H	0	0		Cyclohexyl	−2.03	0.87	6.25
F	−0.46	0.27	1.22	*i*-Bu	−2.17	0.98	5.26
CN	−0.51			*sec*-Bu	−2.37	1.02	6.21
OH	−0.55			CF_3	−2.4	0.91	3.54
OMe	−0.55		3.39	*t*-Bu	−2.78	1.24	7.16
NH_2	−0.61			NMe_3^+	−2.84		
Cl	−0.97	0.55	2.54	Neopentyl	−2.98	1.34	5.75
Me	−1.24	0.52	2.84	CCl_3	−3.3	1.38	6.43
Et	−1.31	0.56	4.31	CBr_3	−3.67	1.56	7.29
I	−1.4	0.78	4.08	$(Me_3CCH_2)_2CH$	−4.42	2.03	
Pr	−1.6	0.68	4.78	Et_3C	−5.04	2.38	
*i*Pr	−1.71	0.76	5.74	Ph_3C	−5.92	2.92	

Reprinted with permission from Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173, Copyright © 1988, with permission from Elsevier Science.

[a]See Ref. 68.

to steric effects (and any others[67] that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

Some E_s values are given in Table 9.7,[68] where hydrogen is taken as standard, with a value of 0.[69] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton[70] show that E_s values for substituents of types CH_2X, CHX_2, and CX_3 are linear functions of the *van der Waals radii* for these groups.

Two other steric parameters are independent of any kinetic data. Charton's υ values are derived from van der Waals radii,[71] and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.[72] The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives υ and V^a values for some groups.[73] As can be seen in the table, there is a fair, but not perfect, correlation among the E_s, υ, and V^a values. Other sets of steric values (e.g., E_S^1,[74] E_S^*,[75] Ω_s[76] and δ_f,[77] have also been proposed.[73]

[67] See McClelland, R.A.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 5860.

[68] Taken from Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91. Charton, M. *J. Org. Chem.* ***1976***, *41*, 2217; and Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[69] In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the orginal values by adding 1.24.

[70] Charton, M. *J. Am. Chem. Soc.* ***1969***, *91*, 615.

[71] Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217. See also, Charton, M. *J. Org. Chem.* ***1978***, *43*, 3995; Idoux, J.P.; Schreck, J.O. *J. Org. Chem.* ***1978***, *43*, 4002.

[72] Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[73] See DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[74] MacPhee, J.A.; Panaye, A.; Dubois, J.E. *J. Org. Chem.* ***1980***, *45*, 1164; Dubois, J.E.; MacPhee, J.A.; Panaye, A. *Tetrahedron* ***1980***, *36*, 919. See also, Datta, D.; Sharma, G.T. *J. Chem. Res. (S)* ***1987***, 422.

[75] Fellous, R.; Luft, R. *J. Am. Chem. Soc.* ***1973***, *95*, 5593.

[76] Komatsuzaki, T.; Sakakibara, K.; Hirota, M. *Tetrahedron Lett.* ***1989***, *30*, 3309; *Chem. Lett.* ***1990***, 1913.

[77] Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 593.

Since the *Hammett equation* has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.[78] The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.[79] Despite the many attempts made to quantify ortho effects, no set of values has so far commanded general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC_6H_4Y is separated from the ring; for example, ionization constants of *o*-$XC_6H_4OCH_2CO_2H$ can be successfully correlated.[80]

Linear free energy relationships can have mechanistic implications. If $\log k/k_0$ is linear with the appropriate σ, it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,[81] although nonlinear plots can also be due to other causes (e.g., complications arising from side reactions). If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.[82]

Information can also be obtained from the magnitude and sign of ρ. For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.[83] The σρ relationship even applies to free radical reactions, because free radicals can have some polar character (Sec. 14.A.ii), though ρ values here are usually small (less than ∼1.5) whether positive or negative. Reactions involving cyclic transition states (Sec. 6.B) also exhibit very small ρ values.

9.D. EFFECT OF MEDIUM ON REACTIVITY AND RATE

There is no question that the solvent chosen for a given reaction has a profound influence on the course of that reaction. Protic versus aprotic solvents, as well as polar versus nonpolar solvents, can have effects ranging from solubility to solvent assisted ionization or stabilization of transition states. Reactions can also be done neat in one of the reactants, in the gas phase, on solid support, or in the solid phase. Environmental friendly chemistry (green chemistry) is becoming increasingly important, and chemical reactions in non-polluting (often non-organic) solvents are of particular interest.[84] This section will describe alternative reaction media as well as other medium-related things that influence chemical reactions.

[78] See Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* ***1976***, *12*, 49; Charton, M. *Prog. Phys. Org. Chem.* ***1971***, *8*, 235. See also, Robinson, C.N.; Horton, J.L.; Fosheé, D.O.; Jones, J.W.; Hanissian, S.H.; Slater, C.D. *J. Org. Chem.* ***1986***, *51*, 3535.

[79] This is not the same as the ortho effect discussed in Section 11.B.iv.

[80] Charton, M. *Can. J. Chem.* ***1960***, *38*, 2493.

[81] See Schreck, J.O. *J. Chem. Educ.* ***1971***, *48*, 103.

[82] See, however, Gawley, R.E. *J. Org. Chem.* ***1981***, *46*, 4595.

[83] Also see Williams, A. *Acc. Chem. Res.* ***1984***, *17*, 425.

[84] Clark, J.H. *Green Chem.* ***1999***, *1,* 1; Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159.

9.D.i High Pressure

Acceleration of some chemical reactions is possible when high-pressure techniques are employed.[85,86] The effects on a given reaction can be predicted to a certain extent because the thermodynamic properties of solutions are well known. The rate of a reaction can be expressed in terms of the activation volume, ($\Delta V^{\ddagger}$)

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

so rate constants vary with pressure.[86] "The activation volume[87] is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view, this could be approximated by the molar volume."[86] If the volume of activation is negative, the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of $\Delta V^{\ddagger}$ decreases and the system does not strictly obey the equation shown above at pressures > 10 kbar ($1\text{ bar} = 0.986924\text{ atm} = 1.1019716\text{ kg cm}^{-2}$). If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. There is a correlation between pressure and steric interactions in organic reactions.[88] Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto et al. summarized the reactions for which rate enhancement is expected at high pressure.[86]

1. Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions and condensations.
2. Reactions that proceed via cyclic transition states.
3. Reactions that take place through dipolar transition states.
4. Reactions with steric hindrance.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.[86,89] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

[85] Jenner, G. *Tetrahedron* ***2002****, 58*, 5185; Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, New York, ***1991***.

[86] Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis.* ***1985***, 999. Also see Benito-López, F.; Egberink, R.J.M.; Reinhoudt, D.N.; Verboom, W. *Tetrahedron* ***2008****, 64,* 10023.

[87] See le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967****, 5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978,*** *78*, 407.

[88] Jenner, G. *Tetrahedron* ***2005****, 61,* 3621.

[89] Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981****, 46*, 2160.

9.D.ii Water and Other Non-Organic Solvents

Although some reactions may be done in water,[90] chemical reactions of organic substrates usually employ an organic solvent (e.g., a hydrocarbon, ether, dichloromethane, small molecular weight alcohols, and so on), but other more exotic solvents are available. For example, poly(ethylene glycol), or PEG, has been used as a solvent medium for catalytic hydrogenation (Reaction **15-11**).[91] For some reactions in organic solvents, the presence of water may cause unwanted side reactions, and methods have been developed to detect the presence of water in those solvents.[92]

With the exception of small molecular weight molecules with polar functional groups and polyfunctional molecules or salts, organic chemicals have poor solubility in water. Nonetheless, some reactions show a faster rate of reaction in water or in aqueous media.[93] The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,[94] who reported that yields in the *Diels–Alder Reaction* (**15-60**) were enhanced in aqueous detergent solutions. In an early study, Berson et al.[95] showed a clear relationship between the endo/exo product ratio and solvent polarity, in the Diels–Alder reaction of cyclopentadiene and acrylates. Breslow and Rideout.[96] showed there was a hydrophobic acceleration for an intermolecular *Diels–Alder reaction* in which cyclopentadiene reacted with methyl vinyl ketone. Clearly, there is an accelerating effect on some chemical reactions when done in water that is useful in organic chemistry.[97]

When nonpolar compounds are suspended in water, their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a hydrophobic effect).[98] This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate.[96]

Organic chemical reactions have been done is supercritical fluids, including supercritical water.[99] A supercritical fluid can be either liquid or gas, but it is used in a state above the temperature and pressure where gases and liquids can coexist. The properties of a supercritical fluid are different from those of either gases or liquids under standard conditions, with no distinct liquid and gas phases at temperatures and pressures above its critical point. The critical point is the temperature, pressure, and so on, at which there are no phase boundaries. Carbon dioxide can be used as a reaction solvent when pressurized (supercritical carbon dioxide, $scCO_2$). Carbon dioxide is nontoxic,

[90] *Organic Reactions in Water: Principles, Strategies and Applications*, Lindström, U.M. (Ed.), Blackwell, Oxford, ***2007***; Chanda, A.; Fokin, V.V. *Chem. Rev.* ***2009***, *109*, 725.

[91] Chandrasekhar, S.; Prakash, S.J.; Rao, C.L. *J. Org. Chem.* ***2006****, 71,* 2196. PEG has also been used for the synthesis of β-amino sulfides. See Kamal, A.; Reddy, D.R.; Rajendar *Tetrahedron Lett.* ***2006****, 47,* 2261.

[92] Sun, H.; Wang, B.; DiMagno, S.G. *Org. Lett.* ***2008****, 10,* 4413.

[93] See Pirrung, M.C. *Chemistry: European J.* ***2006****, 12,* 1312.

[94] Hopff, H.; Rautenstrauch, C.W. *U.S. Patent* 2,262,002, ***1939*** [*Chem. Abstr. 36*: 1046^9, ***1942***].

[95] Berson, J.A.; Hamlet, Z.; Mueller, W.A. *J. Am. Chem. Soc.* ***1962****, 84*, 297.

[96] Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* ***1980****, 102*, 7816.

[97] Engberts, J.B.F.N.; Blandamer, M.J. *Chem. Commun.* ***2001***, 1701; Lindström, U.M. *Chem. Rev.* ***2002****, 102*, 2751; Ribe, S.; Wipf, P. *Chem. Commun.* ***2001***, 299.

[98] For a review of chemical reactions in aqueous media with a focus on C—C bond formation, see Li, C.-J. *Chem. Rev.* ***2005****, 105,* 3095. For microwave assisted synthesis in water, see Dallinger, D.; Kappe, C.O. *Chem. Rev.* ***2007****, 107,* 2563.

[99] Weingärtner, H.; Franck, E.U. *Angew. Chem. Int. Ed.* **2005**, 44, 2672; Fraga-Dubreuil, J.; Poliakoff, M. *Pure Appl. Chem.* ***2006****, 78*,1971.

inexpensive, abundant, and easily recycled. These properties have made it attractive as an extraction solvent.[100] The low critical temperature of CO_2 (T_c) 31.1 °C ensures that $scCO_2$ is a safe solvent for many applications.[101] There are solubility issues that suggest $scCO_2$ is a rather polar solvent.[102] For example, many systems with hydrocarbon chains are not very soluble in CO_2.[103] Water/carbon dioxide emulsions have also been employed.[104] The use of ($scCO_2$) has been explored in many reactions,[105] including catalysis.[106] Some applications of this technique include the electrochemical synthesis of conducting polymers[107] and highly cross-linked polymers[108] in $scCO_2$, the synthesis of octyl palmitate,[109] of carbonated fatty methyl esters,[110] and of methyl carbamates.[111] A carbonylation reaction was done is $scCO_2$ in the course of a synthesis of trisubstituted cyclopentanes and cyclohexanes as key components of substance P antagonists.[112] A continuous flow acid-catalyzed dehydration of alcohols was accomplished in $scCO_2$.[113] Supercritical fluids are playing an increasingly important role in synthetic organic chemistry.[114]

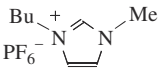
Other supercritical fluids can be used for chemical reactions, such as supercritical ammonia in the synthesis of labeled guanidines.[115]

9.D.iii Ionic Solvents

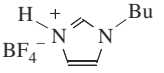
Environmentally friendly solvents,[116] which include ionic liquids, are of great interest.[117] An ionic liquid is a salt in which the ions are poorly coordinated, usually leading to their being liquid at <100 °C and sometimes at room temperature.[118] In such ionic species, there is usually at least one ion with a delocalized charge, whereas the other component is usually organic. This combination inhibits the formation of a stable crystal lattice. The structure and solvation properties of solutes in ionic liquids have been studied.[119] It was discovered

[100] See Raynie, D.E. *Anal. Chem.* ***2004****, 76,* 4659.
[101] Subramaniam, B.; Rajewski, R. A.; Snavely, K. *J. Pharm. Sci.* ***1997***, *86*, 885.
[102] Raveendran, P.; Ikushima, Y.; Wallen, S.L. *Acc. Chem. Res.* ***2005****, 38,* 478.
[103] Consani, K.A.; Smith, R.D.J. *Supercrit. Fluids* ***1990****, 3,* 51.
[104] Jacobson, G.B.; Lee, Jr., C.T.; da Rocha, S.R.P.; Johnston, K.P. *J. Org. Chem.* ***1999****, 64,* 1207; Jacobson, G.B.; Lee, Jr., C.T.; Johnston, K.P. *J. Org. Chem.* ***1999****, 64,* 1201.
[105] Gopalan, A.D.; Wai, C.M.; Jacobs, H.K. *Supercritical Carbon Dioxide: Separations and Processes*, American Chemical Society (distributed by Oxford University Press), Washington, DC. ***2003***; Beckman, E.J. *Ind. Eng. Chem. Res.* ***2003****, 42,* 1598; Wang, S.; Kienzle, F. *Ind. Eng. Chem. Res.* ***2000****, 39*, 4487.
[106] Leitner, W. *Acc. Chem. Res.* ***2002****, 35*, 746.
[107] Anderson, P.E.; Badlani, R.N.; Mayer, J.; Mabrouk, P.A. *J. Am. Chem. Soc.* ***2002****, 124,* 10284.
[108] Cooper, A.I.; Hems, W.P.; Holmes, A.B. *Macromolecules* ***1999****, 32*, 2156.
[109] Madras, G.; Kumar, R.; Modak, J. *Ind. Eng. Chem. Res.* ***2004****, 43,* 7697,1568.
[110] Doll, K.M.; Erhan, S.Z. *J. Agric. Food Chem.* ***2005****, 53,* 9608.
[111] Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* ***2005****, 70,* 2771.
[112] Kuethe, J.T.; Wong, A.; Wu, J.; Davies, I.W.; Dormer, P.G.; Welch, C.J.; Hillier, M.C.; Hughes, D.L.; Reider, P.J. *J. Org. Chem.* ***2002****, 67,* 5993.
[113] Gray, W.K.; Smail, F.R.; Hitzler, M.G.; Ross, S.K.; Poliakoff, M. *J. Am. Chem. Soc.* ***1999****, 121,* 10711.
[114] See Prajapati, D.; Gohain, M. *Tetrahedron* ***2004****, 60*, 815.
[115] Jacobson, G.B.; Westerberg, G.; Markides, K.E.; Langstrom, B. *J. Am. Chem. Soc.* ***1996****, 118,* 6868.
[116] *Alternative Solvents for Green Chemistry,* Kerton, F.M.; Clark J.M.; Kraus, G.A. Royal Society of Chemistry, Cambridge, ***2009***.
[117] But also see Scammells, P.J.; Scott, J.L.; Singer, R.D. *Austr. J. Chem.* ***2005****, 58*, 155.
[118] For a discussion of physical properties, see Ludwig, R.; Kragl, U. *Angew. Chem. Int. Ed. 2007, 46,* 6582.
[119] Hardacre, C.; Holbrey, J.D.; Nieuwenhuyzen, M.; Youngs, T.G.A. *Acc. Chem. Res.* ***2007****, 40*, 1146; Greaves, T.L.; Drummond, C.J. *Chem. Rev.* ***2008***, *108*, 206. See also Lungwitz, R.; Strehmel, V.; Spange, S. *New J. Chem.* ***2010****, 34,* 1135.

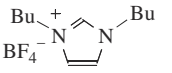
that some ionic liquids are suitable as a medium for chemical reactions.[120] Both methylimidazolium and pyridinium ions form the basis of common ionic liquids that have been used in organic chemistry.[121] One of the most common ionic liquids used as a solvent is 1-butyl-3-methylimidazolium as the hexafluorophosopahte, (**10**, Bmim PF_6).[122] Hydrogenbutylimidazolium tetrafluoroborate (HBuIm, **11**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **12**), for example,[123] have been reported to facilitate *Diels–Alder Reactions* (**15-60**).[124] It is known that a proton on C-2 of imidazolium cations (e.g., **10-12**) is relatively acidic.[125] Carbene formation is common and the anion generated by treatment with base can undergo substitution reactions.[125] These facts lead to a caution that undesired side reactions are possible when these ionic liquids are employed as solvents.[125,126] Pyridinium-based ionic liquids [e.g., ethylpyridinium tetrafluoroborate (**13**)] have also been used.[127] Several room temperature ionic liquids have been synthesized from amino acids.[128]



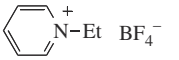
10



11



12



13

Ionic solvents have been used to facilitate heterocyclic reactions,[129] several catalytic reactions,[130] the *Heck Reaction* (**13-9**)[131] and other Pd catalyzed C—C bond-forming reactions,[132] the oxidation of alcohols with hypervalent iodine reagents (**19-3**),[133] and the catalytic asymmetric dihydroxylation of alkenes (**15-48**) using a recoverable and reusable Os/ligand complex.[134] The camphorsulfonate anion has been used as a counterion for imidazolium salts, and shown to increase the number of unsolvated imidazolium cations.[135] This ionic liquid was then shown to influence the endo/exo ratio in a stereoselective *Diels–Alder Reaction* (**15-60**).[135] Other catalytic reactions in ionic liquids are known.[136] Other chiral ionic

[120] Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* ***2000****, 39,* 3772; Earle, M.J.; Seddon, K.R. *Pure. Appl. Chem.* ***2000****, 72*, 1391; *Ionic Liquids in Synthesis*, Wasserscheid, P.; Welton, T.; Wiley–VCH, NY, ***2002***; *Chemistry in Alternative Reaction Media*, Adams, D.J.; Dyson, P.J.; Taverner, S.J.; Wiley, ***2003***. For a discussion of the solvating ability, see Chiappe, C.; Malvaldi, M.; Pomelli, C.S. *Pure Appl. Chem.* ***2009***, ***81***, 767.

[121] Rogers, R.D.; Voth, G.A. A*cc. Chem. Res.* ***2007****, 40,*1077;

[122] Dupont, J.; Consorti, C.S.; Suarez, P.A.Z.; de Souza, R.F. *Org. Synth. Coll. Vol. X*, 184.

[123] For discussion of HBuIM and DiBuIm, see Harlow, K.J.; Hill, A.F.; Welton, T. *Synthesis* ***1996***, 697; Holbrey, J.D.; Seddon, K.R. *J. Chem. Soc., Dalton Trans.* ***1999***, 2133; Larsen, A.S.; Holbrey, J.D.; Tham, F.S.; Reed, C.A. *J. Am. Chem. Soc.* ***2000****, 122*, 7264.

[124] Jaegar, D.A.; Tucker, C.E. *Tetrahedron Lett.* ***1989****, 30,* 1785.

[125] Handy, S.T.; Okello, M. *J. Org. Chem.* ***2005****, 70,* 1915.

[126] For a discussion of the reactivity of ionic liquids, see Chowdhury, S.; Mohan, R.S.; Scott, J.L. *Tetrahedron* ***2007****, 63,* 2363.

[127] See Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* ***2004****, 45*, 8339.

[128] Fukumoto, K.; Yoshizawa, M.; Ohno, H. *J. Am. Chem. Soc.* ***2005****, 127,* 2398. Also see Chen, X.; Li, X.; Hu, A.; Wang, F. *Tetrahedron Asymmetry* ***2008****, 19*, 1.

[129] Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Zanatta, N.; Bonacorso, H.G. *Chem. Rev.* ***2008****, 108,* 2015.

[130] See Toma, Š.; Mečiarová. M.; Šebesta, R. *Eur. J. Org. Chem.* ***2009***, 321.

[131] Handy, S.T.; Okello, M.; Dickenson, G. *Org. Lett.* ***2003****, 5,* 2513.

[132] Calò, V.; Nacci, A.; Monopoli, A. Eur. J. Org. Chem. 2006, 3791.

[133] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron* ***2004****, 60,* 2131.

[134] Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004****, 69*, 4381.

[135] Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* ***2005****, 70,* 10106.

[136] Pârvulescu, V.I.; Hardacre, C. *Chem. Rev.* ***2007****, 107,* 2615.

liquids are known.[137] Reactions performed in an ionic liquid are a rapidly growing area of organic chemistry, and has been expanded to include microwave reactions (see Sec. 7.C) in ionic solvents.[138] The development and use of ionic solvents is a growth area of organic chemistry.[139] Also note that some ionic liquids are categorized as Lewis base (Sec. 8.E), which will influence the acidity of dissolved compounds.[140] There are also acidic Brønsted ionic liquids.[141]

9.D.iv. Solventless Reactions

In some cases, it should be possible to accomplish a chemical transformation without the use of a solvent. Dry media reaction under microwave irradiation is an important area of study (see Sec. 7.C).[142] There are several advantages of solventless reactions: (1) the possibility of direct formation of high-purity compounds, (2) the possibility of sequential reactions, (3) fast kinetics, (4) lower energy usage, (5) minimal need for preformed salts and metal–metalloid complexes, (6) simplicity and low equipment cost, and (7) the possibility of avoiding functional group protection–deprotection.[143] Potential difficulties include the possibility of hot spots and runaway reactions, and difficulties in handling solid or highly viscous materials.[144] An example of this approach is the aldol condensation, where a single aldol product was obtained in high yield.[145] 3-Carboxylcoumarins have been produced via a solventless aldol.[143]

[137] Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.C. *Tetrahedron Asymmetry* ***2005****, 16,* 3921; Pernak, J.; Feder-Kubis, J. *Tetrahedron Asymmetry* ***2006****, 17,* 1728; Luo, S.-P.; Xu, D.-Q.; Yue, H.-D.; Wang, L.-P.; Yang, W.-L.; Xu, Z.-Y. *Tetrahedron Asymmetry* ***2006****, 17,* 2028.

[138] See Leadbeater, N.E.; Torenius, H.M. *J. Org. Chem.* ***2002****, 67*, 3145.

[139] For studies to expand the polarity range of ionic solvents see Dzyuba, S.V.; Bartsch, R.A. *Tetrahedron Lett.* ***2002****, 43*, 4657. See *Ionic Liquids: From Knowledge to Application*, Plechkova, N.V.; Rogers, R.D.; Seddon, K.R. (Eds.), American Chemical Society, Washington, DC (distributed by Oxford University Press), ***2010***.

[140] MacFarlane, D.R.; Pringle, J.M.; Johansson, K.M.; Forsyth, S.A.; Forsyth, M. *Chem. Commun.* ***2006***, 1905.

[141] Hajipour, A.R.; Rafiee, F. *Org. Prep. Proceed. Int.* ***2010****, 42,* 285.

[142] Kidwai, M. *Pure Appl. Chem.* ***2001****, 73*, 147.

[143] Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159; Toda, F.; Tanaka, K. *Chem. Rev.* ***2000****, 100,* 1025.

[144] Raston, C.L. *Chemistry in Australia* ***2004***, 10.

[145] Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 3207.

PART II

INTRODUCTION

Part II of this book will be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation–reduction reactions. Substitutions are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon–carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation–reduction reactions. This last chapter covers only those oxidation–reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part II consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry that can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. However, certain special areas have been covered only lightly or not at all. Among these are polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

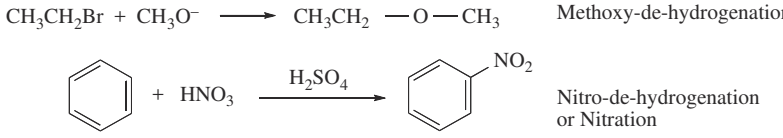
Each reaction is discussed in its own numbered section.[1] These are numbered consecutively within a chapter, each section number is preceded by the chapter number, so that Reaction **16-1** is the first reaction of Chapter 16 and Reaction **13–21** is the 21st reaction of Chapter 13. The order in which the reactions are presented is not arbitrary, but is based on an orderly outline that depends on the type of reaction. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

II.A. IUPAC NOMENCLATURE FOR TRANSFORMATIONS

There has long been a need for a method of naming reactions. Many reactions have been given the names of their discoverers or those who popularized them (e.g., *Claisen*, *Diels–Alder*, *Stille*, *Wittig*, *Cope*, *Dess–Martin*). In the past, this was necessary because mechanisms were not well understood, and a *named reaction* was a convenient way to identify certain transformations. Nowadays, the reasons for assigning a name are less clear and there may be as many as 800–1000 named reactions. Some believe that this practice has gotten out of hand, while others believe it to be the best way to organize key reactions. Named reactions are useful to a point, but each name must be individually memorized, and there are many reactions that do not have such names. The IUPAC Commission on Physical Organic Chemistry produced a *system* for naming, not reactions, but transformations (a reaction includes all reactants; a transformation shows only the substrate and product, omitting the reagents). The advantages of a systematic method are obvious. Once the system is known, no memorization is required; the name can be generated directly from the equation. The system includes rules for naming eight types of transformation: substitutions, additions, eliminations, attachments and detachments, simple rearrangements, coupling and uncoupling, insertions and extrusions, and ring opening and closing. Only the most basic rules are given for the first three of these types, which, however, will suffice for naming many transformations.[2]

II.A.i. Substitutions

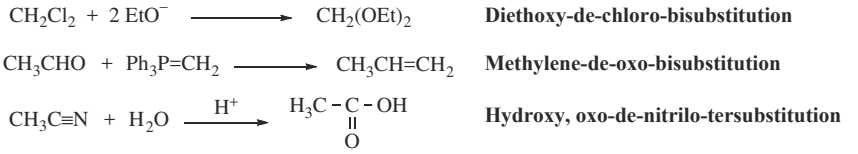
A name consists of the entering group, the syllable "de", and the leaving group. If the leaving group is hydrogen, it may be omitted (in all examples, the substrate is written on the left).



[1] The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction is different, and custom generally decides how we group them together. Individual preferences also play a part. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita, S. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 597.

[2] For a more complete set of rules, see Jones, R.A.Y.; Bunnett, J.F. *Pure Appl. Chem.* ***1989***, *61*, 725.

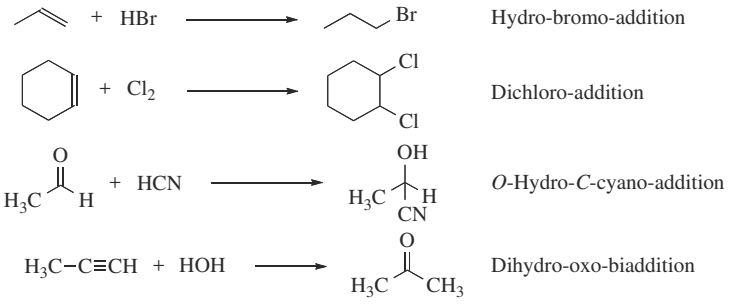
Multivalent substitutions are named by a modification of this system that includes suffixes (e.g., "bisubstitution" and "tersubstitution").



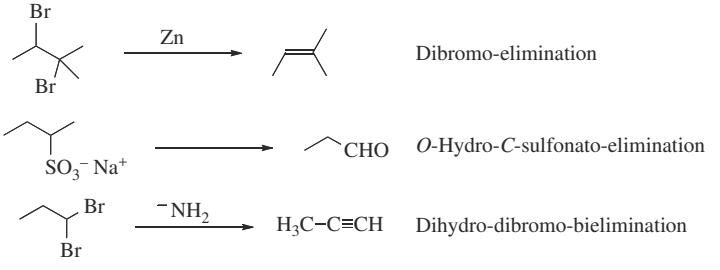
(*Note*: The nitrilo group is ≡N.)

II.A.ii. Additions

For simple 1,2-additions, the names of both addends are given followed by the suffix "addition". The addends are named in order of priority in the *Cahn–Ingold–Prelog system* (Sec. 4.E.i), the lower-ranking addend coming first. Multivalent addition is indicated by "biaddition", and so on,



Eliminations are named the same way as additions, except that "elimination" is used instead of "addition".



In the reaction sections of this book, IUPAC names are used for most transformations (these names will be printed in the same typeface used above), including examples of all eight types.[3] As will become apparent, some transformations require more rules than we have given here.[2] However, it is hoped that the simplicity of the system will also be apparent.

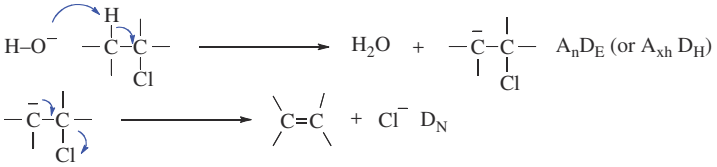
[3] For some examples, see: attachments (**18-27**, **19-29**), detachments (**19-72**), simple rearrangements (**18-7**, **18-29**), coupling (**10-56**, **19-34**), uncoupling (**19-9**, **19-75**), insertions (**12-21**, **18-9**), extrusions (**17-35**, **17-38**), ring opening (**10-14**, **10-35**), ring closing (**10-9**, **15-60**).

Two further notes: (1) Many transformations can be named using either of two reactants as the substrate. For example, the transformation methylene-de-oxo-bisubstitution above, can also be named ethylidene-de-triphenylphosphoranediyl-bisubstitution. In this book, unless otherwise noted, we will show only those names in which the substrate is considered to undergo the reactions indicated by the titles of the chapters. Thus the name we give to Reaction **11-11** ($ArH + RCl \rightarrow ArR$) is alkyl-de-hydrogenation, not aryl-de-chlorination, although the latter name is also perfectly acceptable under the IUPAC system. (2) The IUPAC rules recognize that some transformations are too complex to be easily fitted into the system, so they also include a list of names for some complex transformations, which are IUPAC approved, but nonsystematic (for some examples, see Reactions **12–44**, **18–34**).

II.B. IUPAC SYSTEM FOR SYMBOLIC REPRESENTATION OF MECHANISMS

In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.[4] As will be seen, many mechanisms (but by no means all) are commonly referred to by designations (e.g., S_N2, $A_{AC}2$, $E1_{cB}$, and $S_{RN}1$), many of them devised by C.K. Ingold and co-workers. While these designations have been useful (and we will continue to use them in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how S_N2' is related to S_N2 (see Sec. 10.A.i). The IUPAC system is based on a very simple description of bond changes.[5] The letter A represents formation of a bond (association); D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism, the *core atoms* are defined as (1) the two atoms in a multiple bond that undergoes addition, or (2) the two atoms that will be in a multiple bond after elimination, or (3) the single atom at which substitution takes place.

As an example of the system, this is how an $E1_{cB}$ mechanism (Sec. 17.A.iii) would be represented:



Overall designation: $A_nD_E + D_N$ (or $A_{xh}D_H + D_N$). In this case, the overall reaction is



and the core atoms are the two carbons in boldface.

[4] Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23. For a briefer description, see Guthrie, R.D.; Jencks, W.P. *Acc. Chem. Res.* ***1989***, *22*, 343.

[5] There are actually two IUPAC systems. The one used in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler, J.S. *Pure Appl. Chem.* ***1989***, *61*, 57. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

Step 1, First Symbol.
A bond is being formed between O and H. Bond formation is represented by A. For this particular case, the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_N) or breaking a bond to a nucleofuge (D_N). If a noncore atom is doing the same thing, lowercase n is used instead. Since H and O are noncore atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n. However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the term A_{xh} means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh, would be used if the outside atom were any other nucleophilic atom, say, N or S.

Step 1, Second Symbol.
A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E. Alternatively, the symbol could be D_H. The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+. Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1. Combined Symbols.
In Step 1, two bond changes take place simultaneously. In such cases, they are written together with no space or punctuation: A_nD_E or $A_{xh}D_H$

Step 2.
Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system, bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N.

The overall designation can be either $A_nD_N + D_N$ or $A_{xh}D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol. In this case, if the first step is the slow step [old designation $(E1_{cB})_I$], the designation would be $A_nD_E + D_N$ or $A_{xh}D_H + D_N$.

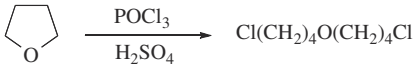
For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_nD_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

Here, we have given only a brief description of the system. Other IUPAC designations will be shown in Part II, where appropriate. For more details, further examples, and additional symbols, see Ref. 4.

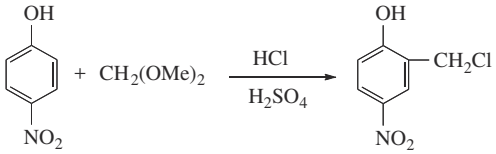
II.C. ORGANIC SYNTHESES REFERENCES

At the end of many numbered sections there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**12-3**, **12–23**, **12–24**,

and **12–38**), and to the extent that it is possible, the list includes *all* OS references for each reaction. The volumes of OS that have been covered are Collective Volumes **I**–**XI**. There are indices to OS.[6] Organic Syntheses can now be accessed online.[7] Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS **IV**, 266 is



This reaction is treated as Reaction **10–49** followed by Reaction **10–12** and is listed in both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS **III**, 468:



This is a chloromethylation reaction and is consequently listed in Reaction **11–14**. However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed in Reaction **10-6** (hydrolysis of acetals), because it is not really a preparation of formaldehyde.

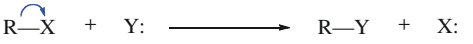
[6] Smith, M.B. Fieser and Fieser's Reagents For Organic Syntheses, Collective Index For Volumes 1–22, Wiley, New York, **2005**; Smith, J.G.; Fieser, M. Fieser and Fieser's Reagents for Organic Synthesis: Collective Index for, Volumes 1–12, Wiley, New York, **1990**; Liotta, D.C.; Volmer, M. Organic Syntheses Reaction Guide, Wiley: NY, **1991**, which covers the series through Vol. 68. For an older index to Organic Syntheses (through Vol. 45), see Sugasawa, S.; Nakai, S. Reaction Index of Organic Syntheses, Wiley: NY, **1967**.

[7] Available at http://www.orgsyn.org/.

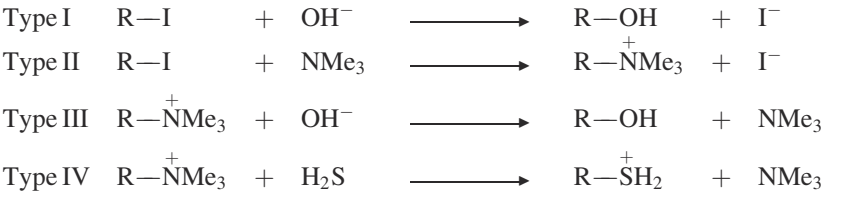
CHAPTER 10

Aliphatic Substitution, Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:



As written, this equation says nothing about charges. Nucleophile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which follows:



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe_3 is an *alkylation* of trimethylamine. Nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile, and such reactions are found in Chapter 16.

10.A. MECHANISMS

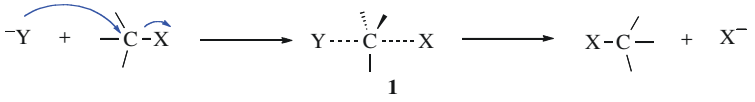
Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the *attacking* reagent carries the electron pair with it. Mechanisms that

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

occur at a saturated carbon atom are considered first.[1] By far the most common are the S_N1 and S_N2 mechanisms.

10.A.i. The S_N2 Mechanism

The designation S_N2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (Sec. 9.F) is A_ND_N. In this mechanism, there is *backside attack*,[2] which means that the nucleophile approaches the substrate from a position 180° away from the leaving group. This approach will minimize steric and electronic repulsion of the substrate and the incoming nucleophile. The reaction is a one-step process with no intermediate (see below, and Sec. 10.A.iv). The C—Y bond is formed as the C—X bond is broken to generate *pentacoordinate transition state* **1**.



1

The energy necessary to break the C—X bond is supplied by the collision of the nucleophile (Y) with the carbon bearing the leaving group (X). The top of the curve of free energy of activation is taken to be the transition state, and the position of the atoms for this reaction are shown in transition state **1**. The transition state is not a real structure, of course, but the energetic midpoint of the reaction. There are various computational methods to ascertain characteristics of a given transition state, and the experimental examination of kinetic isotope effects has been used to infer information about the transition state.[3] The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial sp^3 hybridization to essentially sp^2 with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is the reason a frontside S_N2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. At the energy point of the transition state, the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and leaving group are the same.

There is a large amount of evidence for the S_N2 mechanism. First, there is the kinetic evidence.[4] Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order

[1] See Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, ***1973***; Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* ***1990***, *19*, 83; Richard, J.P. *Adv. Carbocation Chem.* ***1989***, *1*, 121; Streitwieser, A. *Solvolytic Displacement Reactions,* McGraw-Hill, NY, ***1962***.

[2] See Sun, L.; Hase, W. L.; Song, K. *J. Am. Chem. Soc.* ***2001***, *123,* 5753. Nucleophlicity and leaving group ability for frontside and backside attack have been studied. See Bento, A.P.; Bickelhaupt, F.M. *J. Org. Chem.* ***2008***, *73,* 7290.

[3] Hasanayn, F.; Streitwieser, A.; Al-Rifai, R. *J. Am. Chem. Soc.* ***2005***, *127*, 2249. See also Cruickshank, F.R.; Hyde, A.J.; Pugh, D. *J. Chem. Ed.* ***1977***, *54*, 288.

[4] For a theoretical investigation of a kinetic isotope effect, see Matsson, O.; Dybala-Defratyka, A.; Rostkowski, M.; Paneth, P.; Westaway, K.C. *J. Org. Chem.* ***2005***, *70,* 4022.

in each component, second order overall, and satisfy the rate expression shown in Eq. (10-1).

$$\text{Rate} = k[\text{RX}][\text{Y}] \tag{10-1}$$

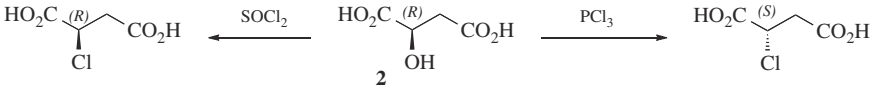
This rate law has been found to apply. Note that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see Sec. 6.J.vi). If a large excess of nucleophile is present (e.g., if it is the solvent[5]) the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order, Eq. (10-2).

$$\text{Rate} = k[\text{RX}] \tag{10-2}$$

As previously mentioned (Sec. 6.J.vi), such kinetics are called *pseudo-first order*.

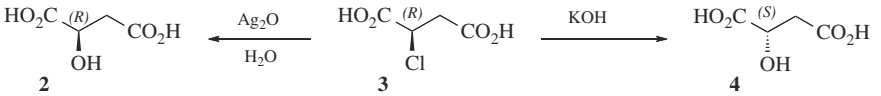
The kinetic evidence is a necessary but not a sufficient condition; other mechanisms will be encountered that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (see Sec. 4.E.ii) that proceeds through transition state **1** is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.[6]

At this point, it is useful to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples[7] in which inversion *must* have taken place. For example, (+)-malic acid (**2**) could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (−)-chlorosuccinic acid by phosphorus pentachloride.



2

One was an inversion and the other a retention of configuration, but the question was which was which? The signs of rotation are of no help in answering this question since rotation need not be related to configuration (Sec. 4.F). Another example discovered by Walden is formation of **3** from **4**.[8]



2 **3** **4**

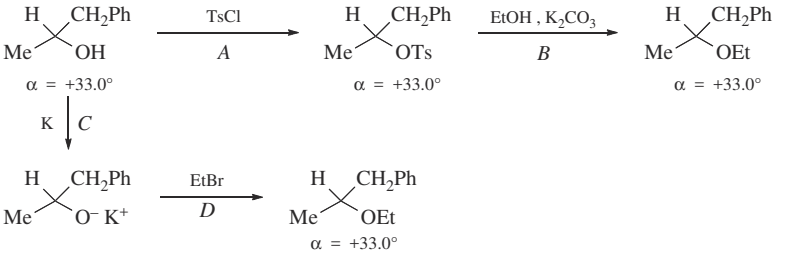
[5] For a discussion of this type of solvent effect, see Arnaut, L.G.; Formosinho, S.J. *Chemistry: European J.* ***2007***, *13,* 8018.

[6] Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis, G.N. in *Valence and the Structure of Atoms and Molecules,* Chemical Catalog Company, NY, ***1923***, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen, A.R. *J. Chem. Phys.* ***1933***, *1*, 418.

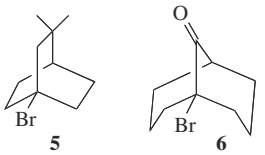
[7] Walden, P. *Ber.* ***1893***, *26*, 210; ***1896***, *29*, 133; ***1899***, *32*, 1855.

[8] For a discussion of these cycles, see Kryger, L.; Rasmussen, S.E. *Acta Chem. Scand.* ***1972***, *26*, 2349.

A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips,[9] Kenyon,[10] and co-workers. In 1923, Phillips and co-workers[9] carried out the following cycle based on (+)-1-phenyl-2-propanol. In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.[10] These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.



Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group.[11] Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.[12] High-pressure mass spectrometry has been used to probe the energy surface for gas-phase S_N2 reactions, which have two transition states (a "loose" and a "tight" transition state.[13]



5 **6**

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[14] are treatment of the [2.2.2] system (**5**) with ethoxide

[9] Phillips, H. *J. Chem. Soc.* ***1923***, *123*, 44. See Garwood, D.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4575; Cram, D.J.; Cram, J.M. *Fortschr. Chem. Forsch.* ***1972***, *31*, 1.

[10] See Kenyon, J.; Phillips, H.; Shutt, G.R. *J. Chem. Soc.* ***1935***, 1663 and references cited therein.

[11] Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1953***, *75*, 5014.

[12] Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* ***1980***, *102*, 3115 and references cited therein; Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209. See Riveros, J.M.; José, S.M.; Takashima, K. *Adv. Phys. Org. Chem.* ***1985***, *21*, 197.

[13] Li, C.; Ross, P.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1996***, *118*, 9360.

[14] See Müller, P.; Mareda, J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 189–217; Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283.

ion[15] and treatment of the [3.3.1] system (**6**) with sodium iodide in acetone.[16] In these cases, open-chain analogues underwent the reactions readily. As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

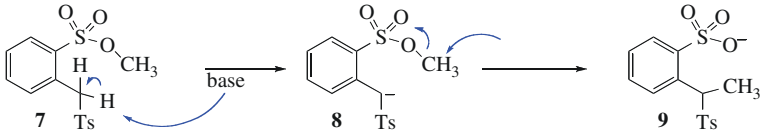
$$C_6H_{13}CHMeI + {}^{*}I^{-} \longrightarrow C_6H_{13}CHMe{}^{*}I + I^{-}$$

Racemization is expected in this reaction, since if the pure *R* isomer is the starting material each exchange will produce an (*S*) isomer. With increasing concentration of (*S*) isomer, *it* will begin to compete for I^- with the *R* isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ${}^{*}I^{-}$. It was found[17] that the rates were identical within experimental error:

$$\text{Rate of inversion} \quad 2.88 \pm 0.03 \times 10^{-5}$$
$$\text{Rate of exchange} \quad 3.00 \pm 0.25 \times 10^{-5}$$

The rate of racemization was the parameter actually measured, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers[18] provided strong evidence that the transition state in an S_N2 reaction must be linear. Base treatment of methyl α-tosyl-*o*-toluenesulfonate (**7**) gives the *o*-(l-tosylethyl)benzenesulfonate ion (**9**). The role of the base is to remove the benzylic proton α- to the tosyl group to give the ion **8**. It might be supposed that the negatively charged carbon of **8** attacks the methyl group in an internal S_N2 process, but this is not the case. Crossover experiments[18] (See **11-27**) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule; that is, the reaction is intermolecular (see **8**) and not intramolecular, despite the more favorable entropy of the latter pathway (Sec. 6.D). It is likely that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (Sec. 10.C), where intramolecular S_N2 mechanisms operate freely.



There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge-type I reactions, where a negative ion nucleophile attacks a neutral substrate.[19] Two energy minima, one before and one after the

[15] Doering, W. von E.; Levitz, M.; Sayigh, A.; Sprecher, M.; Whelan, Jr., W.P. *J. Am. Chem. Soc.* ***1953***, *75*, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.
[16] Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.* ***1950***, *72*, 5228.
[17] Hughes, E.D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* ***1935***, 1525.
[18] Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1970***, *53*, 2059. See also, King, J.F.; McGarrity, M.J. *J. Chem. Soc., Chem. Commun.* ***1979***, 1140.
[19] See Angel, L.A; Ervin, K.M. *J. Am. Chem. Soc.* ***2003***, *125*, 1014.

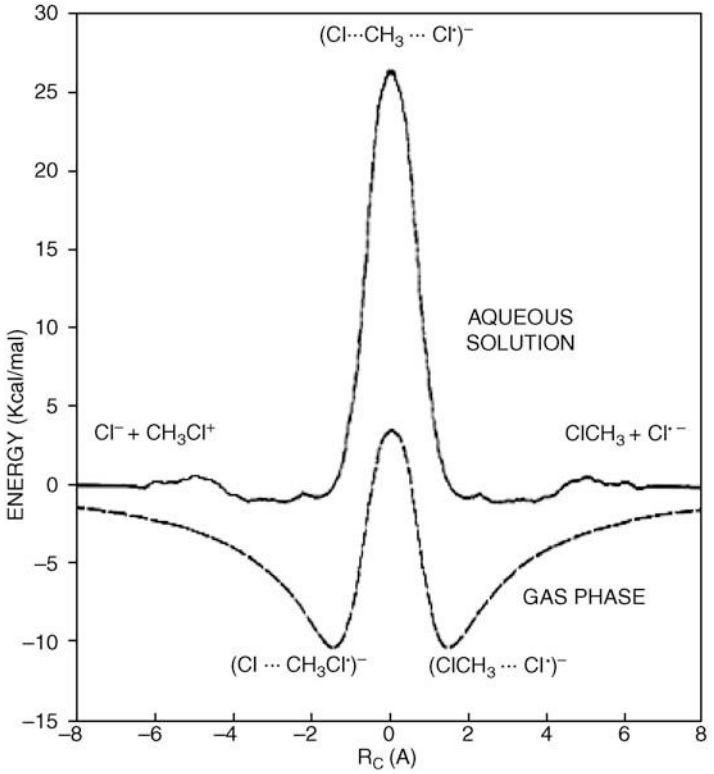


FIG. 10.1. Free energy profile for the gas phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH_3Cl and Cl^-, from molecular orbital calculations.[20] [Reprinted with permission from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985****, 107*,154. Copyright © 1985 American Chemical Society.

transition state, appear in the reaction coordinate (Fig. 10.1).[20] The energy surface for the S_N2 *Menshutkin reaction* (**10-31**) has been examined. It was shown that charge separation was promoted by the solvent.[21] An *ab initio* study of the S_N2 reaction at primary and secondary carbon centers has looked at the energy barrier (at the transition state) to the reaction.[22] These minima correspond to unsymmetrical ion–dipole complexes.[23] Theoretical calculations also show such minima in certain solvents (e.g., *N*, *N*-dimethylformamide DMF), but not in water.[24] In general, polar aprotic solvents (those that do not have an acidic hydrogen X—H, where X—O, S, N, etc.), favor polarized transition state 1.[25] The rate of the reaction is generally slower in protic solvents (e.g., alcohol or water).

[20] Taken from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 154.
[21] Gao, J.; Xia, X. *J. Am. Chem. Soc.* ***1993***, *115*, 9667.
[22] Lee, I.; Kim, C.K.; Chung, D.S.; Lee, B.-S. *J. Org. Chem.* ***1994***, *59*, 4490.
[23] Evanseck, J.D.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2349; Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* ***1989***, *111*, 1547; Jorgensen, W.L. *Acc. Chem. Res.* ***1989***, *22*, 184.
[24] Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 2974.
[25] For a discussion of environmentally benign substitution reactions, see Vogel, P.; Figueira, S.; Muthukrishnan, S.; Mack, J. *Tetrahedron Lett.* ***2009***, *50*, 55.

The S_N2 reactions can occur at atoms other than carbon, X (e.g., nitrogen or sulfur[26]), and analogous to the phenomenon observed for S_N2 reactions at carbon.[27] the valence of the element X, controls the intrinsic barrier for the reaction in accord with the properties seen in the periodic table.[28]

For a list of some of the more important reactions that operate by the S_N2 mechanism, see Table 10.7.

Note that in some reactions, (e.g., bromine transfer between carbanions via nucleophilic attack on bromine), anomalous kinetic behavior is observed. The largest rate constants are associated with bromine transfer between cyano-activated carbanions and the smallest relate to the removal of bromine from the nitromethane and nitroethane moieties.[29] The Brønsted plot (log k vs ΔpK_a) for this reaction shows that unlike any normal Brønsted plot, which by definition displays a positive slope, the plot for $MeNO_2$ and $EtNO_2$ is negative. In deprotonation reactions of carbon compounds, the reactivity of nitroethane and nitromethane were shown to be anomalous.[30] In the series nitromethane, ethane, and isopropane, compounds with higher acidity undergo slower deprotonation (i.e., the Brønsted plot displays a negative slope), contrary to expectations.[31]

10.A.ii. The S_N1 Mechanism

The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps[32] (once again, possible charges on the substrate and nucleophile are not shown):

$$\text{Step 1} \quad \text{R—X} \underset{}{\overset{\text{slow}}{\rightleftharpoons}} \text{R}^+ + \text{X}$$

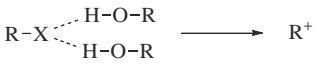
$$\text{Step 2} \quad \text{R}^+ + \text{Y} \xrightarrow{\text{fast}} \text{R—Y}$$

The first step is a slow ionization of the substrate and is the rate-determining step. The second is a rapid reaction between the intermediate carbocation and the nucleophile. There are, of course, transition states for both step 1 ($R\cdots X$) and step 2 ($R^+\cdots Y$).[33] The reactive nature of the carbocation can be expressed by its electrophilic character, or *electrophilicity*. A theoretical discussion concerning the origin of the electrophilicity concept was proposed by Parr et al.[34] In general, a good electrophile was characterized by having a high value of electronegativity (or a high value of electronic chemical potential), and a low value of chemical hardness (Sec. 8.E.i). The effect of substitution has been studied[35] in the context of superelectrophilicity (where carbocations are generated in superacidic media). Solvent effects have also been studied.[36] Electrophilicity scales

[26] See Reactions **10-60–10-68** and Bachrach, S.M.; Gailbreath, B.D. *J. Org. Chem.* ***2001***, *66*, 2005.
[27] Hoz, S.; Basch, H.; Wolk, J.L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* ***1999***, *121,* 7724.
[28] Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2002***, *67*, 5891.
[29] Grinblat, J.; Ben-Zion, M.; Hoz, S. *J. Am. Chem. Soc.,* ***2001***, *123*, 10738.
[30] Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.
[31] Yamataka, H.; Mustanir; Mishima, M. *J. Am. Chem. Soc.* ***1999***, *121,* 10223.
[32] See Mayr, H.; Minegishi, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4493. For a discussion of dynamic processes associated with the S_N1 mechanism, see Peters, K.S. *Chem. Rev.* ***2007***, *107,* 859.
[33] For a related computational study, see Ruff, F.; Farkas, Ö; Kucsman, Á *Eur. J. Org. Chem.* ***2006***, 5570.
[34] Parr, R. G.; Szentpály, L.V.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121,* 1922. Also see Denekamp, C.; Sandlers, Y. *Angew. Chem. Int. Ed.* ***2006***, *45,* 2093.
[35] See Pérez, P. *J. Org. Chem.* ***2004***, *69*, 5048.
[36] Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* ***2001***, *123,* 5527.

have been proposed using other carbocations,[37] and there is an electrophilicity index.[38] Carbocation intermediates have been studied for the reaction $Ar_2CH—O_2CR \rightarrow Ar_2CH^+$, and the relative ionization rates with the same anionic leaving group does not correlate with the corresponding relative reactivities of the carbocation toward a common nucleophile.[39]

Returning to the S_N1 mechanism, ionization of a leaving group to form the carbocation is always assisted by the solvent,[40] since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of *t*-BuCl to *t*-Bu^+ and Cl^- in the gas phase without a solvent requires 150 kcal mol^{-1} (630 kJ mol^{-1}). In the absence of a solvent, such a process simply would not take place, except at very high temperatures. In water, this ionization requires only 20 kcal mol^{-1} (84 kJ mol^{-1}). The difference is solvation energy. This means that the water is effectively "pulling" the leaving group away from the substrate. In cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside the mechanism is called *limiting* S_N1. In other words, there is a complete absence of backside (S_N2) participation by solvent molecules. There is kinetic and other evidence[41] that two molecules of a protic solvent form weak hydrogen bonds with X in order to pull the leaving group X away from RX.



In the IUPAC system, the S_N1 mechanism is $D_N + A_N$ or $D_N^{\ddagger} + A_N$ (where ‡ denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: A_ND_N indicates that bond breaking is concurrent with bond formation; $D_N + A_N$ shows that the former happens first.

In looking for evidence for the S_N1 mechanism, the first thought is that it should be a first-order reaction following the rate law:

$$\text{Rate} = k[\text{RX}] \tag{10-3}$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (10-3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. This fact can be explained by taking into account the

[37] Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* ***2002***, *67*, 4747.
[38] Chattaraj, P.K.; Sarkar, U.; Roy, D.R. *Chem. Rev.* ***2006***, *106*, 2065.
[39] Schaller, H.F.; Tishkov, A.A.; Feng, X.; Mayr, H. *J. Am. Chem. Soc.* ***2008***, *130*, 3012.
[40] See Okamoto, K. *Adv. Carbocation Chem.* ***1989***, *1*, 171; Blandamer, M.J.; Scott, J.M.W.; Robertson, R.E. *Prog. Phys. Org. Chem.* ***1985***, *15*, 149. Also see Dvorko, G.F.; Ponomareva, E.A.; Kulik, N.I. *Russ. Chem. Rev.* ***1984***, *53*, 547.
[41] Blandamer, M.J.; Burgess, J.; Duce, P.P.; Symons, M.C.R.; Robertson, R.E.; Scott, J.M.W. *J. Chem. Res. (S)* ***1982***, 130.

reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as shown (see Chap 6).

$$\begin{aligned} &RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+ + X \\ &R^+ + Y \xrightarrow{k_2} RY \\ &\text{Rate} = \frac{k_1 k_2 [RX][Y]}{k_{-1}[X] + k_2[Y]} \end{aligned} \tag{10-4}$$

At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[X]$ is negligible compared with $k_2[Y]$ and the rate law is reduced to Eq. (10-3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, [X] becomes large and Eq. (10-4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,[42] although not for *tert*-butyl halides, which follow Eq. (10-3) for the entire reaction.[43] An explanation for this difference is that *tert*-butyl cations are less selective than the relatively stable diarylmethyl type (Sec. 5.A.ii). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[44] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide. However, some of the collisions with solvent lead to product, so despite the fact that the halide ion is more reactive, the slower reaction with solvents leads to product because of the overwhelming number of solvent molecules.

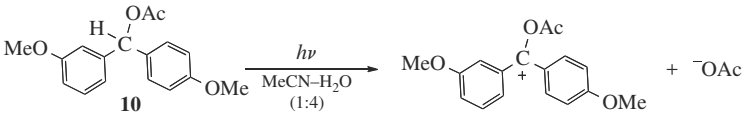
If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl, but not for *tert*-butyl halides.

One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an S_N1 reaction (Sec. 10.G.iv). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most S_N1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

Note that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y [Eq. (10-1)] is the same as that for an ordinary S_N1 reaction [Eq. (10-3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, they can often be distinguished by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as seen above, not all S_N1 reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

[42] Benfey, O.T.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1952***, 2488.
[43] Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 960.
[44] In the experiments mentioned, the solvent was actually "70" or "80%" aq acetone. The "80%" aq acetone consists of 4 vol of dry acetone and 1 vol of water.

Kinetic studies also provide other evidence for the S_N1 mechanism. One technique used ^{19}F NMR to follow the solvolysis of trifluoroacetyl esters.[45] If this mechanism operates essentially as shown above, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment, benzhydryl chloride (Ph_2CHCl) was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.[46] In each case, the initial rate of the reaction was approximately the same when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see Sec. 10.G.ii) as H_2O and HO^-.

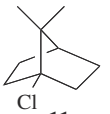


It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4-dimethoxydiphenylmethyl acetate (**10**), and certain other substrates in polar solvents, it was possible to initiate the reaction photolytically, and under these conditions the UV spectra of the intermediate carbocations could be obtained,[47] providing additional evidence for the S_N1 mechanism. Further, addition of water to a colorless solution of $Ar_2CH—OAc$ (Ar = morpholinophenyl) in acetone, leads to direct observation of the intermediate carbocation.[48]

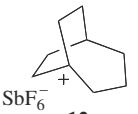
Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions[13] of [2.2.1] (norbornyl) systems[49] (e.g., 1-chloroapocamphane, **8**). If S_N1 reactions require carbocations and if carbocations must be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **11**, boiled 21 h with 30% KOH in 80% ethanol or 48 h with aq ethanolic silver nitrate, gave no reaction in either case,[50] although analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, although the reaction is still slower than with open-chain systems.[51] Proceeding to a still larger system, the bridgehead [3.2.2] cation (**12**) is actually stable enough to be kept in solution in SbF_5-SO_3ClF at temperatures below $-50\,^\circ C$[52] (see also, Sec. 10.G, category 6). Other small bridgehead systems that undergo S_N1 reactions are the [3.1.1] (e.g., **13**)[53] and

[45] Creary, X.; Wang, Y.-X. *J. Org. Chem.* ***1992***, *57*, 4761. Also see, Farcasiu, D.; Marino, G.; Harris, J.M.; Hovanes, B.A.; Hsu, C.S. *J. Org. Chem.* ***1994***, *59*, 154.
[46] Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 1011.
[47] McClelland, R.A.; Kanagasabapathy, V.M.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 6913.
[48] Schaller, H.F.; Mayr, H. *Angew. Chem. Int. Ed.* ***2008***, *47*, 3958.
[49] Fort, Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1973***, pp. 1783–1835.
[50] Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184.
[51] For synthetic examples, see Kraus, G.A.; Hon, Y. *J. Org. Chem.* ***1985***, *50*, 4605.
[52] Olah, G.A.; Liang, G.; Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1972***, *74*, 4927.
[53] Della, E.W.; Pigou, P.E.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* ***1987***, 833.

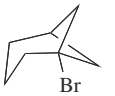
the cubyl (e.g., **14**)[54] systems. *Ab initio* calculations show that the cubyl cation, although it cannot be planar, requires less energy to form than the 1-norbornyl cation.[55] There are reactions where the cationic carbon is not coplanar with conjugating substituents (e.g., phenyl), and formation of the carbocation is more difficult but the reaction proceeds.[56]



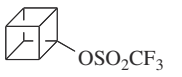
11



12

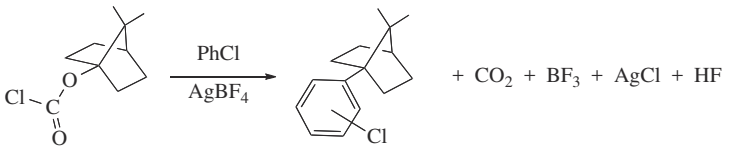


13



14

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads[57] (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone, and in the displacement of $ClCO_2$ in **15**. In this example,[58] chlorobenzene is the nucleophile (see Reaction **11-10**).



15

Additional evidence for the S_N1 mechanism, in particular, for the intermediacy of carbocations, is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities, as determined by heats of ionization measured in superacid solutions (Sec. 5.A.ii).[59] It is important to note that some solvolysis reactions proceed by an S_N2 mechanism.[60]

10.A.iii. Ion Pairs in the S_N1 Mechanism[61]

Like the kinetic evidence, the stereochemical evidence for the S_N1 mechanism is less clear-cut than it is for the S_N2 mechanism.[62] If there is a free carbocation, it is planar (Sec. 5.A.ii), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5–20% inversion, although in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S_N1 reactions at least some of the products are not formed from free carbocations, but rather from *ion pairs*. According to this

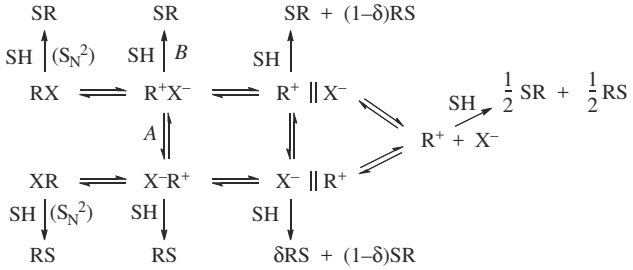
[54] Eaton, P.E.; Yang, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 3225; Moriarty, R.M.; Tuladhar, S.M.; Penmasta, R.; Awasthi, A.K. *J. Am. Chem. Soc.* ***1990***, *112*, 3228.
[55] Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1990***, *112*, 3227.
[56] Lee, I.; Kim, N.D.; Kim, C.K. *Tetrahedron Lett.* ***1992***, *33*, 7881.
[57] White, E.H.; McGirk, R.H.; Aufdermarsh, Jr., C.A.; Tiwari, H.P.; Todd, M.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8107; Beak, P.; Harris, B.R. *J. Am. Chem. Soc.* ***1974***, *96*, 6363.
[58] For a review of reactions with the OCOCl leaving group, see Beak, P. *Acc. Chem. Res.* ***1976***, *9*, 230.
[59] See Arnett, E.M.; Molter, K.E. *Acc. Chem. Res.* ***1985***, *18*, 339.
[60] Lee, I.; Lee, Y.S.; Lee, B.-S.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1441.
[61] See Beletskaya, I.P. *Russ. Chem. Rev.* ***1975***, *44*, 1067; Harris, J.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 89; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. in Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Vol. 2, Wiley, NY, ***1974***, pp. 247–374.
[62] For an alternative view, See Uggerud, E. *J. Org. Chem.* ***2001***, *66,* 7084.

concept,[63] S_N1 reactions proceed in this manner:

$$R{-}X \rightleftharpoons \underset{\mathbf{16}}{R^+X^-} \rightleftharpoons \underset{\mathbf{17}}{R^+||X^-} \rightleftharpoons \underset{\mathbf{18}}{R^+} + X^-$$

where **16** (an *intimate*, *contact*, or *tight ion pair*), **17** (a *loose*, or *solvent-separated ion pair*),[64] or **18** (the dissociated ions, which means that each is surrounded by molecules of solvent).[65] The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair (**16**), R^+ does not behave like the free cation of **18**. There is probably significant bonding between R^+ and X^- and asymmetry may well be maintained.[66] Here, X^- "solvates" the cation on the side from which it departed, while solvent molecules near **16** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **16** thus leads to inversion. Note that there is evidence for concerted pathways in some ion pairing reactions.[67]

Ignoring the possibilities of elimination or rearrangement (see Chapters 17 and 18), a complete picture of the possibilities for solvolysis reactions[68] in a solvent SH is represented by the following scheme,[69] although in any particular case it is unlikely that all these reactions occur:



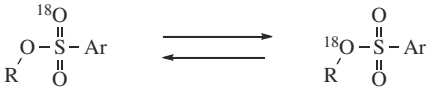
In this scheme, (RS) and (SR) represent enantiomers, and so on, and δ represents some fraction. The following are the possibilities: (1) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (2) If the intimate ion pair $R^+ X^-$ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (3) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly and more racemization (perhaps total) is expected. (4) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence

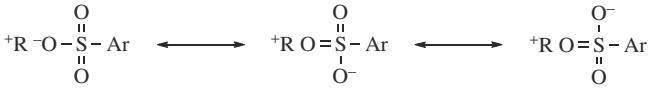
[63] Proposed by Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328.
[64] Marcus, Y.; Hefter, G. *Chem. Rev.* ***2006***, *106,* 4585.
[65] See Kessler, H.; Feigel, M. *Acc. Chem. Res.* ***1982***, 15, 2.
[66] Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538.
[67] Savéant, J.-M. *J. Am. Chem. Soc.* ***2008***, *130,* 4732.
[68] See Richard, J.P.; Toteva, M.M.; Amyes, T.L. *Org. Lett.* ***2001***, *3*, 2225.
[69] Shiner Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553.

that ion pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs,[70] including ion–molecule pairs.[71]

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, although not completely, scrambled:[72]



In an intimate ion pair, the three oxygen atoms become equivalent:



Similar results were obtained with several other sulfonate esters.[73] The possibility must be considered that the scrambling resulted from ionization of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbocation or perhaps on a molecule of $ROSO_2Ar$ in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3–20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters ($R—^{18}O—COR'$), where the leaving group is $R'COO^-$[74]. Also in this case, the external addition of $RCOO^-$ did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.[75]

2. The *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).[76] This result is interpreted as: the ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $R^+ \,||\, ClO_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.[77]

[70] See McManus, S.P.; Safavy, K.K.; Roberts, F.E. *J. Org. Chem.* ***1982***, *47*, 4388; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875; Ronco, G.; Petit, J.; Guyon, R.; Villa, P. *Helv. Chim. Acta* ***1988***, *71*, 648; Kevill, D.N.; Kyong, J.B.; Weitl, F.L. *J. Org. Chem.* ***1990***, *55*, 4304.

[71] Jia, Z.S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 182.

[72] Diaz, A.F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1904.

[73] Paradisi, C.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1985***, *107*, 8223; Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* ***1988***, *29*, 93.

[74] Goering, H.L.; Hopf, H. *J. Am. Chem. Soc.* ***1971***, *93*, 1224 and references cited therein.

[75] Dietze, P.E.; Wojciechowski, M. *J. Am. Chem. Soc.* ***1990***, *112*, 5240.

[76] Cristol, S.J.; Noreen, A.L.; Nachtigall, G.W. *J. Am. Chem. Soc.* ***1972***, *94*, 2187.

[77] Simon, J.D.; Peters, K.S. *J. Am. Chem. Soc.* ***1982***, *104*, 6142.

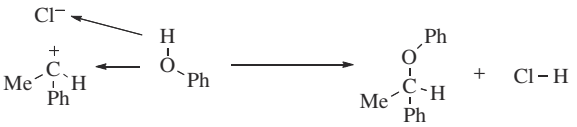
3. The possibilities of racemization or inversion of the *product* (*RS*) of a solvolysis reaction were discussed previously. However, the formation of an ion pair followed by internal return can also affect the stereochemistry of the *substrate* molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aq acetone of α-*p*-anisylethyl *p*-nitrobenzoate,[78] while in other cases partial or complete retention is found (e.g., solvolysis in aq acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate).[79] Racemization of RX is presumably caused by the equilibrium pathway:

$$R-X \rightleftharpoons R^+X^- \rightleftharpoons X^-R^+ \rightleftharpoons X-R$$

Evidence for ion pairs includes some cases where internal return involves racemization, it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes ∼ 30 times faster than it solvolyzes in acetic acid.[80]

Molecular orbital calculations[81] on *tert*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at ∼ 5.5 Å (cf. the C—Cl bond length of 1.8 Å).

In a few cases, S_N1 reactions have been found to proceed with partial retention (20–50%) of configuration. Ion pairs have been invoked to explain some of these.[82] For example, it has been proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.[83] Partial retention can also arise when the ion pair is shielded at the backside by an additive (e.g., acetonitrile, acetone, or aniline).[84]

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first X leaves, then Y attacks. In the S_N2 case, the two

[78] Goering, H.L.; Briody, R.G.; Sandrock, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7401.
[79] Goering, H.L.; Briody, R.G.; Levy, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 3059.
[80] Winstein, S.; Gall, J.S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* ***1960***, *82*, 1010. See also, Shiner, Jr., V.J.; Hartshorn, S.R.; Vogel, P.C. *J. Org. Chem.* ***1973***, *38*, 3604.
[81] Jorgensen, W.L.; Buckner, J.K.; Huston, S.E.; Rossky, P.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1891.
[82] Okamoto, K. *Pure Appl. Chem.* ***1984***, *56*, 1797. Also see Lee, I.; Kim, H.Y.; Kang, H.K.; Lee, H.W. *J. Org. Chem.* ***1988***, *53*, 2678; Lee, I.; Kim, H.Y.; Lee, H.W.; Kim, I.C. *J. Phys. Org. Chem.* ***1989***, *2*, 35.
[83] Okamoto, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1545.
[84] Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3273; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875.

things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean that there are more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (Sec. 10.F and Chap 13).

10.A.iv. Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.[85] At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" S_N1 nor "pure" S_N2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen et al.[86] The formulation is in fact very broad and applies not only to borderline behavior, but to all nucleophilic substitutions at a saturated carbon.[87] According to Sneen, et al.[88] all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair that is then converted to products:

$$\mathrm{RX} \underset{}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+X^-} \overset{k_2}{\rightleftharpoons} \text{Products}$$

The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its *destruction* (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.[88] However, a number of investigators have asserted that these results could also be explained in other ways.[89]

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case, there is a cation–molecule pair ($\mathrm{RX^+ \rightarrow R^+\ X^-}$).[90] instead of the ion pair that would be present if the leaving group were uncharged. Katritzky et al.[91] found that

[85] For an essay on borderline mechanisms in general, see Jencks, W.P. *Chem. Soc. Rev.* ***1982***, *10*, 345.

[86] Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46.

[87] See Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1465.

[88] See Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Blandamer, M.J.; Robertson, R.E.; Scott, J.M.W.; Vrielink, A. *J. Am. Chem. Soc.* ***1980***, *102*, 2585; Stein, A.R. *Can. J. Chem.* ***1987***, *65*, 363.

[89] See Raber, D.J.; Harris, J.C.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4821; McLennan, D.J. *Acc. Chem. Res.* ***1976***, *9*, 281; Stein, A.R. *J. Org. Chem.* ***1976***, *41*, 519; Katritzky, A.R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* ***1981***, *46*, 3831. For a reply, see Sneen, R.A.; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868. See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 442–450.

[90] See Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1629.

[91] Katritzky, A.R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 1879.

when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant versus pressure. A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,[92] who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an S_N2 (intermediate) mechanism.[93]

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aq acetone.[94] In this solvent, hydrolysis[95] (i.e., conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect), but *decreases* the rate of hydrolysis. If more carbocations are produced, but fewer go to the alcohol, then some azide must be formed by reaction with carbocations: an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.[94] Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.[96]

Some nucleophilic substitution reactions that seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, this type of stereochemical behavior is quite consistent with a strictly S_N2 process.[97] The reaction of optically active 2-octyl brosylate in 75% aq dioxane, gave inverted 2-octanol in 77% optical purity.[97] When sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted*. It is apparent that, in the original case, 2-octanol was produced by two different processes: An S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought, it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or 2-octanol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aq dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (Sec. 10.G.iii), it is

[92] Bentley, T.W.; Bowen, C.T.; Morten, D.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 5466.

[93] Also see Laureillard, J.; Casadevall, A.; Casadevall, E. *Tetrahedron* ***1984***, *40*, 4921; *Helv. Chim. Acta* ***1984***, *67*, 352. For evidence against the S_N2 (intermediate) mechanism, see Richard, J.P.; Amyes, T.L.; Vontor, T. *J. Am. Chem. Soc.* ***1991***, *113*, 5871.

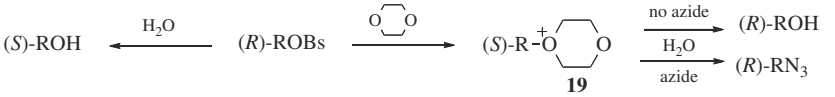
[94] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1990***, *112*, 9507. Also see Richard, J.P.; Rothenberg, M.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1361; Richard, J.P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1373, 1383; Katritzky, A.R.; Brycki, B.E. *J. Phys. Org. Chem.* ***1988***, *1*, 1; Stein, A.R. *Can. J. Chem.* ***1989***, *67*, 297.

[95] The relationship between electropilicity and rate coefficients is discussed in Aizman, A.; Contreras, R.; Pérez, P. *Tetrahedron* ***2005***, *61,* 889.

[96] See, however, Sneen, R.A.; Larsen, J.W. *J. Am. Chem. Soc.* ***1969***, *91*, 6031.

[97] Weiner, H.; Sneen, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 287.

extremely unlikely that any S_N1 process could occur in 75% aq dioxane. The intermediate in the second process is thus not a carbocation. It's nature is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion (**19**) formed by an S_N2 attack *by dioxane*. This ion is not a stable product, but reacts with water in another S_N2 process to produce 2-octanol with retained configuration.



That part of the original reaction that resulted in retention of configuration[98] is thus seen to stem from two successive S_N2 reactions and not from any "borderline" behavior.[99]

10.B. SET MECHANISMS

In certain reactions, where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.[100] The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:

$$\text{Step 1} \qquad R{-}X + Y^- \longrightarrow R{-}X^{\bullet -} + Y^{\bullet}$$

Mechanisms that begin this way are called SET *mechanisms*.[101] Once formed, the radical ion cleaves:

$$\text{Step 2} \qquad R{-}X^{\bullet -} \longrightarrow R^{\bullet} + X^-$$

The radicals formed in this way can go on to product by reacting with the Y• produced in Step 1 or with the original nucleophilic ion Y^-, in which case an additional step is necessary:

$$\text{or Step 3} \qquad R^{\bullet} + Y^{\bullet} \longrightarrow R{-}Y$$

$$\text{Step 3} \qquad R^{\bullet} + Y^- \longrightarrow R{-}Y^{\bullet -}$$

$$\text{Step 4} \qquad R{-}Y^{\bullet -} + R{-}X \longrightarrow R{-}Y + R{-}X^{\bullet -}$$

In the latter case, the radical ion $R{-}X^{\bullet -}$ is formed by Step 4, as well as by Step 1, so that a chain reaction (Sec. 14.A.i) can take place.

[98] According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs.

[99] See Streitwieser, Jr., A.; Walsh, T.D.; Wolfe, Jr., J.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3682; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Beronius, P.; Nilsson, A.; Holmgren, A. *Acta Chem. Scand.* ***1972***, *26*, 3173. See also, Knier, B.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1980***, *102*, 6789.

[100] Bank, S.; Noyd, D.A. *J. Am. Chem. Soc.* ***1973***, *95*, 8203; Ashby, E.C.; Goel, A.B.; Park, W.S. *Tetrahedron Lett.* ***1981***, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis, E.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7576; Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

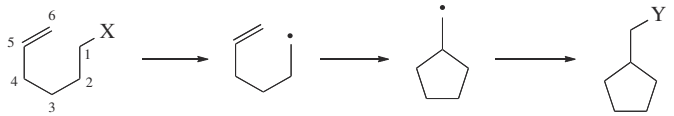
[101] See Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414. See also, Pross, A. *Acc. Chem. Res.* ***1985***, *18*, 212; Chanon, M. *Acc. Chem. Res.* ***1987***, *20*, 214. See Rossi, R.A.; Pierini, A.B.; Peñéñory, A.B. *Chem. Rev.* ***2003***, *103*, 71.

One type of evidence for an SET mechanism is the finding of some racemization. A free radical would likely result in a completely racemized product RY, but it has been suggested[102] that inversion can also take place in some SET processes. The suggestion is that in Step 1 the Y^- still approaches from the back side, even though an ordinary S_N2 mechanism will not follow, and that the radical $R^\bullet$, once formed, remains in a solvent cage with $Y^\bullet$ still opposite X^-, so that Steps 1–3 can lead to inversion.

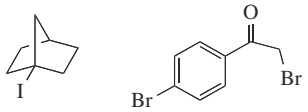
$$Y^- + R{-}X \longrightarrow \underset{\text{Solvent cage}}{[Y^\bullet R{-}X^{\bullet -}]} \longrightarrow \underset{\text{Solvent cage}}{[Y^\bullet R^\bullet X^-]} \longrightarrow Y{-}R + X^-$$

Reactions with SET mechanisms typically show predominant, although not 100%, inversion.

Other evidence cited[103] for SET mechanisms has been detection of radical or radical-ion intermediates by ESR[104] or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;[105] and the formation of cyclic side products when the substrate has a double bond in the 5,6-position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (Sec. 15.A.iii).[106]



20 **21**

The SET mechanism is chiefly found where X = I or NO_2 (see Reaction **10-67**). A closely related mechanism, the $S_{RN}1$, takes place with aromatic substrates (Chap 13).[107] In that mechanism, the initial attack is by an electron donor, rather than a nucleophile. The $S_{RN}1$ mechanism has also been invoked for reactions of enolate anions with 2-iodobicyclo [4.1.0]heptane.[108] An example is the reaction of 1-iodobicyclo[2.2.1]heptane (**20**) with $NaSnMe_3$ or $LiPPh_2$, and some other nucleophiles, to give the substitution product.[109] Another is the reaction of bromo 4-bromoacetophenone (**21**) with Bu_4NBr in cumene.[110] The two mechanisms, S_N2 versus SET, have been compared and contrasted.[111] There are

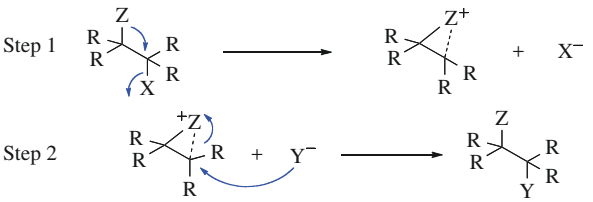
[102] Daasbjerg, K.; Lund, T.; Lund, H. *Tetrahedron Lett.* ***1989***, *30*, 493.
[103] See also, Fuhlendorff, R.; Lund, T.; Lund, H.; Pedersen, J.A. *Tetrahedron Lett.* ***1987***, *28*, 5335.
[104] See, for example, Russell, J.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* ***1979***, *101*, 3331.
[105] Santiago, A.N.; Morris, D.G.; Rossi, R.A. *J. Chem. Soc., Chem. Commun.* ***1988***, 220.
[106] See Newcomb, M.; Curran, D.P. *Acc. Chem. Res.* ***1988***, *21*, 206; Newcomb, M. *Acta Chem. Scand.* ***1990***, *44*, 299. For replies to this criticism, see Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Ashby, E.C.; Pham, T.N.; Amrollah-Madjdabadi, A.A. *J. Org. Chem.* ***1991***, *56*, 1596.
[107] In this book, there is a distinction between the SET and $S_{RN}1$ mechanisms. However, many workers use the designation SET to refer to the $S_{RN}1$, the chain version of the SET, or both.
[108] Nazareno, M.A.; Rossi, R.A. *J. Org. Chem.* ***1996***, *61*, 1645.
[109] Ashby, E.C.; Sun, X.; Duff, J.L. *J. Org. Chem.* ***1994***, *59*, 1270.
[110] Haberfield, P. J. *Am. Chem. Soc.* **1995**, 117, 3314.
[111] Shaik, S.S. *Acta Chem. Scand.* **1990**, 44, 205.

also reactions where it is reported that radical, carbanion, and carbene pathways occur simultaneously.[112]

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

10.C. THE NEIGHBORING-GROUP MECHANISM[113]

It is occasionally found with certain substrates that (1) the rate of reaction is greater than expected, and (2) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases, there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration.[114] In the first step of this reaction, the neighboring group acts as a nucleophile, pushing out the leaving group, but still retaining attachment to the molecule. In the second step, the external nucleophile displaces the neighboring group by a backside attack:



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (10-2) or (10-3); that is, Y does not take part in the rate-determining step.

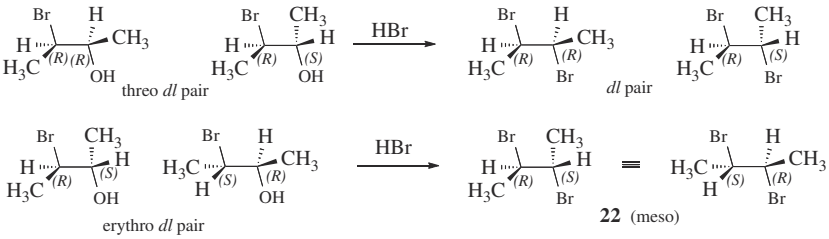
The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation ($\Delta S^{\ddagger}$), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of $\Delta S^{\ddagger}$ (see Sec. 6.D).[115]

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. An obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, (e.g., $HOCH_2CH_2Br$ vs CH_3CH_2Br). However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the

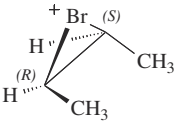
[112] Ashby, E.C.; Park, B.; Patil, G.S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* ***1993***, *58*, 424.
[113] See Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***.
[114] See McCortney, B.A.; Jacobson, B.M.; Vreeke, M.; Lewis, E.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3554.
[115] See Page, M.I. *Chem. Soc. Rev.* ***1973***, *2*, 295.

nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably > 50-fold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo *dl* pair of 3-bromo-2-butanol when treated with HBr gave *dl*-2,3-dibromobutane, while the erythro pair gave the meso isomer (**22**).[116]

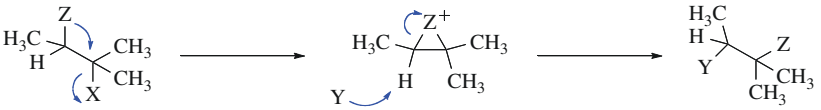


This result indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**23**) is symmetrical, so the external nucleophile Br^- can attack both carbon atoms equally well. Intermediate **23** is a *bromonium ion*, the existence of which has been demonstrated in several types of reactions (see Reaction **15-39**).



23

Although **23** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product, but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:

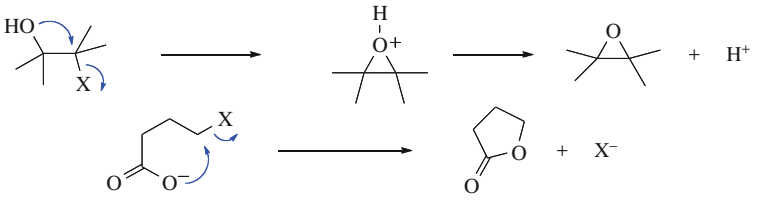


In such cases, substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

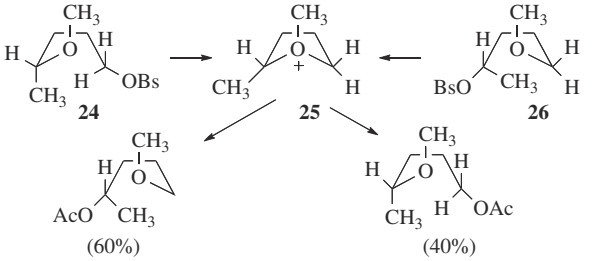
Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal S_N2 reactions.[117] Two examples are formation of epoxides and lactones:

[116] Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* ***1939***, *61*, 1576, 2845.

[117] For a theoretical treatment of strain energy release and intrinsic barriers for internal S_N2 reactions, see Wolk, J.L.; Rozental, E.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2006***, *71*, 3876.



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**24**) and 5-methoxy-2-pentyl brosylate (**25**) gave the same mixture of products is further evidence for participation by a neighboring group.[118] In this case, the intermediate **26** is common to both substrates.

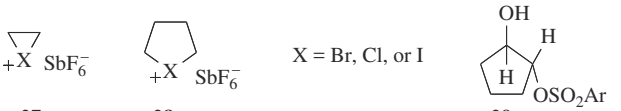


The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $MeO(CH_2)_nOBs$, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate), but not for $n = 2$, 3, or 6.[119] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups α or β to the neighboring group.[120]

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR, COAr, OCOR,[121] OR, OH, O^-,[122] NH_2, NHR, NR_2, NHCOR, SH, SR, S^-,[123] SO_2Ph,[124] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[125] The Cl substituents is a very weak neighboring group, and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl, but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction

[118] Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998.
[119] Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 4012.
[120] Eliel, E.L.; Clawson, L.; Knox, D.E. *J. Org. Chem.* ***1985***, *50*, 2707; Eliel, E.L.; Knox, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 2946.
[121] See Wilen, S.H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* ***1987***, *43*, 5089.
[122] See Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127. Also see Francl, M.M.; Hansell, G.; Patel, B.P.; Swindell, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3535.
[123] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 141–145.
[124] Lambert, J.B.; Beadle, B.M.; Kuang, K. *J. Org. Chem.* ***1999***, *64*, 9241.
[125] Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407, and references cited therein.

pathway.[126] Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see Sec. 10.C.i).



27 **28** **29**

A number of intermediates of halogen participation (halonium ions),[127] (e.g., **27** and **28**), have been prepared as stable salts in $SbF_5—SO_2$ or $SbF_5—SO_2ClF$ solutions.[128] Some have even been crystallized. Attempts to prepare four-membered homologues of **27** and **28** were not successful.[129] There is no evidence that F can act as a neighboring group.[123]

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, *p*-$NO_2C_6H_4SO_2O$ (the nosylate group) is a better leaving group than *p*-$MeC_6H_4SO_2O$ (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates (**29**) acts as a neighboring group when the leaving group is tosylate, but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[130]

10.C.i. Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations[131]

For all the neighboring groups listed in Section 10.C, the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section, neighboring-group participation by C=C π bonds and C—C and C—H σ bonds will be considered. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In *classical carbocations* (Chap 5), the positive charge is *localized* on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a *nonclassical carbocation*,[132] the positive charge is *delocalized* by a double or triple bond that is not in the allylic position or by a single bond. Examples are

[126] Peterson, P.E.; Bopp, R.J.; Chevli, D.M.; Curran, E.L.; Dillard, D.E.; Kamat, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5902. See also, Reich, I.L.; Reich, H.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2654.

[127] See Olah, G.A. *Halonium Ions*, Wiley, NY, ***1975***; Koster, G.F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1265–1351.

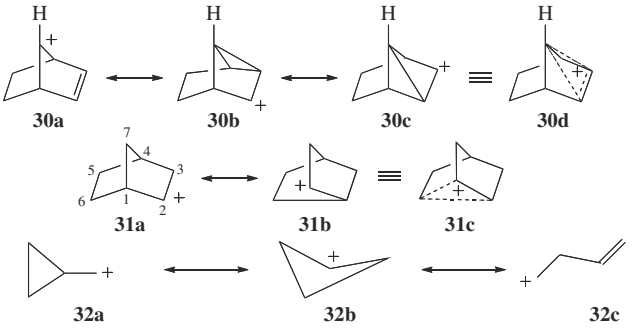
[128] See Henrichs, P.M.; Peterson, P.E. *J. Org. Chem.* ***1976***, *41*, 362; Vancik, H.; Percac, K.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 807.

[129] Olah, G.A.; Bollinger, J.M.; Mo, Y.K.; Brinich, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 1164.

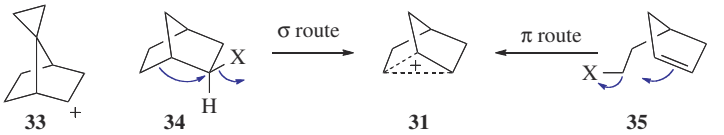
[130] Haupt, F.C.; Smith, M.R. *Tetrahedron Lett.* ***1974***, 4141.

[131] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***; Bartlett, P.D. *Nonclassical Ions*, W.A. Benjamin, NY, ***1965***. Barkhash, V.A. *Top. Curr. Chem.* ***1984***, *116/117*, 1; McManus, S.P.; Pittman Jr., C.U. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 302–321.

[132] Olah, G.A. *J. Org. Chem.* ***2005***, *70,* 2413.



the 7-norbornenyl cation (**30**), the norbornyl cation (**31**),[133] and the cyclopropylmethyl cation (**32**). A cyclopropyl group (as in **33**) is capable of stabilizing the norbornyl cation, inhibiting this rearrangement.[134] Carbocation **30** is called a *homoallylic* carbocation, because in **30a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **31** can be generated by the departure of a leaving group



from **34** or from **35**.[135] The first of these pathways is called the *σ route* to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the *π route*.[136] The argument against the existence of nonclassical carbocations is essentially that the structures **30a**–**30c** (or **31a**, **31b**, etc.) are not canonical forms, but real structures and that there is rapid equilibration among them. This debate remained an active area of interest for some reactions for many years.[137] In one study, the solvolysis and rearrangement of 2-bicyclo[3.2.2]nonanyl tosylate in methanol generated ethers derived from the 2-bicyclo [3.2.2]-nonanyl and 2-bicyclo[3.3.1]nonanyl systems that were rationalized in terms of a classical carbocation.[138] Density functional and *ab initio* calculations indicated that the products of the 2-bicyclo[3.2.2]nonanyl tosylate solvolysis were found to have non-classical structures.[139]

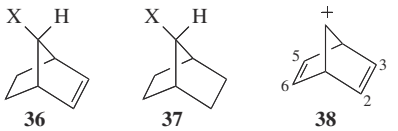
In discussing nonclassical carbocations, care must be taken to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.[140] If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon–carbon double or single bond participates in the departure of the leaving group to

[133] Sieber, S.; Schleyer, P.v.R.; Vancik, H.; Mesic, M.; Sunko, D.E. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1604; Schleyer, P.v.R.; Sieber, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1606.
[134] Herrmann, R.; Kirmse, W. *Liebigs Ann. Chem.* ***1995***, 703.
[135] Bartlett, P.D.; Bank, S.; Crawford, R.J.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *88*, 1288.
[136] Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.
[137] For example, see Brunelle, P.; Sorensen, T.S.; Taeschler, C. *J. Org. Chem.* ***2001***, *66,* 7294.
[138] Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2000***, *65,* 1680.
[139] Smith, W. B. J. Org. Chem. **2001**, 66, 376.
[140] This was pointed out by Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 3767.

form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case, either or both of these possibilities are possible.

In the following pages, some of the evidence bearing on the questions of the participation of π and σ bonds is considered, which bears on the existence of nonclassical carbocations,[141] although a thorough discussion is beyond the scope of this book.[100]

1. C=C *as a Neighboring Group*.[142] The most striking evidence that C=C can act as a neighboring group is that acetolysis of **36**–OTs is 10^{11} times faster than that of **37**–OTs and *proceeds with retention of configuration*.[143] The rate data alone do not necessarily prove that acetolysis of **36**–OTs involves a nonclassical intermediate (**30d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs.



36 **37** **38**

Evidence that **30** is indeed a nonclassical ion comes from an NMR study of the relatively stable norbornadienyl cation (**38**). The ^{1}H NMR spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[144] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **30d**.[145] In the case of **36**, the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,[146] as well as in positions farther away,[147] can also lend anchimeric assistance, although generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**39**), which at 25°C undergoes acetolysis ~ 140,000 times faster than the saturated analogue **40**.[148] Triple bonds[149] and allenes[150] can also act as neighboring groups.

[141] See Brown, H.C. *The Nonclassical Ion Problem*, Plenum, NY, ***1977***. This book also includes rebuttals by Schleyer, P.v.R. See also, Brown, H.C. *Pure Appl. Chem.* ***1982***, *54*, 1783.

[142] See Story, P.R.; Clark, Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1007–1060; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 77–101.

[143] Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* ***1956***, *78*, 592.

[144] Story, P.R.; Snyder, L.C.; Douglass, D.C.; Anderson, E.W.; Kornegay, R.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3630. See Story, P.R.; Clark, Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1026–1041; Lustgarten, R.K.; Brookhart, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2347.

[145] See Gassman, P.G.; Doherty, M.M. *J. Am. Chem. Soc.* ***1982***, *104*, 3742 and references cited therein; Laube, T. *J. Am. Chem. Soc.* ***1989***, *111*, 9224.

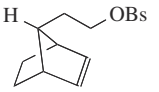
[146] See Schleyer, P.v.R.; Bentley, T.W.; Koch, W.; Kos, A.J.; Schwarz, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6953; Fernández-Mateos, A.; Rentzsch, M.; Sánchez, L.R.; González, R.R. *Tetrahedron* ***2001***, *57*, 4873.

[147] See Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 1051; Orlovic, M.; Borcic, S.; Humski, K.; Kronja, O.; Imper, V.; Polla, E.; Shiner, Jr., V.J. *J. Org. Chem.* ***1991***, *56*, 1874.

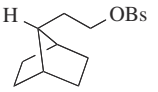
[148] Bly, R.S.; Bly, R.K.; Bedenbaugh, A.O.; Vail, O.R. *J. Am. Chem. Soc.* ***1967***, *89*, 880.

[149] See Peterson, P.E.; Vidrine, D.W. *J. Org. Chem.* ***1979***, *44*, 891; Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 440.

[150] Von Lehman, T.; Macomber, R. *J. Am. Chem. Soc.* ***1975***, *97*, 1531.

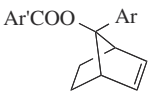


39

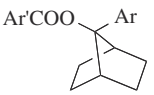


40

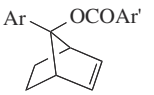
Evidence has been presented to show that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (see above), or if a sufficiently good leaving group is present (see above). In another example of the principle of increasing electron demand, Gassman et al.[151] showed that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **36** and **37** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85 °C of **38** was only ~ 2.5 times faster than that of the saturated compound **42**. Furthermore, both **41** and its stereoisomer **43** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **36** is not present here. The difference between **41** and **36** is that in the case of **41** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently, the stabilization by the *p*-anisyl group is so great that further stabilization that would come from participation by the C=C bond is not needed.[152] The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, although it does reduce it.[153] These results essentially emphasize the previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it*.[154] The π-bond of a neighboring alkene group can assist solvolysis via π-participation.[155]



41



42

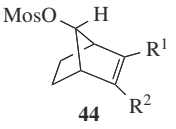


43

Ar = *p*-$MeOC_6H_4$
Ar' = *p*-$NO_2C_6H_4$

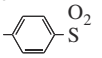
The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF_3 group was attached to a double-bond carbon of **44**, the solvolysis rate was lowered by a factor of ~ 10^6.[156] A second CF_3 group had an equally strong effect. In this case, two CF_3 groups decrease the electron density of the C=C bond to the point that the solvolysis rate for **44** ($R^1 = R^2 = CF_3$) was about the same as (actually ~ 17 times slower than) the rate for the saturated substrate **37** (X = OMos). Thus, the two CF_3 groups completely remove the ability of the C=C bond to act as a neighboring group.

[151] Gassman, P.G.; Zeller, J.; Lamb, J.T. *Chem. Commun.* ***1968***, 69.
[152] See Olah, G.A.; Berrier, A.L.; Arvanaghi, M.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 1122.
[153] Gassman, P.G.; Fentiman, Jr., A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1545; ***1970***, *92*, 2549.
[154] See Lambert, J.B.; Mark, H.W.; Holcomb, A.G.; Magyar, E.S. *Acc. Chem. Res.* ***1979***, *12*, 317.
[155] Malnar, I.; Juric, S.; Vrcek, V.; Gjuranovic, Z.; Mihalic, Z.; Kronja, O. *J. Org. Chem.* ***2002***, *67,* 1490.
[156] Gassman, P.G.; Hall, J.B. *J. Am. Chem. Soc.* ***1984***, *106*, 4267.

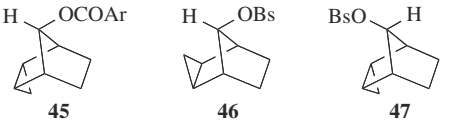


44

Substituents	Relative Rates
$R^1 = R^2 = H$	1.4×10^{12}
$R^1 = H, R^2 = CF_3$	1.5×10^{6}
$R^1 = R^2 = CF_3$	1

Mos = MeO  O_2S

2. *Cyclopropyl*[157]*as a Neighboring Group*.[158] In Section 4.Q.i, the properties of a cyclopropane ring were shown to be similar to those of a double bond in some ways. Therefore it is not surprising that a suitably placed

Ar = *p*-$NO_2C_6H_4$ 

45 **46** **47**

cyclopropyl ring can also be a neighboring group. Thus *endo–anti*-tricyclo [3.2.1.$0^{2,4}$]octan-8-yl *p*-nitrobenzoate (**45**) solvolyzed $\sim 10^{14}$ times faster that the *p*-nitrobenzoate of **37**–OH.[159] Obviously, a suitably placed cyclopropyl ring can be even more effective[160] as a neighboring group than a double bond.[161] The need for suitable placement is emphasized by the fact that **47** solvolyzed only about five times faster than **37**–OBs,[162] while **46** solvolyzed three times *slower* than **37**–OBs.[163] In the case of **45** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.[164] An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.[164] This result is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (Sec. 5.A.ii, and category 4.b below). Rate enhancements, although considerably smaller, have also been reported for suitably placed cyclobutyl rings.[165]

3. *Aromatic Rings as Neighboring Groups*.[166] There is a great deal of evidence that aromatic rings in the β position can function as neighboring groups.[167]

[157] In this section, systems are considered in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see below, category 4.b.

[158] For a review, see Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

[159] Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1953; Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954.

[160] For a competitive study of cyclopropyl versus double-bond participation, see Lambert, J.B.; Jovanovich, A.P.; Hamersma, J.W.; Koeng, F.R.; Oliver, S.S. *J. Am. Chem. Soc.* ***1973***, *95*, 1570.

[161] Also see Gassman, P.G.; Creary, X. *J. Am. Chem. Soc.* ***1973***, *95*, 2729; Takakis, I.M.; Rhodes, Y.E. *Tetrahedron Lett.* ***1983***, *24*, 4959.

[162] Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

[163] Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. Also see Rhodes, Y.E.; Takino, T. *J. Am. Chem. Soc.* ***1970***, *92*, 4469; Hanack, M.; Krause, P. *Liebigs Ann. Chem.* ***1972***, *760*, 17.

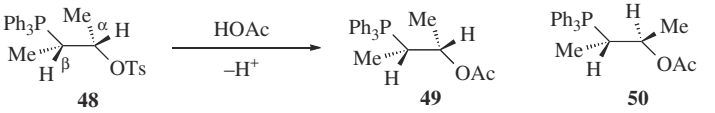
[164] Gassman, P.G.; Seter, J.; Williams, F.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1673. See Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020; Chenier, P.J.; Jenson, T.M.; Wulff, W.D. *J. Org. Chem.* ***1982***, *47*, 770.

[165] See Schipper, P.; Driessen, P.B.J.; de Haan, J.W.; Buck, H.M. *J. Am. Chem. Soc.* ***1974***, *96*, 4706; Ohkata, K.; Doecke, C.W.; Klein, G.; Paquette, L.A. *Tetrahedron Lett.* ***1980***, *21*, 3253.

[166] See Lancelot, L.A.; Cram, D.J.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1347–1483.

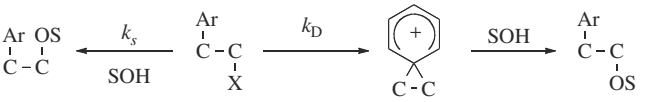
[167] Kevill, D.N.; D'Souza, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 257.

Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**48**) in acetic acid.[168] Of the acetate product, 96% was the threo isomer and only ~ 4% was erythro. Moreover, both the (+) and (-) threo isomers (**49** and **50**) were produced in



48 **49** **50**

approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (Sec. 10.C) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β-aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general, they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.[169] In one of these (designated k_Δ), the aryl, behaving as a neighboring group, pushes out the leaving



51

group to give a bridged ion, called a *phenonium ion* (**51**), and is in turn pushed out by the solvent (SOH), so the net result is substitution with retention of configuration (or rearrangement, if **51** is opened from the other side). The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no cross over between these pathways; they are completely independent.[170] Both the k_Δ and k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases, the mechanism is S_N1 and open carbocations $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c. Which of the two pathways (k_s or k_Δ) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (see above), the k_Δ/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents, the k_Δ/k_s ratio increases in the order $EtOH < CH_3CO_2H < HCO_2H < CF_3CO_2H$.[171] In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50 °C: solvolysis in EtOH 7%, CH_3CO_2H 35%, and HCO_2H 85%.[171] This finding indicates that k_s predominates in EtOH (phenyl participates very little),

[168] Cram, D.J. *J. Am. Chem. Soc.* **1949**, 71, 3863; **1952**, 74, 2129.
[169] Brookhart, M.; Anet, F.A.L.; Cram, D.J.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 5659; Lee, C.C.; Unger, D.; Vassie, S. *Can. J. Chem.* ***1972***, *50*, 1371.
[170] Brown, H.C.; Kim, C.J. *J. Am. Chem. Soc.* ***1971***, *93*, 5765.
[171] Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1969***, *91*, 4300. See also, Schadt, F.L.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1978***, *100*, 228.

TABLE 10.1 Approximate k_Δ/k_s Ratios for Acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ at 90 °C[a]

Z	k_Δ/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

Reprinted with permission Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. Copyright © 1969 American Chemical Society.

[a]See Ref. 145.

while k_Δ predominates in HCO_2H. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_Δ;[172] deuterium labeling showed 100% retention.[173] This case provides a clear example of neighboring-group rate enhancement by phenyl. The rate of solvolysis of $PhCH_2CH_2OTs$ at 75 °C in CF_3COOH is 3040 times the rate for CH_3CH_2OTs.[172]

With respect to the aromatic ring, the k_Δ pathway is electrophilic aromatic substitution (Chapter 11). Groups on the ring that activate that reaction (Sec. 11.B.i) are predicted to increase, and deactivating groups will decrease the rate of this pathway. This prediction has been borne out by several investigations. The *p*-nitro derivative of **48** solvolyzed in acetic acid 190 times slower than **48**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.[174] At 90 °C, acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ gave the rate ratios shown in Table 10.1.[175] Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_Δ that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group. For some groups (e.g., *p*-nitrophenyl), in some solvents (e.g., acetic acid), there is essentially no neighboring-group participation at all,[176] while for others (e.g., *p*-methoxyphenyl),neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2, where the figures shown were derived by three different methods.[177] The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of C=C bonds substituted by CF_3 groups (see above, category 1).

[172] Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996.
[173] Jablonski, R.J.; Snyder, E.I. *J. Am. Chem. Soc.* ***1969***, *91*, 4445.
[174] Thompson, J.A.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1778. See also Kingsbury, C.A.; Best, D.C. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 3440.
[175] Coke, J.L.; McFarlane, F.E.; Mourning, M.C.; Jones, M.G. *J. Am. Chem. Soc.* ***1969***, *91*, 1154; Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. See also, Harris, J.M.; Schadt, F.L.; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 7508.
[176] See Ando, T.; Shimizu, N.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Tetrahedron Lett.* ***1973***, 117.
[177] Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4291, 4296; Lancelot, C.J.; Harper, J.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4294; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 4297.

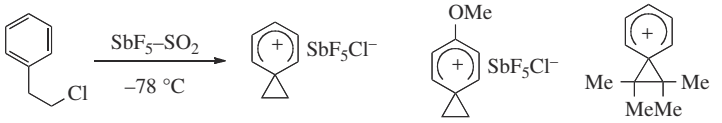
TABLE 10.2 Percent of Product Formed by the k_Δ Pathway in Solvolysis of p-$ZC_6H_4CH_2CH_2OTs$[a]

Z	Solvent	Percent by k_Δ
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

Reprinted with permission Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969****, 91*, 4296. Copyright © 1969 American Chemical Society.

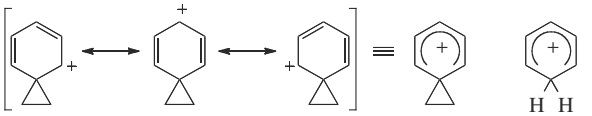
[a]See Ref. 177.

Several phenonium ions have been prepared as stable ions in solution where they can be studied by NMR, among them **52**,[178] **53**,[179] and the unsubstituted **51**.[180] These were prepared[181] by the method shown for **51**: treatment of the corresponding β-arylethyl chloride with SbF_5—SO_2 at low temperatures. These conditions are even more



51 **52** **53**

extreme than the solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile eliminates not only the k_s pathways but also nucleophilic attack on **51**. Although **51** is not in equilibrium with the open-chain ion $PhCH_2CH_2^+$, which is primary and hence unstable, **53** is in equilibrium with the open-chain tertiary ions $PhCMe_2C^+Me_2$ and PhC^+MeCMe_3, although only **53** is present in appreciable concentration. Proton and ^{13}C NMR show that **51**–**53** are classical carbocations where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nuclear magnetic resonance spectra show that the six-membered rings have no aromatic character, but are similar in structure to the arenium ions (e.g., **54**), that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **51**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ^{13}C labeling.[182]



54

[178] Ramsey, B.; Cook Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[179] Olah, G.A.; Comisarow, M.B.; Kim, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1458. See, however, Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[180] Olah, G.A.; Spear, R.J.; Forsyth, D.A. *J. Am. Chem. Soc.* ***1976***, *98*, 6284.

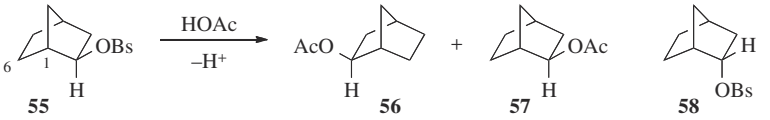
[181] See Olah, G.A.; Singh, B.P.; Liang, G. *J. Org. Chem.* ***1984***, *49*, 2922; Olah, G.A.; Singh, B.P. *J. Am. Chem. Soc.* ***1984***, *106*, 3265.

[182] Mishima, M.; Tsuno, Y.; Fujio, M. *Chem. Lett.* ***1990***, 2277.

It is thus clear that β-aryl groups can function as neighboring groups.[183] Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.[184]

4. *The Carbon–Carbon Single Bond as a Neighboring Group*.[185]

   a. *The 2-Norbornyl System*. In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention has been paid to the 2-norbornyl system.[186] Winstein et al.[187] found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**55**, OB = brosylate) gave a racemic mixture of the two exo acetates; no endo isomers were formed:



55 **56** **57** **58**

Furthermore, **55** solvolyzed ∼ 350 times faster than its endo isomer (**58**). Similar high exo/endo rate ratios have been found in many other [2.2.1] systems. These two results [(1) that solvolysis of an optically active exo isomer gave only racemic exo isomers and (2) the high exo/endo rate ratio] were interpreted by Winstein et al.[187] as indicating that the 1,6-bond assists in the departure of the leaving group and that a nonclassical intermediate (**59**) is involved. They reasoned that solvolysis of the endo isomer (**58**) is not assisted by the 1,6-bond because it is not in a favorable position for backside attack, and that consequently solvolysis of **58** takes place at a "normal" rate. Therefore the much faster rate for the solvolysis of **55** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **59**, since in **59** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the exo direction in either case. Incidentally, acetolysis of **58** also leads exclusively to the exo acetates (**56** and **57**), so that in this case Winstein et al.[187] postulated that a classical ion (**60**) is first formed and then converted to the more stable **59**. Evidence for this interpretation is that the product from solvolysis of **58** is not racemic, but contains somewhat more **57** than **56** (corresponding to 3–13% inversion, depending on the solvent), suggesting that when **60** is formed, some of it goes to give **57** before it can collapse to **59**.

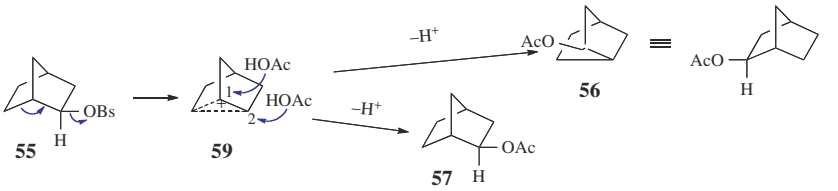
[183] See Tanida, H. *Acc. Chem. Res.* ***1968***, *1*, 239; Shiner, Jr., V.J.; Seib, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 862; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 2217; Fujio, M.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y.; Sawada, M.; Takai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1097. For a discussion of evidence obtained from isotope effects, see Scheppele, S.E. *Chem. Rev.* ***1972***, *72*, 511, p. 522.

[184] Jackman, L.M.; Haddon, V.R. *J. Am. Chem. Soc.* ***1974***, *96*, 5130; Gates, M.; Frank, D.L.; von Felten, W.C. *J. Am. Chem. Soc.* ***1974***, *96*, 5138; Ando, T.; Yamawaki, J.; Saito, Y. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 219.

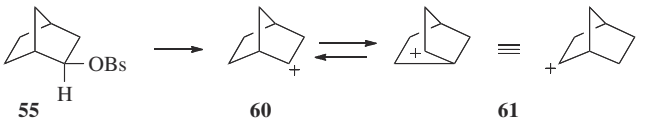
[185] See Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173, pp. 192–198.

[186] See Olah, G.A.; Prakash, G.K.S.; Williams, R.E. *Hypercarbon Chemistry*, Wiley, NY, ***1987***, pp. 157–170; Grob, C.A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 87; Sargent, G.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1099–1200; Sargent, G.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 301; Gream, G.E. *Rev. Pure Appl. Chem.* ***1966***, *16*, 25. Also see Kirmse, W. *Acc. Chem. Res.* ***1986***, *19*, 36. See also, Ref. 190.

[187] Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *J. Am. Chem. Soc.* ***1965***, *87*, 376.



The concepts of σ participation and the nonclassical ion **59** were challenged by H.C. Brown,[141] who suggested that the two results can also be explained by postulating that **55** solvolyzes without participation of the 1,6 bond to give the classical ion **60**, which is in rapid equilibrium with **61**. This rapid interconversion has been likened to the action of a windshield wiper.[188] Obviously, in going from **60** to **61** and back again, **59** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result was that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side. There is a large body of data showing that exo attack on norbornyl systems is fairly general in many reactions. A racemic mixture will be obtained if **60** and **61** are present in equal amounts, since they are equivalent and exo attack on **60** and **61** gives, respectively, **57** and **56**. Brown explained the high exo/endo rate ratios by contending that it is not the endo rate that is normal and the exo rate abnormally high, but the exo rate that is normal and the endo rate abnormally *low*, because of steric hindrance to removal of the leaving group in that direction.[189]



A vast amount of work has been done[190] on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6-bond participates and whether **59** is an intermediate. Most,[191] although not all,[192] chemists now accept the intermediacy of **59**.

Besides the work done on solvolysis, of 2-norbornyl compounds, the 2-norbornyl cation has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers prepared the 2-norbornyl cation in stable solutions at temperatures below -150 °C in SbF_5-SO_2 and FSO_3H—SbF_5—SO_2, where the structure is static

[188] For another view, see Bielmann, R.; Fuso, F.; Grob, C.A. *Helv. Chim. Acta* ***1988***, *71*, 312; Flury, P.; Grob, C.A.; Wang, G.Y.; Lennartz, H.; Roth, W.R. *Helv. Chim. Acta* ***1988***, *71*, 1017.

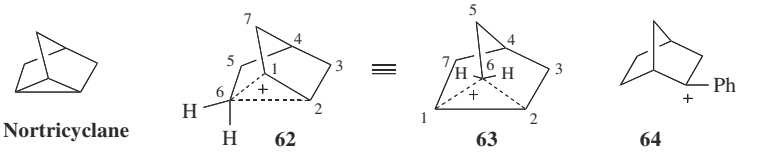
[189] See Menger, F.M.; Perinis, M.; Jerkunica, J.M.; Glass, L.E. *J. Am. Chem. Soc.* ***1978***, *100*, 1503.

[190] See Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661; Grob, C.A. *Acc. Chem. Res.* ***1983***, *16*, 426; Brown, H.C. *Acc. Chem. Res.* ***1983***, *16*, 432; Walling, C. *Acc. Chem. Res.* ***1983***, *16*, 448. Also see Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1985***, *3*, 189, pp. 193–202.

[191] See Lajunen, M. *Acc. Chem. Res.* ***1985***, *18*, 254; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661.

[192] Also see Werstiuk, N.H.; Dhanoa, D.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 2403; Brown, H.C.; Ikegami, S.; Vander Jagt, D.L. *J. Org. Chem.* ***1985***, *50*, 1165; Nickon, A.; Swartz, T.D.; Sainsbury, D.M.; Toth, B.R. *J. Org. Chem.* ***1986***, *51*, 3736.

and hydride shifts are absent.[193,194] Studies by ^{1}H and ^{13}C NMR, as well as by laser Raman spectra and X-ray electron spectroscopy, led to the conclusion[194] that under these conditions the ion is nonclassical.[195] A similar result has been reported for the 2-norbornyl cation in the solid state, where at 77 and even 5 K, ^{13}C NMR spectra gave no evidence of the freezing out of a single classical ion.[196]



Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**62**); the symmetry is better seen when the ion is drawn, as in **63**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements showing that the 2-norbornyl cation is more stable (by $\sim$ 6–10 kcal mol^{-1} or 25–40 kJ mol^{-1}) than would be expected without the bridging.[197] Studies of IR spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.[198] *Ab initio* calculations show that the nonclassical structure corresponds to an energy minimum.[199]

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,[200] and the 2-phenylnorbornyl cation (**64**) is essentially classical,[201] as are the 2-methoxy-[202] and 2-chloronorbornyl cations.[203] Recall (Sec. 5.A.ii) that methoxy and halo groups also stabilize a positive charge. The ^{13}C NMR data show that electron-withdrawing groups on the benzene ring of **64** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.[204]

b. *The Cyclopropylmethyl System*. Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the

[193] The presence of hydride shifts (Reaction **18-01**) under solvolysis conditions has complicated the interpretation of the data.

[194] Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Saunders, M. *Acc. Chem. Res.* ***1983***, *16*, 440. See also, Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112.

[195] See Kramer, G.M.; Scouten, C.G. *Adv. Carbocation Chem.* ***1989***, *1*, 93. See, however, Olah, G.A.; Prakash, G. K.S.; Farnum, D.G.; Clausen, T.P. *J. Org. Chem.* ***1983***, *48*, 2146.

[196] Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8991.

[197] See Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917 and references cited therein.

[198] Koch, W.; Liu, B.; DeFrees, D.J.; Sunko, D.E.; Vancik, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 183.

[199] See, for example, Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1989***, *111*, 1527.

[200] Olah, G.A.; DeMember, J.R.; Lui, C.Y.; White, A.M. *J. Am. Chem. Soc.* ***1969***, *91*, 3958. See also, Forsyth, D. A.; Panyachotipun, C. *J. Chem. Soc., Chem. Commun.* ***1988***, 1564.

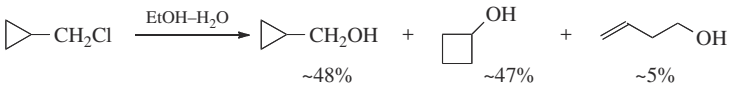
[201] Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41. See also, Farnum, D.G.; Wolf, A.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5166.

[202] Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6861. See also, Montgomery, L.K.; Grendze, M.P.; Huffman, J.C. *J. Am. Chem. Soc.* ***1987***, *109*, 4749.

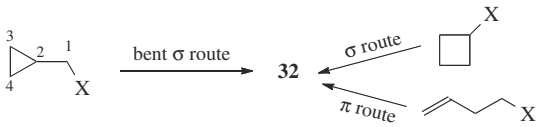
[203] Fry, A.J.; Farnham, W.B. *J. Org. Chem.* ***1969***, *34*, 2314.

[204] Farnum, W.B.; Botto, R.E.; Chambers, W.T.; Lam, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3847. See also, Olah, G.A.; Berrier, A.L.; Prakash, G.K.S. *J. Org. Chem.* ***1982***, *47*, 3903.

cyclopropylmethyl system.[205] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and that the products often include not only unrearranged cyclopropylmethyl, but also cyclobutyl and homoallylic compounds. An example is[206]



Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Indeed, computational studies on the cyclobutylmethyl cation suggest it is nonclassical (Sec. 10.C.i). Furthermore, when the reactions are carried out with labeled substrates, considerable, although not complete, scrambling is observed. For these reasons, it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **32**) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years, much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. although there is much that is still not completely understood, some conclusions can be drawn.

i. In the solvolysis of simple primary cyclopropylmethyl systems, the rate is enhanced because of participation by the σ bonds of the ring.[207] The ion that forms initially is an unrearranged cyclopropylmethyl cation[208] that is *symmetrically* stabilized; that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. As seen previously (Sec. 5.A.ii) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **65**. Among the evidence that **65** is a symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.[209] If only one of the σ bonds (say, the 2,3 bond) stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.[210]

[205] See in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the articles by Richey, Jr., H.G. pp. 1201–1294, and by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1295–1345; Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* ***1968***, *7*, 577.

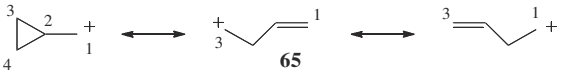
[206] Roberts, D.D.; Mazur, R.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2509.

[207] See Roberts, D.D.; Snyder, Jr., R.C. *J. Org. Chem.* ***1979***, *44*, 2860, and references cited therein.

[208] Wiberg, K.B.; Ashe, III, A.J. *J. Am. Chem. Soc.* ***1968***, *90*, 63.

[209] Schleyer, P.v.R.; Van Dine, G.W. *J. Am. Chem. Soc.* ***1966***, *88*, 2321. See also, Kevill, D.N.; Abduljaber, M.H. *J. Org. Chem.* ***2000***, *65,* 2548.

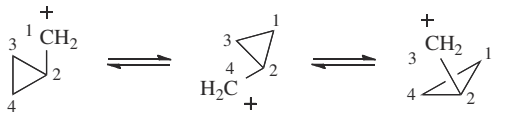
[210] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the article by Wiberg, K.B.; Hess, Jr., B.A.; Ashe, III, A.J. pp. 1300–1303.



65

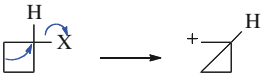
ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown in Section 5.A.ii. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[211]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.[212] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **65** or on the cyclobutyl cation intermediate.[213] A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **65**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl substrates often gives similar product mixtures. There is no evidence that requires cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, although tertiary cyclobutyl cations can be solvolysis intermediates.



v. The unsubstituted cyclopropylmethyl cation has been generated in superacid solutions at low temperatures, where ^{13}C NMR spectra have led to the conclusion that it consists of a mixture of the bicyclobutonium ion (**32**) and the bisected cyclopropylmethyl cation (**65**), in equilibrium with **32**.[214] Molecular orbital calculations show that these two species are energy minima, and that both have nearly the same energy.[213]

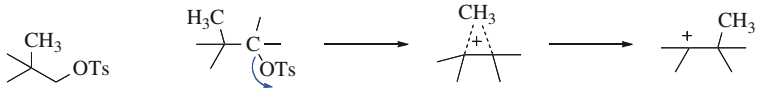
[211] See Rhodes, Y.E.; DiFate, V.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7582. See, however, Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1975***, *97*, 1927.

[212] Majerski, Z.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 665.

[213] Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7325; Saunders, M.; Laidig, K.E.; Wiberg, K. B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1988***, *110*, 7652.

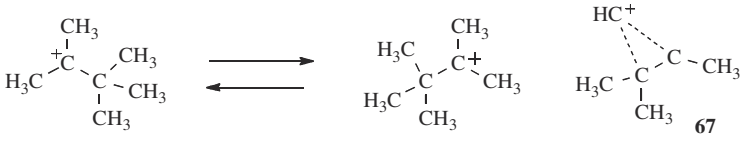
[214] Staral, J.S.; Yavari, I.; Roberts, J.D.; Prakash, G.K.S.; Donovan, D.J.; Olah, G.A. *J. Am. Chem. Soc.* ***1978***, *100*, 8016. See also, Prakash, G.K.S.; Arvanaghi, M.; Olah, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6017; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8992.

c. *Methyl as a Neighboring Group*. Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound, (e.g., neopentyl tosylate). On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **66** must lie on the reaction path, but the two questions



Neopentyl tosylate **66**

that have been asked are (1) Is the departure of the leaving group concerted with the formation of the CH_3—C bond (e.g., does the methyl participate)? (2) Is **66** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, which indicates that the methyl group in the neopentyl system does indeed participate,[215] although it may not greatly enhance the rate. As to the second question, evidence that **66** is an intermediate is that small amounts of cyclopropanes (10–15%) can be isolated in these reactions.[216] Cation **66** is a protonated cyclopropane and would give cyclopropane on loss of a proton.[217] In an effort to isolate a species that has structure **66**, the 2,3,3-trimethyl-2-butyl cation was prepared in superacid solutions at low temperatures.[218] However, ^1H and ^{13}C NMR, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions. Of course, **67** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from X-ray photoelectron spectroscopy (XPS) has shown that the 2-butyl cation is substantially methyl bridged.[219]



67

d. *Silylalkyl as a Neighboring Group.* Rates of solvolysis are enhanced in molecules that contain a silylalkyl or silylaryl group β-to the carbon bearing the leaving group. This is attributed to formation of a cyclic transition state involving the silicon.[220]

[215] See Yamataka, H.; Ando, T.; Nagase, S.; Hanamura, M.; Morokuma, K. *J. Org. Chem.* ***1984***, *49*, 631. For an opposing view, see Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 11.

[216] Silver, M.S.; Meek, A.G. *Tetrahedron Lett.* ***1971***, 3579; Dupuy, W.E.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1715.

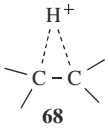
[217] For further discussions of protonated cyclopropanes, see Sec. 15.B.iv, 18.A.ii.

[218] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459.

[219] Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112. See also, Carneiro, J.W.; Schleyer, P.v.R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* ***1990***, *112*, 4064.

[220] Fujiyama, R.; Munechika, T. *Tetrahedron Lett.* ***1993***, *34*, 5907.

5. *Hydrogen as a Neighboring Group*. The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are (1) Does the hydrogen atom



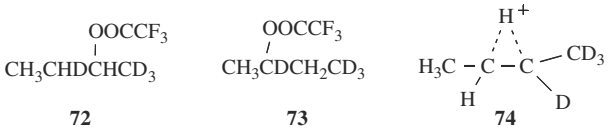
68

participate in the departure of the leaving group? (2) Is **68** an intermediate or only a transition state? There is some evidence that a β hydrogen can participate.[221] Evidence that **68** can be an intermediate in solvolysis



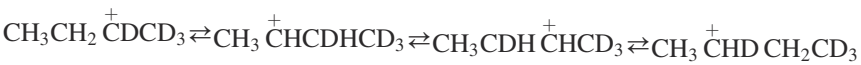
69 **70** **71**

reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **69**. In this solvent of very low nucleophilic power, the products were an equimolar mixture of **70** and **71**,[222] but



72 **73** **74**

no **72** or **73** was found. If this reaction did not involve neighboring hydrogen at all (pure S_N2 or S_N1), the product would be only **70**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:



leading not only to **70** and **71**, but also to **72** and **73**. The results are most easily compatible with the intermediacy of the bridged ion **74**, which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **68** as a stable ion in superacid solutions at low temperatures have not been successful.[221]

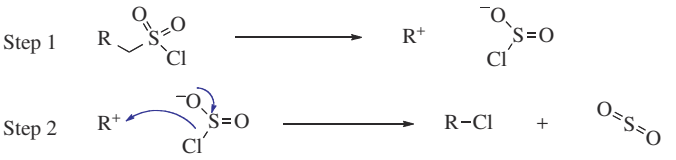
10.D. THE S_Ni MECHANISM

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC

[221] See Buzek, P.; Schleyer, P.v.R.; Sieber, S.; Koch, W.; Carneiro, J.W. de M.; Vancik, H.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 671; Imhoff, M.A.; Ragain, R.M.; Moore, K.; Shiner, V.J. *J. Org. Chem.* ***1991***, *56*, 3542.

[222] Dannenberg, J.J.; Barton, J.K.; Bunch, B.; Goldberg, B.J.; Kowalski, T. *J. Org. Chem.* ***1983***, *48*, 4524; Allen, A.D.; Ambidge, I.C.; Tidwell, T.T. *J. Org. Chem.* ***1983***, *48*, 4527.

designation is $D_N + A_N D_e$. The first step is the same as the very first step of the S_N1 mechanism: dissociation into an intimate ion pair.[223] But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.



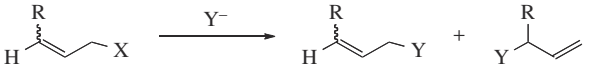
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: The addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $ROSONC_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[224]

The S_Ni mechanism is relatively rare. Another example is the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[225]

10.E. NUCLEOPHILIC SUBSTITUTION AT AN ALLYLIC CARBON: ALLYLIC REARRANGEMENTS

Allylic substrates rapidly undergo nucleophilic substitution reactions (see Sec. 10.G.i, category 3), but we discuss them in a separate section because they are commonly accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.[226] When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



Two products are formed because an allylic type of carbocation is a resonance hybrid

$$R{-}CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow R{-}\overset{+}{C}H{-}CH{=}CH_2$$

[223] Lee, C.C.; Clayton, J.W.; Lee, C.C.; Finlayson, A.J. *Tetrahedron* ***1962***, *18*, 1395.
[224] Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* ***1952***, *74*, 308.
[225] Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198. Also see Kice, J.L.; Hanson, G.C. *J. Org. Chem.* ***1973***, *38*, 1410; Cohen, T.; Solash, J. *Tetrahedron Lett.* ***1973***, 2513; Verrinder, D.J.; Hourigan, M.J.; Prokipcak, J.M. *Can. J. Chem.* ***1978***, *56*, 2582.
[226] See DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 417–437. For comprehensive older reviews, see DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753; in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, the sections by Mackenzie, K. pp. 436–453 and DeWolfe, R.H.; Young, W.G. pp. 681–738.

so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is $1/D_N + 3/A_N$, the numbers 1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

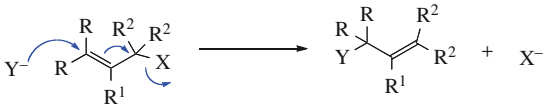
As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,

$$\underset{\mathbf{75}}{CH_3CH{=}CHCH_2Cl} \qquad \text{and} \qquad \underset{\mathbf{76}}{CH_3CHClCH{=}CH_2}$$

should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 M aq NaOH at 25 °C, **75** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **76** gave the products in yields of 38 and 62%, respectively.[227] This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent,[228] the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent completely stabilizes free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_3$,[229] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **75** and **76**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.[230]

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:[231]

S_N2' Mechanism

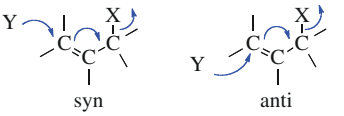


[227] DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753 give several dozen such examples.
[228] Katritzky, A.R.; Fara, D.C.; Yang, H.; Tämm, K.; Tamm, T.; Karelson, M. *Chem. Rev.* ***2004***, *104*, 175.
[229] Young, W.G.; Winstein, S.; Goering, H.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1958.
[230] See Kantner, S.S.; Humski, K.; Goering, H.L. *J. Am. Chem. Soc.* ***1982***, *104*, 1693; Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 313.
[231] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1901–1910.

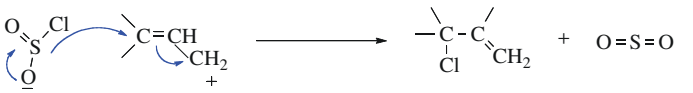
The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where a substitution sterically retards the normal S_N2 mechanism.[232] There are few well-established cases of the S_N2' mechanism on substrates of the type $C{=}C{-}CH_2X$, but compounds of the form $C{=}C{-}CR_2X$ give the S_N2' rearrangement almost exclusively[233] when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2.[233] In certain cases, the leaving group can also have an affect on whether the rearrangement occurs. Thus $PhCH{=}CHCH_2X$, treated with $LiAlH_4$, gave 100% S_N2 reaction (no rearrangement) when X = Br or Cl, but 100% S_N2' when $X = PPh_3^+ Br^-$.[234] The solvent also plays a role in some cases, with more polar solvents giving more S_N2' product.[235]

The S_N2' mechanism, as shown above, involves the simultaneous movement of three pairs of electrons. However, Bordwell et al.[236] contended that there is no evidence requiring that this bond making and bond breaking be in fact concerted, and that a true S_N2' mechanism is a myth. There is evidence both for[237] and against[238] this proposal. There is also a review of the S_N' reaction.[239]

The stereochemistry of S_N2' reactions has been investigated. It has been found that both syn[240] (the nucleophile enters on the side from which the leaving group departs) and anti[241] reactions can take place, depending on the nature of X and Y,[242] although the syn pathway predominates in most cases.

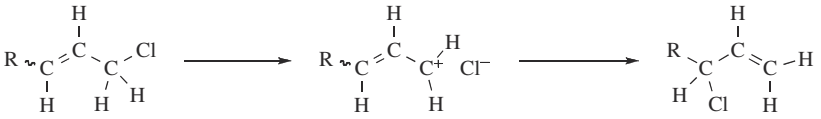


When a molecule has a nucleofuge capable of giving the S_Ni reaction in an allylic position, it is possible for the nucleophile to attack at the γ position instead of the α position. This reaction is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol, both of which gave 100% allylic rearrangement



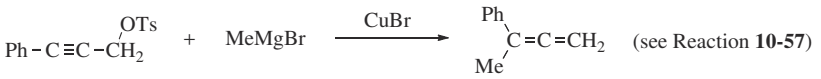
[232] Streitwieser, A.; Jayasree, E.G.; Leung, S.S.-H.; Choy, G.S.-C. *J. Org. Chem.* ***2005***, *70,* 8486.
[233] Bordwell, F.G.; Clemens, A.H.; Cheng, J. *J. Am. Chem. Soc.* ***1987***, *109*, 1773. Also see, Young, J.-j; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* ***2000***, *41*, 3411.
[234] Hirab, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1984***, *49*, 4084.
[235] Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* ***2004***, *45,* 3225.
[236] Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5829. See also Dewar, M.J.S. *J. Am. Chem. Soc.* ***1984***, *106*, 209.
[237] See Uebel, J.J.; Milaszewski, R.F.; Arlt, R.E. *J. Org. Chem.* ***1977***, *42*, 585.
[238] See Fry, A. *Pure Appl. Chem.* ***1964***, *8*, 409; Georgoulis, C.; Ville, G. *Bull. Soc. Chim. Fr.* ***1985***, 485; Meislich, H.; Jasne, S.J. *J. Org. Chem.* ***1982***, *47*, 2517.
[239] Paquette, L.A.; Stirling, C.J.M. *Tetrahedron* ***1992***, *48*, 7383.
[240] See Magid, R.M.; Fruchey, O.S. *J. Am. Chem. Soc.* ***1979***, *101*, 2107; Bäckvall, J.E.; Vågberg, J.O.; Genêt, J.P. *J. Chem. Soc., Chem. Commun.* ***1987***, 159.
[241] See Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* ***1979***, *101*, 5081.
[242] Bach, R.D.; Wolber, G.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1352; Stohrer, W. *Angew. Chem. Int. Ed.* ***1983***, *22*, 613.

when treated with thionyl chloride in ether.[243] Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, (e.g., Cl) comes off to form an ion pair[244] and then returns not to the position where it ougmented but to the allylic position:

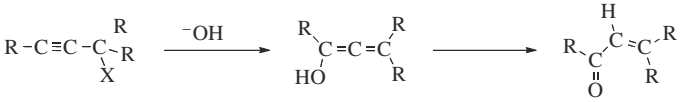


Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[245]



The product in this case is an allene,[246] but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β-unsaturated aldehyde or ketone.



When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer–Schuster rearrangement*.[247] The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.[248]

The S_N2' reaction has been shown to predominate in reactions of mixed cuprates (Reaction **10-58**) with allylic mesylates,[249] and in ring-opening reactions of aziridines.[250] A related reaction is the opening of cyclopropylcarbinyl halides with organocuprates where the cyclopropane ring reacts similarly to the C=C unit of an alkene to give a homoallylic substituted product.[251] This latter reaction is interesting since the reaction of **77** with piperidine leads to the S_N2' product (**78**) in ~ 87% yield, but there is ~ 8% of the direct substitution product, (**79**). Since the carbon bearing the bromine is very hindered,

[243] Young, W.G. *J. Chem. Educ.* ***1962***, *39*, 456. See Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3055.

[244] For a theoretical study, see Streitwieser, A.; Jayasree, E.G.; Hasanayn, F.; Leung, S.S.-H. *J. Org. Chem.* ***2008***, *73,* 9426.

[245] Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 112.

[246] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317, pp. 324–328. See Larock, R.C.; Reddy, Ch.K. *Org. Lett.* ***2000***, *2,* 3325.

[247] See Swaminathan, S.; Narayanan, K.V. *Chem. Rev.* ***1971***, *71*, 429; Andres, J.; Cardenas, R.; Silla, E.; Tapi, O. *J. Am. Chem. Soc.* ***1988***, *110*, 666.

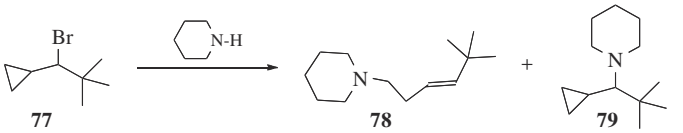
[248] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063.

[249] Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* ***1993***, *58,* 1207.

[250] Wipf, P.; Fritch, P.C. *J. Org. Chem.* ***1994***, *59*, 4875.

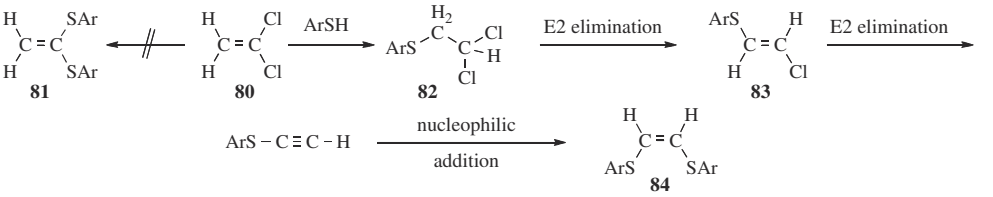
[251] Smith, M.B.; Hrubiec, R.T. *Tetrahedron* ***1984***, *40*, 1457; Hrubiec, R.T.; Smith, M.B. *J. Org. Chem.* ***1984***, *49*, 385.

formation of **72** is somewhat unusual under these conditions. As Bordwell has suggested (see above), this may not be a true S_N2 process.



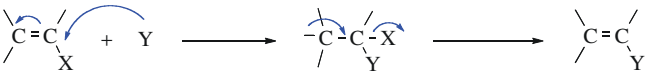
10.F. NUCLEOPHILIC SUBSTITUTION AT AN ALIPHATIC TRIGONAL CARBON: THE TETRAHEDRAL MECHANISM

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. These reactions are discussed in Chapter 16. Nucleophilic substitution at vinylic carbons is considered in Section 10.6 and at aromatic carbons in Chapter 13.



Nucleophilic substitution at a vinylic carbon[252] is difficult (see Sec. 10.G.i), but many examples are known. The most common mechanisms are the tetrahedral mechanism and the closely related *addition–elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition–elimination mechanism has been demonstrated for the reaction between 1,1-dichloroethene (**80**) and ArS^- catalyzed by ^-OEt.[253] The product was not the 1,1-dithiophenoxy compound (**81**), but the "rearranged" compound **84**. Isolation of **82** and **83** showed that an addition-elimination mechanism had taken place. In the first step, ArSH adds to the double bond (nucleophilic addition, Sec. 15.A.ii) to give the saturated **82**. The second step is an E2 elimination reaction (Sec. 17.A.i) to give the alkene **83**. A second elimination and addition give **84**.

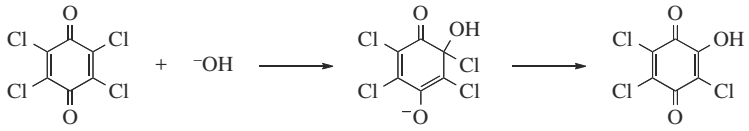
The tetrahedral mechanism, often also called addition–elimination (*AdN-E*), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a C=C double bond (see Chap 15). It

[252] See Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* ***1986***, *104*, 309; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 511; Modena, G. *Acc. Chem. Res.* ***1971***, *4,* 73.
[253] Truce, W.E.; Boudakian, M.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2748.

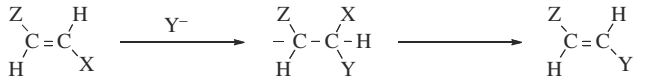
is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[254]



In the case of $Ph(MeO)C{=}C(NO_2)Ph + RS^-$, the intermediate lived long enough to be detected by UV spectroscopy.[255]

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a "rearrangement", but of course the mechanism could still take place even if no rearrangement is found. Evidence[256] that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, e.g., to an S_N1 or S_N2 mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).[257] This finding clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the S_N1 and S_N2 mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the S_N1 and S_N2 reactions (Sec. 10.G.iii). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C—F bond more positive, and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type ZCH=CHX, where Z is an electron-withdrawing group (HCO, RCO,[258] EtOOC, $ArSO_2$, NC, F, etc.), since these β groups stabilize the carbanion:

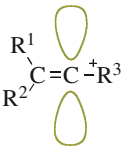


Many such examples are known. In most cases, where the stereochemistry has been investigated, retention of configuration is observed,[259] but stereoconvergence [the same product mixture from an (*E*) or (*Z*) substrate] has also been observed,[260] especially where the carbanionic carbon bears two electron-withdrawing groups. Although rare, nucleophilic substitution with inversion has also been reported as in the intramolecular substitution of the C—Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom, giving

[254] Hancock, J.W.; Morrell, C.E.; Rhom, D. *Tetrahedron Lett.* ***1962***, 987.
[255] Bernasconi, C.F.; Fassberg, J.; Killion, Jr., R.B.; Rappoport, Z. *J. Org. Chem.* ***1990***, *55*, 4568.
[256] See Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* ***1979***, *101*, 2682, and references cited therein.
[257] Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 6687.
[258] See Rybinskaya, M.I.; Nesmeyanov, A.N.; Kochetkov, N.K. *Russ. Chem. Rev.* ***1969***, *38*, 433.
[259] Rappoport, Z. *Adv. Phys. Org. Chem.* ***1969***, *7*, see pp. 31–62; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 516. See also, Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6698.
[260] See Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1986***, *51*, 4112; Park, K.P.; Ha, H. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3006.

2-ethylene aziridines by way of stereochemical inversion.[261] It is not immediately apparent why the tetrahedral mechanism should lead to retention, but this behavior has been ascribed, on the basis of MO calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.[262]

Vinylic substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways:[263] (1) By the use of a group that stabilizes the vinylic cation. For example, α-aryl vinylic halides $ArBrC{=}CR'_2$ have often been shown to give S_N1 reactions.[264] The S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[265] vinylic,[266] alkynyl,[267] and an adjacent double-bond ($R_2C{=}C{=}CR'X$).[268] (2) Even without a stabilization, by the use of a very good leaving group [e.g., OSO_2CF_3 (triflate)].[269] The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,[270] that is, either a cis or a trans substrate gives a 1:1 mixture of cis and trans products, indicating that vinylic cations are linear. Another indication that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.[271] However, a linear vinylic cation need not give random products.[272] The empty *p* orbital lies in the plane of the double bond, so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2.[273] It must be emphasized that even where vinylic substrates do give S_N1 reactions, the rates are generally lower than those of the corresponding saturated compounds.



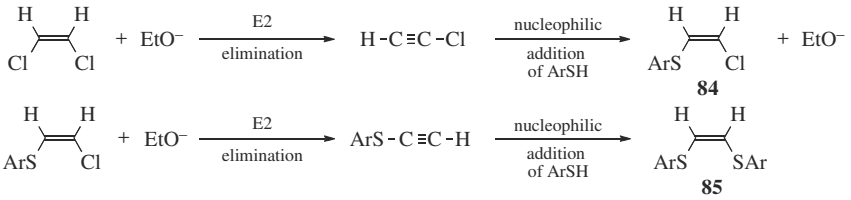
Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.

$$R{-}C{\equiv}C{-}T \xrightarrow{\beta \text{ decay}} R{-}C{\equiv}C{-}{}^3He \xrightarrow[\text{fast}]{\text{very}} R{-}C{\equiv}C^+ + {}^3He$$

[261] Shiers, J.J.; Shipman, M.; Hayes, J.-F.; Slawin, A.M.Z. *J. Am. Chem. Soc.* ***2004***, *126*, 6868.
[262] Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* ***1979***, *101*, 5095.
[263] See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapter 5, Academic Press, NY, ***1979***; Stang, P.J. *Acc. Chem. Res.* ***1978***, *11*, 107; Rappoport, Z. *Acc. Chem. Res.* ***1976***, *9*, 265.
[264] See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chap. 6, Academic Press, NY, ***1979***.
[265] Hanack, M.; Bässler, T.; Eymann, W.; Heyd, W.E.; Kopp, R. *J. Am. Chem. Soc.* ***1974***, *96*, 6686.
[266] Grob, C.A.; Spaar, R. *Helv. Chim. Acta* ***1970***, *53*, 2119.
[267] Hassdenteufel, J.R.; Hanack, M. *Tetrahedron Lett.* ***1980***, 503. See also, Kobayashi, S.; Nishi, T.; Koyama, I.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1980***, 103.
[268] Schiavelli, M.D.; Gilbert, R.P.; Boynton, W.A.; Boswell, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5061.
[269] See Hanack, M.; Märkl, R.; Martinez, A.G. *Chem. Ber.* ***1982***, *115*, 772.
[270] Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1971***, *93*, 1941.
[271] Pfeifer, W.D.; Bahn, C.A.; Schleyer, P.v.R.; Bocher, S.; Harding, C.E.; Hummel, K.; Hanack, M.; Stang, P.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1513.
[272] See Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110
[273] Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* ***1972***, 857.

When the tritium (half-life 12.26 years) decays it is converted to the helium-3 isotope, which, of course, does not form covalent bonds, and so immediately departs, leaving behind the alkynyl cation. When this was done in the presence of benzene, $RC{\equiv}CC_6H_5$ was isolated.[274] The tritium-decay technique has also been used to generate vinylic and aryl cations.[275]

Besides the mechanisms already discussed, another mechanism, involving an *elimination–addition* sequence, has been observed in vinylic systems (a similar mechanism is known for aromatic substrates, Sec. 13.A.iii). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and ^-OEt to produce **84**. The mechanism may be formulated as shown. The steps are the same as in the addition–elimination mechanism, but in reverse order. Evidence for this sequence[276] is as follows: (1) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^-. (2) Under the same reaction conditions, chloroacetylene gave **84** and then **85**. (3) Compound **84**, treated with ArS^-, gave no reaction but, when EtO^- was added, **85** was obtained. It is interesting that the elimination–addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.[277] Note that both the addition–elimination and elimination–addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are anti.



The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates (e.g., $ArSO_2CH_2CH_2SO_2Ar$).[278] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[E^2\ \text{elmination}]{EtO^-} ArSO_2CH{=}CH_2 \xrightarrow[\text{addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see Reaction **16-19**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.[279] The nucleophile replaces the NR_2 group.

The simple S_N2 mechanism has never been convincingly demonstrated for vinylic substrates.[280]

[274] Angelini, G.; Hanack, M.; Vermehren, J.; Speranza, M. *J. Am. Chem. Soc.* ***1988***, *110*, 1298.
[275] See Cacace, F. *Adv. Phys. Org. Chem.* ***1970***, *8*, 79. See also, Fornarini, S.; Speranza, M. *J. Am. Chem. Soc.* ***1985***, *107*, 5358.
[276] Flynn Jr., J.; Badiger, V.V.; Truce, W.E. *J. Org. Chem.* ***1963***, *28*, 2298. See also, Shainyan, B.A.; Mirskova, A. N. *J. Org. Chem. USSR* ***1984***, *20*, 885, 1989; ***1985***, *21*, 283.
[277] Bottini, A.T.; Corson, F.P.; Fitzgerald, R.; Frost II, K.A. *Tetrahedron* ***1972***, *28*, 4883.
[278] See Popov, A.F.; Piskunova, Z.; Matvienko, V.N. *J. Org. Chem. USSR* ***1986***, *22*, 1299.
[279] See Andrisano, R.; Angeloni, A.S.; De Maria, P.; Tramontini, M. *J. Chem. Soc. C* ***1967***, 2307.
[280] See Rappoport, Z. *Acc. Chem. Res.* ***1981***, *14*, 7; Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* ***1982***, *47*, 1397.

Vinylic halides can react by a $S_{RN}1$ mechanism (Sec. 13.A.iv) in some cases. An example is the $FeCl_2$ catalyzed reaction of 1-bromo-2-phenylethene and the enolate anion of pinacolone (t-$BuCOCH_2^-$), which gave a low yield of substitution products along with alkynes.[281]

10.G. REACTIVITY

A large amount of work has been done on this subject. Although a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section, only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.[282]

10.G.i. The Effect of Substrate Structure

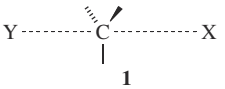
The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α and β Carbons*. For the S_N2 mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom[283] react by the S_N2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[284] Experiments show that methyl halide reacts 30 times faster than ethyl, whereas isopropyl halides react 40 times slower than ethyl.[285] The presence of π bonds accelerates the rate, as illustrated by the fact that allyl halides react 40 times faster than ethyl halides, and benzyl halides react 120 times faster.[285] The reason for the low rates for secondary and especially tertiary is almost certainly steric. This statement includes the primary neopentyl halides, which react 20,000 times slower than ethyl halides[286] The transition state **1** is more crowded when larger groups are close to the central carbon.[287]

   The tetrahedral mechanism for substitution at a carbonyl carbon (Chapter 16) is also slowed or blocked completely by α or β branching for similar reasons. Solvolysis in such systems is linked to relief of B-strain, but solvent participation can overshadow this as steric hindrance increases.[288] Severe steric strain can cause distortion from coplanarity in the carbocation intermediate,[289] although there seems to be no loss of

[281] Galli, C.; Gentili, P.; Rappoport, Z. *J. Org. Chem.* ***1994***, *59*, 6786.
[282] See DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8650.
[283] For a reported example, see Edwards, O.E.; Grieco, C. *Can. J. Chem.* ***1974***, *52*, 3561.
[284] See Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.
[285] See Streitwieser, A. *Solvolytic Displacement Reactions,* McGraw-Hill, NY, ***1962***, p. 13.
[286] For evidence, see Caldwell, G.; Magnera, T.F.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 959.
[287] For a discussion of the interplay between steric and electronic effects, see Fernández, I.; Frenking, G.; Uggerud, E. *Chemistry: Eur. J.* ***2009***, *15,* 2166.
[288] Liu, K.-T.; Hou, S.-J.; Tsao, K.-L. *J. Org. Chem.* ***1998***, *63*, 1360.
[289] Fujio, M.; Nomura, H.; Nakata, K.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Matsushita, T.; Nishimoto, K.; Tsuno, Y. *Tetrahedron Lett.* ***1994***, *35*, 5005.

resonance stability.[290] Adding electron-donating substituents to such molecules improves coplanarity in the cation.[291] For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see Reaction **16-59**), and R_3CCO_2H acids cannot be easily esterified.[292] Synthetic advantage can be taken of this fact, for example, with a molecule containing two ester groups only the less hindered one is hydrolyzed.



1

For the S_N1 mechanism, branching as the α carbon increases the rate, as shown by rate data for alkyl bromides.[293] The secondary bromide isopropyl bromide reacts 11.6 times faster than bromoethane in water at 50 °C, and *tert*-butyle bromide (a tertiary halide) reacts 1.2×10^6 times faster[293]. This result is explained by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. The *Hammond postulate* (Sec. 6.G) is used to make the assumption that the transition states resemble the cations and that anything (e.g., branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates.[294] As previously indicated (Sec. 10.A.iv), secondary substrates generally react by the S_N2 mechanism,[295] except that the S_N1 mechanism may become important at high solvent polarities. Isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (cf. this with the 10^4 ratio for *tert*-butylbromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6.[293] The 2-adamantyl system is an exception; it is a secondary system that reacts by the S_N1 mechanism because backside attack is hindered for steric reasons.[296] Because there is no S_N2 component, this system provides an opportunity for comparing the pure S_N1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for a hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of $\sim 10^8$.[297] Simple primary substrates react by the S_N2 mechanism (or with participation by neighboring alkyl or hydrogen), but not by the

[290] Fujio, M.; Nakata, K.; Kuwamura, T.; Nakamura, H.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *34*, 8309.
[291] Liu, K.T.; Tsao, M.-L.; Chao, I. *Tetrahedron Lett.* ***1996***, *37*, 4173.
[292] See DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1987***, *52*, 2074.
[293] See Streitwieser, A. *Solvolytic Displacement Reactions,* McGraw-Hill, NY, ***1962***, p. 43.
[294] See Zamashchikov, V.V.; Bezbozhnaya, T.V.; Chanysheva, I.R. *J. Org. Chem. USSR* ***1986***, *22*, 1029.
[295] See Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317.
[296] Fry, J.L.; Harris, J.M.; Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2540; Schleyer, P.v.R.; Fry, J.L.; Lam, L.K.M.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2542. Also see Dutler, R.; Rauk, A.; Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1989***, *111*, 9024.
[297] Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 4628. See also, Gassman, P.G.; Pascone, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 7801.

S_N1 mechanism, even when solvolyzed in solvents of very low nucleophilicity[298] (e.g., trifluoroacetic acid or trifluoroethanol[299]), and even when very good leaving groups (e.g., OSO_2F) are present[300] (see, however, Sec. 10.G.iii).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see Sec. 9.B). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., *p*-$NO_2C_6H_4CMe_2Cl$) give very good yields of substitution products when treated with a variety of nucleophiles.[301]

2. *Unsaturation at the α Carbon*. Vinylic, acetylenic,[302] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems, both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and even more, *sp*) carbon atoms have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As seen previously (Sec. 8.F, category 7), an *sp*-H bond has a higher acidity than an sp^3-H bond, with that of an sp^2–H bond in between. This is reasonable; the carbon retains the electrons when the proton is lost and an *sp* carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so the situation is reversed and it is the sp^3 carbon that loses the leaving group and the electron pair most easily. Recall (Sec. 1.J) that bond distances decrease with increasing *s* character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Of course, it has been seen (Sec. 10.F) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (Sec. 10.F).

[298] See Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* ***2004***, *126,* 5174; Kevill, D.N. in Charton, M. *Advances in Quantitative Structure–Property Relationships*, Vol. 1, JAI Press, Greenwich, CT, ***1996***, pp 81–115; Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[299] Dafforn, G.A.; Streitwieser, Jr., A. *Tetrahedron Lett.* ***1970***, 3159.

[300] Cafferata, L.F.R.; Desvard, O.E.; Sicre, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 940.

[301] Kornblum, N.; Cheng, L.; Davies, T.M.; Earl, G.W.; Holy, N.L.; Kerber, R.C.; Kestner, M.M.; Manthey, J.W.; Musser, M.T.; Pinnick, H.W.; Snow, D.H.; Stuchal, F.W.; Swiger, R.T. *J. Org. Chem.* ***1987***, *52*, 196.

[302] See Miller, S.I.; Dickstein, J.I. *Acc. Chem. Res.* ***1976***, *9*, 358.

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X. Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX: (1) The carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles. (2) In an S_N2 reaction, a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (3) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the β Carbon*. The S_N1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (allylic tosylates react more than 30 times faster than ethyl tosylate).[303] The reason is that allylic (Sec. 5.A.ii) and benzylic[304] (Sec. 5.A.ii) cations are stabilized by resonance. The presence of a second or a third phynyl group increases the rate still more (10^5 and 10^{10} times faster, respectively), because these carbocations are more stable yet.[303] Remember that allylic rearrangements are possible with allylic systems.

   In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.[305] Among these are alkyl, aryl, and halo groups.



86

   The S_N2 rates for allylic and benzylic systems are also increased (see above), probably owing to resonance possibilities in the transition state. Evidence for this in benzylic systems is that the rate of the reaction was 8000 times slower than the rate with $(PhCH_2)_2SEt^+$.[306] The cyclic **86** does not have the proper geometry for conjugation in the transition state.

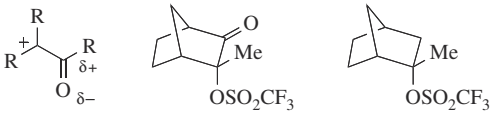
   Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[307] Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. *α Substitution*. Compounds of the formula 2X, where Z = RO, RS, or R_2N undergo S_N1 reactions very rapidly,[308] because of the increased resonance in the carbocation.

[303] Streitwieser, A. *Solvolytic Displacement Reactions,* McGraw-Hill, NY, ***1962***, p. 75.
[304] For a Grunwald–Winstein correlation analysis of the solvolysis of benzyl bromide see Liu, K.-T.; Hou, I.-J. *Tetrahedron* ***2001***, *57*, 3343.
[305] See DeWolfe, R.H.; Young, W.G. in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, ***1964***, pp. 683–688, 695–697.
[306] King, J.F.; Tsang, G.T.Y.; Abdel-Malik, M.M.; Payne, N.C. *J. Am. Chem. Soc.* ***1985***, *107*, 3224.
[307] Jacobs, T.L.; Brill, W.F. *J. Am. Chem. Soc.* ***1953***, *75*, 1314.
[308] See Gross, H.; Höft, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 335.

These groups have an unshared pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (Sec. 5.A.ii). The field effects of these groups would be expected to decrease S_N1 rates (see Sec. 10.G.i, category 6), so the resonance effect is far more important.

When Z in 2X is RCO,[309] HCO, ROCO, NH_2CO, NC, or F_3C,[310] S_N1 rates are decreased compared to CH_3X, owing to the electron-withdrawing field effects of these groups. Furthermore, carbocations[311] with a CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**87**). The S_N1 reactions have been carried out on such compounds,[312] but the rates are very low. For example, from a comparison of the solvolysis rates of **88** and **89**, a rate-retarding effect of 10^{76}



87 **88** **89**

was estimated for the C=O group.[313] However, when a different kind of comparison is made: $RCOCR'_2X$ versus HCR'_2X (where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance[314] may be offsetting the inductive destabilization for this group.[315] For a CN group also, the rate-retarding effect is reduced by this kind of resonance.[316] A carbocation with a COR group has been isolated.[317] When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.[318] For example, α-chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75 °C ∼ 32,000 times faster than 1-chlorobutane,[319] but α-bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.[318] The reasons

[309] See De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, Wiley, NY, ***1988***, pp. 225–368.

[310] Allen, A.D.; Kanagasabapathy, V.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1989***, *111*, 1455.

[311] For reviews of such carbocations, see Bégué, J.; Charpentier-Morize, M. *Acc. Chem. Res.* ***1980***, *13*, 207; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1974***, 343.

[312] For reviews, see Creary, X. *Acc. Chem. Res.* ***1985***, *18*, 3; Creary, X.; Hopkinson, A.C.; Lee-Ruff, E. *Adv. Carbocation Chem.* ***1989***, *1*, 45; Charpentier-Morize, M.; Bonnet-Delpon, D. *Adv. Carbocation Chem.* ***1989***, *1*, 219.

[313] Creary, X. *J. Org. Chem.* ***1979***, *44*, 3938.

[314] The resonance contributor that has the positive charge on the more electronegative atom is less stable, according to rule c in Section 2.E, but it nevertheless seems to be contributing in this case.

[315] Creary, X. *J. Am. Chem. Soc.* ***1984***, *106*, 5568. See, however, Takeuchi, K.; Yoshida, M.; Ohga,Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* ***1990***, *55*, 6063.

[316] Gassman, P.G.; Saito, K.; Talley, J.J. *J. Am. Chem. Soc.* ***1980***, *102*, 7613.

[317] Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* ***1983***, 7. See also, Dao, L.H.; Maleki, M.; Hopkinson, A.C.; Lee-Ruff, E. *J. Am. Chem. Soc.* ***1986***, *108*, 5237.

[318] Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* ***1978***, 327.

[319] Bordwell, F.G.; Brannen, Jr., W.T. *J. Am. Chem. Soc.* ***1964***, *86*, 4645. Sisti, A.J.; Lowell, S. *Can. J. Chem.* ***1964***, *42*, 1896.

for this varying behavior are not clear, but those nucleophiles that form a "tight" transition state (one in which bond making and breaking have proceeded to about the same extent) are more likely to accelerate the reaction.[320]

When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[321] The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group,[322] and the S_N2 mechanism presumably by the steric effect.

5. *β Substitution*. For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in Section 10.F, as well as halogen[323] or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in item 4 are absent, but the field effects are still there, although smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,[324] or unless their size causes the rates to decrease for steric reasons.[325] It has been shown that silicon exerts a β-effect, and that tin exerts a γ-effect.[326] Silcon also exerts a exerts γ-effect.[327]
6. *The Effect of Electron-Donating and Electron-Withdrawing Groups*. If substitution rates for a series of compounds *p*-$ZC_6H_4CH_2X$ are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For S_N1 reactions, electron-withdrawing Z decrease the rate and electron-donating Z increase it,[328] because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, for example,



while electron-withdrawing groups concentrate the charge. The Hammett σρ relationship[329] (Sec. 9.C) fairly successfully correlates the rates of many of these reactions (with σ^+ instead of σ). The ρ values are generally about –4, which is expected for a reaction where a positive charge is created in the transition state.

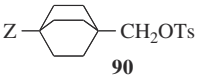
For S_N2 reactions, no such simple correlations are found.[330] In this mechanism, bond breaking is about as important as bond making in the rate-determining step,

[320] See McLLee, I.; Shim, C.S.; Chung, S.Y.; Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 975; Yoh, S.; Lee, H.W. *Tetrahedron Lett.* ***1988***, *29*, 4431.
[321] Cinquini, M.; Colonna, S.; Landini, D.; Maia, A.M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 996.
[322] See Creary, X.; Mehrsheikh-Mohammadi, M.E.; Eggers, M.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2435.
[323] See Gronert, S.; Pratt, L.M.; Mogali, S. *J. Am. Chem. Soc.* ***2001***, *123*, 3081.
[324] See Sedaghat-Herati, M.R.; McManus, S.P.; Harris, J.M. *J. Org. Chem.* ***1988***, *53*, 2539.
[325] See, for example, Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1913.
[326] Sugawara, M.; Yoshida, J.-i. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 1253.
[327] Nakashima, T.; Fujiyama, R.; Kim, H.-J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 429
[328] Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 100; Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* ***1981***, 737.
[329] See Fernández, I.; Frenking, G. *J. Org. Chem.* ***2006***, *71,* 2251.
[330] See Sugden, S.; Willis, J.B. *J. Chem. Soc.* ***1951***, 1360; Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840; Lee, I.; Sohn, S.C.; Oh, Y.J.; Lee, B.C. *Tetrahedron* ***1986***, *42*, 4713.

and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and bromide solvolyze by the S_N2 mechanism.[322]

For Z = alkyl, the *Baker–Nathan order* (Sec. 2.M) is usually observed both for S_N1 and S_N2 reactions.

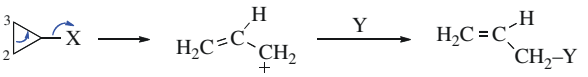
In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock[331] studied a system that removes not only steric effects, but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**90**). In this system, steric effects are completely absent owing to the rigidity of the molecules, and only field effects operate. By this means, Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.



90

For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. *Cyclic Substrates*. Cyclopropyl substrates are extremely resistant to nucleophilic attack.[332] For example, cyclopropyl tosylate solvolyzes $\sim 10^6$ times more slowly than cyclobutyl tosylate in acetic acid at 60 °C.[333] When such attack does take place, the result is generally not normal substitution (though exceptions are known,[334] especially when a stabilizing group, e.g., aryl or alkoxy, is present), but ring opening:[326]

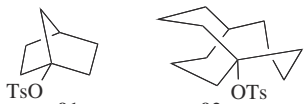


There is much evidence that the ring opening is usually concerted with the departure of the leaving group[335] (as in the similar case of cyclobutyl substrates, Sec. 10.C.i, category 4.b.iv), from which we can conclude that if the 2,3-bond of the cyclopropane ring did not assist, the rates would be lower still. Strain plays a role in the ring-opening process.[336] It has been estimated[337] that without this

[331] Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404.
[332] See Friedrich, E.C. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 633–700; Aksenov, V.S.; Terent'eva, G.A.; Savinykh, Yu.V. *Russ. Chem. Rev.* ***1980***, *49*, 549.
[333] Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5034.
[334] See Banert, K. *Chem. Ber.* ***1985***, *118*, 1564; Vilsmaier, E.; Weber, S.; Weidner, J. *J. Org. Chem.* ***1987***, *52*, 4921.
[335] See Jefford, C.W.; Wojnarowski, W. *Tetrahedron* ***1969***, *25*, 2089; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.
[336] See Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2001***, *66,* 915.
[337] Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7946.

assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12}. For a discussion of the stereochemistry of the ring opening, see Reaction **18-27**, Section B. For larger rings, we have seen (Sec. 9.A) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

8. *Bridgeheads*.[14] The S_N2 mechanism is impossible at most bridgehead compounds (Sec. 10.A.i). Nucleophilic attack in [1.1.1]propellane has been reported, however.[338] In general, a relatively large ring is required for an S_N1 reaction to take place (Sec. 10.A.ii).[339] The S_N1 reactions have been claimed to occur for 1-iodobicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl cation,[340] but this has been disputed and the bicyclo[1.1.0]butylcarbinyl cation was calculated to be the real intermediate.[341] Solvolytic reactivity at



91 **92**

bridgehead positions spans a wide range; for example, from $k = 4 \times 10^{-17}$ s^{-1} for **91** (very slow) to 3×10^{6} s^{-1} for the [3.3.3] compound **92** (very fast);[342] a range of 22 orders of magnitude. Molecular mechanics calculations show that S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.[343]

9. *Deuterium Substitution*. Both α and β secondary isotope effects affect the rate in various ways (Sec. 6.J.vii). The measurement of a secondary isotope effect provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are higher.[344] This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes (e.g., changing a substituent or the polarity of the solvent) may have a much more complex effect.

   Table 10.3 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.4 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl).

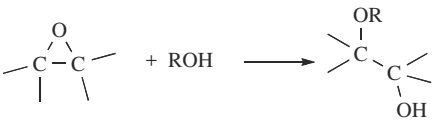
[336] See Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2001***, *66,* 915.
[337] Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7946.
[338] Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* ***1996***, *37*, 5573.
[339] See Kraus, G.A.; Hon, Y.; Thomas, P.J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* ***1989***, *89*, 1591.
[340] Adcock. J.L.; Gakh, A.A. *Tetrahedron Lett*. ***1992***, *33*, 4875.
[341] Wiberg, K.B.; McMurdie, N. *J. Org. Chem.* ***1993***, *58*, 5603.
[342] Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.
[343] Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.
[344] Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553. For a review of secondary isotope effects in S_N2 reactions, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275.

TABLE 10.3 List of Groups in Approximately Descending Order of Reactivity Toward S_N1 and S_N2 Reactions[a]

S_N1 Reactivity	S_N2 Reactivity
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
$ArCH_2X$	$-C{=}C-CH_2X$
$-C{=}C-CH_2X$	$RCH_2X \sim RCHDX \sim RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \sim R_3CCH_2X$	R_3CX
RCHDX	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
$-C{=}C-C-X$	$-C{=}C-C-X$
ZCH_2X	
ZCH_2CH_2X	ArX
ArX	Bridgehead-X
[2.2.1] Bridgehead-X	

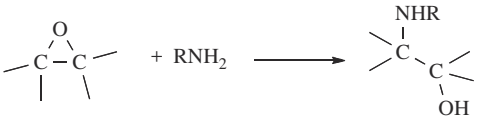
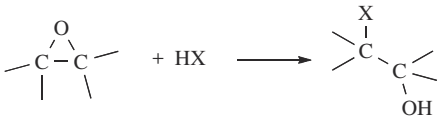
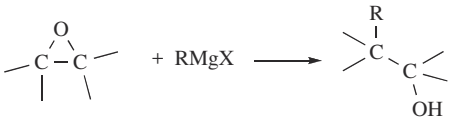
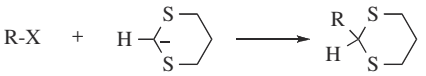
[a]Here Z is RCO, HCO, ROCO, NH_2CO, NC, or a similar group.

TABLE 10.4 The More Important Synthetic Reactions of Chapter 10 That Take Place by an S_N2 Mechanism.[a,b]

Reaction Number	Reactions
10-1	$RX + OH^- \longrightarrow ROH$
10-8	$RX + OR' \longrightarrow ROR'$
10-9	
10-10	$R{-}OSO_2OR'' + OR' \longrightarrow ROR'$
10-12	$2\,ROH \longrightarrow ROR$
10-14	
10-15	$R_3O^+ + R'OH \longrightarrow ROR'$
10-17	$RX + R'COO^- \longrightarrow R'COOR$
10-21	$RX + OOH^- \longrightarrow ROOH$
10-25	$RX + SH^- \longrightarrow RSH$
10-26	$RX + R'S^- \longrightarrow RSR'$
10-27	$RX + S_2^{2-} \longrightarrow RSSR$
10-30	$RX + SCN^- \longrightarrow RSCN$
10-31	$RX + R'_2NH \longrightarrow RR'_2N$
10-31	$RX + R'_3N \longrightarrow RR'_3N^+X^-$

(*continued*)

TABLE 10.4 (*Continued*)

Reaction Number	Reactions
10-35	
10-41	$RX + R'CONH^- \longrightarrow RNHCOR'$
10-42	$RX + NO_2^- \longrightarrow RNO_2 + RONO$
10-43	$RX + N_3^- \longrightarrow RN_3$
10-44	$RX + NCO^- \longrightarrow RNCO$
10-46	$RX + X'^- \longrightarrow RX'$
10-47	$R{-}OSO_2OR' + X^- \longrightarrow RX$
10-48	$ROH + PCl_5 \longrightarrow RCl$
10-49	$ROR' + 2\,HI \longrightarrow RI + R'I$
10-50	
10-51	$R{-}O{-}COR' + LiI \longrightarrow RI + R'COO^-$
10-57	$RX + R'_2CuLi \longrightarrow RR'$
10-65	
10-67	$RX + H\bar{C}(CO_2R')_2 \longrightarrow RCH(CO_2R')_2$
10-68	$RX + R''CH{-}COR' \longrightarrow RCR''{-}COR'$
10-70	$RX + R'CHCOO^- \longrightarrow RR'CHCOO^-$
10-71	
10-74	$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$
10-75	$RX + CN^- \longrightarrow RCN$

[a]Here R = primary, often secondary, alkyl.

[b]Catalysts are not shoure. This is a schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

10.G.ii The Effect of the Attacking Nucleophile[345]

Any species that has an unshared pair (i.e., any Lewis base) can, in principle, be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions

[345] Harris, J.M.; McManus, S.P. *Nucleophilicity*, American Chememical Society, Washington, ***1987***; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 145–167, 181–186; Hudson, R.F. in Klopman, G. *Chemical Reactivity and Reaction Paths*, Wiley, NY, ***1974***, pp. 167–252.

are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.[346] This may be illustrated by the effect of changing the nucleophile from H_2O to ^-OH for a primary and a tertiary substrate. For methyl bromide, which reacts by an S_N2 mechanism, the rate is multiplied > 5000 by the change to the more powerful nucleophile ^-OH, but for *tert*-butylbromide, which reacts by an S_N1 mechanism, the rate is unaffected.[347] A change in nucleophile can, however, change the *product* of an S_N1 reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

Note that the so-called *cation affinity* is used to measure the ability of a cation to interact with an electron-donating species. While this is not formally used to describe S_N1 reactions, it is important for catalytic activity due to different ligands.[348]

For S_N2 reactions in solution, there are four main principles that govern the effect of the nucleophile on the rate. The nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, and so on.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus ^-OH is more powerful than H_2O, $^-NH_2$ is more powerful than NH_3, and so on
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately the same as the order of basicity,[349] although *basicity is thermodynamically controlled and nucleophilicity is kinetically controlled*. So an approximate order of nucleophilicity is $^-NH_2 > RO^- > ^-OH > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and pK values.[350]
3. Going down the periodic table, nucleophilicity increases, although basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (as seen below, this order is solvent dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analogue The same is true for phosphorus versus nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This finding is most important for protic polar solvents in which the solvent may be hydrogen bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones.[351] Also, in DMF, an aprotic solvent, the

[346] See Ritchie, C.D.; Minasz, R.J.; Kamego, A.A.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3747; McClelland, R.A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* ***1986***, *108*, 7023.
[347] Bateman, L.C.; Cooper, K.A.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 925.
[348] See Wei, Y.; Sastry, G.N.; Zipse, H. *J. Am. Chem. Soc.* ***2008***, *130,* 3473.
[349] Uggerud, E. *Chem. Eur. J.* **2006**, 12, 1127.
[350] See Bordwell, F.G.; Hughes, D.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3234.
[351] Parker, A.J. *J. Chem. Soc.* ***1961***, 1328 has a list of $\sim$ 20 such reactions.

order of nucleophilicity was $Cl^- > Br^- > I^-$.[352] Another experiment was the use of $Bu_4N^+ X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+ X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; —, 3.7.[353] In a further experiment, halide ions were allowed to react with the molten salt $(n\text{-}C_5H_{11})_4N^+ X^-$ at 180 °C in the absence of a solvent.[354] Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^-, 620; Br^-, 7.7; I^-, 1. In the gas phase (no solvent), an approximate order of nucleophilicity was found to be $^-OH > F^- \sim MeO^- > MeS^- >> Cl^- > {}^-CN > Br^-$,[355] providing further evidence that solvation[356] is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.[357] To explain these cases, the principle of hard and soft acids and bases (Sec. 8.E) may be used.[358] The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given in Section 8.F, an alkyl group is expected to prefer softer nucleophiles than the proton. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

4. The freer the nucleophile, the greater the rate.[359] One instance of this has already been discussed.[353] Another is that the rate of attack by $(EtOOC)_2CBu^- Na^+$ in benzene was increased by the addition of substances (e.g., 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.[360] In a nonpolar solvent (e.g., benzene), salts, [e.g., $(EtOOC)_2CBu^- Na^+$], usually exist as ion-pair aggregations of large molecular weights.[361] Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion: K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[362] Presumably, the potassium ion leaves

[352] Weaver, W.M.; Hutchison, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 261; See also, Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1981***, *46*, 3570. For a contrary result in liquid sulfur dioxide, see Lichtin, N.N.; Puar, M.S.; Wasserman, B. *J. Am. Chem. Soc.* ***1967***, *89*, 6677.

[353] Winstein, S.; Savedoff, L.G.; Smith, S.G.; Stevens, I.D.R.; Gall, J.S. *Tetrahedron Lett.* ***1960***, no. 9, 24.

[354] Gordon, J.E.; Varughese, P. *Chem. Commun.* ***1971***, 1160. See also, Ford, W.T.; Hauri, R.J.; Smith, S.G. *J. Am. Chem. Soc.* ***1974***, *96*, 4316.

[355] Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219. See also, Tanaka, K.; Mackay, G.I.; Payzant, J.D.; Bohme, D.K. *Can. J. Chem.* ***1976***, *54*, 1643.

[356] See Kormos, B.L.; Cramer, C.J. *J. Org. Chem.* ***2003***, *68,* 6375.

[357] Parker, A.J. *J. Chem. Soc.* ***1961***, 4398.

[358] Pearson, R.G. *Surv. Prog. Chem.* ***1969***, *5*, 1, pp. 21-38.

[359] See Guibe, F.; Bram, G. *Bull. Soc. Chim. Fr.* ***1975***, 933.

[360] Zaugg, H.E.; Leonard, J.E. *J. Org. Chem.* ***1972***, *37*, 2253. See also, Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1987***, *23*, 1243; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.

[361] See, for example Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462.

[362] Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386. See also, Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* ***1988***, *53*, 2579.

the negative ion freest to attack most rapidly. Further evidence is that in the gas phase,[363] where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.[364] It has proven possible to measure the rates of reaction of $^-$OH with methyl bromide in the gas phase, with $^-$OH either unsolvated or solvated with one, two, or three molecules of water.[365] The rates were, with the number of water molecules in parentheses: (0) 1.0×10^{-9}; (1) 6.3×10^{-10}; (2) 2×10^{-12}; (3) 2×10^{-13} cm^3 $molecule^{-1}$ s^{-1}, evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is 2.3×10^{-25} cm^3 $molecule^{-1}$ s^{-1}. Similar results were found for other nucleophiles and other solvents.[366] Also, solution studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. Indeed, hydrogen bonding lowers the intrinsic nucleophilicity.[367] When the salt $(n\text{-}C_6H_{13})_4N^+F^-$ reacted with *n*-octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.[368]

In Chapter 3, cryptands were seen to specifically solvate the alkali metal portion of salts like KF, KOAc, and so on. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (see Sec. 10.G.v).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *tert*-butoxide ion Me_3CO^- is a stronger base than $^-$OH or $^-$OEt, but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for S_N2 mechanisms (in protic solvents) was given by Edwards and Pearson[369]: $RS^- > ArS^- > I^- > CN^- > {}^-OH > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship[370] (the *Swain–Scott equation*, which can be derived from *Marcus theory*[371]) has been worked out similar to the linear free-energy equations considered in Chapter 9:[372]

$$\log(k, k_o) = sn$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. The parameter s is defined as 1.0 for bromomethane.

[363] See Barlow, S.E.; Van Doren, J.M.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1988***, *110*, 7240; Merkel, A.; Havlas, Z.; Zahradník, R. *J. Am. Chem. Soc.* ***1988***, *110*, 8355.
[364] Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219.
[365] Bohme, D.K.; Raksit, A.B. *J. Am. Chem. Soc.* ***1984***, *106*, 3447. See also, Hierl, P.M.; Ahrens, A.F.; Henchman, M.; Viggiano, A.A.; Paulson, J.F.; Clary, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 3142.
[366] Bohme, D.K.; Raksit, A.B. *Can. J. Chem.* ***1985***, *63*, 3007.
[367] Chen, X.; Brauman, J.I. *J. Am. Chem. Soc.* ***2008***, *130,* 15038.
[368] Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* ***1989***, *54*, 328.
[369] Edwards, J.O.; Pearson, R.G. *J. Am. Chem. Soc.* ***1962***, *84*, 16.
[370] Swain, C.G.; Scott, C.B. *J. Am. Chem. Soc.* ***1953***, *75*, 141.
[371] Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87, pp. 113–115.
[372] Also see Ritchie, C.D. *Pure Appl. Chem.* ***1978***, *50*, 1281; Duboc, C. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry, Recent Advances*, Plenum, NY, ***1978***, pp. 313–355; Ibne-Rasa, K.M. *J. Chem. Educ.* ***1967***, *44*, 89; Kawazoe, Y.; Ninomiya, S.; Kohda, K.; Kimoto, H. *Tetrahedron Lett.* ***1986***, *27*, 2897; Kevill, D.N.; Fujimoto, E.K. *J. Chem. Res. (S)* ***1988***, 408.

TABLE 10.5 Nucleophiliclties of Some Common Reagents[a]

Nucleophile	*n*	Nucleophile	*n*
SH	5.1	Br^-	3.5
CN^-	5.1	PhO^-	3.5
I^-	5.0	AcO^-	2.7
$PhNH_2$	4.5	Cl^-	2.7
OH	4.2	F^-	2.0
N_3^-	4.0	NO_3^-	1.0
Pyridine	3.6	H_2O	0.0

Reprinted with permission Wells, P.R. *Chem. Rev.* ***1963*** *, 63*, 171. Copyright © 1963 American Chemical Society.
[a]See Ref. 373.

Table 10.5 contains values of *n* for some common nucleophiles.[373] The order is similar to that of Edwards and Pearson.

It is now evident that there is *no* absolute order of either nucleophilicity[374] or leaving-group ability, even in the gas phase where solvation is not a factor because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.[363] Although this effect is smaller than the effects in paragraphs one and four above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability.[375] There has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.[376]

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon has a partial positive charge. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:[377] $Me_2C{=}NO^- > EtO^- > MeO^- > {}^-OH > {}^-OAr > N_3^- > F^- > H_2O > Br^- \sim I^-$. Soft bases are ineffective at a carbonyl carbon.[378] In a reaction carried out in the gas phase with alkoxide nucleophiles OR^- solvated by only one molecule of an alcohol R′OH, it was found that both RO^- and $R'O^-$ attacked the formate substrate (HCO_2R'') about equally, although in the unsolvated case, the more basic alkoxide is the better nucleophile.[379] In this study, the product ion R^2O^- was also solvated by one molecule of ROH or R′OH.

If an atom containing one or more unshared pairs is adjacent to the attacking atom on the nucleophile, the nucleophilicity is enhanced.[380] Examples of such nucleophiles are HO_2^-,

[373] From Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 212. See also, Koskikallio, J. *Acta Chem. Scand.* ***1969***, *23*, 1477, 1490.
[374] See Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1983***, *105*, 2672.
[375] For reference scales for the characterization of cationic electrophiles and neutral nucleophiles see Mayr, H.; Bug, T.; Gotta, M.F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A.R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* ***2001***, *123,* 9500.
[376] For discussions, see Dietze, P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 5880.
[377] Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2622.
[378] For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncel, E.; Shaik, S.S.; Um, I.; Wolfe, S. *J. Am. Chem. Soc.* ***1988***, *110*, 1275, and references cited therein.
[379] Baer, S.; Stoutland, P.O.; Brauman, J.I. *J. Am. Chem. Soc.* ***1989***, *111*, 4097.
[380] Definition in the *Glossary of Terms used in Physical Organic Chemistry*, *Pure Appl. Chem.* ***1979***, *51,* 1731.

$Me_2C{=}NO^-$, NH_2NH_2, and so on. This is called the *alpha effect* (α-effect),[381] and a broader definition is a positive deviation exhibited by an α-nucleophile from a Brønsted-type nucleophilicity plot,[382] where the reference (or normal) nucleophile is one that possesses the same basicity as the α-nucleophile, but does not deviate from the Brønsted-type plot. Several reviews of the α-effect have been published previously.[72,383] Several possible explanations have been offered.[384] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[385] another is that the transition state is stabilized by the extra pair of electrons;[386] a third is that the adjacent electron pair reduces solvation of the nucleophile.[387] Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,[388] although HO_2^- shows a strong alpha effect in solution. The α-effect has been demonstrated to be remarkably dependent on the nature of the solvent.[389] The α-effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[390] and for reactions of a nucleophile with a carbocation,[391] but is generally smaller or absent entirely for substitution at a saturated carbon.[392]

Attempts have been made to establish a general scale of nucleophilicity,[393] and the nucleophilic reactivity of other moieties have been determined, including alcohols and alkoxides,[394] carbanions,[395] amines,[396] pyridines,[397] pyrroles,[398] indoles,[399] imides and amides,[400] amino acids and peptides,[401] and sulfur ylids.[402]

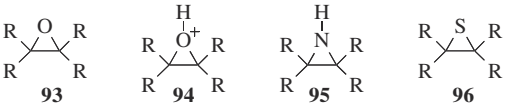
[381] See Ren, Y.; Yamataka, H. *J. Org. Chem.* ***2007***, *72,* 5660; *Org. Lett.* ***2006***, *8,* 119; *Chemistry: European J.* ***2007***, *13,* 677.
[382] Hoz, S.; Buncel, E. *Israel J. Chem.* ***1985***, *26*, 313.
[383] Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, ***1969***; pp 107–111.
[384] See Ho, S.; Buncel, E. *Isr. J. Chem.* ***1985***, *26*, 313.
[385] Buncel, E.; Hoz, S. *Tetrahedron Lett.* ***1983***, *24*, 4777. For evidence that this is not the sole cause, see Oae, S.; Kadoma, Y. *Can. J. Chem.* ***1986***, *64*, 1184.
[386] See Hoz, S. *J. Org. Chem.* ***1982***, *47*, 3545; Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* ***1984***, *25*, 1267.
[387] Also see Hudson, R.F.; Hansell, D.P.; Wolfe, S.; Mitchell, D.J. *J. Chem. Soc., Chem. Commun.* ***1985***, 1406. For a discussion, see Herschlag, D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 1951.
[388] Buncel, E.; Um, I. *J. Chem. Soc., Chem. Commun.* ***1986***, 595; Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* ***1988***, 415. For some evidence against this explanation, see Moss, R.A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun.* ***1987***, 860.
[389] Buncel, E.; Um, I.-H. *Tetrahedron* ***2004***, *60,* 7801.
[390] For example, see Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.
[391] Dixon, J.E.; Bruice, T.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3248, 6592.
[392] McIsaac, Jr., J.E.; Subbaraman, L.R.; Subbaraman, J.; Mulhausen, H.A.; Behrman, E.J. *J. Org. Chem.* ***1972***, *37*, 1037. See, however, Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* ***1982***, *104*, 4896; *Int. J. Chem. Kinet.* ***1982***, *14*, 823.
[393] Phan, T.B.; Breugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3869.
[394] Phan, T.B.; Mayr, H. *Can. J. Chem.* ***2005***, *83,* 1554.
[395] Phan, T.B.; Mayr, H. *Eur. J. Org. Chem.* ***2006***, 2530.
[396] Brotzel, F.; Chu, Y.C.; Mayr, H. *J. Org. Chem.* ***2007***, *72,* 3679; Korzhenevskaya, N.G. *Russ. J. Org. Chem.* ***2008***, *44*, 1255.
[397] Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chemistry: European J.* ***2007***, *13,* 336.
[398] Nigst, T.A.; Westermaier, M.; Ofial, A.R.; Mayr, H. *Eur. J. Org. Chem.* ***2008***, 2369.
[399] Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A.R.; Mayr, H. *J. Org. Chem.* ***2006***, *71,* 9088.
[400] Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* ***2010***, *75*, 5250.
[401] Brotzel, F.; Mayr, H. *Org. Biomol. Chem.* ***2007***, *5,* 3814.
[402] Appel, R.; Mayr, H. *Chemistry: Eur. J.* ***2010***, *16*, 8610.

10.G.iii. The Effect of the Leaving Group

The leaving group at the saturated carbon comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride is the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers, but can come off when the groups are protonated (i.e., converted to ROH_2^+ or $RORH^+$).[403] Reactions in which the leaving group does not come off until it has been protonated have been called S_N1cA or S_N2cA, depending on whether after protonation the reaction is an S_N1 or S_N2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $A_h + D_N + A_N$ and $A_h + A_ND_N$; that is, the same designations as S_N1 and S_N2, with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in superacid solutions.[404] At higher temperatures, they cleave to give carbocations.

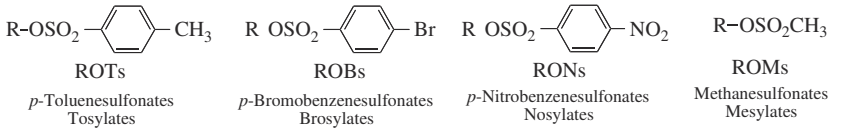
It is obvious that the best nucleophiles (e.g., NH_2^-, ^-OH) cannot take part in S_N1cA or S_N2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[405] Because S_N1 reactions do not require powerful nucleophiles, but do require good leaving groups, most of them take place under acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles, which are generally strong bases, most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides[406] (**93**) are cleaved quite easily and protonated epoxides (**94**) even more easily. Aziridines (**95**)[407] and episulfides (**96**) are also easily cleaved (see Sec. 10.G.viii).[408]

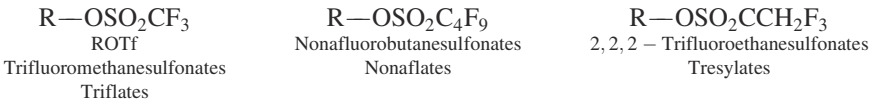


Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better

[403] See Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 22–46.
[404] Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725; Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576; Olah, J.A.; Olah, G.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 743–747.
[405] See Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 610.
[406] See Smith, J.G. *Synthesis* ***1984***, 629; Bartók, M.; Láng, K.L.in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 609–681.
[407] See Hu, X.E. *Tetrahedron* ***2004***, *60,* 2701.
[408] See Di Vona, M.L.; Illuminati, G.; Lillocci, C. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1943; Bury, A.; Earl, H.A.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1985***, 393.



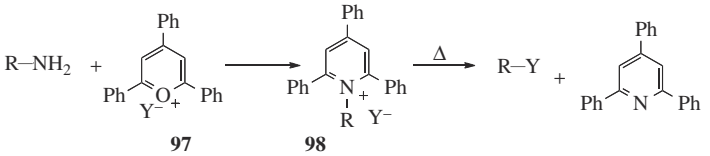
leaving groups than halides and are frequently used.[409] Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[410] and the



fluorinated compounds *triflates*[411] and *nonaflates*.[411] *Tresylates* are $\sim$ 400 times less reactive than triflates, but still $\sim$ 100 times more reactive than tosylates.[412] Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in superacid solutions (Sec. 5.A.ii) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[413] Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

The leaving group ability of NH_2, NHR, and NR_2 are extremely poor,[414] but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine (RNH_2) to the ditosylate ($RNTs_2$). The NTs_2 group has been successfully replaced by a number of nucleophiles.[415] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky et al.[416] In this method, the amine is converted to a pyridinium compound (**98**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **97**).[417] When the salt is heated, the counterion acts as a nucleophile. In some cases, a non-nucleophilic ion (e.g., BF_4^-), is used as the counterion for the conversion **97** $\rightarrow$ **98**, and then Y^- is added to **98**. Among the nucleophiles that have been used successfully in this reaction are I^-, Br^-, Cl^-, F^-, ^-OAc, N_3^-, NHR_2, and H^-. Ordinary NR^2 groups are good leaving groups when the substrate is a *Mannich base* (these are compounds of the form $RCOCH_2CH_2NR_2$; see Reaction **16-19**).[418] The elimination–addition mechanism applies in this case.

[409] Bentley, T.W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2531.
[410] Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127; Perst, H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 1961–2047; Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* ***1971***, *40*, 747; See Curphey, T.J. *Org. Synth.* ***VI***, 1021.
[411] See Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* ***1982***, 85; Howells, R.D.; McCown, J.D. *Chem. Rev.* ***1977***, *77*, 69, pp. 85–87.
[412] Crossland, R.K.; Wells, W.E.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4217.
[413] Olah, G.A.; Mo, Y.K. *J. Am. Chem. Soc.* ***1974***, *96*, 3560.
[414] See Baumgarten, R.J.; Curtis, V.A. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 929–997.
[415] See Müller, P.; Thi, M.P.N. *Helv. Chim. Acta* ***1980***, *63*, 2168; Curtis, V.A.; Knutson, F.J.; Baumgarten, R.J. *Tetrahedron Lett.* ***1981***, *22*, 199.
[416] See Katritzky, A.R.; Marson, C.M. *Angew. Chem. Int. Ed.* ***1984***, *23*, 420; Katritzky, A.R.; Sakizadeh, K.; Musumarra, G. *Heterocycles* ***1985***, *23*, 1765; Katritzky, A.R.; Musumarra, G. *Chem. Soc. Rev.* ***1984***, *13*, 47.
[417] See Katritzky, A.R.; Brycki, B. *J. Am. Chem. Soc.* ***1986***, *108*, 7295, and other papers in this series.
[418] For a review of *Mannich bases*, see Tramontini, M. *Synthesis* ***1973***, 703.



97 **98**

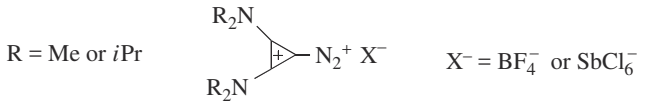
Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[419] of which the two most important are the treatment of primary amines with nitrous acid (see Reaction **13-19**)

$$RNH_2 + HONO \longrightarrow RN_2^+$$

and the protonation of diazo compounds[420]

$$R_2C{=}\overset{+}{N}{=}N^- + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are usually too unstable to be isolable,[421] reacting presumably by the S_N1 or S_N2 mechanism.[422] The simplest aliphatic diazonium ion ($CH_2N_2^+$) has been prepared at $-120\,^\circ C$ in superacid solution, where it lived long enough for an NMR spectrum to be taken.[423] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[424] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, and so on, as carbocations generated in other S_N1 reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[425] as have ion pairs, in which ^-OH (or ^-OAc, etc., depending on how the diazonium ion is generated) is the counterion.[426] One class of aliphatic diazonium salts of which several members have been isolated as stable salts are the cyclopropeniumyldiazonium salts:[427]



[419] See Kirmse, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 251; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315.

[420] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, 1978, pp. 511–591, pp. 571–575; More O'Ferrall, R.A. *Adv. Phys. Org. Chem.* ***1967***, *5*, 331; Studzinskii, O.P.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1970***, *39*, 834.

[421] For aromatic diazoium salts, see Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491); Laali, K.; Olah, G.A. *Rev. Chem. Intermed.* ***1985***, *6*, 237; Bott, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 671–697.

[422] See Mohrig, J.R.; Keegstra, K.; Maverick, A.; Roberts, R.; Wells, S. *J. Chem. Soc., Chem. Commun.* ***1974***, 780.

[423] Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3135

[424] See Manuilov, A.V.; Barkhash, V.A. *Russ. Chem. Rev.* ***1990***, *59*, 179; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 280–317.

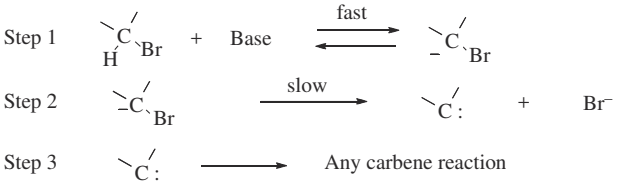
[425] Semenow, D.; Shih, C.; Young, W.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5472. See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, the articles by Keating, J.T.; Skell, P.S. pp. 573–653.

[426] Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1693; Connor, J.K.; Maskill, H. *Bull. Soc. Chim. Fr.* ***1988***, 342.

[427] Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491.

Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[428]

In the S_N1cA and S_N2cA mechanisms (see above) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions, there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see Sec. 5.D.ii). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.[429] Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.6 lists some leaving groups in approximate order of ability to leave.[430–432] The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

10.G.iv. The Effect of the Reaction Medium[433]

The effect of solvent polarity[434] on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged.[435] For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.7[436]) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same

[428] Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1957***, *79*, 2888.
[429] Pearson, R.G.; Edgington, D.N. *J. Am. Chem. Soc.* ***1962***, *84*, 4607.
[430] See Knipe, A.C. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 313–385. See also, Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* ***1984***, II-431.
[431] See McMurry, J.E. *Org. React.* ***1976***, *24*, 187.
[432] For the effect of nitro substitution, see Sinnott, M.L.; Whiting, M.C. *J. Chem. Soc. B* ***1971***, 965. See also, Page, I.D.; Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 906.
[433] See Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 186–203; Bentley, T.W.; Schleyer, P.v.R. *Adv. Phys. Org. Chem.* ***1977***, *14*, 1.
[434] Mu, L.; Drago, R.S.; Richardson, D.E. *J. Chem. Soc. Perkin Trans 2*, ***1998***, 159; Fujio, M.; Saeki, Y.; Nakamoto, K.; Kim, S.H.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 751.
[435] Bentley, T.W.; Llewellyn, G.; Ryu, Z.H. *J. Org. Chem.* ***1998***, *63*, 4654.
[436] This analysis is due to Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 457–463.

TABLE 10.6 Leaving Groups Listed in Approximate Order of Decreasing Ability to Leave.[a]

	Common leaving groups	
Substrate RX	At Saturated Carbon	At Carbonyl Carbon
RN_2^+	x	
ROR'_2^+		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	x	
$ROSO_2F$		
ROTs, etc.[b]	x	
RI	x	
RBr	x	
ROH_2^+	x (conjugate acid of alcohol)	
RCl	x	x (acyl halides)
$RORH^+$	x (conjugate acid of ether)	
$RONO_2$, etc.[b]		
RSR'_2^{+c}		
RNR'_2^+	x	
RF		
ROCOR′[d]	x	x (anhydrides)
RNH_3^+		
ROAr[e]		x (aryl esters)
ROH		x (carboxylic acids)
ROR		x (alkyl esters)
RH		
RNH_2		x (amides)
RAr		
RR		

[a]Groups that are common leaving groups at saturated and carbonyl carbons are indicated;

[b]The ROTs, and so on, includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, and so on, $RONO_2$, and so on, includes inorganic ester leaving groups, such as $ROPO(OH)_2$ and $ROB(OH)_2$.

[c]See Ref. 430.

[d]See Ref. 431.

[e]See Ref. 432.

polarity, there is a difference between protic and aprotic solvents.[437] The S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water,[438] alcohols, and carboxylic acids, while some polar aprotic solvents are DMF, DMSO,[439] acetonitrile, acetone, sulfur dioxide, and HMPA $[(Me_2N)_3PO]$.[440] An algorithm has been developed to accurately

[437] See Ponomareva, E.A.; Dvorko, G.F.; Kulik, N.I.; Evtushenko, N.Yu. *Doklad. Chem.* ***1983***, *272*, 291.

[438] See Bug, T.; Mayr, H. *J. Am. Chem. Soc.* ***2003***, *125*, 12980; Brinchi, L.; DiProfio, P.; Germani, R.; Savelli, G.; Spreti, N.; Bunton, L.A. *Eur. J. Org. Chem.* ***2000***, 3849.

[439] See Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* ***1977***, *14*, 133; Martin, D.; Weise, A.; Niclas, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 318.

[440] See Normant, H. *Russ. Chem. Rev.* ***1970***, *39*, 457; *Angew. Chem. Int. Ed.* ***1967***, *6*, 1046.

TABLE 10.7 Transition States for S_N1 Reactions of Charged and Uncharged Substrates, and for S_N2 Reactions of the Four Charge Types[a]

Reactants and Transition States		Charge in the Transition State Relative to Starting Materials	How an Increase in Solvent Polarity Affects the Rate
Type I	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta-}$	Dispersed	Small decrease
Type II	$RX + Y^- \rightarrow Y^{\delta+} \cdots R \cdots X^{\delta-}$	Increased	Large increase
S_N2			
Type III	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta+}$	Decreased	Large decrease
Type IV	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta+}$	Dispersed	Small decrease
	$RX \rightarrow R^{\delta+} \cdots X^{\delta-}$	Increased	Large increase
S_N1			
	$RX^- \rightarrow R^{\delta-} \cdots X^{\delta-}$	Dispersed	Small decrease

Adapted material from *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 457–463., edited by Ingold, C.K. Copyright © 1969 by Cornell University. Used by permission of the publisher, Cornell University Press.

[a]See Ref. 436.

calculate dielectric screening effects in solvents.[441] The S_N2 reactions have been done in ionic liquids (see Sec. 9.D.iii)[442] and in supercritical carbon dioxide (see Sec. 9.D.ii).[443]

For S_N2 reactions, the effect of the solvent[444] depends on which of the four charge types the reaction belongs to (preceding Sec. 10.A). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III, initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.7.[436] Westaway[445] proposed a "solvation rule" for S_N2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions. The difference between protic and aprotic solvents must be considered for S_N2 reactions as well.[446] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,[447] while (as seen in Sec. 10.G.ii) the original charged nucleophile is less solvated in aprotic solvents[448] (the second factor is generally much greater than the first[449]). So the change from, say, methanol to DMSO should greatly increase the rate. As an example, the relative rates at 25 °C for the reaction between MeI and Cl^- were in MeOH, 1;[351] in $HCONH_2$ (still protic although a weaker acid), 12.5; in HCONHMe, 45.3; and $HCONMe_2$, 1.2×10^6. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the

[441] Klamt, A.; Schüürmann, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 799.
[442] Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2003***, *68*, 4281; Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* ***2003***, *68*, 6710.
[443] DeSimone, J.; Selva, M.; Tundo, P. *J. Org. Chem.* ***2001***, *66*, 4047.
[444] See Craig, S.L.; Brauman, J.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6690.
[445] Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1989***, *67*, 345.
[446] For reviews of the effects of protic and aprotic solvents, see Parker, A.J. *Chem. Rev.* ***1969***, *69*, 1; Madaule-Aubry, F. *Bull. Soc. Chim. Fr.* ***1966***, 1456.
[447] See Magnera, T.F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 6140.
[448] See, for example, Fuchs, R.; Cole, L.L. *J. Am. Chem. Soc.* ***1973***, *95*, 3194.
[449] See, however, Haberfield, P.; Clayman, L.; Cooper, J.S. *J. Am. Chem. Soc.* ***1969***, *91*, 787.

TABLE 10.8 Relative Rates of Ionization of *p*-Methoxyneophyl Toluenesulfonate in Various Solvents[a]

Solvent	Relative Rate	Solvent	Relative Rate
HCOOH	153	Ac_2O	0.020
H_2O	39	Pyridine	0.013
80% EtOH—H_2O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	THF	5.0×10^{-4}
EtOH	0.370	Et_2O	3×10^{-5}
Me_2SO	0.108	$CHCl_3$	Lower still
Octanoic acid	0.043	Benzene	Lower still
MeCN	0.036	Alkanes	Lower still
$HCONMe_2$	0.029		

Reprinted with permission Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618. Copyright © 1961 American Chemical Society.

[a]See Ref. 450.

attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 431 have lists of several dozen reactions of charge types I and III in which yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.8 is a list of solvents in order of ionizing power;[450] a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith et al.,[450] has greater ionizing power[451] than any solvent listed in Table 10.8. Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol (CF_3CH_2OH), and 1,1,1,3,3,3-hexafluoro-2-propanol [$(F_3C)_2CHOH$].[452]

Previously, the influence of the polarity of the solvent on the rates of S_N1 and S_N2 reactions was discussed. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative; different salts have different effects.[453] However, there are exceptions: Although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect)*, addition of the leaving-group ion often decreases the rate (the common-ion effect, Sec. 10.A.ii). There is also the special salt effect of $LiClO_4$, mentioned on Section 10.A.iii, category 2. In addition

[450] Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618.
[451] Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***; Haywood–Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.
[452] Schadt, F.L.; Schleyer, P.v.R.; Bentley, T.W. *Tetrahedron Lett.* ***1974***, 2335.
[453] See Bunton, C.A.; Robinson, L. *J. Am. Chem. Soc.* ***1968***, *90*, 5965.

to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.[454] Especially important are Ag^+, Hg^{2+}, and Hg_2^{2+}, but H^+ helps to pull off F (hydrogen bonding).[455] Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.[456] This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the S_N1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.[457]

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free energy relationship[458]

$$\log(k, k_0) = m\ Y$$

where m is characteristic of the substrate (defined as 1.00 for *t*-BuCl) and is usually near unity, Y is characteristic of the solvent and measures its "ionizing power", and $k_\circ$ is the rate in a standard solvent, 80% aq ethanol at 25 °C. This is known as the *Grunwald–Winstein equation*, and its utility is at best limited. The Y values can of course be measured for solvent *mixtures* as well. This is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.[459] The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons, the treatment is not so good quantitatively, although the Y values do give a reasonably good idea of solvolyzing power.[460] Table 10.9 contains a list of some Y values.[461]

Ideally, Y should measure only the ionizing power of the solvent, and should not reflect any backside attack by a solvent molecule in helping the nucleofuge to leave (nucleophilic assistance; k_s, Sec. 10.C.i, category 3). Actually, there is evidence that many solvents do

[454] See Kevill, D.N. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 933–984.

[455] See Rudakov, E.S.; Kozhevnikov, I.V.; Zamashchikov, V.V. *Russ. Chem. Rev.* ***1974***, *43*, 305. For an example of assistance in removal of F by H^+, see Coverdale, A.K.; Kohnstam, G. *J. Chem. Soc.* ***1960***, 3906.

[456] Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 424. See, however, Kevill, D.N.; Fujimoto, E.K. *J. Chem. Soc., Chem. Commun.* ***1983***, 1149.

[457] Kornblum, N.; Jones, W.J.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1704; Kornblum, N.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1707.

[458] Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846.

[459] See Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***, pp. 339–405; Langhals, H. *Angew. Chem. Int. Ed.* ***1982***, *21*, 724.

[460] For a criticism of the Y scale, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1097.

[461] Y values are from Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1956***, *78*, 2770, except for the value for CF_3CH_2OH which is from Shiner, Jr., V.J.; Dowd, W.; Fisher, R.D.; Hartshorn, S.R.; Kessick, M.A.; Milakofsky, L.; Rapp, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 4838. Y_{OTs} values are from Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, pp. 143–144. Z values are from Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780. $E_T(30)$ values are from Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Laurence, C.; Nicolet, P.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 125; Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 1001; Reichardt, C.; Eschner, M.; Schäfer, G. *Liebigs Ann. Chem.* ***1990***, 57. Also see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***.

TABLE 10.9 The Y, Y_{OTs}, Z, and E_T (30) Values for Some Solvents[a]

Solvent	Y	Y_{OTs}	Z	E_T (30)
CF_3CO_2H		4.57		
H_2O	3.5	4.1	94.6	63.1
$(CF_3)_2CHOH$		3.82		65.3
HCO_2H	2.1	3.04		
H_2O—EtOH (1:1)	1.7	1.29	90	55.6
CF_3CH_2OH	1.0	1.77		59.8
$HCONH_2$	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	−1.1	−0.92	83.6	55.4
AcOH	−1.6	−0.9	79.2	51.7
EtOH	−2.0	−1.96	79.6	51.9
90% dioxane	−2.0	−2.41	76.7	46.7
*i*PrOH	−2.7	−2.83	76.3	48.4
95% Acetone	−2.8	−2.95	72.9	48.3
t-BuOH	−3.3	−3.74	71.3	43.9
MeCN		−3.21	71.3	45.6
Me_2SO			71.1	45.1
$HCONMe_2$		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH_2Cl_2				40.7
Pyridine			64.0	40.5
$CHCl_3$			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et_2O				34.5
C_6H_6			54	34.3
PhMe				33.9
CCl_4				32.4
n-Octane				31.1
n-Hexane				31.0
Cyclohexane				30.9

Reprinted with permission Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1956***, *78*, 2770. Copyright © 1956 American Chemical Society.

[a]See Ref. 461.

lend some nucleophilic assistance,[462] even with tertiary substrates.[463] It was proposed that a better measure of solvent "ionizing power" would be a relationship based on 2-adamantyl substrates, rather than *t*-BuCl, since the structure of this system completely prevents backside nucleophilic assistance (Sec. 10.G.i). Such a scale, called Y_{OTs}, was developed,

[462] A scale of solvent nucleophilicity (as opposed to ionizing power), called the N_T scale, has been developed: Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1991***, *56*, 1845.

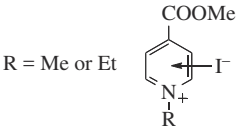
[463] See Kevill, D.N.; Anderson, S.W. *J. Am. Chem. Soc.* ***1986***, *108*, 1579; McManus, S.P.; Neamati-Mazreah, N.; Karaman, R.; Harris, J.M. *J. Org. Chem.* ***1986***, *51*, 4876; Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J. M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 913.

with m defined as 1.00 for 2-adamantyl tosylate.[464] Some values of Y_{OTs} are given in Table 10.9. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power[465]) are called Y_{OTs} because they apply only to tosylates. It has been found that solvent "ionizing power" depends on the leaving group, so separate scales[466] have been set up for OTf,[467] Cl,[433] Br,[468] I,[469] and other nucleofuges,[470] all based on the corresponding adamantyl compounds. A new Y scale has been established based on benzylic bromides.[471] In part, this was done because benzylic tosylates did not give a linear correlation with the 2-adamantyl Y_{OTs} parameter.[472] This is substrate dependent, since solvolysis of 2,2-dimethyl-1-phenyl-1-propanol tosylate showed no nucleophilic solvent participation.[473]

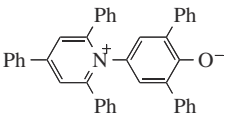
In order to include a wider range of solvents than those in which any of the Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.[474] Kosower et al.[475] found that the position of the charge-transfer peak (see Sec. 3.C.i) in the UV spectrum of the complex (**99**) between iodide ion and 1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.[475] From these peaks, which are very easy to measure, Kosower et al.[475] calculated transition energies that he called Z values. These values are thus measures of solvent polarity analogous to Y values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine (**100**) in various solvents.[476] Solvent polarity values on this scale are called $E_T(30)$[477] values. The $E_T(30)$ values are related to Z values by the expression[478]

$$Z = 1.41\ E_T(30) + 6.92$$

[464] Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.
[465] Bentley, T.W.; Carter, G.E. *J. Org. Chem.* ***1983***, *48*, 579.
[466] For a review of these scales, see Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121.
[467] Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1985***, *50*, 3330. See also, Creary, X.; McDonald, S.R. *J. Org. Chem.* ***1985***, *50*, 474.
[468] Bentley, T.W.; Carter, G.E. *J. Am. Chem. Soc.* ***1982***, *104*, 5741. See also, Liu, K.; Sheu, H. *J. Org. Chem.* ***1991***, *56*, 3021.
[469] Bentley, T.W.; Carter, G.E.; Roberts, K. *J. Org. Chem.* ***1984***, *49*, 5183.
[470] See Kevill, D.N.; Hawkinson, D.C. *J. Org. Chem.* ***1990***, *55*, 5394 and references cited therein.
[471] Fujio, M.; Saeki, Y.; Nakamoto, K.; Yatsugi, K.-i.; Goto, N.; Kim, S.H.; Tsuji, Y.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2603; Liu, K.-T.; Chin, C.-P.; Lin, Y.-S.; Tsao, M.-L. *J. Chem. Res. (S)* ***1997***, 18.
[472] Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Saeki, Y.; Kim, S.H.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 2233.
[473] Tsuji, Y.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *33*, 349.
[474] See Abraham, M.H.; Grellier, P.L.; Abboud, J.M.; Doherty, R.M.; Taft, R.W. *Can. J. Chem.* ***1988***, *66*, 2673; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, pp. 127–172; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Abraham, M.H. *Prog. Phys. Org. Chem.* ***1974***, *11*, 1. See also, Chastrette, M.; Rajzmann, M.; Chanon, M.; Purcell, K.F. *J. Am. Chem. Soc.* ***1985***, *107*, 1.
[475] Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A. G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780.
[476] Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. See also, Haak, J.R.; Engberts, J.B.F.N. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 307.
[477] The symbol E_T comes from *energy*, *transition*. The (30) is used because the ion **100** bore this number in Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. Values based on other ions have also been reported: See, for example, Reichardt, C.; Harbusch-Görnert, E.; Schäfer, G. *Liebigs Ann. Chem.* ***1988***, 839.
[478] Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, p. 32.



99



100

Table 10.9 shows that Z and $E_T(30)$ values are generally in the same order as Y values. Other scales, the π^* scale,[479] the π^*_{azo} scale,[480] and the Py scale,[481] are also based on spectral data.[482]

Carbon dioxide can be liquefied under high pressure (supercritical CO_2). Several reactions have been done using supercritical CO_2 as the medium (Sec. 9.D.ii), but special apparatus is required. This medium offers many advantages,[483] and some disadvantages, but is an interesting new area of research.

The effect of solvent on nucleophilicity has already been discussed (Sec. 10.G.ii).

10.G.v. Phase-Transfer Catalysis

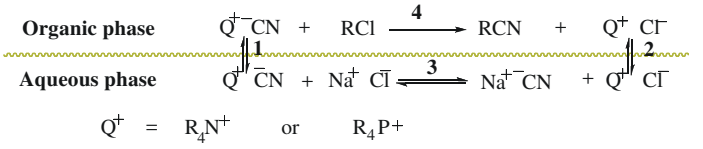
A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place, the reacting molecules must collide. In nucleophilic substitutions, the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water, but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this difficulty is to use a solvent that will dissolve both species. As seen in Section 10.G.iv, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase-transfer catalysis*.[484]

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aqs NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product is quantitatively formed in ~ 2 h.[485] There are two principal types of phase-transfer catalyst, although the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

1. *Quaternary Ammonium or Phosphonium Salts*. In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the $^-$CN ions

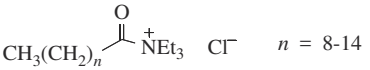
[479] Doherty, R.M.; Abraham, M.H.; Harris, J.M.; Taft, R.W.; Kamlet, M.J. *J. Org. Chem.* ***1986***, *51*, 4872. See also, Bekárek, V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1425; Abe, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2328.
[480] Buncel, E.; Rajagopal, S. *J. Org. Chem.* ***1989***, *54*, 798.
[481] Dong, D.C.; Winnik, M.A. *Can. J. Chem.* ***1984***, *62*, 2560.
[482] For a review of such scales, see Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* ***1990***, *23*, 226.
[483] Kaupp, G. *Angew. Chem. Int. Ed.* **1994**, 33, 1452.
[484] Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 2nd ed., Verlag Chemie, Deerfield Beach, FL, ***1983***; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977*** ; Makosza, M. *Pure Appl. Chem.* ***2000***, *72*, 1399; Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* ***1982***, *101*, 147; Alper, H. *Adv. Organomet. Chem.* ***1981***, *19*, 183; Sjöberg, K. *Aldrichimica Acta* ***1980***, *13*, 55.
[485] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, p. 2.

cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na^+ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The CN^- ions cannot cross without the Na^+ ions because that would destroy the electrical neutrality of each phase. In contrast to Na^+ ions, quaternary ammonium (R_4N^+)[486] and phosphonium (R_4P^+) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na^+ ions remain in the aqueous phase; they cannot cross. The Q^+ ions do cross the interface and carry an anion with them. At the beginning of the reaction, the chief anion present is ^-CN. This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl^-. The Cl^- then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows $Q^+{}^-CN$ to be regenerated. All the equilibria are normally reached much faster than the actual conversion of RCl to RCN, so the latter is the rate-determining step.

In some cases, the Q^+ ions have such a low solubility in water that virtually all remain in the organic phase.[487] In such cases, the exchange of ions (equilibrium 3) takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where ^-OH extracts a proton from an organic substrate.[488] In this mechanism, the ^-OH ions remain in the aqueous phase and the substrate in the organic phase; the deprotonation takes place at the interface.[489] Thermal stability of the quaternary ammonium salt is a problem, limiting the use of some catalysts. The trialkylacyl ammonium halide (**101**) is thermally stable, however, even at high reaction temperatures.[490] The use of molten quaternary ammonium salts as ionic reaction media for substitution reactions has also been reported.[491]

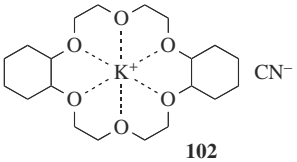


101

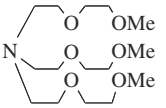
2. *Crown Ethers and Other Cryptands*.[492] As seen in Section 3.C.ii, certain cryptands are able to surround certain cations. In effect, a salt like KCN is converted by

[486] See Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* ***1989***, *30*, 1683.
[487] Landini, D.; Maia, A.; Montanari, F.*J. Am. Chem. Soc.* ***1978***, *100*, 2796.
[488] For a review, see Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* ***1986***, *25*, 960.
[489] See Makosza, M. *Pure Appl. Chem.* ***1975***, *43*, 439. See also, Dehmlow, E.V.; Thieser, R.; Sasson, Y.; Pross, E. *Tetrahedron* ***1985***, *41*, 2927; Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* ***1990***, *55*, 2714.
[490] Bhalerao, U.T.; Mathur, S.N.; Rao, S.N. *Synth. Commun.* ***1992***, *22*, 1645.
[491] Badri, M.; Brunet, J.-J.; Perron R. *Tetrahedron Lett.* ***1992***, *33*, 4435.
[492] See Liotta, C. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 157–174.

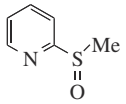
dicyclohexano-18-crown-6 into a new salt (**102**) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a large volume, and hence much less concentrated. This larger cation is much less solubilized by water than K^+ and much more attracted to organic solvents. Although KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases, we do not need an aqueous phase at all but simply add the salt to the organic phase. Suitable cryptands have been used to increase the rates of reactions where F^-, Br^-, I^-, ^-OAc, and ^-CN are nucleophiles.[493] Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**103**), also called TDA-1.[494] Another, not related to the crown ethers, is the pyridyl sulfoxide (**104**).[495]



102



103



104

Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to react with the substrate (Sec. 10.G.ii, category 4). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as "naked" anions.

Not all quaternary salts and cryptands work equally well in all situations. Some experimentation is often required to find the optimum catalyst.

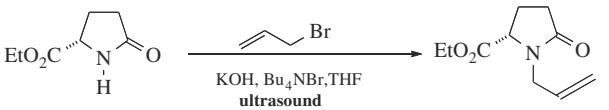
Although phase-transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase-transfer catalyst. Some examples will be seen in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,[496] radicals, and molecules.[497] The reverse type of phase-transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.[498] Microwave activated phase-transfer catalysis has been reported.[499]

[493] See Liotta, C.; Harris, H.P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* ***1974***, 2417; Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1974***, *96*, 2252; Durst, H.D. *Tetrahedron Lett.* ***1974***, 2421.
[494] Soula, G. *J. Org. Chem.* **1985**, 50, 3717.
[495] Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1833. See also, Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 333.
[496] See Iwamoto, H.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 796.
[497] See, for example, Dehmlow, E.V.; Slopianka, M. *Chem. Ber.* ***1979***, *112*, 2765.
[498] Fife, W.K.; Xin, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 1278.
[499] Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* ***1999***, *55*, 10851.

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina[500] and silica gel, have been used as insoluble phase-transfer catalysts. These, called *triphase catalysts*,[501] have the advantage of simplified product work up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

10.G.vi. Influencing Reactivity by External Means

In many cases, reactions are slow. This is sometimes due to poor mixing or the aggregation state of one or more reactants. A powerful technique used to increase reaction rates is *ultrasound* (see Sec. 7.B). In this technique, the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.[502] In an instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. The reaction of pyrrolidinone (**105**) with allyl bromide, under phase-transfer conditions, gave < 10% of the *N*-allyl product, (**106**). When the reaction was done under identical conditions, but with exposure to ultrasound (in an ultrasonic bath), the yield of **106** was 78%.[503] It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free radical intermediates.[504]



105 **106**

As noted in Chapter 7 (see Sec. 7.C), microwave irradiation is used extensively. Reaction times are greatly accelerated in many reactions, and reactions that took hours to be complete in refluxing solvents are done in minutes. Benzyl alcohol was converted to benzyl bromide, for example, using microwave irradiation (650 W) in only 9 min on a doped K-10 Montmorillonite clay.[505] This technique is growing and very useful.

[500] Quici, S.; Regen, S.L. *J. Org. Chem.* ***1979***, *44*, 3436.
[501] See Regen, S.L. *Nouv. J. Chim.* ***1982***, *6*, 629; *Angew. Chem. Int. Ed.* ***1979***, *18*, 421. See also, Bogatskii, A.V.; Luk'yanenko, N.G.; Pastushok, V.N.; Parfenova, M.N. *Doklad. Chem.* ***1985***, *283*, 210; Pugia, M.J.; Czech, B.P.; Czech, B.P.; Bartsch, R.A. *J. Org. Chem.* ***1986***, *51*, 2945.
[502] See Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Giguere, R.J. *Org. Synth. Theory Appl.* ***1989***, *1*, 103.
[503] Keusenkothen, P.F.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3369.
[504] See Einhorn, C.; Einhorn, J.; Dickens, M.J.; Luche, J. *Tetrahedron Lett.* ***1990***, *31*, 4129.
[505] Kad, G.-L.; Singh, V.; Kuar, K.P.; Singh, J. *Tetrahedron Lett.* ***1997***, *38*, 1079.

The rate of many reactions can be increased by application of high pressure.[506] In solution, the rate of a reaction can be expressed in terms of the activation volume $(\Delta V)^{\ddagger}$.[507]

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

The value of $\Delta V^{\ddagger}$ is the difference in partial molal volume between the transition state and the initial state, but it can be approximated by the molar volume.[507] Increasing pressure decreases the value of $\Delta V^{\ddagger}$ and $\Delta V^{\ddagger}$ is negative as the reaction rate is accelerated. This equation is not strictly obeyed > 10 kbar. If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, neutralization of the transition state, and diffusion control lead to a positive volume of activation. Reactions for which rate enhancement is expected at high pressure include[507]:

1. Reactions in which the number of molecules decreases when starting materials are converted to products: cycloadditions [e.g., *the Diels–Alde*r (Reaction **15-60**)] and condensations, [e.g., the *Knoevenagel condensation* (**16-38**)].
2. Reactions that proceed via cyclic transition states: *Claisen* (Reaction **18-33**) and *Cope* (Reaction **18-32**) rearrangements.
3. Reactions that take place through dipolar transition states: *Menshutkin reaction* (Reaction **10-31**), electrophilic aromatic substitution.
4. Reactions with steric hindrance.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, which influences the viscosity of the medium (viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important.[508] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place.

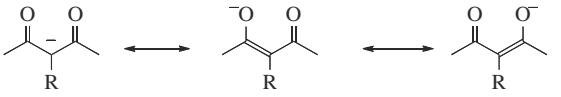
10.G.vii. Ambident (Bidentant) Nucleophiles: Regioselectivity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases, the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.[509] In most cases, a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, although this is not always the case. For example, the

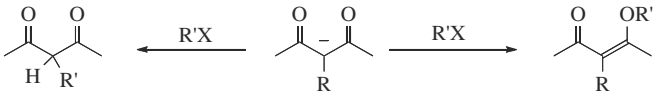
[506] Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, NY, ***1991***; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1, 999.
[507] Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.
[508] Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981***, *46*, 2160.
[509] See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***. For a review, see Black, T.H. *Org. Prep. Proced. Int.* ***1989***, *21*, 179.

nucleophile (NCO^-) usually gives only isocyanates (RNCO) and not the isomeric cyanates (ROCN).[510] When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO), but actually produces only one, the reaction is said to be *regioselective*[511] (cf. the definitions of stereoselective, Sec. 4.N and enantioselective, Sec. 4.H., category 2). Some important ambident nucleophiles follow:

1. *Ions of the Type* —CO—$^-$CR—CO—. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, and so on, are resonance hybrids:



Attack is therefore possible at a saturated carbon via the carbon atoms (*C*-alkylation) or the oxygen atoms (*O*-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo *C*- or *O*-acylation.

2. *Compounds of the Type* $CH_3CH—CH_2—CO—$. *Can Give Up Two Protons*, if treated with 2 molar equivalents of a strong enough base, to give dicarbanions:

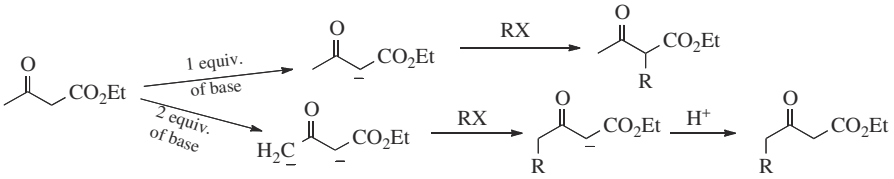
$$CH_3—CO—CH_2—CO— \xrightarrow{2 \text{ equiv } \textit{of base}} {}^- CH_2—CO—\bar{C}H—CO—$$

107

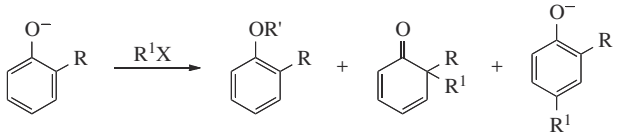
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.[512] Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chap 8), the CH group of **107** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: Whenever the goal is to remove a proton at a given position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if the goal is to attack with the more acidic position, all that is necessary is to remove just one proton.[513] For example, ethyl acetoacetate can be

[510] See Holm, A.; Wentrup, C. *Acta Chem. Scand.* ***1966***, *20*, 2123.
[511] This term was introduced by Hassner, A. *J. Org. Chem.* ***1968***, *33*, 2684.
[512] For an exception, see Trimitsis, G.B.; Hinkley, J.M.; TenBrink, R.; Faburada, A.L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G.; Erdman, J.; Rop, D. *J. Org. Chem.* ***1983***, *48*, 2957.
[513] See Hauser, C.R.; Harris, C.M. *J. Am. Chem. Soc.* ***1958***, *80*, 6360. For reviews, see Thompson, C.M.; Green, D. L.C. *Tetrahedron* ***1991***, *47*, 4223; Harris, T.M.; Harris, C.M. *Org. React.* ***1969***, *17*, 155.

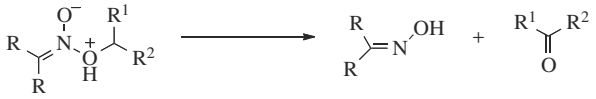
alkylated at either the methyl or the methylene group (Reaction **10-67**):



3. *The CN^- Ion*. This nucleophile can give nitriles (RCN, Reaction **10-75**) or isocyanides (RN≡C).
4. *The Nitrite Ion*. This ion can give nitrite esters R—O—N=O (Reaction **10-22**) or nitro compounds RNO_2 (Reaction **10-76**), which are not esters.
5. *Phenoxide ions*. These ions, (which are analogous to enolate anions) can undergo *C*- or *O*-alkylation:



6. *Removal of a Proton from an Aliphatic Nitro Compound*. This reaction gives a carbanion ($R_2C^-—NO_2$) that can be alkylated at oxygen or carbon.[514] *O*-Alkylation gives a nitronic ester, and such compounds are generally unstable to heat and break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.[515] Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (Sec. 6.F), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., C > N > O > S).[516] However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (Sec. 10.G.ii), there are two major factors: the polarizability (hard–soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (Sec. 8.E.i). In an S_N1 mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile

[514] For a review, see Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 719.
[515] See Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737; Reutov, O.A.; Kurts, A.L. *Russ. Chem. Rev.* ***1977***, *46*, 1040; Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 321.
[516] See Bégué, J.; Charpentier-Morize, M.; Née, G. *J. Chem. Soc., Chem. Commun.* ***1989***, 83.

attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. Therefore, as the character of a given reaction changes from S_N1 to S_N2 like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[517] Thus, changing from S_N1 to S_N2 conditions should favor C attack by ^-CN, N attack by NO_2^-, C attack by enolate or phenoxide ions, and so on. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of $CH_3COCH_2CO_2Et$, while α-chloro ethers, which react by the S_N1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all S_N2 reactions and by the more electronegative atom in all S_N1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the S_N2 character of the transition state makes attack by the less electronegative atom more likely.

2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, Sec. 10.G.iv), rather than the more usual Na^+ or K^+, then the transition state is more S_N1 like. Therefore the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN generally give mostly RCN, but the use of AgCN increases the yield of isocyanides (RNC).[518]
3. In many cases, the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely it is to attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β-naphthoxide on benzyl bromide, which resulted in 95% O-alkylation in DMSO and 85% C-alkylation in 2,2,2-trifluoroethanol.[519] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors O- over C-alkylation[520] for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (Sec. 3.C.ii).[521] Alkylation of the enolate anion of cyclohexanone in the gas phase,

[517] This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, N.; Smiley, R.A.; Blackwood, R.K.; Iffland, D.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6269.

[518] See Austad, T.; Songstad, J.; Stangeland, L.J. *Acta Chem. Scand.* ***1971***, *25*, 2327; Carretero, J.C.; García Ruano, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3381.

[519] Kornblum, N.; Berrigan, P.J.; le Noble, W.J. *J. Chem. Soc.* ***1963***, *85*, 1141; Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148. For other examples, see le Noble, W.J.; Puerta, J.E. *Tetrahedron Lett.* ***1966***, 1087; Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* ***1982***, *38*, 1279.

[520] Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148; Kurts, A.L.; Beletskaya, I.P.; Masias, A.; Reutov, O.A. *Tetrahedron Lett.* ***1968***, 3679. See, however, Sarthou, P.; Bram, G.; Guibe, F. *Can. J. Chem.* ***1980***, *58*, 786.

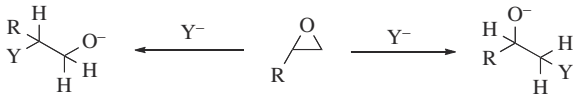
[521] Smith, S.G.; Hanson, M.P. *J. Org. Chem.* ***1971***, *36*, 1931; Akabori, S.; Tuji, H. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 1197. See also, le Noble, W.J.; Palit, S.K. *Tetrahedron Lett.* ***1972***, 493.

where the nucleophile is completely free, showed only O-alkylation and no C-alkylation.[522]

4. In extreme cases, steric effects can govern the regioselectivity.[523]

10.G.viii. Ambident Substrates

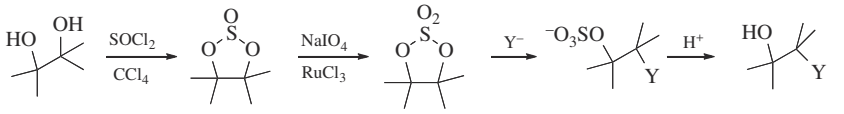
Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions, and these may be called *ambident substrates*. In the example given, there happen to be two leaving groups in the molecule. Apart from dichlorobutane, and in general, there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (Sec. 10.E). The other is the epoxy (or the similar aziridine[524] or episulfide) substrate.[525] Selectivity for one or the other position is usually called regioselectivity.



Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, attack may be expected be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by what is expected to be an S_N2 mechanism, attack is usually at the more highly substituted position.[526] This result probably indicates significant carbocation character at the carbon (ion pairing, for example). Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of $Ti(OiPr)_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.[527] When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.[528]

[522] Jones, M.E.; Kass, S.R.; Filley, J.; Barkley, R.M.; Ellison, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 109.
[523] See, for example O'Neill, P.; Hegarty, A.F. *J. Org. Chem.* ***1987***, *52*, 2113.
[524] Chechik, V.O.; Bobylev, V.A. *Acta Chem. Scand. B*, ***1994***, *48*, 837.
[525] Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* ***1983***, *39*, 2323; Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* ***1983***, *16*, 67; Enikolopiyan, N.S. *Pure Appl. Chem.* ***1976***, *48*, 317; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 206–273.
[526] Biggs, J.; Chapman, N.B.; Finch, A.F.; Wray, V. *J. Chem. Soc. B* ***1971***, 55.
[527] Caron M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1557. See also, Chong, J.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1560; Behrens, C.H.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 5696.
[528] Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. *J. Am. Chem. Soc.* ***1969***, *91*, 2649. For a method of overriding this preference, see McKittrick, B.A.; Ganem, B. *J. Org. Chem.* ***1985***, *50*, 5897.

Cyclic sulfates (**108**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly:[529]



108

10.H. REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group. For the most part, only alkyl substrates are considered, since acyl substrates are considered in Chapter 16. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases, the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases, conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

10.H.i. Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

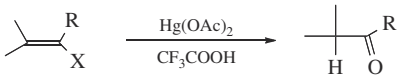
10-1 Hydrolysis of Alkyl Halides

Hydroxy-de-halogenation

$$RX + H_2O \longrightarrow ROH_2^+ \xrightarrow{-H^+} ROH + H^+$$
$$RX + OH^- \longrightarrow ROH$$

Alkyl halides can be converted to alcohols. Hydroxide ion is usually required, although particularly active substrates (e.g., allylic or benzylic alcohols) can be hydrolyzed by water. Ordinary halides can be hydrolyzed by water,[530] if the solvent is HMPA or *N*-methyl-2-pyrrolidinone,[531] or if the reaction is done in an ionic solvent.[532] If the hydrolysis (solvolysis) reaction proceeds via ionization, by an S_N1 type mechanism, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. Tertiary alkyl α-halocarbonyl compounds can be converted to the corresponding alcohol with silver oxide in aq acetonitrile.[533] The reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

[529] Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7538; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 655.
[530] See, however, Kurz, J.L.; Lee, J.; Love, M.E.; Rhodes, S. *J. Am. Chem. Soc.* ***1986***, *108*, 2960.
[531] Hutchins, R.O.; Taffer, I.M. *J. Org. Chem.* ***1983***, *48*, 1360.
[532] Kim, D.W.; Hong, D.J.; Seo, J.W.; Kim, H.S.; Kim, H.K.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69,* 3186.
[533] Cavicchioni, G. *Synth. Commun.* ***1994***, *24*, 2223.

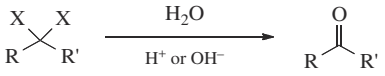


Vinylic halides are unreactive (Sec. 10.F), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either trifluoroacetic acid or acetic acid containing BF_3 etherate.[534] Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide ($Bu_3Sn—O—SnBu_3$) in the presence of silver salts.[535]

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

10-2 Hydrolysis of gem-Dihalides

Oxo-de-dihalo-bisubstitution



gem-Dihalides can be hydrolyzed using either acid or basic catalysis to give aldehydes or ketones.[536] Formally, the reaction may be regarded as giving R—C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. For aldehydes derived from $RCHX_2$, strong bases cannot be used, because the product undergoes the *aldol reaction* (**16-34**) or the *Cannizzaro reaction* (**19-81**). A mixture of calcium carbonate and sodium acetate is effective,[537] and heating to 100 °C in DMSO gives good yields.[538] A simple method heats a *gem*-dibromide with pyridine, and subsequent treatment with water gives the aldehyde.[539] Heating 1,1-dihaloalkenes ($C=CX_2$) with zinc and water leads to the corresponding methyl ketone.[540]

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see, OS **III**, 737.

10-3 Hydrolysis of 1,1,1-Trihalides

Hydroxy,oxo-de-trihalo-tersubstitution

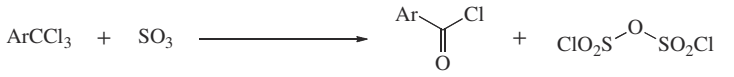
$$RCX_3 + H_2O \longrightarrow RCO_2H$$

This reaction is similar to **10-2**. The utility of the method is limited by the lack of availability of trihalides, although these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (Reaction **15-38**) and by the free radical halogenation of methyl groups on aromatic rings (Reaction **14-1**). When the reaction is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.[541] 1,1-Dichloroalkenes

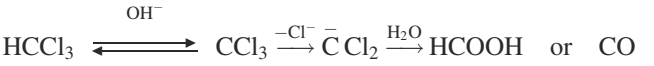
[534] Martin, S.F.; Chou, T. *Tetrahedron Lett.* ***1978***, 1943; Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* ***1979***, 3489.
[535] Gingras, M.; Chan, T.H. *Tetrahedron Lett.* ***1989***, *30*, 279.
[536] Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 177–210.
[537] Mataka, S.; Liu, G.-B.; Sawada, T.; Tori-i, A.; Tashiro, M. *J. Chem. Res. (S)* ***1995***, 410.
[538] Li, W.; Li, J.; DeVincentis, D.; Masour, T.S. *Tetrahedron Lett.* ***2004***, *45*, 1071.
[539] Augustine, J.K.; Naik, Y.A.; Mandal, A.B.; Chowdappa, N.; Praveen, V.B. *Tetrahedron* ***2008***, *64,* 688.
[540] Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* ***2003***, *44*, 4685.
[541] See, for example, Le Fave, G.M.; Scheurer, P.G. *J. Am. Chem. Soc.* ***1950***, *72*, 2464.

can also be hydrolyzed to carboxylic acids, by treatment with aq H_2SO_4. In general 1,1,1-trifluorides do not undergo this reaction,[542] although exceptions are known.[543]

Aryl 1,1,1-trihalomethanes can be converted to acyl halides by treatment with sulfur trioxide.[544] Hydrolysis of the acid chloride gives the carboxylic acid (Reaction **16-57**).



Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid, but also carbon monoxide.[545] Hine[546] showed that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, although superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^-, which then loses Cl^- to give dichlorocarbene (CCl_2), which is hydrolyzed to formic acid or carbon monoxide.

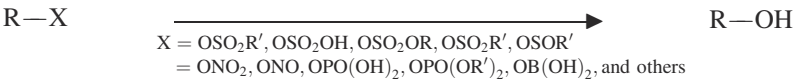


This is an example of an S_N1cB mechanism (Sec. 10.G.iii, category 1). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

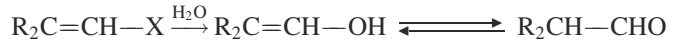
OS **III**, 270; **V**, 93. Also see, OS **I**, 327.

10-4 Hydrolysis of Alkyl Esters of Inorganic Acids

Hydroxy-de-sulfonyloxy-substitution, and so on



Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). When vinylic substrates are hydrolyzed, the products are enols, which tautomerize to aldehydes or ketones (Sec. 2.N), as shown.



These reactions are all considered at one place because they are formally similar. Although some of them involve R—O cleavage and are thus nucleophilic substitutions at

[542] Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 410–411; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 273–274.

[543] See, for example, Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* ***1978***, *11*, 197.

[544] Rondestvedt, Jr., C.S. *J. Org. Chem.* ***1976***, *41*, 3569, 3574, 3576. For another method, see Nakano, T.; Ohkawa, K.; Matsumoto, H.; Nagai, Y. *J. Chem. Soc., Chem. Commun.* ***1977***, 808.

[545] See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 129–141.

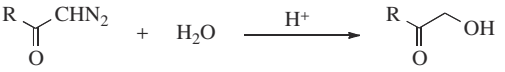
[546] Hine, J. *J. Am. Chem. Soc.* ***1950***, *72*, 2438. Also see, le Noble, W.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2434.

a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, and so on. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[547] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters ($ROSO_2R'$) generally give C—O cleavage,[548] while nitrous acid esters (RONO) usually give N—O cleavage.[549] Esters of sulfonic acids that are frequently hydrolyzed are mentioned in Section 10.G.iii. For hydrolysis of sulfonic acid esters (see also, Reaction **16-100**).

OS **VI**, 852. See also, **VIII**, 50.

10-5 Hydrolysis of Diazoketones

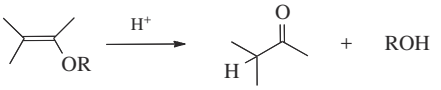
Hydro, hydroxy-de-diazo-bisubstitution



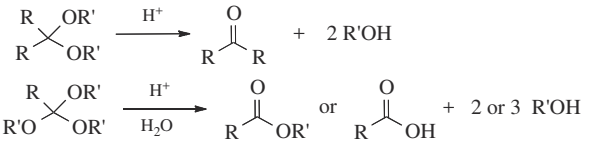
Diazoketones are relatively easy to prepare (see Reaction **16-89**). When treated with acid, they add a proton to give α-keto diazonium salts, which are hydrolyzed to the alcohols by the S_N1 or S_N2 mechanism.[550] Relatively good yields of α-hydroxy ketones can be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α-carbonyl carbocation.

10-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds[551]

3/Hydro-de-*O*-alkylation



***O*-Alkyl-*C*-alkoxy-elimination**



The alkoxyl group (OR) is not a leaving group in these reactions, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[552] the only

[547] Batts, B.D. *J. Chem. Soc. B* ***1966***, 551.

[548] Barnard, P.W.C.; Robertson, R.E. *Can. J. Chem.* ***1961***, *39*, 881. See also, Drabicky, M.J.; Myhre, P.C.; Reich, C.J.; Schmittou, E.R. *J. Org. Chem.* ***1976***, *41*, 1472.

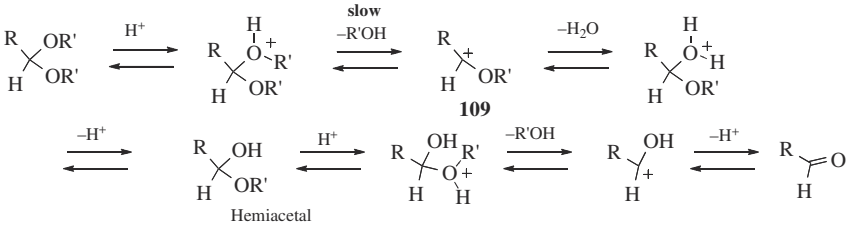
[549] SeeWilliams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 162–163.

[550] Dahn, H.; Gold, H. *Helv. Chim. Acta* ***1963***, *46*, 983; Thomas, C.W.; Leveson, L.L. *Int. J. Chem. Kinet.* ***1983***, *15*, 25. See Smith, III, A.B; Dieter, R.K. *Tetrahedron* ***1981***, *37*, 2407.

[551] Bergstrom, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 881–902; Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups*, *Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 149–329; Cordes, E.H.; Bull, H.G. *Chem. Rev.* ***1974***, *74*, 581; Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75 (ortho esters); DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 134–146 (ortho esters); Rekasheva, A.F. *Russ. Chem. Rev.* ***1968***, *37*, 1009 (enol ethers).

[552] Jaques, D.; Leisten, J.A. *J. Chem. Soc.* ***1964***, 2683. See also, Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725.

acids used preparatively for this purpose are HBr and HI (Reaction **10-49**). However, acetals, ketals, and ortho esters[553] are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of type $R_2(RO)C^+$ are greatly stabilized by resonance (Sec. 5.A.ii). The reactions therefore proceed by the S_N1 mechanism,[554] as shown for acetals:[555]

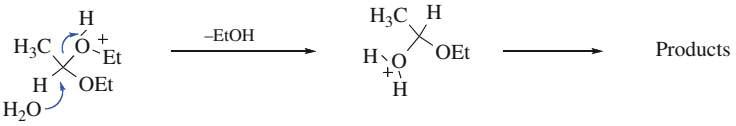


This mechanism, which is an S_N1cA or A1 mechanism, is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (Reaction **16-5**). Among the facts supporting the mechanism are[556] (1) The reaction proceeds with *specific* H_3O^+ catalysis (see Sec. 8.D). (2) It is faster in D_2O. (3) Optically active ROH are not racemized. (4) Even with *tert*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling.[557] (5) In the case of acetophenone ketals, the intermediate corresponding to **109** [$ArCMe(OR)_2$] could be trapped with sulfite ions (SO_3^{2-}).[558] (6) Trapping of this ion did not affect the hydrolysis rate,[558] so the rate-determining step must come earlier. (7) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **109** were isolated as stable ions in superacid solution at −75 °C, where their spectra could be studied.[559] (8) Hydrolysis rates greatly increase in the order $CH_2(OR')_2 < RCH(OR')_2 < R_2C(OR')_2 < RC(OR')_3$, as would be expected for a carbocation intermediate.[560] Formation of **109** is usually the rate-determining step (as marked above), but there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of R′OH from the protonated hemiacetal.[561] Rate-determining addition of water to **109** has also been reported.[562]

While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.[563] In one of these mechanisms, the second and third of the above steps are concerted, so that the

[553] See Pavlova, L.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1986***, *55*, 1026.
[554] See Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 55.
[555] Kreevoy, M.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1955***, *77*, 3146, 5590.
[556] For a discussion of these, and of other evidence, see Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1.
[557] Cawley, J.J.; Westheimer, F.H. *Chem. Ind. (London)* ***1960***, 656.
[558] Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8238. See also, Jencks, W.P. *Acc. Chem. Res.* ***1980***, *13*, 161; Young, P.R.; Bogseth, R.C.; Rietz, E.G. *J. Am. Chem. Soc.* ***1980***, *102*, 6268. However, see Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 3677.
[559] See White, A.M.; Olah, G.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2943; Akhmatdinov, R.T.; Kantor, E.A.; Imashev, U.B.; Yasman, Ya.B.; Rakhmankulov, D.L. *J. Org. Chem. USSR* ***1981***, *17*, 626.
[560] See Belarmino, A.T.N.; Froehner, S.; Zanette, D.; Farah, J.P.S.; Bunton, C.A.; Romsted, L.S. *J. Org. Chem.* ***2003***, *68*, 706.
[561] Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050; McClelland, R.A.; Sørensen, P.E. *Acta Chem. Scand.* ***1990***, *44*, 1082.
[562] Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050.
[563] See Fife, T.H. *Acc. Chem. Res.* ***1972***, *5*, 264; Wann, S.R.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 419.

mechanism is S_N2cA (or A2). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:[564]



In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown[565] demonstrating that the substrate is protonated in the rate-determining step (Sec. 8.D). Reactions in which a substrate is protonated in the rate-determining step are called A-S_E2 reactions.[566] However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (Sec. 8.D). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only about halfway. This can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion drawn is that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.[567]

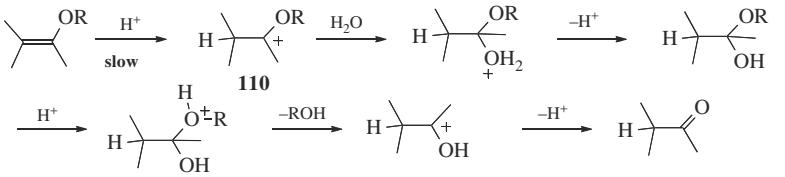
The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor discussed in Section 16.A.i, category 4,[568] although the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems. There is evidence for synplanar stereoselection in the acid hydrolysis of acetals.[569] The mechanism of Lewis acid mediated cleavage of chiral acetals is also known.[570]

Convenient reagents for the hydrolysis of acetals are wet silica gel[571] and Amberlyst-15 (a sulfonic acid based polystyrene cation exchange resin).[572] Both cyclic and acyclic acetals and ketals can be converted to aldehydes or ketones under nonaqueous conditions by treatment with TESOTf-2,6-lutidine (or 2,4,6-collidine) in dichloromethane followed by treatment with water,[573] with Lewis acids e.g., 0.8% $In(OTf)_3$ in acetone,[574] ceric ammonium nitrate in aq acetonitrile,[575] or $Bi(OTf)_3 \bullet xH_2O$.[576]

[564] Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.
[565] Fife, T.H.; Brod, L.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1681; Jensen, J.L.; Herold, L.R.; Lenz, P.A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* ***1979***, *101*, 4672.
[566] See Williams Jr., J.M.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1968***, *6*, 63.
[567] Chiang, Y.; Kresge, A.J.; Lahti, M.O.; Weeks, D.P. *J. Am. Chem. Soc.* ***1983***, *105*, 6852 and references cited therein; Fife, T.H.; Przystas, T.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 143.
[568] See, for example, Kirby, A.J. *Acc. Chem. Res.* ***1984***, *17*, 305; Bouab, O.; Lamaty, G.; Moreau, C. *Can. J. Chem.* ***1985***, *63*, 816. See, however, Ratcliffe, A.J.; Mootoo, D.R.; Andrews, C.W.; Fraser-Reid, B. *J. Am. Chem. Soc.* ***1989***, *111*, 7661.
[569] Li, S.; Kirby, A.J.; Deslongchamps, P. *Tetrahedron Lett.* ***1993***, *34*, 7757.
[570] Sammakia, T.; Smith, R.S. *J. Org. Chem.* ***1992***, *57*, 2997.
[571] Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.M. *Synthesis* ***1978***, 63. See Caballero, G.M.; Gros, E.G. *Synth. Commun.* ***1995***, *25*, 395.
[572] Coppola, G.M. *Synthesis* ***1984***, 1021.
[573] Fujioka, H.; Okitsu, T,; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* ***2006***, *128,* 5930.
[574] Gregg, B.T.; Golden, K.C.; Quinn, J.F. *J. Org. Chem.* ***2007***, *72,* 5890.
[575] Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.M.; Quesnel, Y.; Markó, I.E. *Tetrahedron Lett.* ***1999***, *40*, 1799.
[576] Carringan, M.D.; Sarapa, D.; Smith, R.C.; Wieland, L.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 1027.

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (Reaction **16-5**), and then can be cleaved with acid. Pyridine–HF has also been used for this conversion.[577] Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR_2, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Thioacetals [$RCH(SR')_2$] and thioketals [$R_2C(SR')_2$] are among those compounds generally resistant to acid hydrolysis.[578] Because conversion to these compounds (Reaction **16-11**) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents[579] used for this purpose are $HgCl_2$,[580] $FeCl_2 \bullet 6\ H_2O$,[581] cetyltrimethylammonium tribromide in dichloromethane,[582] *m*-chloroperoxybenzoic acid, the *Dess–Martin periodinane*[583] (see Reaction **19-03**), and sodium nitrite in aqueous acetyl chloride.[584] Mixed acetals and ketals (RO—C—SR) can be hydrolyzed with most of the reagents mentioned above, including *N*-bromosuccinimide (NBS) in aq acetone,[585] and glyoxylic acid on Amberlyst-15 with microwave irradiation.[586]

Enol ethers (vinyl ethers) are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate.[587] However, protonation does not take place at the oxygen, but at the β carbon,[588] because that gives rise to the stable carbocation (**110**).[589] After that, the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.

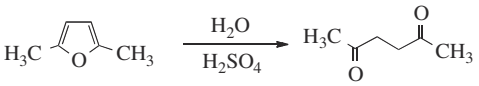


Among the facts supporting this mechanism, which is an A-S_E2 mechanism because the substrate is protonated in the rate-determining step, are (1) the ^{18}O labeling shows that in $ROCH{=}CH_2$ it is the vinyl–oxygen bond and not the RO bond that cleaves;[590] (2) the

[577] Watanabe, Y.; Kiyosawa, Y.; Tatsukawa, A.; Hayashi, M. *Tetrahedron Lett.* ***2001***, *42*, 4641.
[578] Ali, M.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 219; ***1993***, 1825; Ali, M.; Satchell, D.P.N.; Le, V.T. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 917.
[579] See Gröbel, B.; Seebach, D. *Synthesis* ***1977***, 357, see pp. 359–367; Cussans, N.J.; Ley, S.V.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1654.
[580] Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 513.
[581] Kamal, A.; Laxman, E.; Reddy, P.S.M.M. *Synlett* ***2000***, 1476.
[582] Mondal, E.; Bose, G.; Khan, A.T. *Synlett* ***2001***, 785.
[583] Langille, N.F.; Dakin, L.A.; Panek, J.S. *Org. Lett.* ***2003***, *5*, 575. See also, Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 287.
[584] Khan, A.T.; Mondal, E.; Sahu, P.R. *Synlett* ***2003***, 377.
[585] Karimi, B.; Seradj, H.; Tabaei, M.H. *Synlett* ***2000***, 1798.
[586] Chavan, S.P.; Soni, P.; Kamat, S.K. *Synlett* ***2001***, 1251.
[587] Jones, J.; Kresge, A.J. *Can. J. Chem.* ***1993***, *71*, 38.
[588] See Burt, R.A.; Chiang, Y.; Kresge, A.J.; Szilagyi, S. *Can. J. Chem.* ***1984***, *62*, 74.
[589] See Chwang, W.K.; Kresge, A.J.; Wiseman, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6972.
[590] Kiprianova, L.A.; Rekasheva, A.F. *Dokl. Akad. Nauk SSSR*, ***1962***, *142*, 589.

reaction is subject to general acid catalysis;[591] (3) there is a solvent isotope effect when D_2O is used.[591] A method has been developed to determine primary kinetic isotope effects relating to proton transfer in the hydrolysis of enol ethers.[592] Enantioselective protonation is possible in some cases. Cyclic silyl enol ethers are converted to chiral α-substituted ketones, for example, with high enantioselectivity using a chiral Brønsted acid.[593]

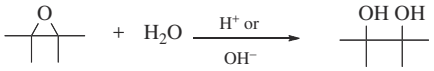
Enamines are also hydrolyzed by acids (see Reaction **16-2**); the mechanism is similar. Ketene dithioacetals [$R_2C{=}C(SR')_2$] also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.[594] Furans represent a special case of enol ethers that are cleaved by acid to give 1,4-diones.[595] Thus oxonium ions are cleaved by water to give an alcohol and an ether:



OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **VI**, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII**, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **VIII**, 19, 155, 241, 353, 373

10-7 Hydrolysis of Epoxides

(3)*OC-seco*-hydroxy-de-alkoxy substitution



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases. A basic reagent will attack the polarized carbon of the epoxide unit to open the ring, whereas an acid-catalyzed reaction leads to a protonated epoxide (an oxonium ion),[596] which is opened by nucleophilic attack at an adjacent carbon. Among acid catalysts, perchloric acid leads to minimal side reactions,[597] and 10% Bu_4NHSO_4 in water is effective.[598] However, water reacts directly with epoxides at 60 °C.[599] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[600]

Cobalt salen [salen = bis(salicylidene)ethylenediamine] catalysts, in the presence of water, open epoxides with high stereoselectivity.[601] The enzyme *epoxide hydrolase* opens epoxides with high enantioselectivity.[602]

OS **V**, 414.

[591] Fife, T.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1084; Kresge, A.J.; Yin, Y. *Can. J. Chem.* ***1987***, *65*, 1753.
[592] Tsang, W.-Y.; Richard, J.P. *J. Am. Chem. Soc.* ***2007***, *129,* 10330.
[593] Cheon, C.H.; Yamamoto, H. *J. Am. Chem. Soc* ***2008***, *130,* 9246. For a different example, see Nakashima, D.; Yamamoto, H. *Synlett* ***2006***, 150.
[594] For a review, see Okuyama, T. *Acc. Chem. Res.* ***1986***, *19*, 370.
[595] See Finlay, J.; McKervey, M.A.; Gunaratne, H.Q.N. *Tetrahedron Lett.* ***1998***, *39*, 5651.
[596] For a density functional analysis of this ion, see Zhao, Y.; Truhlar, D.G. *J. Org. Chem.* ***2007***, *72*, 295.
[597] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, ***1967***, p. 796.
[598] Fan, R.-H.; Hou, X.-L. *Org. Biomol. Chem.* ***2003***, *1,* 1565. For a reaction with $NaHSO_4$, see Cavdar, H.; Saracoglu, N. *Tetrahedron* ***2009***, *65*, 985.
[599] Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* ***2008***, *73*, 2270.
[600] Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* ***1965***, 3421.
[601] Ready, J.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2687.
[602] See Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D.S.; Zhu, Z.; Milan, A.; Robertson, D.E.; Weiner, D.P.; Burk, M. J. *J. Am. Chem. Soc.* ***2004***, *126,* 11156.

10.H.ii Attack by OR at an Alkyl Carbon

10-8 Alkylation with Alkyl Halides: The Williamson Reaction

Alkoxy-de-halogenation

$$RX + OR'^{-} \longrightarrow ROR'$$

The *Williamson reaction* (*Williamson ether synthesis*), discovered in 1850, is still the best general method for the preparation of unsymmetrical or symmetrical ethers.[603] The reaction can also be carried out with aromatic R′, although *C*-alkylation is sometimes a side reaction (see Sec. 10.G.vii).[604] The normal method involves treatment of a primary or secondary alkyl halide with alkoxide or aroxide ion prepared from an alcohol or phenol by reaction with a suitable base, although methylation using dimethyl carbonate has been reported.[605] The solvent is usually an aprotic solvent (THF, ether, etc.,) rather than an alcohol solvent, which typically promotes elimination reactions in the presence of alkoxides (see Chap. 17). It is also possible to mix the halide and alcohol or phenol directly with Cs_2CO_3 in acetonitrile,[606] or with NaH in the presence of DMF.[607] The reaction can also be carried out in a dry medium,[608] neat,[609] or in solvents using microwave irradiation.[610] Williamson ether synthesis in ionic liquids has also been reported.[611] The reaction is *not* successful for tertiary R (elimination predominates), and low yields are often obtained with secondary R. Monoethers can be formed from diols and alkyl halides.[612] It is possible to selectively alkylate the primary hydroxyl in a diol [$HOCH_2CH(OH)R$] using a tin complex.[613]

Many other functional groups can be present in the molecule without interference. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (Reaction **10-10**) with a tertiary alkoxide ($R'O^-$). Di-*tert*-butylether was prepared in high yield by direct attack by *t*-BuOH on reaction with the *tert*-butyl cation (at −80 °C in SO_2ClF).[614] Di-*tert*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag_2CO_3 or Ag_2O.[615] Alcohols react with $Mg(ClO_4)_2$ and an excess of Boc (Boc = *t*-butoxycarbonyl) anhydride (Boc_2O) to give the *tert*-butyl ether.[616]

[603] See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 446–450, 460–468.
[604] For a list of reagents used to convert alcohols and phenols to ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 890–893.
[605] Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. *Tetrahedron Lett.* ***2002***, *43*, 2661.
[606] Lee, J.C.; Yuk, J.Y.; Cho, S.H. *Synth. Commun.* ***1995***, *25*, 1367.
[607] Jin, C.H.; Lee, H.Y.; Lee, S.H.; Kim, I.S.; Jung, Y.H. Synlett ***2007***, 2695.
[608] Bogdal, D.; Pielichowski, J.; Jaskot, K. *Org. Prep. Proceed. Int.* ***1998***, *30*, 427.
[609] Yuncheng, Y.; Yulin, J.; Jun, P.; Xiaohui, Z.; Conggui, Y. *Gazz. Chim. Ital.* ***1993***, *123*, 519.
[610] Paul, S.; Gupta, M. *Tetrahedron Lett.* ***2004***, *45*, 8825.
[611] Xu, Z.Y.; Xu, D.Q.; Liu, B.Y. *Org. Prep. Proceed. Int.* ***2004***, *36*, 156. Also see More, S.V.; Ardhapure, S.S.; Naik, N.H.; Bhusare, S.R.; Jadhav, W.N.; Pawar, R.P. *Synth. Commun.* ***2005***, *35,* 3113.
[612] See Jha, S.C.; Joshi, N.N. *J. Org. Chem.* ***2002***, *67*, 3897.
[613] Boons, G.-J.; Castle, G.H.; Clase, J.A.; Grice, P.; Ley, S.V.; Pinel, C. *Synlett*, ***1993***, 913.
[614] Olah, G.A.; Halpern, Y.; Lin, H.C. *Synthesis* ***1975***, 315. Also see Masada, H.; Yonemitsu, T.; Hirota, K. *Tetrahedron Lett.* ***1979***, 1315.
[615] Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 866.
[616] Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* ***2005***, *7,* 427.

Active halides (e.g., Ar_3CX) may react directly with the alcohol.[617] Hindered alcohols may react as well.[618] The mechanism for these cases is of course S_N1. *tert*-Butyl halides can be converted to aryl *tert*-butyl ethers by treatment with phenols and an amine (e.g., pyridine).[619] Aryl alkyl ethers can be prepared from alkyl halides by treatment with an aryl acetate (instead of a phenol) in the presence of K_2CO_3 and a crown ether.[620] The Pd-catalyzed displacement of allylic acetates with aliphatic alcohols has been shown to give the corresponding alkyl allyl ether.[621] A Rh-catalyst[622] Ir catalyst,[623] and an In-Si combined Lewis acid catalyst[624] have been used in ether forming reactions. Aryl ethers have been prepared using *Mitsunobu conditions* (see Reaction **10-17**).[625]

Vinyl ethers have been formed by coupling tetravinyl tin with phenols, in the presence of cupric acetate and oxygen.[626] The Pd-catalyzed coupling of vinyl triflates and phenols has also been reported.[627]

Both aryl alkyl and dialkyl ethers can be efficiently prepared with the use of phase-transfer catalysis (Sec. 10.G.v)[628] and with micellar catalysis.[629] Symmetrical benzylic ethers have been prepared by reaction of benzylic alcohols with Mg/I_2 followed by triflic anhydride.[630]

A slight variation of the *Williamson ether synthesis* has been used for the protection of hydroxy groups[631] by reaction of their salts with chloromethyl methyl ether.

$$RO^- + CH_3OCH_2Cl \longrightarrow ROCH_2OCH_3$$

This protecting group is known as MOM (methoxymethyl) and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (Reaction **10-7**). Another protecting group, the 2-methoxyethoxy-methyl group (the MEM group), is formed in a similar manner. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides (e.g., Me_2BBr).[632]

[617] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 454–466. Also see Biordi, J.; Moelwyn-Hughes, E.A. *J. Chem. Soc.* ***1962***, 4291.
[618] Aspinall, H.C.; Greeves, N.; Lee, W.-M.; McIver, E.G.; Smith, P.M. *Tetrahedron Lett.* ***1997***, *38*, 4679.
[619] Masada, H.; Oishi, Y. *Chem. Lett.* ***1978***, 57; Camps, F.; Coll, J.; Moretó, J.M. *Synthesis* ***1982***, 186.
[620] Banerjee, S.K.; Gupta, B.D.; Singh, K. *J. Chem. Soc., Chem. Commun.* ***1982***, 815.
[621] Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 3474; Haight, A.R.; Stoner, E.J.; Peterson, M.J.; Grover, V.K. *J. Org. Chem.* ***2003***, *68*, 8092.
[622] Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2002***, *124*, 7882.
[623] Ueno, S.; Hartwig, J.F. *Angew. Chem. Int. Ed.* ***2008***, *47,* 1928.
[624] Saito, T.; Yasuda, M.; Baba, A. *Synlett* ***2005***, 1737.
[625] Lepore, S.D.; He, Y. *J. Org. Chem.* ***2003***, *68*, 8261.
[626] Blouin, M.; Frenette, R. *J. Org. Chem.* ***2001***, *66*, 9043.
[627] Willis, M.C.; Taylor, D.; Gillmore, A.T. *Chem. Commun.* ***2003***, 2222.
[628] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Springer, NY, ***1978***, pp. 128–138; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis,* Springer, NY, ***1977***, pp. 73–84. See also, Eynde, J.J.V.; Mailleux, I. *Synth. Commun.* ***2001***, *31*, 1; de la Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* ***1989***, *45*, 1533.
[629] Jursic, B. *Tetrahedron* ***1988***, *44*, 6677.
[630] Nishiyama, T.; Kameyama, H.; Maekawa, H.; Watanuki, K. *Can. J. Chem.* ***1999***, *77*, 258.
[631] See Greene, T.W. Protective Groups in Organic Synthesis Wiley, New York, **1980**; Wuts, P.G.M.; Greene, T.W. ProtectiveGroups in Organic Synthesis 2nd ed., Wiley, New York, **1991**; Wuts, P.G.M.; Greene, T.W. Protective Groups in OrganicSynthesis 3rd ed., Wiley, New York, **1999**; Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 4th ed., Wiley, New Jersey, **2006**.
[632] Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* ***1984***, *49*, 3912. For other methods, see Hanessian, S.; Delorme, D.; Dufresne,Y. *Tetrahedron Lett.* ***1984***, *25*, 2515; Rigby, J.H.; Wilson, J.Z. *Tetrahedron Lett.* ***1984***, *25*, 1429.

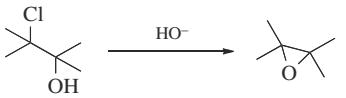
Another common method for the protection of alcohols is conversion to the silyl ether (R—O—SiR'$_3$). The alcohol is generally treated with a base (e.g., trimethylamine or imidazole) and then with a chlorotrialkylsilane (R_3SiCl), or the analogous bromide.[629] There are many variations of this basic procedure. Iodine promotes the reaction, for example.[633] There are also many ways to remove the silyl group to regenerate the alcohol, although fluoride ion, including tetrabutylammonium fluoride in THF, is probably the most common method.[629]

Most Williamson reactions proceed by the S_N2 mechanism, but there is evidence (see Sec. 10.C) that in some cases the SET mechanism can take place, especially with alkyl iodides.[634] Secondary alcohols have been converted to the corresponding methyl ether by reaction with methanol in the presence of ferric nitrate nonahydrate.[635]

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **VIII**, 26, 161, 155, 373; **80**, 227.

10-9 Epoxide Formation (Internal Williamson Ether Synthesis)

(3)*OC-cyclo*-Alkoxy-de-halogenation



This is a special case of Reaction **10-8**. The base removes the proton from the OH group of a halohydrin (chlorohydrin or bromohydrin), and the resulting alkoxide subsequently attacks in an internal S_N2 reaction.[636] Many epoxides have been made in this way.[637] The course of the reaction can be influenced by neighboring group effects.[638] Enantioselective epoxide-forming reactions are known, using chiral additives (e.g., dihydrocinchonidines).[639] Epoxidation of alkenes has also been accomplished using HOF—MeCN in a continuous flow system.[640]

Larger cyclic ethers can be prepared, including five-and six-membered rings (tetrahydrofurans and tetrahydropyrans, respectively).[641] Additional treatment with base yields the glycol (Reaction **10-7**). Thiiranes can be prepared by the reaction of α-chloro ketones with $(EtO)_2P(=O)$-SH and $NaBH_4$-Al_2O_3 with microwave irradiation.[642]

1,2-Diols can be converted to epoxides by treatment with DMF dimethyl acetal, $[(MeO)_2CHNMe_2]$,[643] with diethyl azodicarboxylate ($Et_2OCN{=}NCO_2Et$),

[633] Bartoszewicz, A.; Kalek, M.; Stawinski, J. *Tetrahedron* ***2008***, *64,* 8843.
[634] Ashby, E.C.; Bae, D.; Park, W.; Depriest, R.N.; Su, W. *Tetrahedron Lett.* ***1984***, *25*, 5107.
[635] Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 4593.
[636] See Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.
[637] See Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 187.
[638] Lang, F.; Kassab, D.J.; Ganem, B. *Tetrahedron Lett.* ***1998***, *39*, 5903.
[639] Lygo, B.; Gardiner, S.D.; McLeod, M.C.; To, D.C.M. *Org. Biomol. Chem.* ***2007***, *5,* 2283.
[640] McPake, C.B.; Murray, C.B.; Sandford, G. *Tetrahedron Lett.* ***2009***, *50*, 1674.
[641] See Kim, K.M.; Jeon, D.J.; Ryu, E.K. *Synthesis* ***1998***, 835. Also see Marek, I.; Lefrancois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* ***1992***, *33*, 1747.
[642] Yadav, L.D.S.; Kapoor, R. *Synthesis* ***2002***, 2344.
[643] Neumann, H. *Chimia*, ***1969***, *23*, 267.

and Ph_3P,[644] with a dialkoxytriphenylphosphorane,[645] or with $TsCl^-Na^-OHPhCH_2NEt_2^+Cl^-$.[646]

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **VIII**, 434.

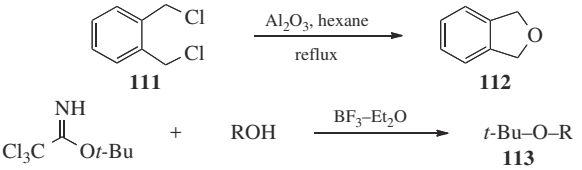
10-10 Alkylation with Inorganic Esters

Alkoxy-de-sulfonyloxy substitution

$$R{-}OSO_2OR^2 + R'O^- \longrightarrow ROR$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to Reaction **10-8** in mechanism and scope. Other inorganic esters can also be used. Methyl ethers of alcohols and phenols are commonly formed by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly with dimethyl sulfate under various conditions.[647] Carboxylic esters sometimes give ethers when treated with alkoxides ($B_{AL}2$ mechanism, Reaction **16-59**) in a very similar process (see also, Reaction **16-64**). A related reaction heated **111** with alumina to give the corresponding benzofuran, (**112**).[648] The reaction of aliphatic alcohols and potassium organotrifluoroborate salts also gives ethers.[649]

tert-Butyl ethers (**113**) can be prepared by treating the compound *tert*-butyl-2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.[650] Trichloroimidates can be used to prepare other ethers as well.[651] *tert*-Butyl ethers can be cleaved by acid-catalyzed hydrolysis.[652]



OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. Also see, OS **V**, 431.

10-11 Alkylation with Diazo Compounds

Hydro, alkoxy-de-diazo-bisubstitution

$$CH_2N_2 + ROH \xrightarrow{HBF_4} CH_3OR$$

$$R_2CN_2 + ArOH \longrightarrow R_2CHOAr$$

[644] Guthrie, R.D.; Jenkins, I.D.; Yamasaki, R.; Skelton, B.W.; White, A.H. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2328 and references cited therein. For a review of diethyl azodicarboxylate–Ph_3P, see Mitsunobu, O. *Synthesis* ***1981***, 1.

[645] Kelly, J.W.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 5490. See also, Hendrickson, J.B.; Hussoin, M.S. *Synlett*, ***1990***, 423.

[646] Szeja, W. *Synthesis* ***1985***, 983.

[647] Cao, Y.-Q.; Pei, B.-G. *Synth. Commun.* ***2000***, *30,* 1759.

[648] Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* ***2002***, 1526.

[649] Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5,* 1381.

[650] Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.* ***1988***, *29*, 2483.

[651] Rai, A.N.; Basu, A. *Tetrahedron Lett.* ***2003***, *44*, 2267.

[652] Lajunen, M.; Ianskanen-Lehti, K. *Acta Chem. Scand. B*, ***1994***, *48*, 861.

Alcohols react with diazo compounds to form ethers, but diazomethane and diazo ketones are most readily available, giving methyl ethers or α-keto ethers,[653] respectively. With diazomethane[654] the method is expensive and requires great caution, but the conditions are mild and high yields are obtained. Diazomethane is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst (e.g., HBF_4[655] or silica gel)[656] is present. The more acidic phenols react very well in the absence of a catalyst. The reaction of oximes, and ketones that have substantial enolic contributions, give O-alkylation to form, respectively, O-alkyl oximes and enol ethers. The mechanism[657] is as in Reaction **10-5**. Note that O-aryloximes are prepared from oximes and aryl halides, mediated by CuI.[658]

Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.[659] Enantioselective insertion into phenolic O—H bond leads to highly substituted ethers.[660] Similar intermediates are involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.[661]

$$R_2CN_2 + 2\,R'OH \xrightarrow{t\text{-BuOCl}} R_2C(OR')_2$$

OS **V**, 245. Also see, OS **V**, 1099.

10-12 Dehydration of Alcohols

Alkoxy-de-hydroxylation

$$2\,ROH \xrightarrow{H_2SO_4} ROR + H_2O$$

The dehydration of alcohols to form symmetrical ethers[662] is analogous to Reactions **10-8** and **10-10**, but the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an S_N1 or S_N2 pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an S_N1 or S_N2 route, be attacked by the nucleophile HSO_4^-, in which case it is converted to $ROSO_2OH$, which in turn may be attacked by an alcohol molecule to give ROR. Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Good yields of ethers were obtained by heating diarylcarbinols [$ArAr'CHOH \rightarrow (ArAr'CH)_2O$] with TsOH in the solid

[653] Pansare, S.V.; Jain, R.P.; Bhattacharyya, A. *Tetrahedron Lett.* ***1999***, *40*, 5255.
[654] For a review of diazomethane, see Pizey, J.S. *Synthetic Reagents*, Vol. 2; Wiley, NY, ***1974***, pp. 65–142.
[655] Neeman, M.; Caserio, M.C.; Roberts, J.D.; Johnson, W.S. *Tetrahedron* ***1959***, *6*, 36.
[656] Ogawa, H.; Hagiwara, H.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 627.
[657] Kreevoy, M.M.; Thomas, S.J. *J. Org. Chem.* ***1977***, *42*, 3979. See also, McGarrity, J.F.; Smyth, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7303.
[658] De, P.; Nonappa; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* ***2007***, *9,* 2767.
[659] Noels, A.F.; Demonceau, A.; Petiniot, N.; Hubert, A.J.; Teyssié, P. *Tetrahedron* ***1982***, *38*, 2733.
[660] Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007***, *129,* 12616.
[661] Baganz, H.; May, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 420.
[662] See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp.457–460, 468–470.

state.[663] Acids (e.g., Nafion-H with silyl ethers)[664] can be used in this transformation, and Lewis acids can be used with alcohols in some cases.[665]

Mixed (unsymmetrical) ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.[666] If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Unsymmetrical ethers have been formed by treatment of two different alcohols with $MeReO_3$[667] or with $BiBr_3$.[668] Unsymmetrical ethers have been prepared under *Mitsunobu conditions* (Reaction **10-17**) with a polymer-supported phosphine and diethyl azadicarboxylate (DEAD).[669] Symmetrical ethers are formed by heating benzylic alcohols with the polymer poly(3,4-ethylenedioxythiophene) in toluene or heptane (a two-phase system), with no other additives.[670] Diols can be converted to cyclic ethers,[671] although the reaction is most successful for five-membered rings, but five-, six-, and seven-membered rings have been prepared.[672] Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination.

Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide[673] (see Reaction **16-63**).

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **VIII**, 116. Also see, OS **V**, 721.

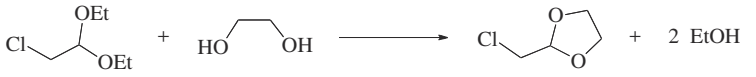
10-13 Transetherification

Hydroxy-de-alkoxylation and **Alkoxy-de-hydroxylation**

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxy group for another is rare for *ethers* without a reactive R group (e.g., diphenylmethyl),[674] or by treatment of alkyl aryl ethers with alkoxide ions: $ROAr + R'O^- \rightarrow ROR' + ArO^-$.[675] 3-(2-Benzyloxyethyl)-3-methyl-oxetane was transformed into 3-benzyloxymethyl-3-methyltetrahydrofuran by an internal transetherification catalyzed by $BF_3{\bullet}OEt_2$.[676]

[663] Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1270.
[664] Zolfigol, M.A.; Mohammadpoor-Baltork, I.; Habibi, D.; Mirjalili, B.B.F.; Bamoniri, A. *Tetrahedron Lett.* ***2003***, *44,* 8165.
[665] See Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* ***2000***, *52*, 575.
[666] See, for example, Jenner, G. *Tetrahedron Lett.* ***1988***, *29*, 2445.
[667] Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1996***, *61*, 324.
[668] Boyer, B.; Keramane, E.-M.; Roque, J.-P.; Pavia, A.A. *Tetrahedron Lett.* ***2000***, *41,* 2891.
[669] Lizarzaburu, M.E.; Shuttleworth, S. *Tetrahedron Lett.* ***2002***, *43*, 2157.
[670] D'Angelo, J.G.; Sawyer, R.; Kumar, A.; Onorato, A.; McCluskey, C.; Delude, C.; Vollenweider, L.; Reyes, N.; French, R.; Warner, S.; Chou, J.; Stenzel, J.; Sotzing, G.A.; Smith, M.B. *J. Polymer Sci., Part A* ***2007***, *45,* 2328.
[671] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 893–894.
[672] See Olah, G.A.; Fung, A.P.; Malhotra, R. *Synthesis* ***1981***, 474.
[673] Vowinkel, E. *Chem. Ber.* ***1962***, *95*, 2997; ***1963***, *96*, 1702; ***1966***, *99*, 42.
[674] Pratt, E.F.; Draper, J.D. *J. Am. Chem. Soc.* ***1949***, *71*, 2846. See Salehi, P.; Irandoost, M.; Seddighi, B.; Behbahani, F.K.; Tahmasebi, D.P. *Synth. Commun.* ***2000***, *30,* 1743.
[675] Zoltewicz, J.A.; Sale, A.A. *J. Org. Chem.* ***1970***, *35*, 3462.
[676] Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* ***1994***, *38*, 2165.



114 **115**

Acetals and ortho esters undergo transetherification readily,[677] as with the transformation of **114** to **115**.[678] As seen in Reaction **10-6**, departure of the leaving group from an acetal gives a particularly stable carbocation. It is also possible to convert a dimethylketal directly to a dithiane by reaction with butane 1,4-dithiol on clay.[679] These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,[680] as shown in the example. *N,N*-Diethylaminoethylthiol reacts with aryl ethers to give the phenol derivative and the corresponding sulfide in what is effectively a transetherification.[681]

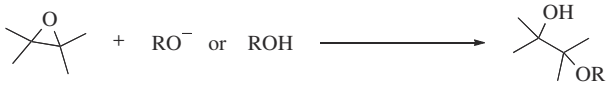
$$\mathrm{ROCH{=}CH_2 + R'OH \xrightarrow{Hg(OAc)_2} R'OCH{=}CH_2 + ROH}$$

1,2-Diketones can be converted to α-keto enol ethers by treatment with an alkoxytrimethylsilane ($ROSiMe_3$).[682]

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **VIII**, 155, 173. Also see, OS **V**, 1080, 1096.

10-14 Alcoholysis of Epoxides

(3)*OC-seco*-alkoxy-de-alkoxylation



This reaction is analogous to **10-7**. It may be acid (including Lewis acid[683]), base, or alumina[684] catalyzed, and may occur by either an S_N1 or S_N2 mechanism. Catalysts (e.g., mesoporous aluminosilicate,[685] $Cu(BF_4)_2{\bullet}nH_2O$,[686] $Al(OTf)_3$,[687] or $BiCl_3$),[688] have been used. β-Cyclodextrin has been used to promote the reaction with phenoxides in aqueous

[677] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pp. 458–463; DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 18–29, 146–148.

[678] McElvain, S.M.; Curry, M.J. *J. Am. Chem. Soc.* ***1948***, *70*, 3781.

[679] Jnaneshwara, G.K.; Barahate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 965.

[680] Watanabe, W.H.; Conlon, L.E. *J. Am. Chem. Soc.* ***1957***, *79*, 2828; Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907; Gareev, G.A. *J. Org. Chem. USSR* ***1982***, *18*, 36.

[681] Magano, J.; Chen, M.H.; Clark, J.D.; Nussbaumer, T. *J. Org. Chem.* ***2006***, *71,* 7103.

[682] Ponaras, A.A.; Meah, M.Y. *Tetrahedron Lett.* ***1986***, *27*, 4953.

[683] Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* ***1996***, 1473. See Moberg, C.; Rákos, L.; Tottie, L. *Tetrahedron Lett.* ***1992***, *33*, 2191 for an example that generates a hydroxy ether with high enantioselectivity. Also see, Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett*, ***1992***, 673.

[684] See Posner, G.H.; Rogers, D.Z. *J. Am. Chem. Soc.* ***1977***, *99*, 8208, 8214.

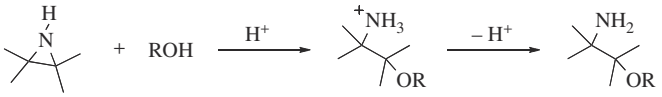
[685] Robinson, M.W.C.; Buckle, R.; Mabbett, I.; Grant, G.M.; Graham, A.E. *Tetrahedron Lett.* ***2007***, *48,* 4723.

[686] Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J.M. *Org. Lett.* ***2002***, *4*, 2817.

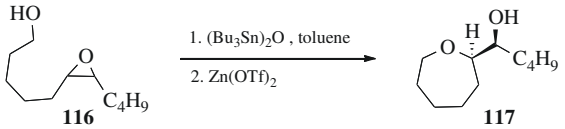
[687] Williams, D.B.G.; Lawton, M. *Org. Biomol. Chem.* ***2005***, *3,* 3269.

[688] Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun.,* ***2000***, *30,* 2365.

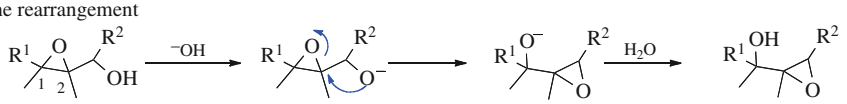
media.[689] Many of the β-hydroxy ethers produced in this way are valuable solvents, [e.g., diethylene glycol and Cellosolve (2-ethoxyethanol)]. Reaction with thiols leads to hydroxy thioethers.[690] Other nucleophilic oxygen or sulfur species have been shown to open epoxides, including thiols[691] (catalyzed by Sc[692] or In[693]). (Phenylseleno)silanes react with epoxides to give β-hydroxy selenides.[694]



Opening an epoxide by an alkoxide moiety can be done intramolecularly, and a new cyclic ether is generated. Ethers of various ring sizes can be produced depending on the length of the tether between the alkoxide unit and the epoxide. Specialized conditions are common, as in the conversion of **116** to **117**.[695] Another variant of this transformation used a Co-salen catalyst.[696] A specialized version has the alkoxide moiety on the carbon adjacent to the epoxide, leading to the *Payne rearrangement* where a 2,3-epoxy alcohol is converted to an isomeric one, by treatment with aqueous base, as shown in the example.[697]



Payne rearrangement



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

The reaction of alcohols with aziridines leads to β-amino ethers,[698] and reaction with thiols gives β-amino thioethers.[699] It has been shown that ring opening of aziridines by

[689] Surendra, K.; Krishnaveni, N.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 4994.
[690] Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* ***2003***, *68*, 8248; Amantini, D.; Friguelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Synlett* ***2003***, 2292.
[691] See also Degl'Innocenti, A.; Capperucci, A.; Cerreti, A.; Pollicino, S.; Scapecchi, S.; Malesci, I.; Castagnoli, G. *Synlett* ***2005***, 3063.
[692] Ogawa, C.; Wang, N.; Kobayashi, S. *Chem. Lett.* ***2007***, *36,* 34.
[693] Nandakumar, M.V.; Tschöp, A.; Krautscheid, H.; Schneider, C. *Chem. Commun.* ***2007***, 2756.
[694] Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Del Verme, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron* ***2008***, *64,* 3337.
[695] Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.-i.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V.P. *Tetrahedron Lett.* ***2000***, *41,* 7701. See also, Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* ***2002***, *43,* 1495.
[696] Wu, M.H.; Hansen, K.B.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***1999***, *38,* 2012.
[697] Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J. *J. Org. Chem.* ***1985***, *50*, 5687. See Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* ***2004***, *6*, 4073.
[698] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 224–227, 256–257.
[699] Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1314.

phenols is promoted by tributylphosphine.[700] Aldehydes open aziridines when catalyzed by nucleophilic carbenes.[701] Metal catalysts [e.g., $Cu(OTf)_2$] mediate the ring opening of *N*-tosylaziridines by alcohols.[702] The reaction of *N*-tosyl aziridines with 10% ceric ammonium nitrate in aq methanol leads to *N*-tosylamino alcohols,[703] and reaction with ethanol and 10% $BF_3{\bullet}OEt_2$ gives *N*-tosyl ethers.[704] In addition, *N*-tosylaziridines are opened by acetic acid in the presence of $In(OTf)_3$ to give *N*-tosylamino acetates.[705] In the presence of Amberlyst-15, *N*-Boc (Boc = *tert*-butoxycarbonyl, $—CO_2t$-Bu) aziridines react with LiBr to give the corresponding bromo amide.[706] Aziridines are opened by potassium thiocyanate, catalyzed by $LiClO_4$.[707] Catalytic enantioselective ring opening of *N*-acyl aziridines with TMSCN and a Gd catalyst leads to amino-nitriles.[708] *aza-Payne rearrangements* are known, based on reactions of aziridines rather than epoxides (see above).[709]

10-15 Alkylation with Onium Salts

Alkoxy-de-hydroxylation

$$R_3O^+ + R'OH \longrightarrow ROR' + R_2O$$

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.[710] Quaternary ammonium salts can sometimes also be used.[711]

OS **VIII**, 536.

10-16 Hydroxylation via Silanes

Hydroxy-de-silylalkylation

$$R—SiR^1_2Ar \xrightarrow{F^-} R—SiR^1_2F \xrightarrow{\text{oxidation}} R—OH$$

$$R—SiR^1_2SiR^1_3 \xrightarrow{F^-} R—SiR^1_2F \xrightarrow{\text{oxidation}} R—OH$$

Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This usually requires either an aryl group[712] or another silyl group[713] attached to silicon. It has

[700] Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* ***2002***, *67,* 5295.
[701] Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* ***2006***, *8,* 1521.
[702] Ghorai, M.K.; Das, K.; Shukla, D. *J. Org. Chem.* ***2007***, *72,* 5859.
[703] Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S.S. *Tetrahedron Lett.* ***2002***, *43*, 7361.
[704] Prasad, B.A.B.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 4677.
[705] Yadav, J.S.; Reddy, B.V.S.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* ***2002***, *43*, 2099.
[706] Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* ***2002***, *43,* 5867.
[707] Yadav, J.S.; Subba Reddy, B.V.; Jyothirmai, B.; Murty, M.S.R. *Tetrahedron Lett.* ***2005***, *46,* 6385. Also in water, with β-cyclodextrin, see Reddy, M.S.; Narender, M.; Nageswar, Y.V.D.; Rao, K.R. *Tetrahedron Lett.* ***2005***, *46,* 6437.
[708] Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127,* 11252.
[709] Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron Asymmetry* ***2006***, *17,* 1394.
[710] Granik, V.G.; Pyatin, B.M.; Glushkov, R.G.*Russ. Chem. Rev.* ***1971***, *40,* 747, see p. 749.
[711] See Vogel, D.E.; Büchi, G.H. *Org. Synth.*, ***66***, 29. With pyridinium salts, see Poon, K.W.C.; Dudley, G.B. *J. Org. Chem.* ***2006***, *71,* 3923. See also Saitoh, T.; Ichikawa, J. J. *Am. Chem. Soc.* ***2005***, *127,* 9696.
[712] Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* ***1983***, *39*, 983; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* ***1984***, 29. For the protodesilylation step see Häbich, D.; Effenberger, F. *Synthesis* ***1979***, 841. Also see Buncel, E.; Davies, A.G. *J. Chem. Soc.* ***1958***, 1550.
[713] Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett*, ***1995***, 941.

been shown that a strained four-membered ring silane (a siletane) also gives the corresponding alcohol upon oxidation.[714] Treatment with a fluorinating agent (e.g., tetrabutylammonium fluoride or CsF) replaces Ar or SiR_3 with F, which is oxidized with hydrogen peroxide or a peroxyacid to give the alcohol. This sequence is often called the *Tamao–Fleming oxidation*.[712] There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.[715] Hydroperoxide oxidation of a cyclic silane leads to a diol.[716]

C. Attack by OCOR at an Alkyl Carbon

10-17 Alkylation of Carboxylic Acid Salts

Acyloxy-de-halogenation

$$RX + R'COO^- \xrightarrow{HMPA} R'COOR$$

Sodium salts of carboxylic acids, including hindered acids (e.g., mesitoic), rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.[717] The mechanism is S_N2. Several bases or basic media have been used to generate the carboxylate salt.[718] Sodium salts are often used, but K, Ag, Cs,[719] and substituted ammonium salts have also been used. An important variation uses phase transfer catalysis,[720] and good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.[721] Without phase-transfer catalysts and in protic solvents, the reaction is useful only for fairly active R [e.g., benzylic and allylic (S_N1 mechanism)], but not for tertiary alkyl, since elimination occurs instead.[722] Solid-state procedures are available. Addition of the dry carboxylate salt and the halide to alumina as a solid support, and microwave irradiation gives the ester in a procedure that is applicable to long-chain primary halides.[723] A similar reaction of hexanoic acid and benzyl bromide on solid benzyltributylammonium chloride

[714] Sunderhaus, J.D.; Lam, H.; Dudley, G.B. *Org. Lett.* ***2003***, *5,* 4571.
[715] See Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* ***1994***, *50*, 335; Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 713.
[716] Liu, D.; Kozmin, S.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4757.
[717] Shaw, J.E.; Kunerth, D.C. *J. Org. Chem.* ***1974***, *39*, 1968; Larock, R.C. *J. Org. Chem.* ***1974***, *39*, 3721; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1976***, *41*, 1373.
[718] Bases include DBU (see Reaction **17-13**): See Mal, D. *Synth. Commun.* ***1986***, *16*, 331. Cs_2CO_3: Lee, J.C.; Oh, Y.S.; Cho, S.H.; Lee, J.I. *Org. Prep. Proceed. Int.* ***1996***, *28*, 480. CsF-Celite: Lee, J.C.; Choi, Y. *Synth. Commun.* ***1998***, *28*, 2021.
[719] See Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J. Org. Chem.* ***1987***, *52*, 4230.
[720] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 140–155; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 85–95.
[721] See Clark, J.H.; Miller, J.M. *Tetrahedron Lett.* ***1977***, 599.
[722] See, however, Moore, G.G.; Foglia, T.A.; McGahan, T.J. *J. Org. Chem.* ***1979***, *44*, 2425.
[723] Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* ***1990***, *46*, 5167. See Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 185; Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc., Chem. Commun.* ***1991***, 853.

gave the ester with microwave irradiation.[724] Ionic liquid solvents have been shown to facilitate this alkylation reaction.[725]

The reaction of an alcohol and a carboxylate anion with diethyl azodicarboxylate (EtOOCN=NCOOEt) and Ph_3P[726] is called the *Mitsunobu reaction*.[727] Other azocarboxylates may be used in this reaction, including diisopropyl azodicarboxylate (DIAD), and di-2-methoxyethyl azodicarboxylate (DMEAD).[728] Other Mitsunobu catalysts are available,[729] including organocatalysts,[730] and polymer-supported reagents have been used.[731] A renewable phosphine ligand has been developed.[732] Note that other functional groups, including azides[733] and thiocyanates[734] can be generated from alcohols using Mitsunobu conditions. This reaction can also be considered as an S_N2 mechanism. Phenol esters can also be formed.[735] Mitsunobu cyclodehydration of 1,2-diols leads to epoxides.[736]

Lactones can be prepared from halo acids by treatment with base (see Reaction **16-63**). This has most often been accomplished with γ and δ lactones, but macrocyclic lactones (e.g., 11-17-members) have also been prepared in this way.[737] An interesting variation treated 2-ethylbenzoic acid with hypervalent iodine and then $I_2/h\nu$ to give the five-membered ring lactone.[738]

Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[739] A simple S_N mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.[740]

A carboxylic acid (not the salt) can be the nucleophile if F^- is present.[741] Mesylates are readily displaced, for example, by benzoic acid/CsF.[742] Dihalides have been converted to

[724] Yuncheng, Y.; Yulin, J.; Dabin, G. *Synth. Commun.* ***1992***, *22*, 3109.
[725] Brinchi, L.; Germani, R.; Savelli, G. *Tetraheron Lett.* ***2003***, *44*, 2027, 6583; Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* ***2004***, 33.
[726] Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2380; Camp, D.; Jenkins, I.D. *Aust. J. Chem.* ***1988***, *41*, 1835.
[727] But, T.Y.S.; Toy, P.H. *Chemistry: Asian J.* ***2007***, *2,* 1340. See Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* ***2002***, *67,* 1751 and references cited therein. See also, Hughes, D.L. *Org. Prep. Proceed. Int.* ***1996***, *28*, 127; Dembinski, R. *Eur. J. Org. Chem.* ***2004***, 2763; Dandapani, S.; Curran, D.P. *Chem. Eur. J.* ***2004***, *10*, 3131. Also see Steinreiber, A.; Stadler, A.; Mayer, S.F.; Faber, K.; Kappe, C.O. *Tetrahedron Lett.* ***2001***, *42,* 6283. For a chromatography-free product separation, see Proctor, A.J.; Beautement, K.; Clough, J.M.; Knight, D.W.; Li, Y. *Tetrahedron Lett.* ***2006***, *47,* 5151.
[728] Sugimura, T.; Hagiya, K. *Chem. Lett.* ***2007***, *36, 566.*
[729] See Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2529; Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2531. For fluorous reactions and reagents see Dandapani, S.; Curran, D.P. *Tetrahedron* ***2002***, *58,* 3855.
[730] But, T.Y.S.; Toy, P.H. *J. Am. Chem. Soc.* ***2006***, *128,* 9636.
[731] Harned, A.M.; He, H.S.; Toy, P.H.; Flynn, D.L.; Hanson, P.R. *J. Am. Chem. Soc.* ***2005***, *127,* 52.
[732] Yoakim, C.; Guse, I.; O'Meara, J.A.; Thavonokham, B. *Synlett* ***2003***, 473.
[733] See Papeo, G.; Poster, H.; Vianello, P.; Varasi, M. *Synthesis* ***2004***, 2886.
[734] Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. *Synthesis* ***2004***, 92.
[735] Fitzjarrald, V.P.; Pongdee, R. *Tetrahedron Lett.* ***2007***, *48*, 3553.
[736] García-Delgado, N.; Riera, A.; Verdaguer, X. *Org. Lett.* ***2007***, *9,* 635.
[737] See Galli, C.; Mandolini, L. *Org. Synth.* ***VI***, 698; Kimura, Y.; Regen, S.L. *J. Org. Chem.* ***1983***, *48*, 1533.
[738] Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* ***1995***, *36*, 7089.
[739] Klumpp, G.W.; Bos, H.; Schakel, M.; Schmitz, R.F.; Vrielink, J.J. *Tetrahedron Lett.* ***1975***, 3429.
[740] Yamaji, M.; Fujiwara, Y.; Asano, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 90.
[741] Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett.* ***2001***, *42*, 9245.
[742] Sato, T.; Otera, J. *Synlett*, ***1995***, 336.

diesters by this method.[741] A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide ($ArCOCH_2Br$).[743] The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see Reaction **16-61**) by phase-transfer catalyzed treatment of primary alkyl halides with dry $KHCO_3$ and K_2CO_3.[744]

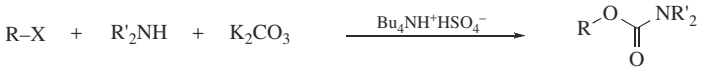
Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. Treatment with oxalyl chloride allows displacement by carboxylate salts.[745] The use of dimethyl sulfate[746] or trimethyl phosphate[747] allows sterically hindered COOH groups to be methylated. The reaction of benzoic acid with aq lithium hydroxide, and then dimethyl sulfate gave methyl benzoate.[748] Dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, see Reaction **17-13**) has been used to prepare methyl esters.[749] With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites [$P(OR)_3$][750] and acetals of DMF.[751]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOH + ROH + HCONMe_2$$

This is an S_N2 process, since inversion is found at R. Another good leaving group is NTs_2 and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[752] $RNTs_2 + OAc^- \rightarrow ROAc$. Ordinary primary amines have been converted to acetates and benzoates by the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.iii).[753] Quaternary ammonium salts can be cleaved by heating with AcO^- in an aprotic solvent.[754] Oxonium ions can also be used as substrates:[755] $R_3O^+ + R'COO^- \rightarrow R'COOR + R_2O$. The reaction of potassium thioacetate with alkyl halides give dithiocarboxylic esters.[756]

In a variation of this reaction, alkyl halides can be converted to carbamates, by treatment with a secondary amine and K_2CO_3 under phase transfer conditions.[757] The reaction of alcohols and alkyl halides can lead to carbonates.[758]

[743] Hendrickson, J.B.; Kandall, L.C. *Tetrahedron Lett.* ***1970***, 343.
[744] Verdecchia, M.; Frochi, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* ***2002***, *67*, 8287. See also, Kadokawa, J.-i.; Habu, H.; Fukamachi, S.; Karasu, M.; Tagaya, H.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2205.
[745] Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Koike, N.; Procopiou, P.A. *J. Org. Chem.* ***1998***, *63*, 6273.
[746] Grundy, J.; James, B.G.; Pattenden, G. *Tetrahedron Lett.* ***1972***, 757.
[747] Harris, M.M.; Patel, P.K. *Chem. Ind. (London)* ***1973***, 1002.
[748] Chakraborti, A.K.; Basak, A.; Grover, V. *J. Org. Chem.* ***1999***, *64,* 8014. See also, Avila–Zárraga, J.G.; Martínez, R. *Synth. Commun.* ***2001***, *31*, 2177.
[749] Shieh, W.-C.; Dell, S.; Repic, O. *Tetrahedron Lett.* ***2002***, *43*, 5607.
[750] Szmuszkovicz, J. *Org. Prep. Proceed. Int.* ***1972***, *4*, 51.
[751] Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 211; Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1963***, *2*, 212.
[752] Curtis, V.A.; Schwartz, H.S.; Hartman, A.F.; Pick, R.M.; Kolar, L.W.; Baumgarten, R.J. *Tetrahedron Lett.* ***1977***, 1969.
[753] See Katritzky, A.R.; Gruntz, U.; Kenny, D.H.; Rezende, M.C.; Sheikh, H. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 430.
[754] Wilson, N.D.V.; Joule, J.A. *Tetrahedron* ***1968***, *24*, 5493.
[755] Raber, D.J.; Gariano, Jr., P.; Brod, A.O.; Gariano, A.; Guida, W.C.; Guida, A.R.; Herbst, M.D. *J. Org. Chem.* ***1979***, *44*, 1149.
[756] Zheng, T.-C.; Burkart, M.; Richardson, D.E. *Tetrahedron Lett.* ***1999***, *40*, 603.
[757] Gómez-Parra, V.; Sánchez, F.; Torres, T. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 695.
[758] Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843. Also see Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* ***2003***, *125,* 4874.



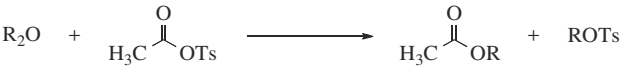
OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580; **VI**, 273, 576, 698.

10-18 Cleavage of Ethers with Acetic Anhydride or Acid Halides

Acyloxy-de-alkoxylation

$$R—O—R' + Ac_2O \xrightarrow{FeCl_3} ROAc + R'OAc$$

Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride,[759] or with Me_3SiOTf in acetic anhydride.[760] In this reaction, both R groups are converted to acetates and yields are moderate to high. Ethers can also be cleaved by the mixed, anhydride acetyl tosylate:[761]



Epoxides give β-hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.[762] Tetrahydrofuran was opened to give *O*-acyl-4-iodo-1-butanol by treatment with acid chlorides and samarium halides[763] or BCl_3.[764] In a highly specialized transformation, the reaction of an epoxide with CO_2 and $ZnCl_2$ in an ionic liquid leads to a cyclic carbonate.[765] Epoxides react with CO and CH_3OH in the presence of 10% of 3-hydroxypyridine and 5% of $Co_2(CO)_8$ to give a β-hydroxy methyl ester.[766]

OS **VIII**, 13.

10-19 Alkylation of Carboxylic Acids with Diazo Compounds

Hydro, **acyloxy-de-diazo-bisubstitution**

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as **10-11**. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, diazomethane (CH_2N_2)[654] is commonly used to prepare methyl esters, and diazo ketones are common. The mechanism is as shown in Reaction **10-11**.

OS **V**, 797.

[759] Ganem, B.; Small, Jr., V.M. *J. Org. Chem.* ***1974***, *39*, 3728.
[760] Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun.* ***1996***, 2625.
[761] Karger, M.H.; Mazur, Y. *J. Am. Chem. Soc.* ***1968***, *90*, 3878. See also, Coffi-Nketsia, S.; Kergomard, A.; Tautou, H. *Bull. Soc. Chim. Fr.* ***1967***, 2788.
[762] See Otera, J.; Matsuzaki, S. *Synthesis* ***1986***, 1019; Deardorff, D.R.; Myles, D.C. *Org. Synth.*, ***67***, 114.
[763] Kwon, D.W.; Kim, Y.H.; Lee, K. *J. Org. Chem.* ***2002***, *67*, 9488.
[764] Malladi, R.R.; Kabalka, G.W. *Synth. Commun.* ***2002***, *32*, 1997.
[765] Li, F.; Xiao, L.; Xia, C.; Hu, B. *Tetrahedron Lett.* ***2004***, *45*, 8307.
[766] Denmark, S.E.; Ahmad, M. *J. Org. Chem.* ***2007***, *72,* 9630.

D. Other Oxygen Nucleophiles

10-20 Formation of Oxonium Salts

Dialkyloxonio-de-halogenation

$$RX + R_2O \longrightarrow R_3O^+ \ {}^-BF_4 + AgX$$

$$RX + R'_2CO \longrightarrow R'_2C{=}O^+{-}R \ BF_4^- + AgX$$

Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X^-.[767] A typical procedure consists of treating the halide with the ether or the ketone in the presence of $AgBF_4$ or $AgSbF_6$. The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid (e.g., $R_2O{\bullet}BF_3 + RX \rightarrow R_3O^+ \ BF_4^-$), although this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:

$$2\,R_3O^+BF_4^- + 3\,R'_2O \rightleftharpoons 2\,R'_3O^+BF_4^- + 3\,R_2O$$

OS **V**, 1080, 1096, 1099; **VI**, 1019.

10-21 Preparation of Peroxides and Hydroperoxides

Hydroperoxy-de-halogenation

$$RX + {}^-OOH \longrightarrow ROOH$$

Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^-.[768] Sodium peroxide is similarly used to prepare dialkyl peroxides ($2RX + Na_2O_2 \rightarrow ROOR$). Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H_2O_2 or a peroxide in the presence of silver trifluoroacetate.[769] Peroxides can also be prepared[770] by treatment of alkyl bromides or tosylates with potassium superoxide (KO_2) in the presence of crown ethers (though alcohols may be side products[771]) and by the reaction between alkyl triflates and germanium or tin peroxide.[772]

Diacyl peroxides and acyl hydroperoxides can similarly be prepared[773] from acyl halides or anhydrides and from carboxylic acids.[774] Diacyl peroxides can also be prepared by the

[767] Meerwein, H.; Hederich, V.; Wunderlich, K. *Arch. Pharm.* ***1958***, *291/63*, 541. See Perst, H. *Oxonium Ions in Organic Chemistry,* Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 22–39.

[768] See Hiatt, R. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 1–151; Pandiarajan, K. in Pizey, J. S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 60–155.

[769] Cookson, P.G.; Davies, A.G.; Roberts, B.P. *J. Chem. Soc., Chem. Commun.* ***1976***, 1022. Also see Bourgeois, M.; Montaudon, E.; Maillard, B. *Synthesis* ***1989***, 700.

[770] Johnson, R.A.; Nidy, E.G.; Merritt, M.V. *J. Am. Chem. Soc.* ***1978***, *100*, 7960.

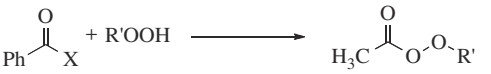
[771] See San Filippo, Jr., J.; Chern, C.; Valentine, J.S. *J. Org. Chem.* ***1975***, *40*, 1678; Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett.* ***1975***, 3183.

[772] Salomon, M.F.; Salomon, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 4290.

[773] See Bouillon, G.; Lick, C.; Schank, K. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 279–309; Hiatt, R.; Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 799–929.

[774] See Silbert, L.S.; Siegel, E.; Swern, D. *J. Org. Chem.* ***1962***, *27*, 1336.

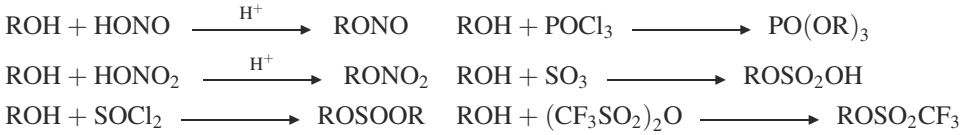
treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,[775] Sulfuric acid, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.



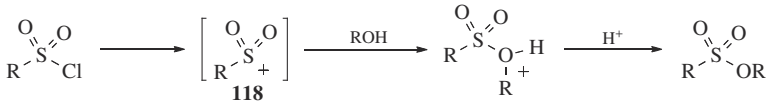
OS **III**, 619, 649; **V**, 805, 904; **VI**, 276.

10-22 Preparation of Inorganic Esters

Nitrosooxy-de-hydroxylation, and so on.



The above transformations show a few of the many inorganic esters that can be prepared by the reaction of an alcohol with an inorganic acid or, better, its acid halide or anhydride[776] These similar reactions are grouped together for convenience, but not all involve nucleophilic substitutions at R. The other possible pathway is nucleophilic substitution at the inorganic central atom, such as the attack of the alcohol oxygen at the electrophilic sulfur atom in **118**,[777] or a corresponding S_N2 type process (see Sec. 16.B.v). In such cases, there



118

is no alkyl-*O* cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO_3, H_2SO_4, $ClSO_2OH$, or SO_3 complexes.[778] It is possible to prepare a primary sulfonate ester (e.g., tosylate), in the presence of a secondary alcohol unit when tosic acid reacts with a 1,2-diol in the presence of Fe^{3+}-Montmorillonite.[779] Polymer-bound reagents have been used to prepared sulfonate esters.[780] Phenolic triflates have been prepared using *N,N*-ditrifylaniline and K_2CO_3 under microwave irradiation.[781] Sulfinic esters are readily prepared from alcohols and sulfinyl chlorides, and in the presence of Cinchona alkaloids the reaction is enantioselective.[782]

[775] Greene, F.D.; Kazan, J. *J. Org. Chem.* ***1963***, *28*, 2168.
[776] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pp. 481–497.
[777] See Aldred, S.E.; Williams, D.L.H.; Garley, M. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 777.
[778] Sandler, S.R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed., Vol 3, Academic Press, NY, ***1989***, pp. 129–151.
[779] Choudary, B.M.; Chowdari, N.S.; Kantam, M.L. *Tetraheron* ***2000***, *56,* 7291.
[780] Vignola, N.; Dahmen, S.; Enders, D.; Bräse, S. *Tetrahedron Lett.* ***2001***, *42*, 7833.
[781] Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* ***2002***, *4*, 1231.
[782] Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett* ***2005***, 1699.

Alkyl nitrites[783] can be conveniently prepared by an exchange reaction ROH + R′ONO → RONO + R′OH, where R = *t*-Bu.[784] Primary amines can be converted to alkyl nitrates ($RNH_2 \rightarrow RONO_2$) by treatment with N_2O_4 at −78 °C in the presence of an excess of amidine base.[785] *Mitsunobu* conditions (Reaction **10-17**) can be used to prepare phosphate ester or phosphonate esters. The reaction can be done intramolecularly for prepare cyclic phosphonate esters.[786]

Alkyl halides are often used as substrates instead of alcohols. In such cases, the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is used as a test for alkyl halides. In some cases, there is competition from the central atom. Thus nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see Reaction **10-42**).[787] Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.[788]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

Here R″ may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R′OH is rapidly converted to R′OR′ by the sulfonic acid (Reaction **10-12**), which in turn is further cleaved to $R'OSO_2R''$ so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids[789] (prepared as in Reaction **16-68**). β-Hydroxyalkyl perchlorates[790] and sulfonates can be obtained from epoxides.[791] Epoxides and oxetanes give α,ω-dinitrates when treated with N_2O_5.[792] Aziridines and azetidines react similarly, giving nitramine nitrates (e.g., *N*-butylazetidine gave $NO_2OCH_2CH_2CH_2N(Bu)NO_2$).[792]

Phosphinate esters are prepared by transesterification-type reactions (**16-64**) from alcohols and other phosphinates.[793]

OS **II**, 106, 108, 109, 112, 204, 412; **III**, 148, 471; **IV**, 955; **V**, 839; **VIII**, 46, 50, 616. Also see, OS **II**, 111.

10-23 Alcohols from Amines

Hydroxy-de-amination

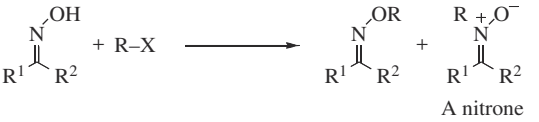
$$RNH_2 \longrightarrow ROH$$

This transformation is rare. A rather direct method was reported whereby a primary amine reacted with KOH in diethylene glycol at 210 °C.[794] The reaction of

[783] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–172.
[784] Doyle, M.P.; Terpstra, J.W.; Pickering, R.A.; LePoire, D.M. *J. Org. Chem.* ***1983***, *48*, 3379. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–156.
[785] Barton, D.H.R.; Narang, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 1114.
[786] Pungente, M.D.; Weiler, L. *Org. Lett.* ***2001***, *3,* 643.
[787] See Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V. *Russ. Chem. Rev.* ***1988***, *57*, 760.
[788] Klamann, D.; Weyerstahl, P. *Chem. Ber.* ***1965***, *98*, 2070.
[789] Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 532, 540.
[790] See Zefirov, N.S.; Zhdankin, V.V.; Koz'min, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 1041.
[791] Zefirov, N.S.; Kirin, V.N.; Yur'eva, N.M.; Zhdankin, V.V.; Kozmin, A.S. *J. Org. Chem. USSR* ***1987***, *23*, 1264.
[792] Golding, P.; Millar, R.W.; Paul, N.C.; Richards, D.H. *Tetrahedron Lett.* ***1988***, *29*, 2731, 2735.
[793] Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* ***2005***, *70,* 10121.
[794] Rahman, S.M.A.; Ohno, H.; Tanaka, T. *Tetrahedron Lett.* ***2001***, *42*, 8007.

(*S*)-phenethylamine and the bis-(sulfonyl chloride) of 1,2-benzenesulfonic acid, followed by KNO_2 and 18-crown-6 gave (*R*)-phenethyl alcohol in 70% yield and 40% enantiomeric excess (ee).[795]

10-24 Alkylation of Oximes[796]



Oximes can be alkylated by alkyl halides or sulfates. *N*-Alkylation is a side reaction, yielding a nitrone.[797] The relative yield of oxime ether and nitrone depends on the nature of the reagents, including the configuration of the oxime, and on the reaction conditions.[798] For example, *anti*-benzaldoximes give nitrones, while the syn isomers give oxime ethers.[799]

OS **III**, 172; **V**, 1031. Also see, OS **V**, 269; **VI**, 199.

10.H.iii. Sulfur Nucleophiles

Sulfur compounds[800] are better nucleophiles than their oxygen analogues (Sec. 10.G.ii), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.[801]

10-25 Attack by SH at an Alkyl Carbon: Formation of Thiols[802]

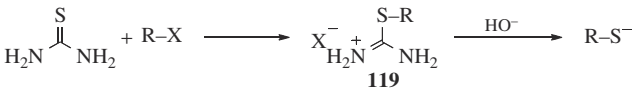
Mercapto-de-halogenation



Sodium sulfhydride (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H_2S and is used much more often. It is easily prepared by bubbling H_2S into an alkaline solution, but hydrosulfide on a supported polymer resin has also been used.[803] The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary

[795] Sørbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetraheron Asymmetry*, ***1998***, *9*, 681.
[796] See Abele, E.; Lukevics, E. *Org. Prep. Proceed. Int.* ***2000***, *32*, 235.
[797] See Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 75–93; Katritzky, A.R.; Cui, X.; Long, Q.; Yanga, B.; Wilcox, A.L.; Zhang, Y.-K. *Org. Prep. Proceed. Int.* ***2000***, *32*, 175.
[798] See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***, pp. 262–272.
[799] Buehler, E. *J. Org. Chem.* ***1967***, *32*, 261.
[800] See Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***; Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***. For selenium compounds, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***; Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.
[801] See Ashby, E.C.; Park, W.S.; Goel, A.B.; Su, W. *J. Org. Chem.* ***1985***, *50*, 5184.
[802] See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 179–211.
[803] Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Chem. Lett.* ***2000***, 1304.

halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.[804] The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide (e.g., $Ph_3SnSSnPh_3$).[805] An indirect method for the preparation of a thiol is the reaction of an alkyl halide with thiourea to give an isothiuronium salt (**119**), and subsequent treatment with alkali or a high-molecular-weight amine gives cleavage to the thiol.



119

Other indirect methods are treatment of the halide with silyl-thiols and KH, followed by treatment with fluoride ion and water,[806] and hydrolysis of *Bunte salts* (see Reaction **10-28**) is another method.

Thiols have also been prepared from alcohols. One method involves treatment with H_2S and a catalyst (e.g., Al_2O_3),[807] but this is limited to primary alcohols. Another method involves treatment with *Lawesson's reagent* (see Reaction **16-10**).[808] Tertiary nitro compounds give thiols ($RNO_2 \rightarrow RSH$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.[809]

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **VIII**, 592. Also see, OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

10-26 Attack by S at an Alkyl Carbon: Formation of Thioethers

Alkylthio-de-halogenation; Alkylthio-de-hydroxylation

$$R{-}X + R'{-}S^- \longrightarrow R{-}S{-}R'$$

$$R{-}OH + R'{-}SH \xrightarrow{\text{additives}} R{-}S{-}R'$$

Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate anions).[810] The R′ group may be alkyl or aryl and organolithium bases can be used to deprotonate the thiol.[811] As in Reaction **10-25**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the *Williamson Reaction* (**10-8**), yields are often improved by phase-transfer catalysis.[812] Thiols react directly with alkyl halides in the presence of bases (e.g., DBU; see Reaction **17-13**)[813] or CsF.[814] Leaving groups other than chloride can be used, as in the Ru catalyzed reaction of thiols

[804] See Vasil'tsov, A.M.; Trofimov, B.A.; Amosova, S.V. *J. Org. Chem. USSR* ***1983***, *19*, 1197.
[805] Gingras, M.; Harpp, D.N. *Tetrahedron Lett.* ***1990***, *31*, 1397.
[806] Miranda, E.I.; Díaz, M.J.; Rosado, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1994***, *35*, 3221; Rane, A.M.; Miranda, E.I.; Soderquist, J. *Tetrahedron Lett.* ***1994***, *35*, 3225.
[807] Lucien, J.; Barrault, J.; Guisnet, M.; Maurel, R. *Nouv. J. Chim.* ***1979***, *3*, 15.
[808] Nishio, T. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1113.
[809] Kornblum, N.; Widmer, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7086.
[810] See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Groups, pt. 2*, Wiley, NY, ***1974***, pp. 721–735.
[811] Yin, J.; Pidgeon, C. *Tetrahedron Lett.* ***1997***, *38*, 5953.
[812] See Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 221–233. Also see Salvatore, R.N.; Smith, R.A.; Nischwitz, A.K.; Gavi, T. *Tetrahedron Lett.* ***2005***, *46,* 8931.
[813] Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Synthesis* ***1980***, 952. See also, Ferreira, J.T.B.; Comasseto, J.V.; Braga, A.L. *Synth. Commun.* ***1982***, *12*, 595; Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Synth. Commun.* ***1982***, *12*, 627.
[814] Shah, S.T.A.; Khan, K.M.; Heinich, A.M.; Voelter, W. *Tetrahedron Lett.* ***2002***, *43*, 8281.

with propargylic carbonates.[815] Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a Ni complex,[816] or in the presence of $Pd(PPh_3)_4$. Alternatively, the Ag salt of an enethiol reacts with iodomethane to give the corresponding methyl vinyl sulfide.[817]

In some cases, alcohols can be converted to thioethers by reaction with thiols. Tertiary alcohols react with thiols in the presence of sulfuric acid to give thioethers, and the reaction works best with tertiary substrates.[818] This reaction is analogous to Reaction **10-12**. Thiophenol reacts with propargylic alcohols in the presence of a Ru catalyst to give propargylic thioethers.[819] Primary and secondary alcohols can be converted to alkyl aryl sulfides ($ROH \rightarrow RSAr$) in high yields by treatment with Bu_3P and an *N*-(arylthio)succinimide in benzene.[820] Iodine catalyzes the allylic alkylation of thiols.[821] Thioethers (RSR') can be prepared from an alcohol ROH and a halide $R'Cl$ by treatment with tetramethylthiourea $Me_2NC(=S)NMe_2$ followed by NaH.[822]

Thiolate ions are also useful for the demethylation of certain ethers,[823] esters, amines, and quaternary ammonium salts. Aryl methyl ethers[824] can be cleaved by heating with EtS^- in the dipolar aprotic solvent DMF: $ROAr + EtS^- \rightarrow ArO^- + EtSR$.[825] Allylic sulfides have been prepared by treating allylic carbonates $ROCO_2Me$ (R = an allylic group) with a thiol and a Pd(0) catalyst.[826] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in 2-butanone to give the amine and methyl phenyl sulfide.[827]

A methyl group is cleaved more readily than other simple alkyl groups (e.g., ethyl), although loss of these groups competes. Benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.[828]

Symmetrical thioethers (R—S—R) can also be prepared by treatment of an alkyl halide (R—X) with sodium sulfide (Na_2S).[829] Symmetrical thioethers have also been prepared by the reaction of $S(MgBr)_2$ with allylic halides.[830] This reaction can be carried out internally, by treatment of sulfide ions with 1,4-, 1,5-, or 1,6-dihalides, to prepare five-, six-, and

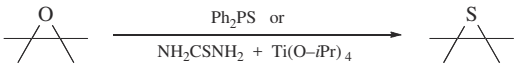
[815] Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2002***, *124,* 12960.
[816] Cristau, H.J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* ***1986***, *51*, 875.
[817] Ochiai, M.; Hirobe, M.; Miyamoto, K. *J. Am. Chem. Soc.* ***2006***, *128,* 9046.
[818] See Cain, M.E.; Evans, M.B.; Lee, D.F. *J. Chem. Soc.* ***1962***, 1694.
[819] Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 15172.
[820] Walker, K.A.M. *Tetrahedron Lett.* ***1977***, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also, Cleary, D.G. *Synth. Commun.* ***1989***, *19*, 737.
[821] Zhang, X.; Rao, W.; Chan, P.W.H. *Synlett* ***2008***, 2204.
[822] Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2429.
[823] See Evers, M. *Chem. Scr.* ***1986***, *26*, 585.
[824] Also see Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* ***1980***, *21*, 2305; Williard, P.G.; Fryhle, C.B. *Tetrahedron Lett.* ***1980***, *21*, 3731; Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1980***, *45*, 4275; Evers, M.; Christiaens, L. *Tetrahedron Lett.* ***1983***, *24*, 377; Tiecco, M. *Synthesis* ***1988***, 749.
[825] Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.* ***1970***, 1327, *Aust. J. Chem.* ***1972***, *25*, 1719, 1731.
[826] Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron* ***1994***, *50*, 10321.
[827] Shamma, M.; Deno, N.C.; Remar, J.F. *Tetrahedron Lett.* ***1966***, 1375. For alternative procedures, see Hutchins, R.O.; Dux, F.J. *J. Org. Chem.* ***1973***, *38*, 1961; Posner, G.H.; Ting, J. *Synth. Commun.* ***1974***, *4*, 355.
[828] Kametani, T.; Kigasawa, T.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* ***1969***, 635.
[829] For another reagent, see Harpp, D.N.; Gingras, M.; Aida, T.; Chan, T.H. *Synthesis* ***1987***, 1122.
[830] Nedugov, A.N.; Pavlova, N.N. *Zhur. Org. Khim.*, ***1992***, *28*, 1401 (Engl. 1103).

seven-membered[831] sulfur-containing heterocyclic rings. Certain larger rings have also been closed in this way.[832]

gem-Dihalides can be converted to dithioacetals [$RCH(SR')_2$],[833] and acetals have been converted to monothioacetals [$R_2C(OR')(SR^2)$],[834] and to dithioacetals.[835] The combination of carbon disulfide and $NaBH_4$ converted 1,3-dibromopropane to 1,3-dithiane.[836]

When epoxides are substrates,[837] reaction with $PhSeSnBu_3/BF_3{\bullet}OEt_2$[838] gives the corresponding β-hydroxy selenide in a manner analogous to that mentioned in Reaction **10-25**. Reaction of an epoxide with Ph_3SiSH followed by treatment with Bu_4NF gives hydroxy-thiols.[839]

Epoxides can also be directly converted to episulfides (thiiranes)[840] by treatment with a phosphine sulfide (e.g., Ph_3PS),[841] with thiourea and titanium tetraisopropoxide[842] or thiourea and $LiBF_4$ in acetonitrile,[843], with NH_4SCN and TiO $(tfa)_2$ (tfa = trifluoacetyl),[844] with $(EtO)_2P(=O)H/S/Al_2O_3$,[845] with KSCN and $InBr_3$,[846] and with KSCN in ionic liquids (Sec. 9.D.iii).[847] 2,4,6-Trichloro-1,3,5-triazine catalyzes this conversion under solvent-free conditions.[848]



Selenides (selenoethers) and tellurides can be prepared via RSe^- and RTe^- species,[849] and Se and borohydride exchange resin followed by the halide give the selenoether.[850] The La/I_2 catalyzed reaction of diphenyl diselenide with primary alkyl iodides gave arylalkyl

[831] Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* ***1992***, *33*, 7709.
[832] See Singh, A.; Mehrotra, A.; Regen, S.L. *Synth. Commun.* ***1981***, *11*, 409.
[833] See, for example Wähälä, K.; Ojanperä, I.; Häyri, L.; Hase, T.A. *Synth. Commun.* ***1987***, *17*, 137.
[834] Sato, T.; Kobayashi, T.; Gojo, T.; Yoshida, E.; Otera, J.; Nozaki, H. *Chem. Lett.* ***1987***, 1661.
[835] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* ***2001***, *66*, 7527 and references cited therein; Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* ***2002***, 727.
[836] Wan, Y.; Kurchan, A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* ***2000***, *2*, 1133.
[837] Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett*, ***1992***, 303.
[838] Nishiyama, Y.; Ohashi, H.; Itoh, K.; Sonoda, N. *Chem. Lett.* ***1998***, 159.
[839] Brittain, J.; Gareau, Y. *Tetrahedron Lett.* ***1993***, *34*, 3363.
[840] See Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1975***, *44*, 138. Key intermediates have been isolated: Kleiner, C.M.; Horst, L.; Würtele, C.; Wende, R.; Schreiner, P.R. *Org. Biomol. Chem.* ***2009, 7***, 1397. See Das, B.; Reddy, V.S.; Krishnaiah, M. *Tetrahedron Lett.* ***2006***, *47,* 8471.
[841] Chan, T.H.; Finkenbine, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 2880.
[842] Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4114. Also see Bouda, H.; Borredon, M.E.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1987***, *17*; 943, ***1989***, *19*, 491.
[843] Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 595.
[844] Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1998***, *28*, 3913. See also, Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett.* ***2004***, *45*, 1535.
[845] Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* ***2004***, *45*, 1283.
[846] Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *Synlett.* ***2003***, 396.
[847] Yadav, J.S.; Reddy, B.V.S.; Reddy, Ch.S.; Rajasekhar, K. *J. Org. Chem.* ***2003***, *68,* 2525.
[848] Bandgar, B.P.; Joshi, N.S.; Kamble, V.T. *Tetrahedron Lett.* ***2006***, *47,* 4775.
[849] Cohen, R.J.; Fox, D.L.; Salvatore, R.N. *J. Og. Chem.* ***2004***, *69,* 4265. Also see Monahan, R.; Brown, D.; Waykole, L.; Liotta, D. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 207–241.
[850] Yanada, K.; Fujita, T.; Yanada, R. *Synlett*, ***1998***, 971.

selenides,[851] Indium has been used with alkyl halides.[852] A Zn mediated synthesis of tertiary alkyl selenides from tertiary alkyl halides is known.[853] Diaryl selenides (Ar—Se—Ar′) have been prepared by coupling aryl iodides with tin reagents ($ArSeSnR_3$) with a Pd catalyst.[854] α-Seleno aldehydes are prepared by the reaction of an aldehyde with PhSe(N(phthalimide).[855]

OS **II**, 31, 345, 547, 576; **III**, 332, 751, 763; **IV**, 396, 667, 892, 967; **V**, 562, 780, 1046; **VI**, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; **VII**, 453; **VIII**, 592. See also, OS **VI**, 776.

10-27 Formation of Disulfides[856]

Dithio-de-dihalo- *aggre* -substitution

$$2\,RX + S_2^{2-} \longrightarrow RSSR + 2\,X^-$$

Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of *Bunte salts* (see Reaction **10-28**) with acid solutions of iodide, thiocyanate ion, or thiourea,[857] or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when heated to reflux with sulfur and NaOH.[858] Some molybdenum compounds convert alkyl halides to disulfides, including $(BnNEt_3)_6Mo_7S_{24}$.[859]

There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV**, 295.

10-28 Formation of Bunte Salts

Sulfonatothio-de-halogenation

$$RX + S_2O_3^{2-} \longrightarrow R{-}S{-}SO_3^- + X^-$$

Primary and secondary, but not tertiary, alkyl halides are easily converted to *Bunte salts* ($RSSO_3^-$) by treatment with thiosulfate ion.[860] Bunte salts can be hydrolyzed with acids to give the corresponding thiols[861] or converted to disulfides, tetrasulfides, or pentasulfides.[862]

OS **VI**, 235.

[851] Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 8696. Zinc in aqueous media has also been used: see Bieber, L.W.; de Sá, A.C.P.F.; Menezes, P.H.; Goncalves, S.M.C. *Tetrahedron Lett.* ***2001***, *42,* 4597.

[852] Munbunjong, W.; Lee, E.H.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* ***2005***, *46*, 8769.

[853] Krief, A.; Derock, M.; Lacroix, D. *Synlett* ***2005***, 2832.

[854] Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* ***1999***, *1*, 1725.

[855] Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* ***2005***, *70,* 5678.

[856] See Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2004***, *125*, 6624.

[857] Milligan, B.; Swan, J.M. *J. Chem. Soc.* ***1962***, 2712.

[858] Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* ***1977***, *319*, 1036. For an example using microwave irradiation, see Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* ***2002***, *32*, 963.

[859] See Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M.P. *Tetrahedron Lett.* ***2003***, *44*, 887.

[860] For a review of Bunte salts, see Distler, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 544–553.

[861] Kice, J.L. *J. Org. Chem.* ***1963***, *28*, 957.

[862] Milligan, B.; Saville, B.; Swan, J.M. *J. Chem. Soc.* ***1963***, 3608.

10-29 Alkylation of Sulfinic Acid Salts

Alkylsulfonyl-de-halogenation

$$RX + R'SO_2^- \longrightarrow R{-}SO_2{-}R' + X^-$$

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.[863] A Pd catalyzed reaction with a chiral complexing agent led to sulfones with modest asymmetric induction.[864] Alkyl sulfinates ($R'SO{-}OR$) may be side products.[865] Sodium tosylsulfinate reacted with allylic acetates in the presence of a Pd catalyst to give the corresponding sulfone.[866] Sulfonic acids themselves can be used, if DBU (see Reaction **17-13**) is present.[867] Sulfonyl halides react with allylic halides in the presence of $AlCl_3{-}Fe$[868] and with benzyl halides in the presence of $Sm/HgCl_2$.[869] Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.[870] The copper(II)-catalyzed cross-coupling of organoboronic acids and sulfinate salts leads to sulfones.[871] Vinyl sulfones were prepared from $PhSO_2Na$ and vinyl iodinium salts $C{=}C{-}I^+Ph\ BF_4^-$.[872]

OS **IV**, 674; **IX**, 497. See also, OS **VI**, 1016.

10-30 Formation of Alkyl Thiocyanates

Thiocyanato-de-halogenation

$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides[873] or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[874] although the attack by the analogous cyanate ion (Reaction **10-44**) gives exclusive *N*-alkylation. Primary amines can be converted to thiocyanates by the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.iii).[875] Tertiary chlorides are converted to tertiary thiocyanates with $Zn(SCN)_2$ in pyridine and ultrasound.[876]

OS **II**, 366.

[863] See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, pp. 177–188. For a reaction using the MgBr salt of an aryl sulfinate, see Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* ***2005***, *7,* 1223.

[864] Eichelmann, H.; Gais, H.-J. *Tetrahedron Asymmetry*, ***1995***, *6*, 643.

[865] See Kielbasinski, P.; Zurawinski, R.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron* ***1988***, *44*, 6687.

[866] Felpin, F.-X.; Landais, Y. *J. Org. Chem.* ***2005***, *70,* 6441. Also see Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* ***2005***, *70,* 6506.

[867] Biswas, G.; Mal, D. *J. Chem. Res. (S)* ***1988***, 308.

[868] Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2001***, 512.

[869] Zhang, J.; Zhang, Y. *J. Chem. Res. (S)* ***2001***, 516.

[870] Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* ***1989***, *45*, 6791.

[871] Huang, F.; Batey, R.A. *Tetrahedron* ***2007***, *63,* 7667.

[872] Ochiai, M.; Oshima, K.; Masaki, Y.; Kunishima, M.; Tani, S. *Tetrahedron Lett.* ***1993***, *34*, 4829.

[873] Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* ***2001***, *42,* 8479. The reagent $Ph_3P(SCN)_2$ has also been used: see Iranpoor, N.; Firouzabadi, H.; Shaterian, H.R. *Tetrahedron Lett.* ***2002***, *43*, 3439. Also see Mohanazadeh, F.; Aghvami, M. *Tetrahedron Lett.* ***2007***, *48*, 7240.

[874] See Guy, R.G. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, pp. 819–886, Wiley, NY, ***1977***, pp. 819–886.

[875] Katritzky, A.R.; Gruntz, U.; Mongelli, N.; Rezende, M.C. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1953. See Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* ***1977***, 4417.

[876] Bettadaiah, B.K.; Gurudutt, K.N.; Srinivas, P. *Synth. Commun.* ***2003***, *33*, 2293.

10.H.iv. Nitrogen Nucleophiles

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

10-31 Alkylation of Amines

Amino-de-halogenation (alkyl)

$$3\,RX + NH_3 \longrightarrow R_3N + RX \longrightarrow R_4N^+X^-$$
$$2\,RX + R'NH_2 \longrightarrow R_2R'N + RX \longrightarrow R_3R'N^+X^-$$
$$RX + R''R'NH_2 \longrightarrow RR'R''N + RX \longrightarrow R_2R'R''N^+X^-$$
$$RX + RR'R''N \longrightarrow RR'R''R'''N^+X^-$$

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines[877] and quaternary ammonium salts. If ammonia is the nucleophile,[878] the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.[879] It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. Metal-catalyzed methods are available to convert primary amines to secondary amines,[880] and secondary amines can be converted to tertiary amines.[881] Ionic liquids have been used to facilitate amination reactions.[882] The use of ammonia in methanol with microwave irradiation has also been effective.[883] Microwave irradiation has also been used in reactions of aniline with allyl iodides.[884] Bromides react faster than chlorides, and secondary amines reaction with 3-chloro-1-bromopropane via the bromide, in the presence of Zn and THF.[885] *N*-Alkylation has been accomplished using alkyl halides in aqueous media.[886]

Bases other than amine can be used. Both sodium carbonate[887] and lithium hydroxide[888] have been used. Cesium hydroxide was successfully used as a base in the presence of

[877] See Gibson, M.S. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 45–55; Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 14–29.
[878] See Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.
[879] For a discussion of solvent effects see Sola, M.; Lledos, A.; Duran, M.; Bertran, J.; Abboud, J.L.M. *J. Am. Chem. Soc.* ***1991***, *113,* 2873. For other parameters, see Bottini, A.T. *Sel. Org. Transform.* ***1970***, *1*, 89; Persson, J.; Berg, U.; Matsson, O. *J. Org. Chem.* ***1995***, *60*, 5037; Zoltewicz, J.A.; Deady, L.W. *Adv. Heterocycl. Chem.* ***1978***, *22*, 71; Shaik, S.; Ioffe, A.; Reddy, A.C.; Pross, A. *J. Am. Chem. Soc.* ***1994***, *116*, 262.
[880] Lorentz-Petersen, L.L.R.; Jensen, P.; Madsen, R. *Synthesis* ***2009***, 4110.
[881] Kurosu, M.; Dey, S.S.; Crick, D.C. *Tetrahedron Lett.* ***2006***, *47,* 4871.
[882] Lyubimov, S.E.; Davankov, V.A.; Gavrilov, K.N. *Tetrahedron Lett.* ***2006***, *47*, 2721.
[883] Saulnier, M.G.; Zimmermann, K.; Struzynski, C.P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D.B. *Tetrahedron Lett.* ***2004***, *45,* 397.
[884] Romera, J.L.; Cid, J.M.; Trabanco, A.A. *Tetrahedron Lett.* ***2004***, *45,* 8797.
[885] Murty, M.S.R.; Jyothirmai, B.; Krishna, P.R.; Yadav, J.S. *Synth. Commun.* ***2003***, *33*, 2483.
[886] Singh, C.B.; Kavala, V.; Samal, A.K.; Patel, B.K. *Eur. J. Org. Chem.* ***2007***, 1369; Simion, A.M.; Arimura, T.; Miyazawa, A.; Simion, C.; Prakash, G.K.S.; Olah, G.A.; Tashiro, M. *Synth. Commun.* ***2009***, *39*, 2859.
[887] Faul, M.M.; Kobierski, M.E.; Kopach, M.E. *J. Org. Chem.* ***2003***, *68,* 5739.
[888] Cho, J.H.; Kim, B.M. *Tetrahedron Lett.* ***2002***, *43*, 1273.

molecular sieve 4 Å,[889] and cesium fluoride has been used with benzylic halides.[890] Potassium carbonate in DMSO has been used for the alkylation of aniline.[891]

The limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, which gave 34.2% of the primary amine (at a 1:1 ratio the yield was 11.3%).[892] α-Halo acids are one type of substrate that give reasonable yields of primary amine (provided a large excess of NH_3 is used) and are subsequently converted to amino acids. *N*-Chloromethyl lactams also react with amines to give good yields to the *N*-aminomethyl lactam.[893] An indirect method to prepare primary amines from alkyl halides uses Reaction **10-43**, followed by reduction of the azide (**19-32**),[894] and the *Gabriel synthesis* (**10-41**) is effective.

The immediate product in any particular step is the protonated amine, but it rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, for example,

$$RX + R_2NH \longrightarrow R_3\overset{+}{N}H + R_2NH \rightleftharpoons R_3N + R_2\overset{+}{N}H_2$$

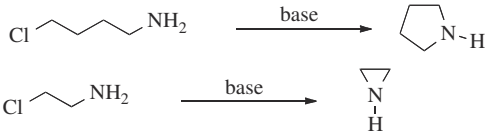
When a primary or secondary amine must be converted directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a non-nucleophilic strong base that serves to remove the proton from $RR'NH_2^+$ or $RR'R^2NH^+$ and thus liberates the amine to attack another molecule of RX.[895]

The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^- R_2N^-) are generically known as *amide bases*, and are sometimes used as nucleophiles,[896] including amide bases generated from organolithium reagents and amines (R_2NLi).[897] This is in contrast to analogous methods **10-1**, **10-8**, **10-25**, and **10-26**. Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl)amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.[898] Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[899] Sulfates or sulfonates can be used instead of halides. *N*-Alkylation of heterocycles is sometimes problematic, but pyrrole is converted to *N*-methylpyrrole with KOH, iodomethane in ionic liquids.[900]

The reaction can be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives

[889] Salvatore, R.N.; Schmidt, S.E.; Shin, S.I.; Nagle, A.S.; Worrell, J.H.; Jung, K.W. *Tetrahedron Lett.* ***2000***, *41*, 9705.
[890] Hayat, S.; Rahman, A.-u.; Choudhary, M.I.; Khan, K.M.; Schumann, W.; Bayer, E. *Tetrahedron* ***2001***, *57*, 9951.
[891] Salvatore, R.N.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2002***, *67,* 674.
[892] Werner, E.A. *J. Chem. Soc.* ***1918***, *113*, 899.
[893] Chen, P.; Suh, D.J.; Smith, M.B. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 1317; Deskus, J.; Fan, D.-p.; Smith. M.B. *Synth. Commun.* ***1998***, *28*, 1649.
[894] See Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.S. *Synlett.* ***1999***, 551.
[895] Sommer, H.Z.; Lipp, H.I.; Jackson, L.L. *J. Org. Chem.* ***1971***, *36*, 824. See also, Chuang, T.-H.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 3555.
[896] See DePue, J.S.; Collum, D.B. *J. Am. Chem. Soc.* ***1988***, *110*, 5524.
[897] Vitale, A.A.; Chiocconi, A.A. *J. Chem. Res. (S)* ***1996***, 336.
[898] Bestmann, H.J.; Wölfel, G. *Chem. Ber.* ***1984***, *117*, 1250.
[899] Patai, S.; Weiss, S. *J. Chem. Soc.* ***1959***, 1035.
[900] Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 1951.

aziridine[901] (analogous to Reaction **10-9**):



Reduction of *N*-(3-bromopropyl) imines gives a bromoamine *in situ*, which cyclizes to the aziridine.[902] Five-membered ring amines (pyrrolidines) can be prepared from alkenyl amines via treatment with *N*-chlorosuccinimide (NCS) and then Bu_3SnH.[903] The Pd catalyzed internal addition of amine to allylic acetates leads to cyclic products via a S_N2' reaction.[904] Three-membered cyclic amines (aziridines) can be prepared from chiral conjugated amides via bromination and reaction with an amine.[905] Four-membered cyclic amines (azetidines) have been prepared from the ditosylate of 1,3-propanediol[906] and from 1,3-dichloropropane.[907] This reaction was also used to close five-, six-, and seven-membered rings.



As usual, tertiary substrates do not give the reaction at all, but undergo preferential elimination upon treatment with a basic amine. However, tertiary (but not primary or secondary) halides (e.g., R_3CCl) can be converted to primary amines (R_3CNH_2) by treatment with NCl_3 and $AlCl_3$[908] in a reaction related to Reaction **10-39**. Ruthenium(II) complexes have been used for the alkylation of aryl amines.[909]

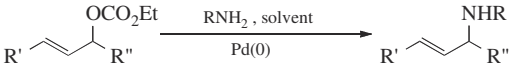
Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine[910] followed by cleavage of the resulting salt with ethanolic HCl. The method called the *Delépine reaction* is most successful for active halides (e.g., allylic and benzylic halides and α-halo ketones).

A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or calcium salt of cyanamide (NH_2—CN) to give disubstituted cyanamides, which are then hydrolyzed and decarboxylated to secondary amines. Good yields are obtained when the reaction is carried out under phase-transfer conditions.[911] The R group may be primary, secondary, allylic, or benzylic. 1,ω-Dihalides give cyclic secondary amines. Aminoboranes react with sulfonate esters to give a derivative that can be hydrolyzed to a tertiary amine.[912] An aminyl-radical

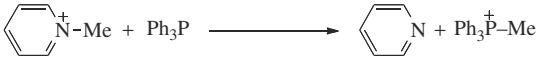
[901] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines,* Academc Press, NY, ***1969***, pp. 1–59.
[902] DeKimpe, N.; DeSmaele, D. *Tetrahedron Lett*. ***1994***, *35*, 8023. Also see, De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* ***1994***, *35*, 1925.
[903] Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 777.
[904] Grellier, M.; Pfeffer, M.; van Koten, G. *Tetrahedron Lett*. ***1994***, *35*, 2877.
[905] Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.*,**1994**, 35, 1653.
[906] Juaristi, E.; Madrigal, D. *Tetrahedron* ***1989***, *45*, 629.
[907] Ju, Y.; Varma, R.S. *J. Org. Chem.* ***2006***, *71,* 135.
[908] Strand, J.W.; Kovacic, M.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2977.
[909] Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* ***2007***, *48,* 3367; Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* ***2008***, *49,* 5742.
[910] See Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* ***1979***, 161.
[911] Jonczyk, A.; Ochal, Z.; Makosza, M. *Synthesis* ***1978***, 882.
[912] Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* ***2001***, *3,* 3915.

cyclization process was used to prepare cyclic amines.[913] *N*-Silylalkyl amines are formed from amines by reaction with halotrialkylsilanes and a suitable base.[914] Amines react directly with triarylsilanes in the presence of Yb catalysts.[915]

Palladium compounds react with allylic halides, acetates, or carbonate derivatives to generate π-allyl Pd intermediates that react with amines to give an allylic amine (see the reaction below).[916] The same reaction is discussed in Reaction **10-60** with other nucleophiles. Propargylic amines can be prepared by similar methodology.[917] Boronic acid derivatives leads to methylation of aniline derivatives in the presence of cupric acetate.[918] *tert*-Butylamines can be prepared from isobutylene, HBr, and the amine by heating a sealed tube.[919]



Phosphines behave similarly to amines, and compounds, such as R_3P and $R_4P^+ X^-$, can be prepared.[920] The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, for example,[921]



Other phosphorus compounds can be alkylated. Phosphinate esters, for example, react with a suitable base and then an alkyl halide to give the P-substituted product.[922]

OS **I**, 23, 48, 102, 300, 488; **II**, 85, 183, 290, 328, 374, 397, 419, 563; **III**, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV**, 84, 98, 383, 433, 466, 582, 585, 980; **V**, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; **VI**, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; **VIII**, 9, 152, 231, 358. Also see, OS **II**, 395; **IV**, 950; OS **V**, 121; OS **I**, 203.

For *N*-arylation of amines see Reaction **13-5**.

[913] Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* ***2003***, *5*, 3767.

[914] Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, New York, ***1980***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 2nd ed., Wiley, New York, ***1991***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 3rd ed., Wiley, New York, ***1999***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 4th ed., Wiley, New Jersey, ***2006***.

[915] Takaki, K.; Kamata, T.; Miura, Y.; Shishido, T.; Takehira, K. *J. Org. Chem.* ***1999***, *64*, 3891.

[916] Faller, J.W.; Wilt, J.C. *Org. Lett*. ***2005***, *7,* 633; Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* ***2009***, *131*, 4200; Watson, I.D.G.; Styler, S.A.; Yudin, A.K. *J. Am. Chem. Soc.* ***2004***, *126*, 5086. See also, Evans, P.A.; Robinson, J.E.; Moffett, K.K. *Org. Lett.* ***2001***, *3,* 3269; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* ***2001***, *42*, 1655. For mechanistic insights, see Watson, I.D.G.; Yudin, A.K. *J. Am. Chem. Soc.* ***2005***, *127,* 17516.

[917] Detz, R.J.; Delville, M.M.E.; Hiemstra, H.; van Maarseveen, J.H. *Angew. Chem. Int. Ed.* ***2008***, *47,* 3777. A Cu(I) mediated reaction in ionic liquids is known, see Park, S.B.; Alper, H. *Chem. Commun.* ***2005***, 1315.

[918] González, I.; Mosquera, J.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Org. Lett.* ***2009***, *11,* 1677. See also, Bariwal, J.B.; Ermolat'ev, D.S.; Van der Eycken, E.V. *Chemistry: Eur. J.* ***2010***, *16*, 3281.

[919] Gage, J.R.; Wagner, J.M. *J. Org. Chem.* ***1995***, *60*, 2613.

[920] See Honaker, M.T.; Sandefur, B.J.; Hargett, J.L.; McDaniel, A.L.; Salvatore, R.N. *Tetrahedron Lett*. ***2003***, *44,* 8373.

[921] See Deady, L.W.; Finlayson, W.L.; Korytsky, O.L. *Aust. J. Chem.* ***1979***, *32*, 1735.

[922] Abrunhosa-Thomas, I.; Sellers, C.E.; Montchamp, J.-L. *J. Org. Chem.* ***2007***, *72,* 2851.

10-32 Replacement of a Hydroxy or Alkoxy by an Amino Group

Amino-de-hydroxylation and Amino-de-alkoxylation

$$R—OH \longrightarrow R—NH_2$$
$$Ar—OR' \longrightarrow R'—NH_2 + ArOH$$

Alcohols can be converted to alkyl halides, which then react with amines (Reaction **10-43**). Alcohols react with various amine reagents that give products convertible to the amine.[923] The conversion $ROH \rightarrow RNH_2$ can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate (*i*Pr—OOCN=NCOO—*i*Pr), and excess Ph_3P in THF, followed by water or aq acid.[924] This is a type of *Mitsunobu Reaction* (see **10-17**).[925] Primary and secondary alcohols (ROH, but not methanol) can be converted to tertiary amines[926] Primary amines can be generated directly from primary alcohols and ammonia.[927] Formation of R'_2NR required treatment with the secondary amine (R'_2NH) with the $(t\text{-BuO})_3Al$ compound in the presence of Raney nickel.[928]

Allylic alcohols (ROH) react with amines in the presence of Pt[929] or Pd[930] complexes, to give allylic amines.[931] Amines can be *N*-alkylated by reaction with alcohols, in a sealed tube with microwave irradiation,[932] and also by Ru-,[933] Ir-,[934] or Au catalyzed[935] reactions, or by Ti mediated[936] reactions. Copper–aluminum hydrotalcite can also be used to generate amines from alcohols.[937] The use of aniline gives secondary amines (PhNHR). Phenols can be converted to aniline derivatives.[938,939] Heating indoles with benzylic alcohols in the presence of $Me_3P{=}CH(CN)$ gives the *N*-benzylindole.[940] Heating an alcohol on $\gamma\text{-}Al_2O_3$

[923] See Katritzky, A.R.; Huang, T.-B.; Voronkov, M.V. *J. Org. Chem.* ***2001***, *66,* 1043; Cami-Kobeci, G.; Williams, J.M.J. *Chem. Commun.* ***2004***, 1072. See also, Salehi, P.; Motlagh, A.R. *Synth. Commun.* ***2000***, *30*, 671; Lakouraj. M.M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* ***2000***, *30*, 821.

[924] Fabiano, E.; Golding, B.T.; Sadeghi, M.M. *Synthesis* ***1987***, 190. See also, Klepacz, A.; Zwierzak, A. *Synth. Commun.* ***2001***, *31,* 1683.

[925] See Edwards, M.L.; Stemerick, D.M.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 3417.

[926] See Arcelli, A.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 95; Huh, K.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* ***1988***, 449.

[927] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8661. For a Ru-catalyzed reaction of primary and secondary alcohols with ammonia, see Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8126.

[928] Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* ***1977***, 722.

[929] Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* ***2007***, *9*, 3371.

[930] Yamashita, Y.; Gopalarathnam, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129,* 7508; Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* ***2006***, *62,* 3949.

[931] Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* ***1986***, 293.

[932] Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W.; Yuan, Y.-C.; Liu, J.-M.; Hao, Q.-S.; Li, D.-P. *Synth. Commun.* ***1996***, *26*, 161.

[933] Hamid, M.H.S.A.; Williams, J.M.J. *Tetrahedron Lett.* ***2007***, *48*, 8263; Malai Haniti S.A.; Hamid, M.H.S.A.; Williams, J.M.J. *Chem. Commun.* ***2007***, 725; Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* ***2008***, 4745.

[934] Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* ***2008***, *64,* 1943; Defieber, C.; Ariger, M.A.; Moriel, P.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2007***, *46*, 3139.

[935] Guo, S.; Song, F.; Liu, Y. *Synlett* ***2007***, 964.

[936] Ramanathan, B.; Odom, A.L. *J. Am. Chem. Soc.* ***2006***, *128,* 9344.

[937] Likhar, P.R.; Arundhathi, R.; Kantam, M.L.; Prathima, P.S. *Eur. J. Org. Chem.* ***2009***, 5383.

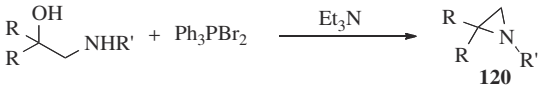
[938] Mizuno, M.; Yamano, M. *Org. Lett.* ***2005***, *7,* 3629.

[939] Kaboudin, B. *Tetrahedron Lett.* ***2003***, 44, 1051.

[940] Bombrun, A.; Casi, G. *Tetrahedron Lett.* ***2002***, *43*, 2187.

leads to an amine,[941] as does treatment with the amine, $SnCl_2$, and $Pd(PPh_3)_4$.[942] The Ru catalyzed reaction of amines and diols leads to cyclic amines.[943]

β-Amino alcohols give aziridines (**120**) when treated with triphenylphosphine dibromide in the presence of triethylamine.[944] The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with $OPPh_3$ as the leaving group.



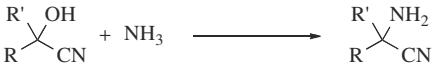
120

Alcohols can be converted to amines in an indirect manner.[945] The alcohols are converted to alkyloxyphosphonium perchlorates, which in DMF successfully *monoalkylate* not only secondary but also primary amines.[946]

$$\mathrm{ROH} \xrightarrow[2.\,NH_4ClO_4]{1.\,CCl_4-P(NMe_2)_3} \mathrm{RO\overset{+}{P}(NMe_2)_3}\quad ClO_4^- \xrightarrow[R'R^2NH]{DMF} \mathrm{RR'R^2N + O{=}P(NMe_2)_3}$$

Thus by this means secondary as well as tertiary amines, can be prepared in good yields. Benzylic alcohols can be converted to an azide and then treated with triphenylphosphine to give the amine (Reaction **19-50**).[947]

Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see Reaction **16-52**). α-Hydroxy ketones (acyloins and benzoins) behave similarly.[948]



A solution of the sodium salt of *N*-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:[949] $\mathrm{ArOMe + PhNMe^- \rightarrow ArO^- + PhNMe_2}$. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide (Ph_2PLi).[950] This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with

[941] Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* ***1999***, *40*, 3689. See Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* ***2003***, *68*, 7374.
[942] Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* ***1995***, 1121.
[943] Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 3525.
[944] Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1185. See also, Pfister, J.R. *Synthesis* ***1984***, 969; Suzuki, H.; Tani, H. *Chem. Lett.* ***1984***, 2129; Marsella, J.A. *J. Org. Chem.* ***1987***, *52*, 467.
[945] Also see Hendrickson, J.B.; Joffee, I. *J. Am. Chem. Soc.* ***1973***, *95*, 4083; Trost, B.M.; Keinan, E. *J. Org. Chem.* ***1979***, *44*, 3451; Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487.
[946] Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* ***1971***, 4368. For a similar method, see Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* ***1975***, 471.
[947] Reddy, G.V.S.; Rao, G.V.; Subrmanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 2233.
[948] See Klemmensen, P.; Schroll, G.; Lawesson, S. *Ark. Kemi*, ***1968***, *28*, 405.
[949] Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* ***1980***, 638.
[950] Ireland, R.E.; Walba, D.M. *Org. Synth.* ***VI***, 567.

high selectivity. Phenyl allyl ethers react with secondary amines in the presence of a Pd catalyst to give phenol and the tertiary allyl amine.[951]

OS **II**, 29, 231; **IV**, 91, 283; **VI**, 567, 788; **VII**, 501. Also see, OS **I**, 473; **III**, 272, 471.

10-33 Transamination

Alkylamino-de-amination

$$RNH_2 + R'NH^- \longrightarrow RR'NH + NH_2^-$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[952] In another process, primary amines are converted to secondary amines in which both R groups are the same ($2\ RNH_2 \rightarrow R_2NH + NH_3$)[953] by refluxing in xylene in the presence of Raney nickel.[954] Quaternary salts can be dealkylated with ethanolamine.[955]

$$R_4N^+ + NH_2CH_2CH_2OH \longrightarrow R_3N + \overset{+}{R}NH_2CH_2CH_2OH$$

In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a *Mannich base* (see Reaction **16-19**) and a secondary amine, where the mechanism is elimination–addition (see Sec. 10.F). Transamination has been accomplished using yeast alcohol dehydrogenase.[956]

See also, Reaction **19-5**.

OS **V**, 1018.

10-34 Alkylation of Amines With Diazo Compounds

Hydro, dialkylamino-de-diazo-bisubstitution

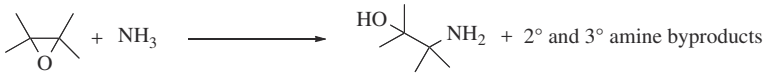
$$CR_2N_2 + R'_2NH \xrightarrow{BF_3} CHR_2NR'_2$$

The reaction of diazo compounds with amines is similar to Reaction **10-11**.[957] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B{-}NHR'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.[958] Ammonia has been used rather than an amine but, as in the case of Reaction **10-31**, mixtures of primary, secondary, and tertiary amines are obtained. However, a highly chemoselective reaction of amines in water has been reported.[959] Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

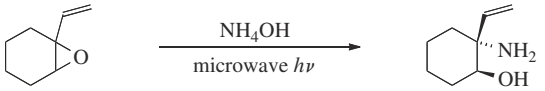
[951] Widehem, R.; Lacroix, T.; Bricout, H.; Monflier, E. *Synlett* ***2000***, 722.
[952] Baltzly, R.; Blackman, S.W. *J. Org. Chem.* ***1963***, *28*, 1158.
[953] See Geller, B.A. *Russ. Chem. Rev.* ***1978***, *47*, 297.
[954] De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* ***1979***, 70; See also, Tsuji, Y.; Shida, J.; Takeuchi, R.; Watanabe, Y. *Chem. Lett.* ***1984***, 889; Bank, S.; Jewett, R. *Tetrahedron Lett.* ***1991***, *32*, 303.
[955] Hünig, S.; Baron W. *Chem. Ber.* ***1957***, *90*, 395, 403.
[956] Cassimjee, K.E.; Branneby, C.; Abedi, V.; Wells, A.; Berglund, P. *Chem. Commun.* ***2010***, 5569.
[957] Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* ***1959***, *623*, 34.
[958] Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* ***1966***, 6131.
[959] Azizi, N.; Saidi, M.R. *Org. Lett.* ***2005***, *7,* 3649.

10-35 Reaction of Epoxides with Nitrogen Reagents[960]

(3)*OC-seco*-Amino-de-alkoxylation

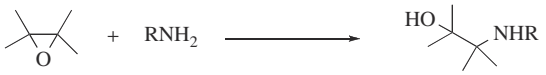


The reaction between epoxides and ammonia[961] (or ammonium hydroxide)[962] is a general and useful method for the preparation of β-hydroxyamines. With epoxides derived from terminal alkenes, the reaction with ammonia gives largely the primary amine, but secondary and tertiary amine products are possible from the appropriate epoxide. The reaction of **121** with ammonium hydroxide with microwave irradiation, for example,



121 **122**

gave **122**.[963] Ethanolamines, which are useful solvents, as well as synthetic precursors, are prepared by this reaction. Similar ring-opening occurs with alkyl and aromatic amines.[964] For another way of accomplishing this conversion, see Reaction **10-40**. Ring opening has been accomplished with aniline on silica gel,[965] and with aromatic amines in the presence of heteropoly acids in water.[966]



Primary and secondary amines give, respectively, secondary and tertiary amines (**121**). Aniline reacts with epoxides in the presence of aq β-cyclodextrin[967] in 5 M $LiClO_4$ in ether,[968] or in fluoro-alcohol solvents.[969] Aniline reacts with epoxides in the presence of a VCl_3 catalyst[970] or a Cu(II) catalyst.[971] *N*-Boc-amine ($H_2N—CO_2t$-Bu) reacted with epoxides in the presence of a cobalt–salen catalyst to give the amido alcohol.[972] Solvent-free reactions using a catalytic amount of $SnCl_4$ are known.[973] Other metal-catalyzed

[960] Lu, P. *Tetrahedron* ***2010***, *66*, 2549.
[961] See Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* ***2000***, *41,* 7347.
[962] Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M.A. *Tetrahedron Lett.* ***2003***, *44*, 8369.
[963] Lindström, U.M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* ***1999***, *40,* 9273.
[964] See Harrack, Y.; Pujol, M.D. *Tetrahedron Lett.* ***2002***, *43,* 819; Steiner, D.; Sethofer, S.G.; Goralski, C.T.; Singaram, B. *Tetrahedron Asymmetry* ***2002***, *13*, 1477. For a reaction catalyzed by LiBr, see Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* ***2004***, 3597.
[965] Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* ***2004***, *2,* 1277.
[966] Azizi, N.; Saidi, M.R. *Tetrahedron* ***2007***, *63,* 888.
[967] Reddy, L.R.; Reddy, M.A.; Chanumathi, N.; Rao, K.R. *Synlett* ***2000***, 339.
[968] Heydari, A.; Mehrdad, M.; Malecki, A.; Ahmadi, N. *Synthesis* ***2004***, 1563.
[969] Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégue, J.P. *J. Org. Chem.* ***2000***, *65,* 6749.
[970] Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. *Synthesis* ***2003***, 2298.
[971] Kamal, A.; Ramu, R.; Azhar, M.A.; Khanna, G.B.R. *Tetrahedron Lett.* ***2005***, *46,* 2675.
[972] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mechiorre, P.; Sambri, L. *Org. Lett.* ***2004***, *6*, 3973.
[973] Zhao, P.-Q.; Xu, L.-W.; Xia, C.-G. *Synlett* ***2004***, 846.

ring-opening reactions of epoxides with amines have been reported,[974] often with high enantioselectivity.

Enantioselective ring-opening reactions typically use a metal catalyst in the presence of a chiral additive. Amines react with epoxides using a catalytic amount of a Nb complex, in the presence of a 1,1-bi-2-naphthol (BINOL) derivative, to give chiral amino alcohols.[975] Other enantioselective ring-opening reactions include a V–salen-catalyzed reaction,[976] and a Mg–BINOL complex.[977]

Tetrahydropyrimidones can be used to mediate the addition of indole to epoxides.[978] Amide bases react differently with epoxides. Lithium 2,2,6,6-tetramethylpiperidide (LTMP), for example, reacted with epoxides, but the product was the corresponding enamine.[979] This latter reaction follows a very different mechanism. Initial formation of the lithio-epoxide is followed by rearrangement to give the aldehyde,[980] and subsequent reaction with the amine byproduct of the lithiation leads to the enamine.

An indirect method for generating an amino alcohol (**124**) is to open an epoxide with azide to give the azido-alcohol (**123**),[981] and subsequent reduction (Reaction **19-50**) gives the amine group.[982] The cerium ammonium nitrate catalyzed reaction of epoxides and sodium azide, for example, gave the azido alcohol with selectivity for the azide group on the more substituted position.[983] Cerium chloride has also been used, giving the azide on the less substituted carbon.[984] Under *Mitsunobu conditions* (Reaction **10-17**), epoxides are converted to 1,2-diazides with HN_3.[985] The reaction of trimethylsilyl azide and an epoxide was reported using an ionic solvent.[986] In the presence of $AlCl_3$ in water at pH 4, sodium azide reacts with epoxy acids to give the β-azido-α-hydroxycarboxylic acid.[987] Silylazides can be used as well.[988]

[974] Examples include **Al compounds**: Williams, D.B.G.; Lawton, M. *Tetrahedron Lett.* ***2006***, *47,* 6557; Robinson, M.W.C.; Timms, D.A.; Williams, S.M.; Graham, A.E. *Tetrahedron Lett.* ***2007***, *48,* 6249. **Bi compounds**: McCluskey, A.; Leitch, S.K.; Garner, J.; Caden, C.E.; Hill, T.A.; Odell, L.R.; Stewart, S.G. *Tetrahedron Lett*. ***2005***, *46,* 8229; Ollevier, T.; Nadeau, E. *Tetrahedron Lett.* ***2008***, *49,* 1546. **Ce compounds**: Reddy, L.R.; Reddy, M.A.; Bhanumathi, N.; Rao, K.R. *Synthesis* ***2001***, 831. **Co compounds**: Sundararajan, G.; Viyayakrishna, K.; Varghese, B. *Tetrahedron Lett.* ***2004***, *45,* 8253. **Er compounds**: Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Rosati, O. *Tetrahedron Lett.* ***2008***, *49,* 2289. **In compounds:** Rodríguez, J.R.; Navarro, A. *Tetrahedron Lett.* ***2004***, *45*, 7495. **Sc cmpounds:** Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett*. ***2005***, *7,* 4593; Placzek, A.T.; Donelson, J.L.; Trivedi, R.; Gibbs, R.A.; De, S.K. *Tetrahedron Lett.* ***2005***, *46,* 9029. **Sm compounds:** Carrée, F.; Gil, R.; Collin, J. *Org. Lett*. ***2005***, *7,* 1023;. **Sn compounds**: Sekar, G.; Singh, V. K. *J. Org. Chem.* ***1999***, *64*, 287. **Zn compounds:** Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* ***2008***, 1574. **Zr compounds**: Charkraborti, A.K.; Kondaskar, A. *Tetrahedron Lett.* ***2003***, *44*, 8315.

[975] Arai, K.; Lucarini, S.; Salter, M.M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2007***, *129*, 8103; Arai, K; Salter, K.M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2007***, *46,* 955.

[976] Sun, J.; Dai, Z.; Yang, M.; Pan, X.; Zhu, C. *Synthesis* ***2008***, 2100.

[977] Bao, H.; Wu, J.; Li, H.; Wang, Z.; You; T.; Ding, K. *Eur. J. Org. Chem.* ***2010***, 6722.

[978] Fink, D.M. *Synlett* ***2004***, 2394.

[979] Hodgson, D.M.; Bray, C.D.; Kindon, N.D. *J. Am. Chem. Soc.* ***2004***, *126,* 6870. For a similar reaction with $LiNTf_2$, see Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* ***2002***, *43,* 7083.

[980] Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 2103.

[981] Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 999. For a reaction done under phase transfer conditions, see Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* ***2001***, *42*, 8721.

[982] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, p. 815.

[983] Iranpoor, N.; Kazemi, F. *Synth. Commun.* ***1999***, *29*, 561.

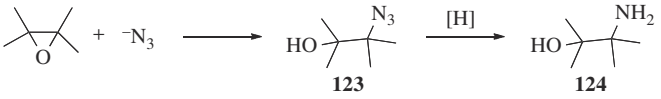
[984] Sabitha, G.; Babu, R.S.; Rajkumar, M.; Yadav, J.S. *Org. Lett.* ***2002***, *4*, 343.

[985] Göksu, S.; Socen, H.; Sütbeyaz, Y. *Synthesis* ***2002***, 2373.

[986] Song, C.E.; Oh, C.R.; Roh, E.J.; Choo, D.J. *Chem. Commun.* ***2000***, 1743.

[987] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* ***2001***, *42,* 1131.

[988] Schneider, C. *Synlett* ***2000***, 1840.



123 **124**

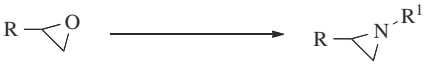
Sodium nitrate ($NaNO_2$) reacts with epoxides in the presence of $MgSO_4$ to give the nitro alcohol.[989] The nitro group can also be reduced to give the amine (Reaction **19-45**).[990]

Episulfides (thiiranes), which can be generated *in situ* in various ways, react similarly to give β-amino thiols,[991] and aziridines react with amines to give 1,2-diamines (Reaction **10-38**). Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give alkenes (see the *Wittig Reaction*, **16-44**).

OS **X**, 29. See OS **VI**, 652 for a related reaction.

10-36 Formation of Aziridines from Epoxides

Amino-de-alkoxylation



It is possible to prepare aziridines, which are synthetically important molecules, directly from the corresponding epoxide. Reaction of $Ph_3P{=}NPh$ with an epoxide in the presence of $ZnCl_2$ gives the *N*-phenyl aziridine.[992] Guanidines have also been used to prepare aziridines from epoxides.[993] Tosylamines react with epoxides to give the *N*-tosylaziridine.[994]

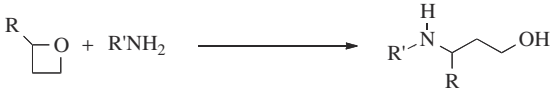
Various methods are available to convert an aminomethyl epoxide to a hydroxymethyl aziridine (**125**).[995]



125

10-37 Amination of Oxetanes

(4)*OC-homoseco*-Amino-de-alkoxylation

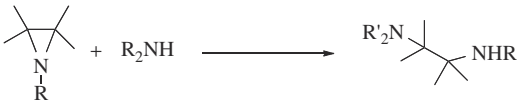


Oxetanes are significantly less reactive with nucleophiles due to diminished ring strain. Under certain conditions, however, amines can open oxetanes to give amino alcohols. *tert*-Butyl amine reacts with oxetanes in the presence of $Yb(OTf)_3$, for example, to give 3-hydroxy amines.[996] Lithium tetrafluoroborate has also been used for this purpose.[997]

[989] Kalita, B.; Barua, N.C.; Bezbarua, M.; Bez, G. *Synlett* ***2001***, 1411.
[990] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, p. 821.
[991] Dong, Q.; Fang, X.; Schroeder, J.D.; Garvey, D.S. *Synthesis* ***1999***, 1106.
[992] Kühnau, D.; Thomsen, I.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 1*, ***1996***, 1167.
[993] Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* ***2004***, *69,* 8504.
[994] Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* ***1999***, *55*, 6387.
[995] Najime, R.; Pilard, S.; Vaultier, M. *Tetrahedron Lett.* ***1992***, *33*, 5351; Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1993***, *34*, 2315.
[996] Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* ***1994***, *35*, 7089.
[997] Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* ***1994***, *35*, 761.

10-38 Reaction of Aziridines with Nitrogen

(3)*NC-seco*-Amino-de-aminoalkylation



Just as epoxides can be opened by amines to give hydroxy amines, aziridines can be opened to give diamines.[998] With bicyclic aziridines, the major product is usually the trans diamine. *N*-Aryl or *N*-alkyl aziridines react with amines in the presence of T-Binolate,[999] $Sn(OTf)_2$[1000] or $B(C_6F_5)_3$[1001] to give the diamine. Activated aziridines undergo regioselective ring opening with organoalanes.[1002] Amines react with *N*-tosylaziridines, in the presence of various catalysts or additives to give the corresponding diamine derivative.[1003] This reaction also takes place on activated silica.[1004] The reaction of $LiNTf_2$ and an amine, in the presence of an *N*-alkyl aziridine gives the diamine.[1005]

Tosyl-aziridines react with azide ion to generate azido tosylamines,[1006] and a clay-catalyzed variation[1007] has been reported. Reduction of the azide (Reaction **19-50**) gives the diamine. Silylazides (e.g., Me_3SiN_3) also react with aziridine derivatives to give the azido-amine.[1008] This latter reaction can be catalyzed by $InCl_3$.[1009]

10-39 Amination of Alkanes

Amino-de-hydrogenation or Amination

$$R_3CH + NCl_3 \xrightarrow[0-10\ ^\circ C]{AlCl_3} R_3CNH_2$$

Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0–10 °C.[1010] For example, *p*-$MeC_6H_4CHMe_2$ gives *p*-$MeC_6H_4CMe_2NH_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields.

[998] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines,* Academic Press, NY, ***1969***, pp. 262–268. See also, Scheuermann, J.E.W.; Ilyashenko, G.; Griffiths, D.V.; Watkinson, M. *Tetrahedron Asymmetry* ***2002***, *13,* 269.

[999] Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem. Int. Ed.* ***2009***, *48*, 4849.

[1000] Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64,* 2537.

[1001] Watson, I.D.G.; Yudin, A.K. *J. Org. Chem.* ***2003***, *68*, 5160.

[1002] Bertolini, F.; Woodward, S.; Crotti, S.; Pineschi, M. *Tetrahedron Lett.* ***2009***, *50*, 4515.

[1003] Examples include **Aqueous media with β-cyclodextrin:** Reddy, M.A.; Reddy, L.R.; Bhanamathi, N.; Rao, K.R. *Chem. Lett*. ***2001***, 246. **$BiCl_3$:** Swamy, N.R.; Venkateswarlu, Y. *Synth. Commun.* ***2003***, *33*, 547. **$InBr_3$:** Yadav, J.S.; Reddy, B.V.S.; Rao, K.; Raj, K.S.; Prasad, A.R. *Synthesis* ***2002***, 1061. **$InCl_3$**: Yadav, J.S.; Reddy, B.V.S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* ***2002***, *43,* 1565; **$LiClO_4$**: Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Synlett* ***2002***, 53; Yadav, J.S.; Reddy, B.V.S.; Parimala, G.; Reddy, P.V. *Synthesis* ***2002***, 2383. **PBu_3**: Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* ***2003***, *68*, 726. **$TaCl_5/SiO_2$:** Chandrasekhar, S.; Prakash, S.J.; Shyamsunder, T.; Ramachandar, T. *Synth. Commun.* ***2004***, *34*, 3865. **$Yb(OTf)_3$**: Meguro, M.; Yamamoto, Y. *Heterocycles* ***1996***, *43*, 2473.

[1004] Kumar, G.D.K.; Baskaran, S. *Synlett* ***2004***, 1719.

[1005] Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J.-R. *Synthesis* ***2002***, 2211.

[1006] Bisai, A.; Pandey, G.; Pandey, M.K.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5839.

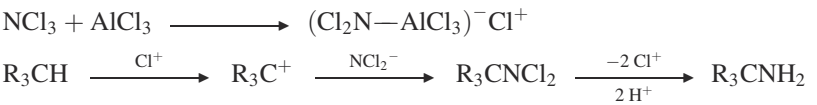
[1007] Nadir, U.K.; Singh, A. *Tetrahedron Lett.* ***2005***, *46,* 2083.

[1008] Rowland, E.B.; Rowland, G.B.; Rivera-Otero, E.; Antilla, J.C. *J. Am. Chem. Soc.* ***2007***, *129,* 12084; Chandrasekhar, M.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 10079.

[1009] Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Synth. Commun.* ***2002***, *32*, 1797.

[1010] Wnuk, T.A.; Chaudhary, S.S.; Kovacic, P. *J. Am. Chem. Soc.* ***1976***, *98*, 5678, and references cited therein.

A Ag catalyzed reaction has also been reported.[1011] There are not many other methods for the preparation of *tert*-alkyl amines. The mechanism has been rationalized as an S_N1 process with H^- as the leaving group:[1010]

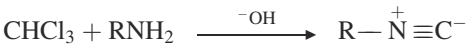


Note that under photochemical conditions, ammonia opens cyclopropane derivatives to give the corresponding alkyl amine.[1012] See also Reaction, **12-12**.

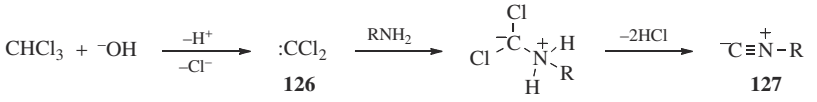
OS **V**, 35.

10-40 Formation of Isonitriles (Isocyanides)

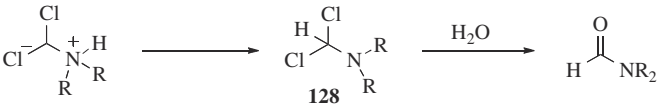
Haloform-isocyanide transformation



There are several methods available for the preparation of isonitriles, otherwise known as isocyanides.[1013] Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isonitriles (**126**) have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene (**127**) as an intermediate.



Yields are generally not high,[1014] but an improved procedure has been reported.[1015] When secondary amines are involved, the adduct **128** cannot lose two molar equivalents of HCl. Instead it is hydrolyzed to an *N,N*-disubstituted formamide.[1016]



A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide to give the isocyanide **129**.[1017]

[1011] Li, Z.; Capretto, D.A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* ***2007***, *46,* 5184.

[1012] Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T.; Yamashita, T. *J. Org. Chem.* ***2003***, *68,* 7618.

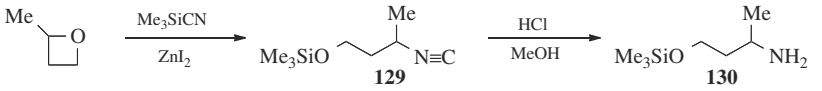
[1013] For a method for the preparation of benzyl isocyanides, see Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. *Synthesis* ***2006***, 405.

[1014] See Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* ***1979***, *11*, 293.

[1015] Weber, W.P.; Gokel, G.W. *Tetrahedron Lett.* ***1972***, 1637; Weber, W.P.; Gokel, G.W.; Ugi, I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 530.

[1016] Saunders, M.; Murray, R.W. *Tetrahedron* ***1959***, *6*, 88; Frankel, M.B.; Feuer, H.; Bank, J. *Tetrahedron Lett.* ***1959***, no. 7, 5.

[1017] Gassman, P.G.; Haberman, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4971, and references cited therein.



The products can be hydrolyzed to protected hydroxy-amines (e.g., **130**). OS **VI**, 232.

B. Attack by NHCOR

10-41 N-Alkylation or N-Arylation of Amides and Imides

Acylamino-de-halogenation

$$RX + {}^{-}NHCOR' \longrightarrow RNHCOR'$$
$$ArX + {}^{-}NHCOR' \longrightarrow ArNHCOR'$$

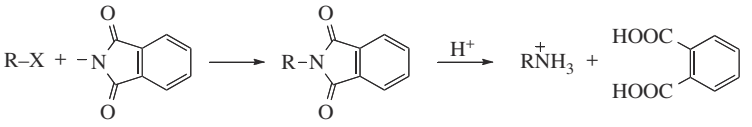
Amides are very weak nucleophiles,[1018] far too weak to attack alkyl halides, so they first must be converted to their conjugate bases, the anion. By this method, unsubstituted amides can be converted to *N*-substituted, or *N*-substituted to *N,N*-disubstituted, amides.[1019] Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination and O-Alkylation is at times a side reaction.[1020] Both amides and sulfonamides have been alkylated under phase-transfer conditions.[1021] Metal-catalyzed amidations are known, including an Ir(I) catalyzed allylic amidation.[1022]

Lactams can be alkylated using similar procedures. Ethyl pyroglutamate (5-carboethoxy 2-pyrrolidinone) and related lactams were converted to *N*-alkyl derivatives via treatment with NaH (short contact time) followed by addition of the halide.[1023] Other 2-pyrrolidinone derivatives can be alkylated using a similar procedure.[1024] *N*-Cyclopropyl lactams are prepared using a Bi reagent in the presence of cupric acetate.[1025] *N*-Aryl lactams can be prepared using Ph_3Bi and $Cu(OAc)_2$.[1026] *N*-Arylation of sulfonamides has been reported using a Pd catalyst,[1027] and this method has been applied to an intramolecular arylation leading to bicyclic lactams.[1028]

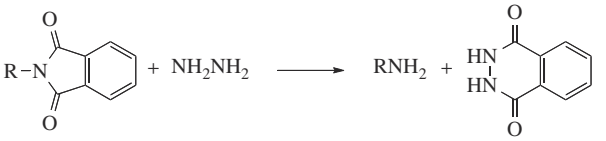
N-Alkenyl amides have been prepared from vinyl iodides and primary amides, using 10% CuI and two molar equivalents of cesium carbonate.[1029] A related Pd catalyzed vinylation of lactams was repeated using vinyl ethers as a substrate.[1030] Oxazolidin-2-ones (a cyclic carbamate) can be *N*-alkylated using an alkyl halide with KF/Al_2O_3.[1031]

[1018] Brace, N.O. *J. Org. Chem.* ***1993***, *58*, 1804.
[1019] For procedures, see Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* ***1981***, 1143; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 838.
[1020] See Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 734–754.
[1021] Salvatore, R.N.; Shin, S.I.; Flanders, V.L.; Jung, K.w. *Tetrahedron Lett.* ***2001***, *42*, 1799.
[1022] Singh, O.V.; Han, H. *Tetrahedron Lett.* ***2007***, *48,* 7094.
[1023] Simandan, T.; Smith, M.B. *Synth. Commun.* ***1996***, *26*, 1827.
[1024] Liu, H.; Ko, S.-B.; Josien, H.; Curran, D.P. *Tetrahedron Lett.* ***1995***, *36*, 8917.
[1025] Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* ***2007***, *129,* 44.
[1026] Chan, D.M.T. *Tetrahedron Lett.* ***1996***, *37*, 9013.
[1027] Ikawa, T.; Barder, T.E.; Biscoe, M.R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2007***, *129,* 13001.
[1028] Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2008***, *130*, 14058. See also, Poondra, R.R.; Turner, N.J. *Org. Lett.* ***2005***, *7,* 863.
[1029] Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* ***2004***, *6*, 1809.
[1030] Brice, J.L.; Meerdink, J.E.; Stahl, S.S. *Org. Lett.* ***2004***, *6*, 1845.
[1031] Blass, B.E.; Drowns, M.; Harris, C.L.; Liu, S.; Portlock, D.E. *Tetrahedron Lett.* ***1999***, *40*, 6545.

The *Gabriel synthesis*[1032] for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the resulting product hydrolyzed (Reaction **16-60**)



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike Reaction **10-31**). The reaction is usually rather slow, but the rate can be conveniently increased by the use of a dipolar aprotic solvent (e.g., DMF)[1033] or with a crown ether.[1034] Hydrolysis of the phthalimide, whether acid or base catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the *Ing–Manske procedure*,[1035] in which the phthalimide is heated with hydrazine in an exchange reaction,[1036] but other methods have been introduced, using Na_2S in aq THF or acetone,[1037] and 40% aq methylamine.[1038] *N*-Aryl imides can be prepared from $ArPb(OAc)_3$ and NaH.[1039]



An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.[1040] There are several other alternative procedures.[1041]

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide (Ph_3P) and diethyl azodicarboxylate ($EtO_2CN{=}NCO_2Et$) at room temperature (the *Mitsunobu Reaction*, **10-17**).[1042] A related reaction treats an alcohol with $ClCH{=}NMe_2{}^+Cl^-$, followed by potassium phthalimide and treatment with hydrazine give the amine.[1043] Metal-catalyzed syntheses of amides via oxidative coupling of alcohols and amines are known. Variations include the use

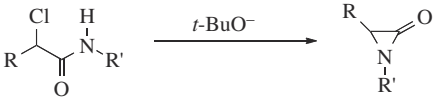
[1032] For a review, see Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed.* ***1968***, *7*, 919.
[1033] See Sheehan, J.C.; Bolhofer, W.A. *J. Am. Chem. Soc.* ***1950***, *72*, 2786. See also, Landini, D.; Rolla, F. *Synthesis* ***1976***, 389.
[1034] Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1671.
[1035] Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* ***1926***, 2348.
[1036] See Khan, M.N. *J. Org. Chem.* ***1995***, *60*, 4536 for the kinetics of hydrazinolysis of phthalimides.
[1037] Kukolja, S.; Lammert, S.R. *J. Am. Chem. Soc.* ***1975***, *97*, 5582.
[1038] Wolfe, S.; Hasan, S.K. *Can. J. Chem.* ***1970***, *48*, 3572.
[1039] López-Alvarado, P.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6875.
[1040] Hebrard, P.; Olomucki, M. *Bull. Soc. Chim. Fr.* ***1970***, 1938.
[1041] See Grehn, L.; Ragnarsson, U. *Synthesis* ***1987***, 275; Dalla Croce, P.; La Rosa, C.; Ritieni, A. *J. Chem. Res. (S)* ***1988***, 346; Yinglin, H.; Hongwen, H. *Synthesis* ***1990***, 122.
[1042] Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* ***1972***, *94*, 679; Grunewald, G.L.; Kolasa, T.; Miller, M.J. *J. Org. Chem.* ***1987***, *52*, 4978; Sammes, P.G.; Thetford, D. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 655.
[1043] Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Procopiou, P.A. *Chem. Commun.* ***1997***, 433.

of a Ru complex,[1044] a $RuCl_3$ catalyzed reaction,[1045] an $FeCl_3$ catalyzed reaction,[1046] an Ir complex catalyzed reaction,[1047] and an $InCl_3$ catalyzed coupling of alcohols with ToSMIC (ToSMIC = toluene sulfonyl methyl cyanide).[1048]

Amides can also be alkylated with diazo compounds, as in Reaction **10-34**. Salts of sulfonamides ($ArSO_2NH^-$) can be used to attack alkyl halides to prepare *N*-alkyl sulfonamides ($ArSO_2NHR$) that can be further alkylated to $ArSO_2NRR'$. Hydrolysis of the latter is a good method for the preparation of secondary amines. Secondary amines can also be made by crown-ether assisted alkylation of $F_3CCONHR$ (R = alkyl or aryl) and hydrolysis of the resulting $F_3CCONRR'$.[1049]

The reaction of a primary amide and benzaldehyde, in the presence of a silane and trifluoroacetic acid, leads to the corresponding *N*-benzylamide.[1050] This transformation is a reductive alkylation (Reaction **16-17**). *N*-Alkynyl amides have been prepared by the copper-catalyzed reaction of 1-bromoalkynes and secondary amides.[1051] 1-Haloalkynes are typically prepared by base-induced elimination of 1,1-dihaloalkenes[1052] or by direct halogenation of an alkyne with sodium or potassium hypohalite, prepared by reaction of the appropriate base with the halogen.[1053]

Internal *N*-alkylation has been used to prepare the highly strained compounds α-lactams.[1054]



OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

C. Other Nitrogen Nucleophiles

10-42 Formation of Nitro Compounds[1055]

Nitro-de-halogenation

$$RX + NO_2^- \longrightarrow RNO_2$$

[1044] Nordstrøm, L.U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* ***2008***, *130,* 17672. See also, Watson, A.J.A.; Maxwell, A.C.; Williams, J.M.J. *Org. Lett.* ***2009***, *11*, 2667; Dam, J.H.; Osztrovszky, G.; Nordstrøm, L.U.; Madsen, R. *Chemistry: Eur. J.* ***2010***, *16*, 6820.

[1045] Ghosh, S.C.; Hong, S.-H. *Eur. J. Org. Chem.* ***2010***, 4266.

[1046] Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* ***2008***, *49,* 858.

[1047] Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* ***2009***, *65*, 3624.

[1048] Krishna, P.R.; Sekhar, E.R.; Prapurna, Y.L. *Tetrahedron Lett.* ***2007***, *48,* 9048.

[1049] Nordlander, J.E.; Catalane, D.B.; Eberlein, T.H.; Farkas, L.V.; Howe, R.S.; Stevens, R.M.; Tripoulas, N.A. *Tetrahedron Lett.* ***1978***, 4987. For other methods, see Briggs, E.M.; Brown, G.W.; Jiricny, J.; Meidine, M.F. *Synthesis* ***1980***, 295; Zwierzak, A.; Brylikowska-Piotrowicz, J. *Synthesis* ***1982***, 922

[1050] Dubé, D.; Scholte, A.A. *Tetrahedron Lett.* ***1999***, *40*, 2295.

[1051] Zhang, Y.; Hsung, R.P.; Tracey, M.R.; Kurtz, K.C.M.; Vera, E.L. *Org. Lett.* ***2004***, *6*, 1151; Frederick, M.O.; Mulder, J.A.; Tracey, M.R.; Hsung, R.P.; Huang, J.; Kurtz, K.C.M.; Shen, L.; Douglas, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 2368.

[1052] For an example involving bromine see Besstmann, H.-J.; Frey, H. *Liebigs Ann. Chem.* ***1980***, *12*, 2061.

[1053] For examples with hypobromite, see Mozuraitis, R.; Buda, V.; Liblikas, I.; Unelius, C.R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* ***2002***, *28*, 1191; Barbu, E.; Tsibouklis, J. *Tetrahedron Lett.* ***1996***, *37*, 5023.

[1054] See Quast, H.; Leybach, H. *Chem. Ber.* ***1991***, *124*, 849. For a review of α-lactams, see Lengyel, I.; Sheehan, J.C. *Angew. Chem. Int. Ed.* ***1968***, *7*, 25.

[1055] See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 325–339; Kornblum, N. *Org. React.* ***1962***, *12*, 101.

Sodium nitrite can be used to prepare nitro compounds from primary or secondary alkyl bromides or iodides, but the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide.[1056] Nitrite esters are an important side product in all these cases (Reaction **10-22**) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite. Alkyl nitro compounds can be prepared from the alkyl halide via the corresponding azide, by treatment with HOF in acetonitrile.[1057]

Nitro compounds can be prepared from alcohols using $NaNO_2$/AcOH/HCl.[1058]

OS **I**, 410; **IV**, 368, 454, 724.

10-43 Formation of Azides

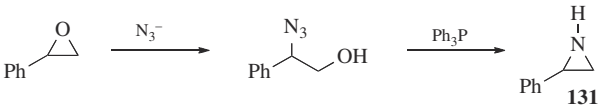
Azido-de-halogenation

$$RX + N_3^- \longrightarrow RN_3$$
$$RCOX + N_3^- \longrightarrow RCON_3$$

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.[1059] Phase-transfer catalysis,[1060] ultrasound,[1061] and the use of reactive clays[1062] are important variations. Substrates with leaving groups other than halogen have been used,[1063] including OMs (Ms = methanesulfonyl), OTs (Ts = tosyl),[1064] and OAc (Ac = acetyl).[1065] There are protocols for the conversion of alcohols to azides[1066] Boronic acids are precursors to azides.[1067] Aryl azides are prepared from aryl amines by reaction with *t*-BuONO and moist NaN_3 in *t*-BuOH.[1068]

Ring-opening reactions of epoxides with nitrogen nucleophiles were discussed in Reaction **10-35**. However, it is appropriate to discuss epoxide-opening reactions involving azides. Epoxides react with NaN_3 (**10-35**), under various conditions and media, including in ionic liquids.[1069] Other reagents include $TMSN_3$ (TMS = trimethylsilyl) and Ph_4SbOH[1070] or SmI_2[1071] or $(i\text{-}Bu)_2AlHN_3Li$[1072] to give β-azido alcohols; these are easily converted to aziridines (**131**).[1073]

[1056] See Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* ***2004***, *69*, 6907.
[1057] Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* ***2003***, *125*, 8118.
[1058] Baruah, A.; Kalita, B.; Barua, N.C. *Synlett* ***2000***, 1064.
[1059] See Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297; Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 57–119; Alvarez, S.G.; Alvarez, M.T. *Synthesis* ***1997***, 413. Also see Kim, J.-G.; Jang, D.O. *Synlett* ***2008***, 2075.
[1060] See Reeves, W.P.; Bahr, M.L. *Synthesis* ***1979***, 823; Marti, M.J.; Rico, I.; Ader, J.C.; de Savignac, A.; Lattes, A. *Tetrahedron Lett.* ***1989***, *30*, 1245.
[1061] Priebe, H. *Acta Chem. Scand. Ser. B*, **1984**, 38, 895.
[1062] See, for example, Varma, R.S.; Naicker, K.P.; Aschberger, J. *Synth. Commun.* ***1999***, *29,* 2823.
[1063] See Murahashi, T.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* ***1986***, *27*, 227.
[1064] Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297, see p. 306.
[1065] Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* ***1989***, *54*, 3292.
[1066] Rad, M.N.S.; Behrouz, S.; Khalafi-Nezhad, A. *Tetrahedron Lett.* ***2007***, *48*, 3445; Hajipour, A.R.; Rajaei, A.; Ruoho, A.E. *Tetrahedron Lett.* ***2009***, *50*, 708.
[1067] Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* ***2007***, *48,* 3525.
[1068] Das, J.; Patil, S.N.; Awasthi, R.; Narasimhulu, C.P.; Trehan, S. *Synthesis* ***2005***, 1801.
[1069] Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Tetrahedron Lett.* ***2005***, *46,* 6559.
[1070] Fujiwara, M.; Tanaka, M.; Baba, A.; Ando, H.; Souma, Y. *Tetrahedron Lett.* ***1995***, *36*, 4849.
[1071] Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1995***, *36*, 1649.
[1072] Youn, Y.S.; Cho, I.S.; Chung, B.Y. *Tetrahedron Lett.* ***1998***, *39*, 4337.
[1073] See Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* ***1978***, *43*, 4271. For the mechanism of the conversion to aziridines, see Pöchlauer, P.; Müller, E.P.; Peringer, P. *Helv. Chim. Acta* ***1984***, *67*, 1238.



131

This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by Reaction **15-48**).[1074] Even hydrogen can be the leaving group. Benzylic hydrogen atoms have been replaced and N_3 and treatment with HN_3 in $CHCl_3$ in the presence of DDQ (see Reaction **19-01**).[1075]

Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2[1076] or by treating tertiary alcohols with NaN_3 and CF_3COOH[1077] or with HN_3 and $TiCl_4$[1078] or BF_3.[1079] Aryl azides can be prepared from aniline and aniline derivatives.[1080]

Acyl azides, which can be used in the *Curtius Reaction* (**18-14**), are generally prepared from acyl halides, anhydrides,[1081] esters,[1082] or other acyl derivatives.[1083] Acyl benzotriazoles are also precursors to acyl azides.[1084] Acyl azides also can be prepared from aldehydes using $SiCl_4/NaN_3—MnO_2$,[1085] $TMSN_3/CrO_3$[1086] or the *Dess–Martin periodinane* (see Reaction **19-03**, category 5) with NaN_3.[1087]

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **VIII**, 116; **IX**, 220; **X**, 378. See also, OS **VII**, 206.

10-44 Formation of Isocyanates and Isothiocyanates

Isocyanato-de-halogenation

$$RX + NCO^- \longrightarrow RNCO$$
$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, *S*-alkylation is an important side reaction (**10-30**), but the cyanate ion practically always gives exclusive *N*-alkylation.[509] Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide ($NaNCNNO_2$) and *m*-chloroperoxybenzoic acid, followed by heating of the initially

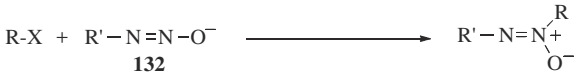
[1074] Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 2623.
[1075] Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* ***1988***, 900.
[1076] Miller, J.A. *Tetrahedron Lett.* ***1975***, 2959. See also, Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* ***1987***, *28*, 6513.
[1077] Balderman, D.; Kalir, A. *Synthesis* ***1978***, 24.
[1078] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.
[1079] See, for example, Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* ***1985***, *41*, 399.
[1080] Liu, Q.; Tor, Y. *Org. Lett.* ***2003***, *5*, 2571.
[1081] See Lwowski, W. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 503–554.
[1082] Rawal, V.H.; Zhong, H.M. *Tetrahedron Lett.* ***1994***, *35*, 4947.
[1083] Affandi, H.; Bayquen, A.V.; Read, R.W. *Tetrahedron Lett.* ***1994***, *35*, 2729. For a preparation using triphosgene see Gumaste, V.K.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2002***, *43*, 1345.
[1084] Katritzky, A.R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* ***2007***, *72,* 5802.
[1085] Elmorsy, S.S. *Tetrahedron Lett*. **1995**, 36, 1341.
[1086] Lee, J.G.; Kwak, K.H. *Tetrahedron Lett.* ***1992***, *33*, 3165.
[1087] Bose, D.S.; Reddy, A.V.N. *Tetrahedron Lett.* ***2003***, *44*, 3543.

produced $RN(NO_2)CN$.[1088] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see Reaction **16-8**).[1089] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[1090] For the formation of isocyanides (isonitriles), see Reaction **10-75**. Isonitriles, in the presence of sulfur and a Rh catalyst, are converted to isothiocyanate,[1091] as are amines.[1092]

OS **III**, 735.

10-45 Formation of Azoxy Compounds

Alkyl-*NNO*-azoxy-de-halogenation

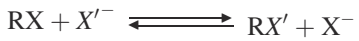


The reaction between alkyl halides and alkanediazotates (**132**) gives azoxyalkanes.[1093] The R and R′ groups may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

10.H.v. Halogen Nucleophiles[1094]

10-46 Halide Exchange

Halo-de-halogenation



Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.[1095] The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS_2, and $ZnCl_2$ as catalyst.[1096] Vinylic bromides give vinylic iodides with

[1088] Manimaran, T.; Wolford, L.T.; Boyer, J.H. *J. Chem. Res. (S)* ***1989***, 331.
[1089] Effenberger, F.; Drauz, K.; Förster, S.; Müller, W. *Chem. Ber.* ***1981***, *114*, 173.
[1090] See Tsuge, O. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 445–506; Nuridzhanyan, K.A. *Russ. Chem. Rev.* ***1970***, *39*, 130; Lozinskii, M.O.; Pel'kis, P.S. *Russ. Chem. Rev.* ***1968***, *37*, 363.
[1091] Arisawa, M.; Ashikawa, M.; Suwa, A.; Yamaguchi, M. *Tetrahedron Lett.* ***2005***, *46*, 1727.
[1092] Munch, H.; Hansen, J.S.; Pittelkow, M.; Christensen, J.B.; Boas, U. *Tetrahedron Lett.* ***2008***, *49,* 3117.
[1093] See Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1980***, *49*, 237; Moss, R.A. *Acc. Chem. Res.* ***1974***, *7*, 421.
[1094] See Hudlicky, M.; Hudlicky, T. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D,* pt. 2, Wiley, NY, ***1983***, pp. 1021–1172.
[1095] For a list of reagents for alkyl halide interconversion, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 667–671.
[1096] Miller, J.A.; Nunn, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 416.

retention of configuration when treated with KI and a nickel bromide-zinc catalyst,[1097] or with KI and CuI in hot HMPA.[1098]

Fluorides[1099] are prepared by treatment of other alkyl halides with any of a number of fluorinating agents,[1100] among them anhydrous HF (which is useful only for reactive substrates, e.g., benzylic or allylic), AgF, KF,[1101] HgF_2, $Et_3N{\bullet}2HF$,[1102] 4-Me—$C_6H_4IF_2$,[1103] and $Me_3SiF_2Ph^{+-}NBu_4$.[1104] The Pd catalyzed conversion of chlorides to fluorides has also been reported.[1105] The equilibria in these cases are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase-transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.[1106]

Primary alkyl chlorides can be converted to bromides with ethyl bromide, *N*-methyl-2-pyrrolidinone and a catalytic amount of NaBr,[1107] with LiBr under phase-transfer conditions,[1108] and with Bu_4N^+ Br^-.[1109] Primary bromides were converted to chlorides with TMSCl/imidazole in hot DMF.[1110] For secondary and tertiary alkyl chlorides, treatment with excess gaseous HBr and an anhydrous $FeBr_3$ catalyst in CH_2Cl_2 has given high yields[1111] (this procedure is also successful for chloride-to-iodide conversions). Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO_3, making use of the fact that the leaving I^- is oxidized to I_2 by the HNO_3.[1112] Primary iodides give the chlorides when treated with PCl_5 in $POCl_3$.,[1113] Primary alkyl halides are converted to the corresponding fluoride with tetrabutylammonium fluoride in *tert*-butanol.[1114] Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.[1115]

OS **II**, 476; **IV**, 84, 525; **VIII**, 486; **IX**, 502.

[1097] Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* ***1978***, 1435.
[1098] Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* ***1988***, 236.
[1099] See Mann, J. *Chem. Soc. Rev.* ***1987***, *16*, 381; Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 24–169; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430.
[1100] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125; Hudlicky, M. *Chemistry of Organic Fluorine Compunds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 91–136.
[1101] See Makosza, M.; Bujok, R. *Tetrahedron Lett.* ***2002***, *43*, 2761.
[1102] Giudicelli, M.B.; Picq, D.; Veyron B. *Tetrahedron Lett.* ***1990***, *31*, 6527. Also see Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, J.; Hara, S.; Yoneda, N. *Synlett* ***2000***, 999.
[1103] Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Kukuhara, T.; Yoneda, N. *Tetrahedron* ***2001***, 57, 3315.
[1104] Kvícala, J.; Mysík, P.; Paleta, O. *Synlett* ***2001***, 547.
[1105] Katcher, M.H.; Doyle, A.G. *J. Am. Chem. Soc.* ***2010***, *132,* 17402.
[1106] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 112–125; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis.* Springer, NY, ***1977***, pp. 117–124. See also, Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* ***1988***, *18*, 1661.
[1107] Willy, W.E.; McKean, D.R.; Garcia, B.A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 1989. See also, Babler, J.H.; Spina, K.P. *Synth. Commun.* ***1984***, *14*, 1313.
[1108] Loupy, A.; Pardo, C. *Synth. Commun.* ***1988***, *18*, 1275.
[1109] Bidd, I.; Whiting, M.C. *Tetrahedron Lett.* ***1984***, *25*, 5949.
[1110] Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* ***1996***, *26*, 4563.
[1111] Yoon, K.B.; Kochi, J.K. *J. Org. Chem.* ***1989***, *54*, 3028.
[1112] Svetlakov, N.V.; Moisak, I.E.; Averko-Antonovich, I.G. *J. Org. Chem. USSR* ***1969***, *5*, 971.
[1113] Bartley, J.P.; Carman, R.M.; Russell-Maynard, J.K.L. *Aust. J. Chem.* ***1985***, *38*, 1879.
[1114] Kim, D.W.; Jeong, H.-J.; Lim, S.T.; Sohn, M.-H. *Tetrahedron Lett.* ***2010***, *51*, 432.
[1115] Namavari, M.; Satyamurthy, N.; Phelps, M.E.; Barrio, J.R. *Tetrahedron Lett.* ***1990***, *31*, 4973.

10-47 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

Halo-de-sulfonyloxy-substitution, and so on

$$ROSO_2R' + X^- \longrightarrow RX$$

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.[1116] Neopentyl tosylate, for example, reacts with Cl^-, Br^-, or I^- without rearrangement in HMPA.[1117] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[1118] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, and so on (Reaction **10-48**), but those esters are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

10-48 Formation of Alkyl Halides from Alcohols

Halo-de-hydroxylation

$$ROH + HX \longrightarrow RX$$
$$ROH + SOCl_2 \longrightarrow RCl$$

Alcohols can be converted to alkyl halides with several reagents,[1119] the most common of which are halogen acids (HX) and inorganic acid halides, (e.g., $SOCl_2$,[1120] PCl_5, PCl_3, and $POCl_3$).[1121] When the reagent is HX, the mechanism is S_N1cA or S_N2cA; that is, the leaving group is not ^-OH, but OH_2 (Sec. 10.G.iii). The leaving group is not ^-OH with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester (e.g., ROSOCl) with $SOCl_2$ (Reaction **10-22**). The leaving group is therefore ^-OSOCl or a similar group (Reaction **10-47**). These may react by the S_N1 or S_N2 mechanism and, in the case of ROSOCl, by the S_Ni mechanism[1122] (Sec. 10.D).

The reagent HBr is usually used for alkyl bromides[1123] and HI for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid (e.g., phosphoric or sulfuric). The use of HI sometimes results in reduction of the alkyl iodide to the alkane (Reaction **19-53**) and, if the substrate is unsaturated, can also reduce the double bond.[1124] The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products.[1125] Tertiary chlorides are easily made with concentrated HCl, but primary and secondary

[1116] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 697–700.
[1117] Stephenson, B.; Solladié, G.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.
[1118] Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393.
[1119] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 689–697.
[1120] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.
[1121] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pt. 1, pp. 595–622.
[1122] Schreiner, P.R.; Schleyer, P.v.R.; Hill, R.K. *J. Org. Chem.* ***1993***, *58*, 2822.
[1123] Chong, J.M.; Heuft, M.A.; Rabbat, P. *J. Org. Chem.* ***2000***, *65,* 5837.
[1124] Jones, R.; Pattison, J.B. *J. Chem. Soc. C* ***1969***, 1046.
[1125] See Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M.C.; Bosco, M.; Sambri, L. *J. Org. Chem.* ***2000***, *65,* 2830.

alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.[1126] Primary alcohols give good yields of chlorides upon treatment with HCl in HMPA.[1127]

The inorganic acid chlorides ($SOCl_2$,[1128] PCl_3, etc.) give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl. Inorganic bromides and iodides, especially PBr_3, have also been used, but they are more expensive and used less often than HBr or HI, although some of them may also be generated *in situ* (e.g., PBr_3 from phosphorous and bromine). Secondary alcohols always give *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using Reaction **10-47**,[1129] or by the use of phase-transfer catalysis.[1130] Tertiary alcohols can be converted to the bromide with BBr_3 at 0 °C.[1131] Iodides have been prepared by simply heating the alcohol with iodine.[1132] Trichloroisocyanuric acid (1,3,5-trichlorohexahydrotriazin-2,4,6-trione) and triphenylphosphine converts primary alcohols to the corresponding chloride.[1133] Pivaloyl chloride–DMF has been used to convert alcohols to chlorides.[1134] Sodium iodide and Amberlyst-15[1135] or tosic acid and KI with microwave irradiation[1136] converts primary alcohols to the iodide.

The preparation of alkyl fluorides can be problematic, and specialized reagents are usually required. Hydrogen fluoride does not generally convert alcohols to alkyl fluorides.[1137] The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride (Et_2NSF_3, DAST),[1138] which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[1139] Fluorides have also been prepared from alcohols by treatment with nonaflyl fluoride,[1140] tetrabutylammonium difluoride,[1141] CsI/BF_3,[1142] $TMSI/ZnCl_2$,[1143] and indirectly, by conversion to a sulfate or tosylate, and so on (Reaction **10-47**). A mixture of IF_5, NEt_3, and excess KF[1144] or $(Cl_3CO)_2C{=}O$ [bis(trichloromethyl)carbonate] and KF (which gives COF_2*in situ*) with 18-crown-6[1145] also converts primary alcohols to primary fluorides.

[1126] Other phase-transfer catalysts have been used: Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1974***, 37.
[1127] Fuchs, R.; Cole, L.L. *Can. J. Chem.* ***1975***, *53*, 3620.
[1128] See Chaudhari, S.S.; Akamanchi, K.G. *Synlett* ***1999***, 1763.
[1129] Cason, J.; Correia, J.S. *J. Org. Chem.* ***1961***, *26*, 3645.
[1130] Dakka, G.; Sasson, Y. *Tetrahedron Lett.* ***1987***, *28*, 1223.
[1131] Pelletier, J.D.; Poirier, D. *Tetrahedron Lett.* ***1994***, *35*, 1051.
[1132] Joseph, R.; Pallan, P.S.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* ***1995***, *36*, 609.
[1133] Hiegel, G.A.; Rubino, M. *Synth. Commmun.* ***2002***, *32*, 2691.
[1134] Dubey, A.; Upadhyay, A.K.; Kumar, P. *Tetrahedron Lett.* ***2010***, *51*, 744.
[1135] Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* ***2004***, 635.
[1136] Lee, J.C.; Park, J.Y.; Yoo, E.S. *Synth. Commun.* ***2004***, *34*, 2095.
[1137] For an exception, see Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* ***1962***, *652*, 96; See also, Politanskii, S.F.; Ivanyk, G.D.; Sarancha, V.N.; Shevchuk, V.U. *J. Org. Chem. USSR* ***1974***, *10*, 697.
[1138] See Hudlicky, M. *Org. React.* ***1988***, *35*, 513.
[1139] Middleton, W.J. *J. Org. Chem.* ***1975***, *40*, 574.
[1140] Vorbrüggen, H. *Synthesis* ***2008***, 1165.
[1141] Kim, K.-Y.; Kim, B.C.; Lee, H.B.; Shin, H. *J. Org. Chem.* ***2008***, *73,* 8106. See also Zhao, X.; Zhuang, W.; Fang, D.; Xue, X.; Zhou, J. *Synlett* ***2009***, 779.
[1142] Hayat, S.; Atta-ur-Rahman; Khan, K.M.; Choudhary, M.I.; Maharvi, G.M.; Zia-Ullah; Bayer, E. *Synth. Commun.* ***2003***, *33*, 2531.
[1143] Manickam, GF.; Siddappa, U.; Li, Y. *Tetrahedron Lett.* ***2006***, *47,* 5867.
[1144] Yoneda, N.; Fukuhara, T. *Chem. Lett.* ***2001***, 222.
[1145] Flosser, D.A.; Olofson, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4275.

Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX, KX, or NH_4X in polyhydrogen fluoride–pyridine solution.[1146] This method is even successful for neopentyl halides. Ionic liquids can be used for halogenation, and bmim-Cl (1-*n*-butyl-3-methylimidazolium chloride) generates the chloride directly from the alcohol without any additional reagent.[1147] Triphenylphosphine and iodine will convert alcohols to iodides in ionic liquids, under solvent-free conditions.[1148] *tert*-Butyl halides halogenate alcohols in the ionic liquid [pmim]Br with sonication.[1149]

Other reagents[1150] have also been used, including $ZrCl_4$/NaI,[1151] Me_3SiCl and $BiCl_3$,[1152] or Me_3SiCl and $InCl_3$[1153] or $GaCl_3$–tartrate,[1154] or simply Me_3SiCl in DMSO.[1155] 1,2-Dipyridiniumditribromide ethane is an efficient brominating agent, and simply grinding the reagent and an alcohol in a porcelain mortar at room temperature with no solvent gives the product.[1156] Other specialized reagents include $(RO)_3PRX$[1157] and R_3PX_2[1158], which give good yields for primary (including neopentyl), secondary, and tertiary halides without rearrangements,[1159] Similarly, a mixture of PPh_3 and CCl_4[1160] (or CBr_4[1161]) give good results, and PPh_3/Cl_3CCONH_2 is an efficient chlorinating reagent.[1162] The compound PPh_3—CCl_3CN converts neopentyl alcohol to neopentyl chloride, in 95% yield.[1163]

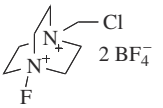
$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3$$

[1146] Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.
[1147] Ren, R. X.; Wu, J. X. *Org. Lett.* ***2001***, *3*, 3727.
[1148] Hajipour, A.R.; Mostafavi, M.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2009***, *41,* 87.
[1149] Ranu, B.C.; Jana, R. *Eur. J. Org. Chem.* ***2005***, 755.
[1150] Also see Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* ***1988***, *53*, 6126; Munyemana, F.; Frisque-Hesbain, A.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* ***1989***, *30*, 3077; Ernst, B.; Winkler, T. *Tetrahedron Lett.* ***1989***, *30*, 3081.
[1151] Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* ***2004***, *45,* 7451.
[1152] Labrouillère, M.; LeRoux, C.; Oussaid, A.; Gaspard-Iloughmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* ***1995*** *132*, 522.
[1153] Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* ***2004***, *126*, 7186.
[1154] Yasuda, M.; Shimizu, K.; Yamasaki, S.; Baba, A. *Org. Biomol. Chem.* ***2008***, *6,* 2790.
[1155] Snyder, D.C. *J. Org. Chem.* ***1995***, *60*, 2638.
[1156] Kavala, V.; Naik, S.; Patel, B.K. *J. Org. Chem.* ***2005***, *70,* 4267.
[1157] Rydon, H.N. *Org. Synth.* ***VI***, 830.
[1158] Sandri, J.; Viala, J. *Synth. Commun.* ***1992***, *22*, 2945.
[1159] See Castro, B.R. *Org. React.* ***1983***, *29*, 1; Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***; pp. 433–466.
[1160] See Appel, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 801; Appel, R.; Halstenberg, M. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 387–431. Also see, Slagle, J.D.; Huang, T.T.; Franzus, B. *J. Org. Chem.* ***1981***, *46*, 3526; Pollasatri, M.P.; Sagal, J.F.; Chang, G. *Tetrahedron Lett.* ***2001***, *42,* 2459.
[1161] Wagner, A.; Heitz, M.; Mioskowski, C. *Tetrahedron Lett.* ***1989***, *30*, 557. See also, Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett.* ***2003***, *44*, 7589.
[1162] Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* ***2006***, *47,* 6821. Also see Pluempanupat, W.; Chantarasriwong, O.; Taboonpong, P.; Jang, D.O.; Chavasiri, W. *Tetrahedron Lett.* ***2007***, *48,* 223.
[1163] Matveeva, E.D.; Yalovskaya, A.I.; Cherepanov, I.A.; Kurts, A.L.; Bundel', Yu.G. *J. Org. Chem. USSR* ***1989***, *25*, 587.

The PPh_3—CCl_4 or CBr_4 method converts allylic alcohols[1164] to the corresponding halides without allylic rearrangements,[1165] and also cyclopropylcarbinyl alcohols to the halides without ring opening.[1166] A mixture of triphenylphosphine and iodine converts alcohols to iodides under solvent-free conditions, using microwave irradiation.[1167] Hexabromoacetone–ethyltribromoacetate is an efficient brominating reagent.[1168] *N*-Bromosaccharin and *N*-iodosaccharin in the presence of PPh_3 gives the corresponding bromide or iodide.[1169]

Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX—BF_3 etherate,[1170] and to iodides with AlI_3.[1171] A mixture of methanesulfonic acid and NaI also converts benzylic alcohols to benzylic iodides.[1172] Allylic alcohols are converted to allylic halides in a procedure that uses acetyl halides, but the reaction proceeds with allylic rearrangement.[1173] A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with NCS or NBS and methyl sulfide.[1174] A mixture of NBS, $Cu(OTf)_2$, and diisopropylcarbodiimide converted primary alcohols to the corresponding bromide.[1175] The use of NCS gave the chloride and *N*-iodosuccinimide (NIS) gave the iodide under identical conditions. Thiols are converted to alkyl bromides by a similar procedure using PPh_3 and NBS.[1176]

Trialkylsilyl ethers (e.g., $ROSiMe_3$) are converted to the corresponding iodide with SiO_2—Cl/NaI.[1177] Hydroxy ketones are converted to the iodide with iodine and iodic acid.[1178] Propargyilc fluorides can be prepared from allenylsilanes by treatment with Selectfluor.[1179]



Selectfluor

OS **I**, 25, 36, 131, 142, 144, 292, 294, 533; **II**, 91, 136, 159, 246, 308, 322, 358, 399, 476; **III**, 11, 227, 370, 446, 698, 793, 841; **IV**, 106, 169, 323, 333, 576, 681; **V**, 1, 249, 608; **VI**, 75, 628, 634, 638, 781, 830, 835; **VII**, 210, 319, 356; **VIII**, 451. Also see, OS **III**, 818; **IV**, 278, 383, 597.

[1164] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, pp. 1924–1926.
[1165] Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1973***, *92*, 2139.
[1166] Hrubiec, R.T.; Smith, M.B. *Synth. Commun.* ***1983***, *13*, 593.
[1167] Hajipour, A.R.; Falahati, A.R.; Ruoho, A.E. *Tetrahedron Lett.* ***2006***, *47,* 4191.
[1168] Tongkate, P.; Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* ***2008***, *49,* 1146.
[1169] Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. *Tetrahedron Lett.* ***2006***, *47,* 1771.
[1170] Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Tetrahedron Lett.* ***2001***, *42,* 951.
[1171] Sarmah, P.; Barua, N.C. *Tetrahedron* ***1989***, *45*, 3569.
[1172] Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* ***2001***, *31,* 827.
[1173] Kishali, N.; Polat, M.F.; Altundas, R.; Kara, Y. *Helv. Chim. Acta* ***2008***, *91,* 67.
[1174] Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* ***1972***, 4339.
[1175] Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* ***2003***, *44,* 8143; Crosignani, S.; Nadal, B.; Li, Z.; Linclau, B. *Chem. Commun.* ***2003***, 260.
[1176] Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synlett* ***2001***, 1176.
[1177] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Tetrahedron Lett.* ***2002***, *43,* 7139.
[1178] Patil, B.R.; Bhusare, S.R.; Pawar, R.P.; Vibhute, Y.R. *Tetrahedron Lett.* ***2005***, *46*, 7179.
[1179] Carroll, L.; Pacheco, M[a] C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* ***2006***, 4113.

10-49 Formation of Alkyl Halides from Ethers

Halo-de-alkoxylation

$$ROR' + HI \longrightarrow RI + R'OH$$

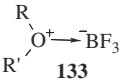
Ethers can be cleaved by heating with concentrated HI or HBr.[1180] Hydrogen chloride is seldom successful,[1181] and HBr reacts more slowly than HI, but is often a superior reagent, since it causes fewer side reactions. Phase-transfer catalysis has also been used,[1182] and 47% HBr in ionic liquids has proven effective.[1183] Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case, the alkyl–oxygen bond is the one broken. As in Reaction **10-48**, the actual leaving group is not OR'^-, but ^-OHR'. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 equiv of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four.

O-Benzyl ethers are readily cleaved to the alcohol and the hydrocarbon via hydrogenolysis, and the most common methods are hydrogenation[1184] or dissolving metal conditions (Na or K in ammonia).[1185] Heating in anisole with 3% $Sc(NTf_2)_3$[1186] or with In metal in aq ethanol[1187] also cleaves benzyl ethers. Isoprenyl alkyl ethers are cleaved using iodine in dichloromethane,[1188] and allyl alkyl ethers are cleaved with Lewis acids under various conditions.[1189] The $OCH_2CH{=}CHPh$ unit of mixed allyl ethers ($O{-}CH_2CH{=}CH_2$ and $OCH_2CH{=}CHPh$) can be cleaved selectively under electrolytic conditions.[1190]

Cyclic ethers (usually THF derivatives) can be similarly cleaved (see Reaction **10-50** for epoxides). Treatment of 2-methyltetrahydrofuran with acetyl chloride and $ZnCl_2$ gave primarily *O*-acetyl-4-chloro-1-pentanol.[1191] A mixture of Et_2NSiMe_3/2 MeI cleaved THF to give the *O*-trimethylsilyl ether of 4-iodo-1-butanol.[1192] Ethers have also been cleaved

[1180] See Bhatt, M.V.; Kulkarni, S.U. *Synthesis* ***1983***, 249; Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, p. 22; Tiecco, M. *Synthesis* ***1988***, 749.
[1181] Also see Jursic, B. *J. Chem. Res. (S)* ***1989***, 284.
[1182] Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1978***, 771.
[1183] Boovanahalli, S.K.; Kim, D.W.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3340.
[1184] Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* ***1971***, *93,* 1746.
[1185] Reist, E.J.; Bartuska, V.J.; Goodman, L. *J. Org. Chem.* ***1964***, *29,* 3725.
[1186] Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2000***, 80.
[1187] Moody, C.J.; Pitts, M.R. *Synlett* ***1999***, 1575.
[1188] Vatèle, J.-M. *Synlett* ***2001***, 1989. For a procedure using DDQ see Vatèle, J.-M. *Synlett* ***2002***, 507
[1189] See Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* ***2003***, *5,* 4085; Bartoli, G.; Cupone, G.; Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* ***2001***, 1897; Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J. *Tetrahedron* ***2001, 57***, 3435; Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* ***2004***, *6*, 1873. See also, Murakami, H.; Minami, T.; Ozawa, F. *J. Org. Chem.* ***2004***, *69*, 4482.
[1190] Solis-Oba, A.; Hudlicky, T.; Koroniak, L.; Frey, D. *Tetrahedron Lett.* ***2001***, *42*, 1241.
[1191] Mimero, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* ***1994***, *35*, 1553.
[1192] Ohshita, J.; Iwata, A.; Kanetani, F.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***1999***, *64,* 8024.

with Lewis acids [e.g., BF_3, $Ce(OTf)_4$,[1193] $SiCl_4/LiI/BF_3$,[1194] BBr_3,[1195] or $AlCl_3$].[1196] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid (see **133**). The reagent NaI—BF_3 etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.[1197]



133

Dialkyl and alkyl aryl ethers are cleaved with Me_3SiI[1198]: $ROR' + Me_3SiI \rightarrow RI + Me_3SiOR$.[1199] A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and NaI.[1200] Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 molar equivalents of alkyl bromide.[1201] Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols[1202] in a reaction similar to Reaction **10-51**. Allyl aryl ethers[1203] are efficiently cleaved with NaI/Me_3SiCl,[1204] or $NbCl_5$.[1205] Aryl benzyl ethers are cleaved with BCl_3 using pentamethylbenzene as a non-Lewis basic cation scavenger.[1206] Cleavage in ionic liquids is also known.[1207]

A closely related reaction is cleavage of oxonium salts.

$$R_3O^+X^- \longrightarrow RX + R_2O$$

For these substrates, HX is not required, and X can be any of the four halide ions.

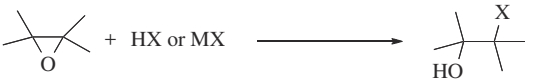
tert-Butyldimethylsilyl ethers ($ROSiMe_2CMe_3$) can be converted to bromides (RBr) by treatment with Ph_3PBr_2,[1208] $Ph_3P—CBr_4$,[1209] BBr_3,[1210] and $CuBr_2$.[1211] Alcohols are often protected by conversion to this kind of silyl ether.[1212]

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also, OS **VIII**, 161, 556.

[1193] Khalafi-Nezhad, A.; Alamdari, R.F. *Tetrahedron* ***2001***, *57,* 6805.
[1194] Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* ***2004***, *45*, 3729.
[1195] Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* ***1981***, *22*, 4239.
[1196] Johnson, F. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 1–109.
[1197] Vankar, Y.D.; Rao, C.T. *J. Chem. Res. (S)* ***1985***, 232. See also, Sharma, G.V.M.; Reddy, Ch.G.; Krishna, P.R. *J. Org. Chem.* ***2003***, *68*, 4574.
[1198] See Olah, G.A.; Prakash, G.K.S.; Krishnamurti, R. *Adv. Silicon Chem.* ***1991***, *1*, 1.
[1199] Jung, M.E.; Lyster, M.A. *J. Org. Chem.* ***1977***, *42*, 3761; *Org. Synth.* ***VI***, 353.
[1200] Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247; Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* ***1987***, 505.
[1201] Anderson, Jr., A.G.; Freenor, F.J. *J. Org. Chem.* ***1972***, *37*, 626.
[1202] Harrison, I.T. *Chem. Commun.* ***1969***, 616.
[1203] See Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* ***2004***, *60,* 7973.
[1204] Kamal, A.; Laxman, E.; Rao, N.V. *Tetrahedron Lett.* ***1999***, *40*, 371.
[1205] Yadav, J.S.; Ganganna, B.; Bhunia, D.C.; Srihari, P. *Tetrahedron Lett.* ***2009***, *50*, 4318.
[1206] Okano, K.; Okuyama, K.; Fukuyama, Y.; Tokuyama, H. *Synlett* ***2008***, 1977. See also, Konieczny, M.T.; Maciejewski, G.; Konieczny, W. *Synthesis* ***2005***, 1575.
[1207] Park, J.; Chae, J. *Synlett* ***2010***, 1651; Cheng, L.; Aw, C.; Ong, S.S.; Lu, Y. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 2008.
[1208] Aizpurua, J.M.; Cossío, F.P.; Palomo, C. *J. Org. Chem.* ***1986***, *51*, 4941.
[1209] Mattes, H.; Benezra, C. *Tetrahedron Lett.* ***1987***, *28*, 1697.
[1210] Kim, S.; Park, J.H. *J. Org. Chem.* ***1988***, *53*, 3111.
[1211] Bhatt, S.; Nayak, S.K. *Tetrahedron Lett.* ***2006***, *47,* 8395.
[1212] See Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* ***1972***, *94*, 6190.

10-50 Formation of Halohydrins from Epoxides

(3)*OC-seco*-Halo-de-alkoxylation



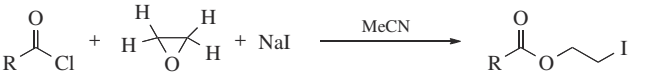
This is a special case of Reaction **10-49** and is frequently used for the preparation of halohydrins.[1213] In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, although with HF[1214] the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.[1215] Hydrogen fluoride does react with more rigid epoxides, such as those in steroid systems. The reaction can be applied to simple epoxides[1216] if polyhydrogen fluoride–pyridine is the reagent. The reagent $NEt_3 \cdot 3HF$ converts epoxides to fluorohydrins with microwave irradiation.[1217] Organocatalysts have been used to convert epoxides to fluorohydrins using an acetyl fluoride/fluorous alcohol combination.[1218] Chloro-, bromo-, and iodohydrins can also be prepared[1219] by treating epoxides with Ph_3P and X_2,[1220] with 3/NaBr/H_2O,[1221] LiBr on Amberlyst-15 resin,[1222] ceric ammonium nitrate/KBr,[1223] I_2 with a SmI_2 catalyst,[1224] and LiI on silica gel.[1225] Epoxides can be converted directly to 1,2-dichloro compounds by treatment with $SOCl_2$ and pyridine,[1226] or with Ph_3P and CCl_4.[1227] These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (Reaction **10-48**). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral B-halodiisopinocampheylboranes (see Reaction **15-16**), where the halogen was Cl, Br, or I.[1228] Diatomic iodine gives an iodohydrin with a 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene catalyst.[1229]

[1213] Wang, T.; Ji, W.-H.; Xu, Z.-Y.; Zeng, B.-B. *Synlett* ***2009***, 1511.
[1214] See Sharts, C.M.; Sheppard, W.A. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430. For a related review, see Yoneda, N. *Tetrahedron* ***1991***, *47*, 5329.
[1215] Shahak, I.; Manor, S.; Bergmann, E.D. *J. Chem. Soc. C* ***1968***, 2129.
[1216] Olah, G.A.; Meidar, D. *Isr. J. Chem.* ***1978***, *17*, 148.
[1217] Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* ***2003***, 1157.
[1218] Kalow, J.A.; Doyle, A.G. *J. Am. Chem. Soc.* ***2010***, *132*, 3268.
[1219] Einhorn, C.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1986***, 1368; Ciaccio, J.A.; Addess, K.J.; Bell, T.W. *Tetrahedron Lett.* ***1986***, *27*, 3697; Spawn, C.; Drtina, G.J.; Wiemer, D.F. *Synthesis* ***1986***, 315. For reviews, see Bonini, C.; Righi, G. *Synthesis* ***1994***, 225; Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* ***1992***, *48*, 3805.
[1220] Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* ***1983***, *24*, 1307. See Afonso, C.A.M.; Vieira, N.M.L.; Motherwell, W.B. *Synlett* ***2000***, 382.
[1221] Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4463.
[1222] Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* ***1992***, *22*, 1863.
[1223] Lu, Z.; Wu, W.; Peng, L.; Wu, L. *Can. J. Chem.* ***2008***, *86, 142*.
[1224] Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2003***, 959. Thiophenol promotes ring openeing by iodine, see Wu, J.; Sun, X.; Sun, W.; Ye, S. *Synlett* ***2006***, 2489.
[1225] Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* ***1996***, *37*, 1845.
[1226] Campbell, J.R.; Jones, J.K.N.; Wolfe, S. *Can. J. Chem.* ***1966***, *44*, 2339.
[1227] Isaacs, N.S.; Kirkpatrick, D. *Tetrahedron Lett.* ***1972***, 3869.
[1228] Srebnik, M.; Joshi, N.N.; Brown, H.C. *Isr. J. Chem.* ***1989***, *29*, 229.
[1229] Nikam, K.; Nashi, T. *Tetrahedron,* ***2002***, *58,* 10259. Also see Sharghi, H.; Niknam, K.; Pooyan, M. *Tetrahedron* ***2001***, *57*, 6057; Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1525.

Epoxides are converted to the corresponding chlorohydrin upon treatment with the ionic liquid [AcMIm]Cl.[1230]

Bicyclic epoxides are usually opened to the *trans*-halohydrin. Unsymmetrical epoxides are usually opened to give mixtures of regioisomers. In a typical reaction, the halogen is delivered to the less sterically hindered carbon of the epoxide. In the absence of this structural feature, and in the absence of a directing group, relatively equal mixtures of regioisomeric halohydrins are expected. The phenyl is such a group, and in 1-phenyl-2-alkyl epoxides reaction with $POCl_3$/DMAP (DMAP = 4-dimethylaminopyridine) leads to the chlorohydrin with the chlorine on the carbon bearing the phenyl.[1231] When done in an ionic liquid with Me_3SiCl, styrene epoxide gives 2-chloro-2-phenylethanol.[1232] The reaction of thionyl chloride and poly(vinylpyrrolidinone) converts epoxides to the corresponding 2-chloro-1-carbinol.[1233] Bromine with a phenylhydrazine catalyst, however, converts epoxides to the 1-bromo-2-carbinol.[1234] An alkenyl group also leads to a halohydrin with the halogen on the carbon bearing the C=C unit.[1235] Epoxy carboxylic acids are another example. When NaI reacts at pH 4, the major regioisomer is the 2-iodo-3-hydroxy compound, but when $InCl_3$ is added, the major product is the 3-iodo-2-hydroxy carboxylic acid.[1236]

Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.[1237]



Acyl chlorides react with epoxides in the presence of a $Eu(dpm)_3$ catalyst[1238] [dpm = 1,1-bis(diphenylphosphino)methane] or a YCp_2Cl catalyst[1239] to give chloro esters.

A related reaction with episulfides leads to 2-chlorothio-esters.[1240] Aziridines have been opened with PPh_3 and halogenating agents,[1241] and also by $MgBr_2$ to give 2-haloamides in a related reaction[1242] *N*-Tosyl aziridines react with KF•2 H_2O to give the 2-fluoro tosylamine product.[1243] Aziridinium salts are opened by bromide ion.[1244]

OS **I**, 117; **VI**, 424; **IX**, 220.

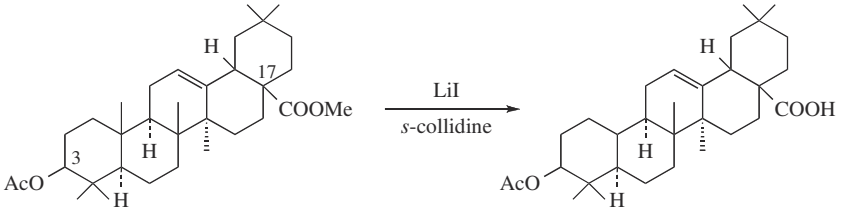
[1230] Ranu, B.C.; Banerjee, S. *J. Org. Chem.* ***2005***, *70*, 4517.
[1231] Sartillo-Piscil, F.; Quinero, L.; Villegas, C.; Santacruz-Juárez, E.; de Parrodi, C.A. *Tetrahedron Lett.* ***2002***, *43*, 15.
[1232] Xu, L.-W.; Li, L.; Xia, C.-G.; Zhao, P.-Q. *Tetrahedron Lett.* ***2004***, *45,* 2435.
[1233] Tamami, B.; Ghazi, I.; Mahdavi, H. *Synth. Commun.* ***2002***, *32*, 3725.
[1234] Sharghi, H.; Eskandari, M.M. *Synthesis* ***2002***, 1519.
[1235] Ha, J.D.; Kim, S.Y.; Lee, S.J.; Kang, S.K.; Ahn, J.H.; Kim, S.S.; Choi, J.-K. *Tetrahedron Lett.* ***2004***, *45*, 5969.
[1236] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4719. Also see Concellón, J.M.; Bardales, E.; Concellón, C.; García-Granda, S.; Díaz, M.R. *J. Org. Chem.* ***2004***, *69*, 6923.
[1237] Belsner, K.; Hoffmann, H.M.R. *Synthesis* ***1982***, 239. See also, Iqbal, J.; Khan, M.A.; Srivastava, R.R. *Tetrahedron Lett.* ***1988***, *29*, 4985.
[1238] Taniguchi, Y.; Tanaka, S.; Kitamura, T.; Fujiwara, Y. *Tetrahedron Lett.* ***1998***, *39*, 4559.
[1239] Qian, C.; Zhu, D. *Synth. Commun.* ***1994***, *24*, 2203.
[1240] Kameyama, A.; Kiyota, M.; Nishikubo, T. *Tetrahedron Lett.* ***1994***, *35*, 4571.
[1241] Kumar, M.; Pandey, S.K.; Gandhi, S.; Singh, V.K. *Tetrahedron Lett.* ***2009***, *50*, 363.
[1242] Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* ***1996***, *37*, 6893.
[1243] Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2004***, *69*, 335.
[1244] D'hooghe, M.; Speybroeck, V.V.; Waroquier, M.; De Kimpe, N. *Chem. Commun.* ***2006***, 1554.

10-51 Cleavage of Carboxylic Esters with Lithium Iodide

Iodo-de-acyloxy-substitution

$$R'COOR + LiI \xrightarrow[\Delta]{\text{pyridine}} RI + R'COOLi$$

Carboxylic esters, where R is methyl or ethyl, can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.[1245] The reaction is useful where a molecule is sensitive to acid and base (so that Reaction **16-59** cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing *O*-acetyloleanolic acid methyl ester with LiI in *s*-collidine



cleaved only the 17-carbomethoxy group, not the 3-acetyl group.[1246] Esters (RCO_2R') and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give R′I and RCO_2H.[1247] The reaction of acetyl chloride and an allylic acetate leads to the allylic chloride.[1248]

10-52 Conversion of Diazo Ketones to α-halo Ketones

Hydro, halo-de-diazo bisubstitution

$$RCOCHN_2 + HBr \longrightarrow RCOCH_2Br$$

When diazo ketones are treated with HBr or HCl, they give the respective α-halo ketones. Hydrogeniodide does not give the reaction, since it reduces the product to a methyl ketone (Reaction **19-67**). α-Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.[1249] This method is also successful for diazoalkanes.

Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro carboxylic acids.[1250] If this reaction is run in the presence of excess KCl or KBr, the corresponding α-chloro or α-bromo acid is obtained instead.[1251]

OS **III**, 119.

[1245] See McMurry, J. *Org. React.* ***1976***, *24*, 187–224.
[1246] Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1960***, *43*, 113.
[1247] Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R.*J. Org. Chem.* ***1979***, *44*, 1247. See also, Kolb, M.; Barth, J. *Synth. Commun.* ***1981***, *11*, 763.
[1248] Yadav, V.K.; Babu, K.G. *Tetrahedron* ***2003***, *59*, 9111.
[1249] Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872.
[1250] Olah, G.A.; Prakash, G.K.S.; Chao, Y.L. *Helv. Chim. Acta* ***1981***, *64*, 2528; Barber, J.; Keck, R.; Rétey, J. *Tetrahedron Lett.* ***1982***, *23*, 1549.
[1251] Olah, G.A.; Shih, J.; Prakash, G.K.S. *Helv. Chim. Acta* ***1983***, *66*, 1028.

10-53 Conversion of Amines to Halides

Halo-de-amination

$$RNH_2 \longrightarrow RNTs_2 \xrightarrow[DMF]{I^-} RI$$

Primary alkyl amines (RNH_2) can be converted[1252] to alkyl halides by (1) conversion to $RNTs_2$ (Sec. 10.G.ii) and treatment of this with I^- or Br^- in DMF,[415] or to N(Ts)—NH_2 derivatives followed by treatment with NBS under photolysis conditions,[1253] (2) diazotization with *tert*-butylnitrite and a metal halide (e.g., $TiCl_4$ in DMF),[1254] or (3) the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.ii).[1255] Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to Reaction **10-49**, for example,[1256]

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR$$

Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate[1257]: $R_3N + ClCOOPh \rightarrow RCl + R_2NCOOPh$. α-Chloroethyl chloroformate behaves similarly.[1258] Alkyl halides may be formed when quaternary ammonium salts are heated: $R_4N^+ X^- \rightarrow R_3N + RX$.[1259]

OS **VIII**, 119. See also, OS **I**, 428.

10-54 Conversion of Tertiary Amines to Cyanamides: The von Braun Reaction

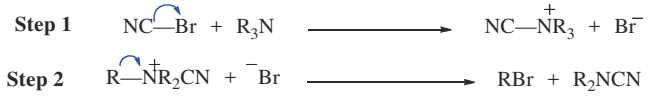
Bromo-de-dialkylamino substitution

$$R_3NH + BrCN \longrightarrow R_2NCN + RBr$$

The *von Braun reaction* involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, and can be applied to many tertiary amines.[1260] Usually, the R group that cleaves is the one that gives the most reactive halide (e.g., benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[1261]

[1252] For another method, see Lorenzo, A.; Molina, P.; Vilaplana, M.J. *Synthesis* ***1980***, 853.
[1253] Collazo, L.R.; Guziec Jr., F.S.; Hu, W.-X.; Pankayatselvan, R. *Tetrahedron Lett.* ***1994***, *35*, 7911.
[1254] Doyle, M.P.; Bosch, R.J.; Seites, P.G. *J. Org. Chem.* ***1978***, *43*, 4120.
[1255] Katritzky, A.R.; Chermprapai, A.; Patel, R.C. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 2901.
[1256] Chambers, R.A.; Pearson, D.E. *J. Org. Chem.* ***1963***, *28*, 3144.
[1257] See Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.
[1258] Olofson, R.A.; Martz, J.T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* ***1984***, *49*, 2081; Olofson, R.A.; Abbott, D.E. *J. Org. Chem.* ***1984***, *49*, 2795. See also, Campbell, A.L.; Pilipauskas, D.R.; Khanna, I.K.; Rhodes, R. A. *Tetrahedron Lett.* ***1987***, *28*, 2331.
[1259] See Ko, E.C.F.; Leffek, K.T. ***1971***, *49*, 129; Deady, L.W.; Korytsky, O.L. *Tetrahedron Lett.* ***1979***, 451.
[1260] See Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1. See Vaccari, D.; Davoli, P.; Spaggiari, A.; Prati, F. *Synlett* ***2008***, 1317.
[1261] See Hageman, H.A. *Org. React.* ***1953***, 205.

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



The intermediate *N*-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[1262] The BrCN in this reaction has been called a *counterattack reagent*; that is, a reagent that accomplishes, in one flask, two transformations designed to give the product.[1263]

OS **III**, 608.

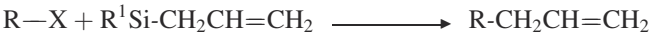
10.H.vi. Carbon Nucleophiles

In any heterolytic reaction in which a new carbon–carbon bond is formed,[1264] one carbon atom attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, Reactions **11-8**–**11-25** and **12-16**–**12-21** are nucleophilic substitutions with respect to one reactant, but following convention, we classify them with respect to the other. Similarly, all the reactions in this section would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

In Reactions **10-56**–**10-65**, the nucleophile is a "carbanion" part of an organometallic compound, often a *Grignard reagent*. There is much that is still not known about the mechanisms of these reactions and many of them are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **10-56**–**10-65** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

10-55 Coupling with Silanes

De-silylalkyl-coupling



Organosilanes ($RSiMe_3$ or $RSiMe_2F$, where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides ($R'X$), in the presence of certain catalysts, to give RR' in good yields.[1265] Allylsilanes react with allylic acetates in the presence of iodine.[1266] The transition metal catalyzed coupling of silanes, particularly allyl

[1262] Fodor, G.; Abidi, S.; Carpenter, T.C. *J. Org. Chem.* ***1974***, *39*, 1507. See also, Paukstelis, J.V.; Kim, M. *J. Org. Chem.* ***1974***, *39*, 1494.
[1263] See Hwu, J.R.; Gilbert, B.A. *Tetrahedron* ***1989***, *45*, 1233.
[1264] See Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Noyori, R. in Alper, H. *Transition Metal Organometallics in Organic Synthesis* Vol. 1, Academic Press, NY, ***1976***, pp. 83–187.
[1265] Cho, Y.S.; Kang, S.-H.; Han, J.-S.; Yoo, B.R.; Jung, I.N. *J. Am. Chem. Soc.* ***2001***, *123,* 5584.
[1266] Yadav, J.S.; Reddy, B.V.S.; Rao, K.V.; Raj, K.S.; Rao, P.P.; Prasad, A.R.; Gunasekar, D. *Tetrahedron Lett.* ***2004***, *45*, 6505.

silanes, is a mild method for incorporating alkyl fragments into a molecule.[1267] Here $PhSiMe_2Cl$ couples to give biphenyl in the presence of CuI and Bu_4NF,[1268] and vinyl silanes react with allylic carbonates and a palladium catalyst to give dienes.[1269] Allylsilanes have been coupled to substrates containing a benzotriazole unit, in the presence of BF_3•etherate.[1270] One variation used a silylmethyltin derivative in a palladium-catalyzed coupling with aryl iodides.[1271] Homoallyl silanes coupled to Ph_3BiF_2 in the presence of BF_3•OEt_2 to give the phenyl coupling product.[1272]

α-Silyloxy methoxy derivatives [$RCH(OMe)OSiR^1{}_3$], react with allyltrimethylsilane ($Me_3SiCH_2CH{=}CH_2$) in the presence of TiX_4 derivatives to give displacement of the OMe group and $RCH(OSiR^1{}_3)CH_2CH{=}CH_2$).[1273] A tertiary silyloxy group was displaced by allyl in the presence of $ZnCl_2$.[1274] Allylic acetates react with $Me_3SiSiMe_3$ and LiCl with a Pd catalyst to give the allyl silane.[1275] The $RSiF_3$ reagents can also be used in coupling reaction with aryl halides.[1276] Allyl silanes react with epoxides, in the presence of BF_3•OEt_2 to give 2-allyl alcohols.[1277] The reaction of α-bromo lactones and $CH_2{=}CHCH_2Si(SiMe_3)_3$ and azoisobutyronitrile (AIBN) leads to the α-allyl lactone.[1278]

Silyl epoxides have been prepared from epoxides via reaction with *sec*-butyllithium and chlorotrimethylsilane.[1279] α-Silyl-*N*-Boc-amines were prepared in a similar manner from the *N*-Boc-amine.[1280] Benzyl silanes coupled with allyl silanes to give $ArCH_2$—R derivatives in the presence of $VO(OEt)Cl_2$[1281] and allyltin compounds couple with allyl silanes in the presence of $SnCl_4$.[1282] Allyl silanes couple to the α-carbon of amines under photolysis conditions.[1283]

Arylsilanes were prepared by reaction of an aryllithium intermediate with $TfOSi(OEt)_3$.[1284] In the presence of BF_3•etherate, allyl silane and α-methoxy *N*-carbobenzoxy (*N*-Cbz) amines were coupled.[1285] Aryl cyanides have been converted to arylsilanes using a Rh catalyst and $Me_3SiSiMe_3$.[1286]

[1267] See Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* ***2004***, *126*, 12792; Nii, S.; Terao, J.; Kambe, N. *Tetrahedron Lett.* ***2004***, *45*, 1699.
[1268] Kang, S.-K.; Kim, T.H.; Pyun, S.-J. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 797.
[1269] Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 1943.
[1270] Katritzky, A.R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* ***2000***, *65*, 4364.
[1271] Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2001***, *123*, 8773.
[1272] Matano, Y.; Yoshimune, M.; Suzuki, H. *Tetrahedron Lett.* ***1995***, *36*, 7475.
[1273] Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1997***, *62*, 6429.
[1274] Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* ***1995***, *36*, 5243.
[1275] Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* ***1996***, *61*, 5779.
[1276] Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6511; Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6507.
[1277] Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41,* 3829.
[1278] Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6387; Chatgilialoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6391.
[1279] Hodgson, D.M.; Norsikian, S.L.M. *Org. Lett.* ***2001***, *3*, 461.
[1280] Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.W. *Chem. Commun.* ***2001***, 1202.
[1281] Hirao, T.; Fujii, T.; Ohshiro, Y. *Tetrahedron Lett.* ***1994***, *35*, 8005.
[1282] Takeda, T.; Takagi, Y.; Takano, H.; Fujiwara, T. *Tetrahedron Lett.* ***1992***, *33*, 5381.
[1283] Pandey, G.; Rani, K.S.; Lakshimaiah, G. *Tetrahedron Lett.* ***1992***, *33*, 5107. See Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* ***1992***, *33*, 73.
[1284] Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 6790.
[1285] Matos, M.R.P.N.; Afonso, C.A.M.; Batey, R.A. *Tetrahedron Lett.* ***2001***, *42*, 7007.
[1286] Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* ***2008***, *130,* 15982.

The reaction of a vinyl iodide with $(EtO)_3SiH$ and a Pd catalyst generated a good yield of the corresponding vinylsilane.[1287]

OSCV 10, 531.

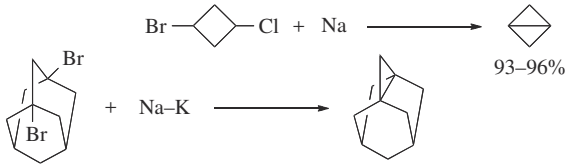
10-56 Coupling of Alkyl Halides: The Wurtz Reaction

De-halogen-coupling

$$2\,RX + Na \longrightarrow RR$$

The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (but still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz–Fittig reaction*).[1288] However, the coupling of two aryl halides with sodium is impractical (but see Reaction **13-11**). Other metals have also been used to effect *Wurtz reactions*,[1289] notably Ag, Zn,[1290] Fe,[1291] activated Cu,[1292] In,[1293] La,[1294] and Mn compounds.[1295] Lithium, under the influence of ultrasound, has been used to couple alkyl, aryl, and benzylic halides.[1296]

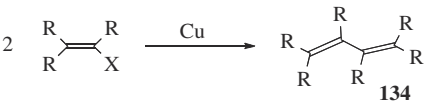
In a related reaction, *Grignard reagents* (Reaction **12-38**) have been coupled in the presence of trifluorosulfonic anhydride.[1297] Tosylates and other sulfonates and sulfates couple with *Grignard reagents*,[1298] most often those prepared from aryl or benzylic halides.[1299] Alkyl sulfates and sulfonates generally make better substrates in reactions with *Grignard reagents* than the corresponding halides (Reaction **10-57**). The method is useful for primary and secondary R.



Tetracyclo[3.3.1.13,7.01,3]decane

[1287] Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* ***1999***, *40,* 9255.
[1288] For an example, see Kwa, T.L.; Boelhouwer, C. *Tetrahedron* ***1970***, *25*, 5771.
[1289] For a list of reagents, including metals and other reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 83–84.
[1290] See, for example, Nosek, J. *Collect. Czech. Chem. Commun.* ***1964***, *29*, 597.
[1291] Onsager, O. *Acta Chem. Scand. Ser. B,* ***1978***, *32*, 15.
[1292] Ginah, F.O.; Donovan, T.A.; Suchan, S.D.; Pfennig, D.R.; Ebert, G.W. *J. Org. Chem.* ***1990***, *55*, 584.
[1293] Ranu, B.C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* ***1998***, *39*, 9557.
[1294] Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67,* 966.
[1295] See Ma, J.; Chan, T.-H. *Tetrahedron Lett.* ***1998***, *39*, 2499; Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* ***1999***, *29*, 2711.
[1296] Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.
[1297] Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K. *Chem. Lett.* ***1996***, 549.
[1298] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1277–1286.
[1299] See Danheiser, R.L.; Tsai, Y.; Fink, D.M. *Org. Synth. 66*, 1.

One type of *Wurtz reaction* that is quite useful is the closing of small rings, especially three-membered rings.[1300] For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.[1301] Two highly strained molecules prepared this way are bicyclobutane[1302] and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.[1303] Three- and four-membered rings can also be closed in this manner with certain other reagents,[1304] including benzoyl peroxide,[1305] *t*-BuLi,[1306] and lithium amalgam,[1307] as well as electrochemically.[1308] The Pd or Ni catalyzed cross-coupling reaction of a *Grignard reagent* and an alkyl halide, is often called *Kumada coupling*.[1309]



134

Vinylic halides can be coupled to give 1,3-butadienes (**134**) by treatment with activated Cu powder in a reaction analogous to the *Ullmann Reaction* (**13-11**).[1310] This reaction is stereospecific, with retention of configuration at both carbons. Vinylic halides can also be coupled[1311] with Zn—$NiCl_2$,[1312] and with *n*-BuLi in ether in the presence of $MnCl_2$.[1313] The coupling reaction with vinyltin reagents and vinyl halides occurs with a Pd catalyst.[1314]

It seems likely that the mechanism of the *Wurtz reaction* consists of two basic steps. The first is halogen–metal exchange to give an organometallic compound ($RX + M \rightarrow RM$), which in many cases can be isolated (Reaction **12-38**). Following this, the organometallic compound reacts with a second molecule of alkyl halide ($RX + RM \rightarrow RR$). This reaction and its mechanism are considered in Section (Reaction **10-57**).

OS **III**, 157; **V**, 328, 1058; **VI**, 133, 153.

[1300] See Freidlina, R.Kh.; Kamyshova, A.A.; Chukovskaya, E.Ts. *Russ. Chem. Rev.* ***1982***, *51*, 368; in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S. pp. 307–373, and Verhé, R.; De Kimpe, N. pp. 445–564.

[1301] For a discussion of the mechanism, see Applequist, D.E.; Pfohl, W.F. *J. Org. Chem.* ***1978***, *43*, 867.

[1302] Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* ***1963***, 2173; Lampman, G.M.; Aumiller, J.C. *Org. Synth.* ***VI***, 133.

[1303] Pincock, R.E.; Schmidt, J.; Scott, W.B.; Torupka, E.J. *Can. J. Chem.* ***1972***, *50*, 3958.

[1304] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 175–184.

[1305] Kaplan, L. *J. Am. Chem. Soc.* **1967**, 89, 1753; J. Org. Chem. **1967**, 32, 4059.

[1306] Bailey, W.F.; Gagnier, R.P. *Tetrahedron Lett.* ***1982***, *23*, 5123.

[1307] Connor, D.S.; Wilson, E.R. *Tetrahedron Lett.* ***1967***, 4925.

[1308] Rifi, M.R. *J. Am. Chem. Soc.* **1967**, 89, 4442; Org. Synth. **VI**, 153.

[1309] Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* ***1972***, *94,* 4374; Terao, J.; Kambe, N. *Acc. Chem. Res.* ***2008***, *41,* 1545; Lopez-Perez, A.; Adrio, J.; Carretero, J.C. *Org. Lett.* ***2009***, *11,* 5514; Frisch, A.C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem.,* ***2002***, *114,* 4218. See Chen, X.; Wang, L.; Liu, J. *Synthesis* ***2009***, 2408; Limmert, M.E.; Roy, A.H.; Hartwig, J.F. *J. Org. Chem.* ***2005***, *70,* 9364; Tsai, F.-Y.; Lin, B.-N.; Chen, M.-J.; Mou, C.-Y.; Liu, S.T. *Tetrahedron* ***2007***, *63,* 4304; Organ, M.G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C.J.; Valente, C. *Chemistry: European J.* ***2007***, *13,* 150; Gauthier, D.; Beckendorf, S.; Gøgsig, T.M.; Lindhardt, A.T.; Skrydstrup, T. *J. Org. Chem. 2009,* ***74***, 3536. For a coupling reaction of aryl iodides with heterocyclic *Grignard reagents*, see Ruben Martin, R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2007***, *129,* 3844.

[1310] Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4363.

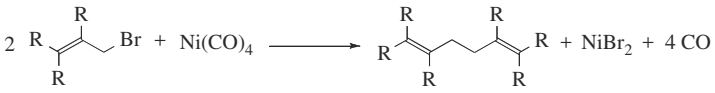
[1311] See Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 971; Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* ***1986***, *27*, 3517.

[1312] Takagi, K.; Mimura, H.; Inokawa, S. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 3517.

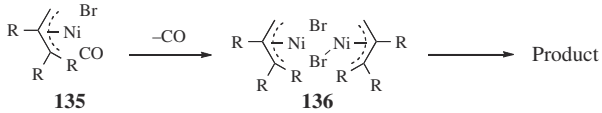
[1313] Cahiez, G.; Bernard, D.; Normant, J.F. *J. Organomet. Chem.* ***1976***, *113*, 99.

[1314] Paley, R.S.; de Dios, A.; de la Pradilla, R.F. *Tetrahedron Lett.* ***1993***, *34*, 2429.

A variation of the *Wurtz coupling* uses other metals to mediate or facilitate the coupling. In certain cases, such variations can be synthetically useful. Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, methods that couple[1315] allylic groups[1316] are quite important. In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl[1317] to give 1,5-dienes.[1318] The order of halide reactivity is I > Br > Cl. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end.



The reaction can be performed intramolecularly; large (11–20-membered) rings can be made in good yields (60–80%) by the use of high dilution.[1319] The mechanism of coupling likely involves reaction of the allylic compound with $Ni(CO)_4$ to give one or more π-allyl complexes, one of which may be the η^3-complex **135**. Loss of CO to give a π-allylnickel bromide (**136**) and ligand transfer leads to coupling and the final product. In some cases, the η^3-complexes (**136**) can be isolated from the solution and crystallized as stable solids.



135 **136**

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **136**, in a polar aprotic solvent,[1320] and coupling occurs at the less substituted end. There is evidence that free radicals are involved in such couplings.[1321] Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **136** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange. For example, allyl bromide treated with **136** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.[1322] A symmetrical coupling of allylic tosylates used $Ni(CO)_4$.



[1315] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1910–1924.

[1316] In this section, methods are discussed in which one molecule is a halide. For other allylic coupling reactions, see **10-57**, **10-63**, and **10-60**.

[1317] See Tamao, K.; Kumada, M. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond* Vol. 4, Wiley, NY, ***1987***, pp. 819–887.

[1318] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R. *Principles and Applications of Organotransition Metal Chemsitry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 739–748; Billington, D.C. *Chem. Soc. Rev.* ***1985***, *14*, 93; Kochi, J.K. *Organometallic Mechanisms and Catalysis,* Academic Press, NY, ***1978***, pp. 398–408; Semmelhack, M.F. *Org. React.* ***1972***, *19,* 115, see pp. 162–170; Baker, R. *Chem. Rev.* ***1973***, *73*, 487, see pp. 512–517.

[1319] Corey, E.J.; Wat, E.K.W. *J. Am. Chem. Soc.* ***1967***, *89,* 2757. See also, Reijnders, P.J.M.; Blankert, J.F.; Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 30.

[1320] See Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, see pp. 147–162; Semmelhack, M.F. *Org. React.* ***1972*** *,199*, 115, see pp. 144–146.

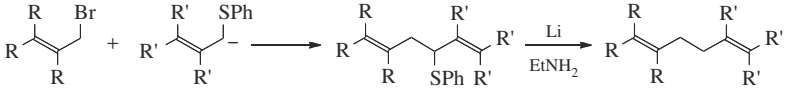
[1321] Hegedus, L.S.; Thompson, D.H.P. *J. Am. Chem. Soc.* ***1985***, *107*, 5663.

[1322] Corey, E.J.; Semmelhack, M.F.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1968***, *90*, 2416.

Symmetrical coupling of allylic halides occurs by heating with magnesium in ether.[1323] The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic *Grignard reagent* in THF containing HMPA,[1324] or with an allylic tin reagent.[1325] This type of coupling can be achieved with almost no allylic rearrangement in the substrate (and almost complete allylic rearrangement in the reagent) by treatment of allylic halides with lithium allylic boron ate complexes ($RCH{=}CHCH_2B{-}R^2{}_3Li^+$).[1326] The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling $RX + CH_2{=}CHCH_2SnBu_3 \rightarrow RCH_2CH{=}CH_2$.[1327]

In another method for the coupling of two different allylic groups,[1328] a carbanion derived from a β,γ-unsaturated thioether couples with an allylic halide to give **137**.[1329] The product (**137**) contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene. Unlike most of the methods previously discussed, this method has the advantage that the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

Treatment of conjugated ketones with SmI_2 in HMPA gave the coupled diketone via *Wurtz-type coupling*.[1330]



137

OS **III**, 121; **IV**, 748; **VI**, 722.

10-57 The Reaction of Alkyl Halides and Sulfonate Esters with Group 1 and 2 Organometallic Reagents[1331]

Alkyl-de-halogenation

$$R{-}Na\,(K)\,(Li) + R'X \longrightarrow R{-}R' + R\text{-}MgX$$

A variety of Group 1 and 2 organometallic compounds[1332] couple with alkyl halides.[1333] Organosodium and organopotassium compounds are more reactive than *Grignard reagents,* and couple even with less reactive halides (see below). Coupling of

[1323] Turk, A.; Chanan, H. *Org. Synth.* ***III***, 121.

[1324] Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393; Grieco, P.A. *J. Am. Chem. Soc.* ***1969***, *91*, 5660.

[1325] Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *J. Organomet. Chem.* ***1985***, *285*, 95. See also, Yanagisawa, A.; Norikate, Y.; Yamamoto, H. *Chem. Lett.* ***1988***, 1899.

[1326] Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1981***, *103*, 1969.

[1327] See Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* ***1982***, *104*, 5829; Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn* ***1983***, *56*, 2480.

[1328] See Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1970***, *92,* 2139; Morizawa, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* ***1982***, *23,* 2953.

[1329] Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1969***, 3707.

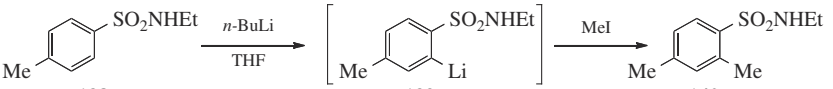
[1330] Cabrera, A.; Rosas, N.; Sharma, P.; LeLagadec, R.; Velasco, L.; Salmón, M. *Synth. Commun.* ***1998***, *28*, 1103.

[1331] See Naso, F.; Marchese, G. in Patai, S.; Rappoport, Z. *The Chemstry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1353–1449.

[1332] For lists of reagents and substrates, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 101–127.

[1333] See Beletskaya, I.P. *J. Organomet. Chem.* ***1983***, *250*, 551; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 249–262.

organolithium compounds with alkyl halides[1334] or aryl halides[1335] is possible.[1336] Unactivated aryl halides couple with alkyllithium reagents in THF.[1337] The reaction of *n*-butyllithium/TMEDA with a homoallylic alcohol [CH_2=C(Me)CH_2CH_2OH] leads to the allyllithium reagent, and subsequent reaction with an alkyl halide gives the substituted homoallylic alcohol [CH_2=C(CH_2R)CH_2CH_2OH].[1338] Organolithium reagents exhibit an important side reaction: They react with ether solvents, and their half-life in such solvents is known.[1339] With highly reactive organolithium reagents, preparing and keeping them long enough for the alkyl halide to be added is sometimes a problem (but usually not with simple primary organolithium reagents). Alkenes can be prepared by the coupling of vinylic lithium compounds with primary halides[1340] or of vinylic halides with alkyllithium reagents in the presence of a Pd or Ru catalyst.[1341] α-Lithioepoxides can also be formed, and reaction with an alkyl halide gives the substituted epoxide.[1342] Arylsilanes (e.g., 2-trimethylsilylpyridine) undergo a deprotonation reaction of a silyl methyl group when treated with *tert*-butyllithium to give the corresponding $ArMe_2SiCH_2Li$ reagent.[1343] Subsequent reaction with an alkyl halide leads to the substituted silane. Organolithium reagents formed by Li—H exchange in the presence of (–)-sparteine couple with alkyl halides with high asymmetric induction.[1344] Exchange of organotin compounds with organolithium reagents generates a new organolithium, and in one case intramolecular coupling in the presence of (–)-sparteine led to chiral pyrrolidine derivatives.[1345] Propargyl lithium reagents formed in the presence of mercuric salts couple with halides.[1346] Note that 1-lithioalkynes were coupled to alkyl halides in the presence of a palladium catalyst.[1347]



138 **139** **140**

Aryllithium reagents are formed by metal–halogen exchange with aryl halides or H–metal exchange with various aromatic compounds, and they react with alkyl halides. The reaction of **138** with *n*-butyllithium, for example, generated the aryllithium (**139**), which reacted with iodomethane to give **140**.[1348] When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base (e.g., an

[1334] Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W.K.; Yum, E.K.; Freskos, J. *Tetrahedron Lett.* ***1994***, *35*, 4067.
[1335] Dieter, R.K.; Li, S.J. *J. Org. Chem.* ***1997***, *62*, 7726. Also see Beak, P.; Wu, S.; Yum, E.K.; Jun, Y.M. *J. Org. Chem.* ***1994***, *59*, 276.
[1336] For example, see Brimble, M.A.; Gorsuch, S. *Aust. J. Chem.* ***1999***, *52*, 965.
[1337] Merrill, R.E.; Negishi, E. *J. Org. Chem.*, ***1974***, *39*, 3452. For another method, see Hallberg, A.; Westerlund, C. *Chem. Lett.*, ***1982***, 1993.
[1338] Yong, K.H.; Lotoski, J.A.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 8248.
[1339] Stanetty, P.; Mihovilovic, M.D. *J. Org. Chem.* ***1997***, *62*, 1514.
[1340] Duhamel, L.; Poirier, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8356.
[1341] Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* ***1979***, *44*, 2408.
[1342] Marié, J.-C.; Curillon, C.; Malacria, M. *Synlett* ***2002***, 553.
[1343] Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J.-i. *J. Org. Chem.* ***2001***, *66*, 3970.
[1344] Basu, A.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 1575; Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 715; Dieter, R.K.; Sharma, R.R. *Tetrahedron Lett.* ***1997***, *38*, 5937.
[1345] Serino, C.; Stehle, N.; Park, Y.S.; Florio, S.; Beak, P. *J. Org. Chem.* ***1999***, *64,*1160.
[1346] Ma, S.; Wang, L. *J. Org. Chem.* ***1998***, *63*, 3497.
[1347] Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* ***2004***, *6,* 1461.
[1348] MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* ***2001***, *66*, 3662.

organolithium reagent) usually leads to an ortho lithiated species.[1349] Subsequent reaction with an electrophilic species gives the ortho substituted product. This phenomenon is known as *directed ortho metalation* (See **13-17**). This selectivity was discovered independently by Gilman and by Wittig in 1939–1940, when anisole was found to give ortho deprotonation in the presence of butyllithium.[1350] Alkylation *ortho* to a carbonyl is possible, and treatment of the acyl hydrazide [PhC(=O)NHNMe$_2$] with *sec*-butyllithium and then iodoethane gave the *ortho* ethyl derivative.[1351] Note that aminonaphthalene derivatives were reacted with *tert*-butyllithium and aryllithium formation occurred on the ring distal to the amino group, and subsequent reaction with iodomethane gave methylation on that ring.[1352]

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (**141**), which is a lithium compound protected by an SiMe$_3$ group.[1353] Reaction at its 1 position (which gives an allene) takes place only to a small extent, because of steric blockage by the large SiMe$_3$ group. The SiMe$_3$ group is easily removed by treatment with Ag^+ followed by CN^-. Propargyl derivative **141** is prepared by treating propynyllithium with Me$_3$SiCl to give MeC≡CSiMe$_3$ from which a proton is removed with BuLi. The R group may be primary or allylic.[1354] On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with *Grignard reagents* and metallic salts,[1355] or with dialkylcuprates (R$_2$Cu).[1356]

$$RX + Li\overset{3}{C}H_2-\underset{\mathbf{141}}{\overset{1}{C}\equiv C}-SiMe_3 \longrightarrow RCH_2-C\equiv C-SiMe_3 \xrightarrow[2.\ CN^-]{1.\ Ag^+} R-CH_2-C\equiv C-H$$

Grignard reagents are generally unreactive with alkyl halides unless allylic and benzylic reagents and substrates are used.[1357] *Grignard reagents* have the advantage that they are usually simpler to prepare than the corresponding R'$_2$CuLi (see Reaction **10-58**), but the reaction is much narrower in scope. *Grignard reagents* couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but generally in low or moderate yields.[1358]

Allylic halides are more reactive than aliphatic alkyl halides, but Cu salts have been used to facilitate coupling with alkylmagnesium halides.[1359] Indeed, *Grignard reagents*

[1349] See Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See also, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453.

[1350] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* ***1939***, *61*, 109; Wittig, G.; Fuhrman, G. *Chem. Ber.* ***1940***, *73*, 1197.

[1351] McCombie, S.W.; Lin, S.-I.; Vice, S.F. *Tetrahedron Lett.* ***1999***, *40*, 8767.

[1352] Kraus, G.A.; Kim, J. *J. Org. Chem.* ***2002***, *67*, 2358.

[1353] Corey, E.J.; Kirst, H.A.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 6314.

[1354] See Ireland, R.E.; Dawson, M.I.; Lipinski, C.A. *Tetrahedron Lett.* ***1970***, 2247.

[1355] Pasto, D.J.; Chou, S.; Waterhouse, A.; Shults, R.H.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1385; Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* ***1980***, *21*, 5019.

[1356] Pasto, D.J.; Chou, S.; Fritzen, E.; Shults, R.H.; Waterhouse, A.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1389. See also, Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* ***1980***, *45,* 4536.

[1357] See Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 161–306, 269–283; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1046–1165.

[1358] See Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* ***1988***, *53*, 729.

[1359] Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* ***2004***, *45*, 7375; Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2426.

may react with alkyl halides in the presence of certain metal catalysts,[1360] and stereocontrol is possible in these reactions.[1361] These catalysts include Cu(I) compounds (see Reaction **10-58**),[1362] Ag compounds,[1363] Pd[1364] complexes, Co compounds,[1365] Fe compounds,[1366] and an Fe–amine complex was shown to catalyze Grignard coupling reactions.[1367] Iron nanoparticles have also been employed to facilitate this type of coupling.[1368] Alkyl triflates have been used rather than alkyl halides.[1369] Chiral Cu complexes have been used with allylic halides to give rearranged alkylated products, with high enantioselectivity.[1370] A similar reaction was reported using a *Grignard reagent* and a chiral imidazolium carbene complex.[1371] As noted above, *Grignard reagents* react with allylic substrates, but if there is steric hindrance at the carbon bearing the leaving group, the reaction may proceed by an S_N2' pathway (Sec. 10.E).[1372]

Aryl halides, even when activated, generally do not couple with *Grignard reagents*, although certain transition metal catalysts do effect this reaction in variable yields,[1373] including V compounds.[1374] The reaction with *Grignard reagents* proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. Aryl triflates couple with arylmagnesium halides in the presence of a Pd catalyst,[1375] as do vinyl halides with RMgX with a Pd[1376] or Ni catalyst.[1377] Alkyl halides are coupled to arylmagnesium bromides in the presence of a Co catalyst.[1378] It is also possible to couple alkynylmagnesium halides with aryl iodides in the presence of Pd catalysts.[1379] A silica-supported phosphine–Pd complex was used to couple arylmagnesium halides with aryl iodides.[1380] Aryl *Grignard reagents* couple with alkyl halides, including neopentyl iodide, in the presence of $ZnCl_2$ and a Ni catalyst.[1381]

[1360] See Erdik, E. *Tetrahedron* ***1984***, *40*, 641; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 374–398.
[1361] Bäckvall, J.-E.; Persson, E.S.M.; Bombrun, A. *J. Org. Chem.* ***1994***, *59*, 4126.
[1362] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2003***, *125*, 5646. See also, Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem. Int. Ed.* ***2008***, *47,* 8246; Cahiez, G.; Gager, O.; Buendia, J. *Synlett* ***2010***, 299.
[1363] Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2008***, *10,* 969.
[1364] López-Pérez, A.; Adrio, J.; Carretero, J.C. *Org. Lett.* ***2009***, *11*, 5514. For other references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 386–392.
[1365] Hamaguchi, H.; Uemura, M.; Yasui, H.; Yorimitsu, H.; Koichiro Oshima, K. *Chem. Lett.* ***2008***, *37,* 1178.
[1366] Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4364; Molander, G.A.; Rahn, B.J.; Shubert, D.C.; Bonde, S.E. *Tetrahedron Lett.* ***1983***, *24*, 5449. See Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Goodby, J.W.; Hird, M. *Chem. Commun.* ***2004***, 2822.
[1367] Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Hird, M. *Chem. Commun.* ***2005***, 4161.
[1368] Bedford, R.B.; Betham, M.; Bruce, D.W.; Davis, S.A.; Frost, R.M.; Hird, M. *Chem. Commun.* ***2006***, 1398.
[1369] Wang, S.; Zhang, A. *Org. Prep. Proceed. Int.* ***2008***, *40,* 293.
[1370] Geurts, K.; Fletcher, S.P.; Feringa, B.L. *J. Am. Chem. Soc.* ***2006***, *128,* 15572.
[1371] Lee, Y.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2006***, *128,* 15604.
[1372] Kar, A.; Argade, N.P. *Synthesis* ***2005***, 2995. For an example, see Sen, S.; Singh, S.; Sieburth, S.McN. *J. Org. Chem.* ***2009***, *74*, 2884.
[1373] See Bell, T.W.; Hu, L.; Patel, S.V. *J. Org. Chem.*, ***1987***, *52,* 3847; Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* ***1989***, *8*, 180.
[1374] Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2008***, *81*, 287.
[1375] Kamikawa, T.; Hayashi, T. *Synlett*, ***1997***, 163.
[1376] Hoffmann, R.W.; Gieson, V.; Fuest, M. *Liebigs Ann. Chem.* ***1993***, 629.
[1377] Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* ***1994***, *35*, 8847.
[1378] Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2006***, *128,* 1886.
[1379] Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* ***1997***, *62*, 8957.
[1380] Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Res. (S)* ***1998***, 264.
[1381] Kondo, S.; Ohira, M.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *J. Org. Chem.* ***1993***, *58*, 5003.

Vinyl[1382] and aryl halides[1383] also couple with alkyl *Grignard reagents* in the presence of a catalytic amount of an Fe catalyst,[1384] as do vinyl triflates with CuI[1385] or vinyl halides with a Co catalyst.[1386] *Grignard reagents* prepared from primary or secondary[1387] alkyl or aryl halides can be coupled with vinylic or aryl halides (see Reaction **13-9**) in high yields in the presence of a Ni(II) catalyst.[1388] When a chiral Ni(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[1389] The Pd catalyzed coupling of arylmagnesium halides and vinyl bromides has also been reported.[1390]

Because *Grignard reagents* react with the C=O group (Reaction **16-24** and **16-82**), they cannot be used to couple with halides containing ketone, CO_2R, or amide functions. Although the coupling of *Grignard reagents* with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while *Grignard reagents* are being prepared.

For symmetrical coupling of organometallic reagents (2RM → RR), see Reaction **14-24** and **14-25**.

Much study has been devoted to the mechanisms of these reactions,[1391] but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free radical mechanism. This could be an SET pathway, or some other route that provides radicals. In either case, the two radicals R• and R′• would be in a solvent cage:

$$MX + RX + R'M \longrightarrow \underset{\text{Solvent cage}}{[R\bullet + R'\bullet]} \longrightarrow RR'$$

It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be ~ 50% RR′, 25% RR, and 25% R′R′. This is generally not the case; in most of these reactions RR′ is the predominant or exclusive product.[1392] An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.[1393] The fact that in some of these cases the reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N process cannot be the only

[1382] Nagano, T.; Hayashi, T. *Org. Lett.* ***2004***, *6*, 1297; Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc.* ***2005***, *127*, 3656.
[1383] Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, 43, 3955.
[1384] Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* ***2001***, 1901. See Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* ***2004***, *69*, 3943.
[1385] Karlström, A.S.E.; Rönn, M.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* ***1998***, *63*, 2517.
[1386] Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* ***1998***, *39*, 6159.
[1387] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* ***1984***, *106*, 158.
[1388] Böhm, V.P.W.; Gstöttmayr, C.W.K.; Weskamp, T.; Hermann, W.A. *Angew. Chem. Int. Ed.* ***2001***, *40,* 3387; Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2002***, *124,* 4222. See Kumada, M. *Pure Appl. Chem.* ***1980***, *52*, 669.
[1389] See Hayashi, T.; Kumada, M. in Morrison, J.D. *Asymmetic Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 147–169. See also, Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2365.
[1390] Rathore, R.; Deselnicu, M.I.; Burns, C.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14832.
[1391] See Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.
[1392] When a symmetrical distribution of products *is* found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.
[1393] Sommer, L.H.; Korte, W.D. *J. Org. Chem.* ***1970***, *35*, 22; Korte, W.D.; Kinner, L.; Kaska, W.C. *Tetrahedron Lett.* ***1970***, 603. See also, Schlosser, M.; Fouquet, G. *Chem. Ber.* ***1974***, *107*, 1162, 1171.

mechanism. One possibility is that the reagents first undergo an exchange reaction: $ArX + RM \rightarrow RX + ArM$, and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free radical mechanisms. Among the evidence[1394] is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[1395] (see Sec. 5.C.i), the detection of free radicals by ESR spectroscopy[1396] (Sec. 5.C.i), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[1397] (this product is formed when a free radical abstracts a hydrogen from cumene to give $PhCMe_2$, which dimerizes). Evidence for free radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (*Wurtz*),[1398] with *Grignard reagents*,[1399] and with lithium dialkylcopper reagents (see Reaction **10-58**).[1400] Free radicals have also been implicated in the metal–ion catalyzed coupling of alkyl and aryl halides with *Grignard reagents*.[1401]

OS **I**, 186; **III**, 121; **IV**, 748; **VI**, 407; **VII**, 77, 172, 326, 485; **VIII**, 226, 396; **IX**, 530; **X**, 332, 396.

10-58 Reaction of Alkyl Halides and Sulfonate Esters with Organocuprates

Alkyl-de-halogenation

$$RX + R'_2CuLi \longrightarrow R{-}R'$$

The reagents lithium dialkylcopper[1402] (known as lithium dialkyl cuprates, also called *Gilman reagents*)[1403] react with alkyl bromides, chlorides, and iodides in ether or THF to give good yields of the cross-coupling products.[1404] They are prepared (see Reaction **12-36**) by the reaction of an organolithium compound with CuI or CuBr, but other Cu(I) compounds can be used.[1405] They are usually generated at temperatures <0 °C due

[1394] See Muraoka, K.; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 761.

[1395] Podoplelov, A.V.; Leshina, T.V.; Sagdeev, R.Z.; Kamkha, M.A.; Shein, S.M. *J. Org. Chem. USSR* ***1976***, *12*, 488; Ward, H.R.; Lawler, R.G.; Cooper, R.A. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 281–322.

[1396] Russell, G.A.; Lamson, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3967.

[1397] Bryce-Smith, D. *Bull. Soc. Chim. Fr.* ***1963***, 1418.

[1398] Garst, J.F.; Hart, P.W. *J. Chem Soc. Chem. Commun.* ***1975***, 215.

[1399] Kasukhin, L.F.; Ponomarchuk, M.P.; Buteiko, Zh.F. *J. Org. Chem. USSR* ***1972***, *8*, 673; Singh, P.R.; Tayal, S.R.; Nigam, A. *J. Organomet. Chem.* ***1972***, *42*, C9.

[1400] Bertz, S.H.; Dabbagh, G.; Mujsce, A.M. *J. Am. Chem. Soc.* ***1991***, *113*, 631.

[1401] Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1483, 1485, 1487; *J. Organomet. Chem.* ***1971***, *31*, 289; ***1972***, *42*, 205; Lehr, G.F.; Lawler, R.G. *J. Am. Chem. Soc.* ***1986***, *106*, 4048.

[1402] See Pearson, R.G.; Gregory, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 4098. See also, Lipshutz, B.H.; Kozlowski, J. A.; Breneman, C.M. *Tetrahedron Lett.* ***1985***, *26*, 5911; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 682–698.

[1403] See Stemmler, T.L.; Barnhart, T.M.; Penner-Hahn, J.E.; Tucker, C.E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* ***1995***, *117*, 12489. Solution compositions of Gilman reagents have also been studied. See Lipshutz, B.H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* ***1993***, *34*, 6693.

[1404] Bergbreiter, D.E.; Whitesides, G.M. *J. Org. Chem.* ***1975***, *40*, 779. See Bertz, S.H.; Eriksson, M.; Miao, G.; Snyder, J.P. *J. Am. Chem. Soc.* ***1998***, *118*, 10906 for the reactivity of β-silyl organocuprates.

[1405] For an example using a Cu(II) salt, see Nguyen, T.T.; Chevallier, F.; Jouikov, V.; Mongin, F. *Tetrahedron Lett.* ***2009***, *50*, 6787.

to the thermal instability of any dialkyl cuprate that has a hydrogen atom on a carbon that is β- to the Cu.

The reaction with alkyl halides is of wide scope[1406] and R in R_2CuLi may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, CO_2H, CO_2R, or $CONR_2$ groups.[1407] The mechanism of these reactions probably involves formation of a Cu(II) intermediate.[1408] Reaction with allylic substrates usually proceeds with high selectivity for the γ-position,[1409] in S_N2'-type reactions.[1410]

Inversion of configuration has been shown in the reaction of 2-bromobutane with Ph_2CuLi,[1411] but the same reaction with 2-iodobutane was reported to proceed with racemization.[1412] The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.[1413] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring[1414] or on a cyclopropane ring,[1415] both halogens can be replaced by R (e.g., $PhCHCl_2 \rightarrow PhCHMe_2$). However, 1,2-dibromides give exclusive elimination (Reaction **17-22**).[1416] Vinylmagnesium halides, upon addition of a catalytic amount of Li_2CuCl_4, couple to alkyl halide.[1416]

Lithium dialkylcopper reagents couple with alkyl tosylates.[1417] High yields are obtained with primary tosylates; secondary tosylates give lower yields,[1418] but aryl tosylates do not react. Vinylic triflates[1419] couple very well to give alkenes[1420] and they also couple with allylic cuprates, to give 1,4-dienes.[1421] Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.[1422]

The R′ in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction so far described, the alkyl groups on the organocuprate or the alkyl halide may *not* be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved

[1406] See Posner, G.H. *Org. React.* ***1975***, *22*, 253; Lipshutz, B.H. *Accts. Chem. Res.* ***1997***, *30*, 277; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. For lists of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 392–399, 599–604, 1564.

[1407] See Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122,* 7294.

[1408] For an extensive discussion of the mechanism of reaction between organocuprates and alkyl haldies or epoxides, see Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122,* 7294; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. See Bertz, S.H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C.A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 7082.

[1409] Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* ***2008***, *130,* 12862.

[1410] Some intermediates in this reaction have been prepared, see Bartholomew, E.R.; Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A. *J. Am. Chem. Soc.* ***2008***, *130,* 11244. For a review, see Falciola, C.A.; Alexakis, A. *Eur. J. Org. Chem.* ***2008***, 3765.

[1411] Posner, G.H.; Ting, J. *Synth. Commun.* ***1973***, *3*, 281.

[1412] Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. *J. Org. Chem.* ***1983***, *48*, 3306.

[1413] Klein, J.; Levene, R. *J. Am. Chem. Soc.* ***1972***, *94*, 2520. For a discussion of the mechanism, see Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 12264.

[1414] Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1972***, 293.

[1415] See Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1600.

[1416] Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* ***2000***, *56*, 2733.

[1417] Johnson, C.R.; Dutra, G.A. *J. Am. Chem. Soc.* ***1973***, *95,* 7777, 7783. See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 85–90.

[1418] Secondary tosylates give higher yields when they contain an O or S atom: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* ***1989***, *54,* 5831.

[1419] See Scott, W.J.; McMurry, J.E. *Acc. Chem. Res.* ***1988***, *21*, 47.

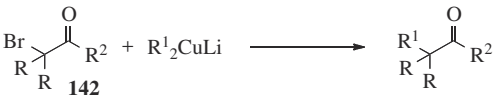
[1420] Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* ***1989***, 1313.

[1421] Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* ***1990***, *55,* 1695.

[1422] Baudouy, R.; Goré, J. *J. Chem. Res. (S)* ***1981***, 278. See also, Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* ***1989***, *54,* 3726.

(on primary RX) by the use of $R'_2CuLi{\bullet}PBu_2$[1423] (but this procedure introduces problems in the workup) or by the use of PhS(R′)CuLi,[1424] which selectively couples a secondary or tertiary R′ with a primary iodide (RI) to give RR′.[1425] It is possible to prepare mixed cuprates, where one ligand is tightly bound to the copper, allowing the other ligand to be transferred in a coupling reaction. A common example is adds a 2-thienyl group to the cuprate to give R(Th)CuLi, where the R group is transferred in lieu of the thienyl unit.[1426] A lithium neopentyl aryl cuprate selectively transferred from an aryl group to an allylic halide.[1427]

Coupling to a secondary alkyl halide (R in RX above = secondary) can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,[1428] where R′ is primary alkyl or vinylic (but not aryl).[1429] This modified reagent is commonly known as a *higher order mixed cuprate*. The reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $RCu(PR'_2)Li$ (R′ = cyclohexyl) are more stable than R_2CuLi and can be used at higher temperatures.[1430] These reagents are rather reactive. Unactivated aryl triflates[1431] ($ArOSO_2CF_3$) react to give ArR in good yields when treated with $R_2Cu(CN)Li_2$,[1432] with R_3Al,[1433] or with R_3SnR and a Pd complex catalyst.[1434] See Reaction **10-59** for other examples involving Al, Sn, and Pd coupling reactions. Both OTf units in $RCH(OTf)_2$ can be replaced with $Me_2(CN)CuLi_2$.[1435] With an allenic substrate, reaction with R(CN)CuLi can give ordinary displacement (with retention of configuration)[1436] or an S_N2' reaction to produce an alkyne.[1437] In the latter case, a chiral allene (see Sec. 4.C, category 5) gave a chiral alkyne. The structures of these "higher order mixed" cuprates has been called into question[1438] by Bertz,[1439] who suggested the reagent actually existed as $R_2CuLi{\bullet}LiCN$ in THF. This was contradicted by Lipshutz and James.[1440]



142

[1423] Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O., *J. Am. Chem. Soc.* ***1969***, *91*, 4871.
[1424] Prepared as in Ref. 1444 or treatment of PhSCu with RLi: Posner, G.H.; Brunelle, D.J.; Sinoway, L. *Synthesis* ***1974***, 662.
[1425] Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.
[1426] See Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* ***1982***, *23*, 3823; Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. *J. Organomet. Chem.* ***1985***, *285,* 437.
[1427] Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3263.
[1428] See Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett* ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.
[1429] Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7672.
[1430] Bertz, S.H.; Dabbagh, G. *J. Org. Chem.* ***1984***, *49*, 1119.
[1431] See Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc*., ***1988***, *110,* 3296.
[1432] McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett*., ***1983***, *24,* 2723.
[1433] Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc*., *Perkin Trans. 1*, ***1989***, 2513.
[1434] Echevarren, E.M.; Stille, J.K. *J. Am. Chem. Soc*., ***1987***, *109,* 5478. For a similar reaction with aryl fluorosulfonates, see Roth, G.P.; Fuller, C.E. *J. Org. Chem*., ***1991***, *56,* 3493.
[1435] Martínez, A.G.; Barcina, J.O.; Díez, B.R.; Subramanian, L.R. *Tetrahedron* ***1994***, *50*, 13231.
[1436] Mooiweer, H.H.; Elsevier, C.J.; Wijkens, P.; Vermeer, P. *Tetrahedron Lett.* ***1985***, *26*, 65.
[1437] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett*. ***1989***, *30*, 4799.
[1438] Bertz, S.H.; Miao, G.; Eriksson, M. *Chem. Commun.* ***1996***, 815; Snyder, J.P.; Bertz, S.H. *J. Org. Chem.* ***1995***, *60*, 4312. Also see, Snyder, J.P.; Tipsword, G.E.; Spangler, D.P. *J. Am. Chem. Soc.* ***1992***, *114*, 1507.
[1439] Bertz, S.H. J. Am. Chem. Soc. **1990**, 112, 4031.
[1440] Lipshutz, B.H.; James, B. *J. Org. Chem.* ***1994***, *59*, 7585 and references cited therein.

The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones via the organocuprate coupling with α-haloketones (e.g., **142**[1441]; see also, Reactions **10-68** and **10-73**). Note that halogen–metal exchange (Reaction **12-39**) is a side reaction and can become the main reaction.[1442] When α,α′-dibromo ketones are treated with Me_2CuLi in ether at −78 °C and the mixture quenched with methanol, monomethylation takes place[1443] (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**10-56**) to a cyclopropanone followed by nucleophilic attack to give the enolate anion, which is protonated by the methanol. If iodomethane is added instead of methanol, an α,α′-dimethyl ketone is obtained, presumably from S_N2 attack (Reaction **10-68**). Primary, secondary, and tertiary monoalkylation can be achieved with a lithium *tert*-butoxy(alkyl)copper reagent[1444] instead of Me_2CuLi, one of the few methods for introducing a tertiary alkyl group to a carbonyl group.

When dialkylcopperzinc reagents ($R_2CuZnCl$) couple with allylic halides, allylic rearrangement occurs (S_N2') almost completely, and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.[1445] Another type of copper reagent was prepared from RZnI/CuCN, and was shown to couple with alkenyl halides.[1446] Diethylzinc in the presence of a catalytic amount of CuBr coupled to allylic chlorides.[1447] When treated with organocopper compounds and Lewis acids (e.g., *n*-BuCu•BF_3), allylic halides give substitution with almost complete allylic rearrangement, independently of the degree of substitution at the two ends of the allylic system.[1448]

OS **IX**, 502.

10-59 Reaction of Alkyl Halides and Sulfonate Esters with Other Organometallic Reagents

Alkyl-de-halogenation

$$RX + R'—M \longrightarrow R—R'$$

In addition of Mg, Li, and Cu, other metals and metal complexes can be used to catalyze or mediate coupling reactions. Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at −78 °C.[1449] This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also, Reaction **10-63**). Vinylic aluminum compounds (in the presence of a suitable transition metal catalyst) couple

[1441] Dubois, J.E.; Fournier, P.; Lion, C. *Bull. Soc. Chim. Fr.* ***1976***, 1871.
[1442] See Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3911; Wakselman, C.; Mondon, M. *Tetrahedron Lett.* ***1973***, 4285.
[1443] Posner, G.H.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3076. See also, Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* ***1975***, *97*, 107; Lion, C.; Dubois, J.E. *Tetrahedron* ***1975***, *31*, 1223. See Lei, X.; Doubleday, Jr., C.; Turro, N.J. *Tetrahedron Lett.* ***1986***, *27*, 4671.
[1444] Prepared by treating CuI with *t*-BuOLi in THF at 0 °C and adding RLi to this solution.
[1445] Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* ***1989***, *111*, 3091.
[1446] Marquais, S.; Cahiez, G.; Knochel, P. *Synlett*, ***1994***, 849.
[1447] Malda, H.; van Zijl, A.W.; Arnold, L.A.; Feringa, B.L. *Org. Lett.* ***2001***, *3,* 1169.
[1448] Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1980***, *102*, 2318. See also, Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 5869.
[1449] Kennedy, J.P. *J. Org. Chem.* ***1970***, *35*, 532. See also, Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* ***1978***, *157*, C30.

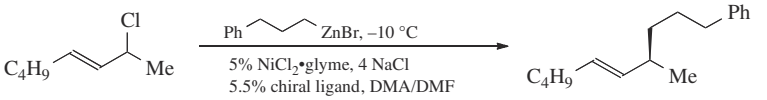
with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,[1450] and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.[1451] Note that alkylboronic acids are coupled in the presence of Ag_2O and a catalytic amount of $CrCl_2$ to give the symmetrical alkyl derivative.[1452]

Products containing a quaternary carbon can also be obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2,[1453] with Me_3Si and $AlCl_3$,[1454] or with alkyltitanium reagents ($RTiCl_3$ and R_2TiCl_2).[1455] Alkyl or aryl triflates (halides) couple with alkyl or ArZn(halide) reagents in the presence of a Pd catalyst.[1456] This organozinc coupling reaction has been done in ionic liquids.[1457] Vinyl halides can be coupled with vinyltin reagents in the presence of CuI,[1458] and aryl tin compounds couple with vinyl halides[1459] or vinyl triflates when a Pd catalyst is present.[1460] When the vinyltin reagent is coupled with a vinyl triflate in the presence of a Pd catalyst, the reaction is known as the *Stille reaction* (Reaction **12-15**). In the *Stille reaction*, vinylic triflates, in the presence of a Pd catalyst and LiCl, couple with organotin compounds ($R'SnMe_3$), where R' can be alkyl, allylic, vinylic, or alkynyl.[1461] The reaction has been performed intramolecularly, to prepare large-ring lactones.[1462]

The coupling of alkyl or alkenyl halides and an organozinc compound with a Ni complex has come to be known as *Negishi coupling*.[1463] Several variations have been reported over the years. Arylzinc compounds[1464] have been used, and also arylvinyl iodides.[1465] The structure of bis(iodozincio)methane in THF solution has been reported.[1466] Pyridylzinc compounds have been used in *Negishi coupling*.[1467]

[1450] See Lee, Y.; Akiyama, K.; Gillingham, D.G.; Brown, M.K.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008,*** *130*, 446.
[1451] Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* ***1987***, *109*, 2393.
[1452] Falck, J.R.; Mohaptra, S.; Bondlela, M.; Venkataraman, S.K. *Tetrahedron Lett.* ***2002***, *43,* 8149.
[1453] Reetz, M.T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* ***1980***, 1202. See also, Klingstedt, T.; Frejd, T. *Organometallics* ***1983***, *2,* 598.
[1454] Bolestova, G.I.; Parnes, Z.N.; Latypova, F.M.; Kursanov, D.N. *J. Org. Chem. USSR* ***1981***, *17*, 1203.
[1455] Reetz, M.T.; Westermann, J.; Steinbach, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 900, 901.
[1456] Takahashi, H.; Hossain, K.M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* ***2006***, *71,* 671. See also Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* ***2008***, *73,* 7380.
[1457] Sirieix, J.; Oßberger, M.; Betzemeier, B.; Knochel, P. *Synlett* ***2000***, 1613.
[1458] Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* ***1997***, *62*, 4208.
[1459] Shen, W.; Wang, L. *J. Org. Chem.* ***1999***, *64*, 8873.
[1460] Fouquet, E.; Rodriguez, A.L. *Synlett* ***1998***, 1323.
[1461] Kwon, H.B.; McKee, B.H.; Stille, J.K. *J. Org. Chem.* ***1990***, *55,* 3114. See Stang, P.J.; Kowalski, M.H.; Schiavelli, M.D.; Longford, D. *J. Am. Chem. Soc.* ***1989***, *111,* 3347; Stang, P.J.; Kowalski, M.H. *J. Am. Chem. Soc.* ***1989***, *111,* 3356.
[1462] Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3785.
[1463] Negishi, E. *Acc. Chem. Res.* ***1982***, *15*, 340; Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* ***1976***, 597; Baba, S.; Negishi, E. *J. Am. Chem. Soc.* ***1976***, *98*, 6729; King, A.O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* ***1977***, 683; Negishi, E.; Okukado, N.; King, A. O.; van Horn, D. E.; Spiegel, B. I. J. *Am. Chem. Soc.* ***1978***, *100,* 2254; Schade, M.A.; Metzger, A.; Hug, S.; Knochel, P. *Chem. Commun.* ***2008***, 3046; Phapale, V.B.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D.J. *Chemistry: Eur. J.* ***2009***, *15*, 12681; Dong, Z.-B.; Manolikakes, G.; Shi, L.; Knochel, P.; Mayr, H. *Chemistry: Eur. J.* ***2010***, *16*, 248. For insights into the mechanism, see Casares, J.A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* ***2007***, *129,* 3508. For coupling with nonactivated secondary halides, see Glorius, F. *Angew. Chem. Int. Ed.* ***2008***, *47,* 8347.
[1464] Mutule, I.; Suna, E. *Tetrahedron* ***2005***, *61,* 11168.
[1465] Kabir, M.S.; Monte, A.; Cook, J.M. *Tetrahedron Lett.* ***2007***, *48,* 7269.
[1466] Matsubara, S.; Oshima, K.; Matsuoka, H.; Matsumoto, K.; Ishikawa, K.; Matsubara, E. *Chem. Lett.* ***2005***, *34,* 952.
[1467] Coleridge, B.M.; Bello, C.S.; Ellenberger, D.H.; Leitner, A. *Tetrahedron Lett.* ***2010***, *51*, 357.

Carbonylative cross coupling reactions have been reported.[1468] Palladium-catalyzed variations are also known for alkyl or vinyl halides with organozinc compounds.[1469] Dialkylzinc compounds can be coupled to alkyl halides in the presence of a nickel catalyst,[1470] but with geminal diiodo compounds without a catalyst.[1471] Asymmetric variations are known using various chiral additives or chiral catalysts,[1472] including the example shown for an allylic chloride (DMA = dimethylactamide).[1473] Coupling with propargylic substrates has also been reported.[1474]



Copper compounds can also be used as catalysts with dialkylzinc reagents.[1475] The reaction of aryl halides with Me_4ZnLi_2 and then $VO(OEt)Cl_2$ leads to the methylated aryl.[1476] Isopropylzinc (*i*PrZn) displaces the iodide in γ-iodo ketones to give the alkyl substitution product, without reaction at the carbonyl.[1477] Reactions of organozinc reagents with a carbonyl compound via acyl addition is presented in **16-31** (the *Reformatsky reaction*). Tertiary halides have also been coupled to allyltin reagents in the presence of AIBN.[1478] Alkyl halides can be treated with SmI_2 and then CuBr to give a reactive species that couples with other alkyl halides.[1479] Trialkylindium compounds couple to allylic bromides in the presence of $Cu(OTf)_2$•$P(OEt)_3$[1480] and vinyl indium compounds are coupled to α-halo esters with a BEt_3 catalyst.[1481] Arylsulfonyl chlorides couple with allyl halides in the presence of bismuth to give allyl-aryls.[1482] Vinyl iodides couple with RMnCl with an iron catalyst[1483] and $Bu_3MnMgBr$ reacted with a geminal dibromocyclopropane to give a dialkylated cyclopropane.[1484] α-Haloketones are coupled with aryl halides using a

[1468] Wang, Q.; Chen, C. *Tetrahedron Lett.* ***2008***, *49,* 2916.
[1469] See Hadei, N.; Kantchev, E.A.B.; O'Brien, C.J.; Organ, M.G. *J. Org. Chem.* ***2005***, *70,* 8503; Andrei, D.; Wnuk, S.F. *J. Org. Chem.* ***2006***, *71,* 405. For a variation using Pd-nanoparticles, see Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T.B.; Yang, Z.; Lei, A. *Org. Lett.* ***2008***, *10,* 2661.
[1470] Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* ***1999***, *64,* 3544; Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67,* 79; Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 14726; Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6180.
[1471] Shibli, A.; Varghese, J.P.; Knochel, P.; Marek, I. *Synlett* ***2001***, 818.
[1472] See Fischer, C.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127,* 4594; Arp, F.O.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127,* 10482.
[1473] Son, S.; Fu, G.C. *J. Am. Chem. Soc.* ***2008***, *130*, 2756.
[1474] Smith, S.W.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2008***, *47,* 9334.
[1475] Shi, W.J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2003***, *14*, 3867.
[1476] Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001***, *66*, 303.
[1477] Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67*, 79.
[1478] Kraus, G.A.; Ansersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* ***1993***, *34*, 1741.
[1479] Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* ***1997***, *38*, 3171.
[1480] Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2003***, *68,* 2518.
[1481] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2004***, *6,* 4555.
[1482] Baruah, M.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett*, ***1998***, 1083.
[1483] Cahiez, G.; Marquais, S. *Tetrahedron Lett.* ***1996***, *37*, 1773.
[1484] Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56,* 2131.

Ni catalyst.[1485] Allylgallium reagents have been coupled to α-bromo esters in the presence of BEt_3/O_2.[1486]

Arylpalladium salts (ArPdX) prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields, although allylic rearrangements can occur.[1487] In most cases, better yields are obtained by addition of a Pd complex to the substrate, sometimes in conjunction with another metal, to facilitate coupling. Under these conditions, any arylpalladium species is generated *in situ*. Allylic, benzylic, vinylic, and aryl halides or triflates (trifluoromethylsulfonates) couple with organotin reagents in a reaction catalyzed by Pd complexes.[1488] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, and so on, which cannot be present in a *Grignard reagent*. Such functional groups as CO_2R, CN, OH, and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Indium metal has been used to mediate the coupling of an allylic halide and an arylpalladium complex.[1489] Organoindium compounds were coupled to 1-iodonaphthalene with a Pd catalyst.[1490] Aryl halides were also coupled to allylic silanes in the presence of a Pd catalyst.[1491]

Dimethylzinc was coupled to aryl halides with a Pd catalyst,[1492] and *Reformatsky-type* zinc derivatives (see Reaction **16-28**) have been coupled to aryl halides using a Pd catalyst and microwave irradiation.[1493] Alkyl halides couple with ArMnCl or RMnCl in the presence of a Pd catalyst.[1494] Cobalt-catalyzed coupling reactions are known.[1495]

In many cases, the organometallic reagent is prepared from the corresponding organolithium reagent (Reaction **10-57**), as in the conversion of an aryllithium to an arylzirconium reagent, which was subsequently coupled to an aryl halide in the presence of a Pd catalyst.[1496] Vinylzirconium reagents can be coupled to allylic halides in the presence of Cu(I) compounds.[1497]

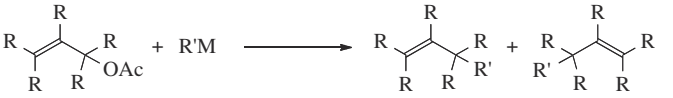
Alkylboranes are coupled to alkyl halides in the presence of a Ni catalyst.[1498]

OS **VII**, 245; **VIII**, 295; **X**, 391.

[1485] Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J. *Synth. Commun.* ***1994***, *24*, 145.
[1486] Usugi, S.-i.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* ***2001***, *42,* 4535.
[1487] Heck, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5531. See Reaction **13-10**. See Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 208–214, 242–249. Also see Yin, L.; Liebscher, J. *Chem. Rev.* ***2007***, *107,* 133.
[1488] See Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1990***, *59*, 1174. See Martínez, A.G.; Barcina, J.O.; Heras, Md.R.C.; Cerezo, A.d.F. *Org. Lett.* ***2000***, *2*, 1377
[1489] Lee, P.H.; Sung, S.-y.; Lee, K. *Org. Lett.* ***2001***, *3*, 3201.
[1490] Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2004***, *69*, 8136.
[1491] Denmark, S.E.; Werner, N.S. *J. Am. Chem. Soc.* ***2008***, *130*, 16382.
[1492] Herbert, J.M. Tetrahedron Lett. **2004**, 45, 817.
[1493] Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* ***2004***, *45,* 7395.
[1494] Riquet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* ***1997***, *38*, 4397.
[1495] Czaplik, W.M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* ***2009***, 2931.
[1496] Frid, M.; Pérez, D.; Peat, A.J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9469. See also, Villiers, P.; Vicart, N.; Ramondenc, Y.; Plé, G. *Tetrahedron Lett.* ***1999***, *40*, 8781.
[1497] Sato, A.; Ito, H.; Taguchi, T. *J. Org. Chem.* ***2005***, *70,* 709.
[1498] Saito, B.; Fu, G.C. *J. Am. Chem. Soc.* ***2008***, *130*, 6694.

10-60 Coupling of Organometallic Reagents with Carboxylic Esters

Alkyl-de-acyloxy-substitution



Several organometallic reagents react with allylic esters and carbonates to give the coupling product. Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.[1499] A mechanism involving a σ-allylic copper(III) complex has been suggested.[1500] Silyl cuprates have also been used, with benzoate esters, to give allyl silanes.[1501] Interestingly, allylic silanes have been coupled to acetates using $B(C_6F_5)_3$[1502] or BF_3.[1503]

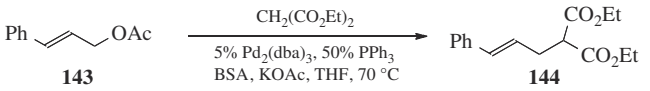
$$RC{\equiv}C{-}CR_2{-}OAc + R'_2CuLi \longrightarrow RR'C{=}C{=}CR_2$$

Allenes are obtained when propargyl acetates are treated with methylmagnesium iodide.[1504] Lithium dialkylcopper reagents give normal coupling products with enol acetates of β-dicarbonyl compounds.[1505] It is also possible to carry out the coupling of allylic acetates with *Grignard reagents*, if catalytic amounts of cuprous salts are present.[1506] Yields are better with this method, and regioselectivity can be controlled by the choice of cuprous salts.

Several metal-catalyzed coupling reactions are known. Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,[1507] and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a Pd catalyst[1508] (see below). Allylic acetates can be symmetrically coupled by treatment with $Ni(CO)_4$ (Reaction **10-56**) or with Zn and a Pd—complex catalyst,[1509] or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane ($R_2C{=}CHCH_2SnR_3$) in the presence of a Pd complex.[1510] Other Ni(0) coupling reactions are known.[1511] Titanium-mediated[1512] coupling, Ir catalyzed,[1513]

[1499] Purpura, M.; Krause, N. *Eur. J. Org. Chem.* ***1999***, 267.
[1500] Goering, H.L.; Kantner, S.S.; Seitz, Jr., E.P. *J. Org. Chem.* ***1985***, *50,* 5495.
[1501] Fleming, I.; Higgins, D.; Lawrence, N.J.; Thomas, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 3331.
[1502] Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2001***, *3*, 2705. See Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1999.
[1503] Smith, D.M.; Tran, M.B.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 14149; Ayala, L.; Lucero, C.G.; Romero, J.A.C.; Tabacco, S.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 15521.
[1504] Roumestant, M.; Gore, J. *Bull. Soc. Chim. Fr.* ***1972***, 591, 598; Crabbé, P.; Barreiro, E.; Dollat, J.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1976***, 183, and references cited therein.
[1505] Casey, C.P.; Marten, D.F. *Tetrahedron Lett.* ***1974***, 925. See also, Posner, G.H.; Brunelle, D.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 907; Kobayashi, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1973***, 1097.
[1506] Karlström, A.S.E.; Huerta, F.F.; Muezelaar, G.J.; Bäckvall, J.-E. *Synlett* ***2001***, 923; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* ***2001***, 927.
[1507] van Klaveren, M.; Persson, E.S.M.; del Villar, A.; Grove, D.M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* ***1995***, *36*, 3059.
[1508] Del Valle, L.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* ***1990***, *55,* 3019. For another method, see Legros, J.; Fiaud, J. *Tetrahedron Lett.* ***1990***, *31*, 7453.
[1509] Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1985***, 315.
[1510] Trost, B.M.; Keinan, E. *Tetrahedron Lett.* ***1980***, *21*, 2595.
[1511] Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* ***2007***, *9*, 4603.
[1512] Mandal, S.K.; Paira, M.; Roy, S.C. *J. Org. Chem.* ***2008***, *73*, 3823.
[1513] Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem. Int. Ed.* ***2008***, *47,* 7652.

and Fe catalyzed[1514] reactions are also known. Aryl halides can be coupled to allylic acetates with $CoBr_2$/Mn/$FeBr_2$.[1515] Allylic phosphonates have been used as substrates for displacement by higher order cuprates[1516] (see Reaction **10-58**) or dialkylzinc reagents.[1517]



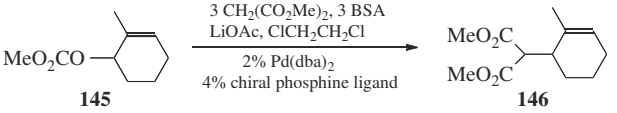
143 **144**

A common method is the reaction of η^3-π-allyl palladium complexes[1518] (see Sec 3.C.i) with various nucleophiles,[1519] where the complex is obtained from allylic esters (acetate is the most common) or allylic carbonates (also see Reaction **10-31**). This coupling reaction is often called the *Tsuji–Trost* reaction.[1520] The mechanism of such π-allyl palladium reactions has been discussed.[1521] The structure and nature of the ligands associated with the metal are important to the reaction, particularly with respect to stereoselectivity of a given reaction.[1522] A typical transformation is shown for the reaction of **143** with diethyl malonate, BSA (N,O-bis(trimethylsilyl)acetamide), and potassium acetate, which gives coupling product **144** in the presence of the Pd catalyst.[1523] This reaction is a variation of the basic transformation reported several years ago by Trost et al.[1524] Enolate anions of active methylene compounds[1525] and also sulfone anions[1526] have been used as nucleophiles most of the time. In most reported cases, the R′M species is the anion of an active methylene compound (e.g., sodium, potassium, or lithium dimethylmalonate) or *Knoevenagel-type* carbanions (see Reaction **16-38**) or amino acid surrogates.[1527] Enolate

[1514] Plietker, B. *Angew. Chem. Int. Ed.* ***2006***, *45, 6053*.
[1515] Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett*. ***2003***, *5*, 1043.
[1516] Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 5552.
[1517] Kacprzynski, M.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126,* 10676.
[1518] See Tsuji, J. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 163–199.
[1519] See Trost, B.M.; Crawley, M.L. *Chem. Rev.* ***2003***, *103*, 2921. For a discussion of the mechanism see Tsurugi, K.; Nomura, N.; Aoi, K. *Tetrahedron Lett.* ***2002***, *43,* 469.
[1520] See Mohr, J.T.; Stoltz, B.M. *Chemistry: Asian J.* ***2007***, *2*, 1476; Trost, B.M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1173; *Acc. Chem. Res.* ***1980***, *13*, 385; Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20*, 140, *Organic Synthesis with Palladium Compounds*, Springer, Berlin, ***1981***, pp. 45, 125; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 130–166; Hegedus, L.S. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 30-44. See Liao, M.-c.; Duan, X.-h.; Liang, Y.-m. *Tetrahedron Lett*. ***2005***, *46*, 3469.
[1521] Trost, B.M.; Toste, F.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4545.
[1522] For example, see Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* ***2007***, *48,* 585; Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron Asymmetry* ***2005***, *16,* 959; Mikhael, I.; Goux-Henry, C.; Sinou, D. *Tetrahedron Asymmetry* ***2006***, *17,* 1853; Ruzziconi, R.; Santi, C.; Spizzichino, S. *Tetrahedron Asymmetry* ***2007***, *18,* 1742; Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron Asymmetry* ***2008***, *19,* 2447; Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* ***2006***, *12,* 3596. Also see Mino, T.; Sato, Y.; Saito, A.; Tanaka, Y.; Saotome, H.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* ***2005***, *70,* 7979.
[1523] Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* ***1999***, *64*, 2962.
[1524] Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3416, 3426. These papers include a discussion of the mechanism of this reaction.
[1525] Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* ***2006***, *45,* 6952.
[1526] Manchand, P.S.; Wong, H.S.; Blount, J.F. *J. Org. Chem.* ***1978***, *43*, 4769.
[1527] Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* ***2001***, *3*, 3329.

anions (see Reaction **10-68**) have also been used.[1528] Other nucleophiles can be used to displace allylic acetates.[1529] The Pd catalyst used, the reaction conditions, and the nature of the organometallic compounds varies widely. Although two allylic coupling products are possible via the π-allyl intermediate, attack at the less substituted position is generally favored. This transformation has been done in ionic liquids[1530] and ionic liquids have been used as additives in catalytic amounts in other solvents.[1531] Palladium nanoparticles have been used to catalyze the reaction.[1532] The S_N2' reactions with allylic substrates have been reported.[1533] Benzoate esters have been used successfully in lieu of the acetate.[1534] Catalyst metals other than Pd have been used for this reaction with allylic acetates.[1535]

The use of chiral ligands[1536] or chiral additives that may act as ligands[1537] lead to asymmetric induction in the coupling product.[1538]



145 **146**

As mentioned above, a common variation is to replace the acetate leaving group with a carbonate (—OCO_2R), where methyl carbonate (—OCO_2Me) is most common.[1539] A representative reaction is the transformation of **145** to **146**,[1540] where the use of a chiral ligand led to modest asymmetric induction. Indeed, as with allylic acetates, chiral ligands and chiral additives lead to asymmetric induction.[1541] A variety of active

[1528] Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* ***2000***, *39,* 3494.
[1529] **$NaN(CHO)_2$:** Wang, Y.; Ding, K. *J. Org. Chem.* ***2001***, *66*, 3238. **Indene**: Hayashi, T.; Suzuka, T.; Okada, A.; Kawatsura, M. *Tetrahedron Asymmetry* ***2004***, *15*, 545.
[1530] See Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* ***1999***, 1247.
[1531] Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* ***2003***, *5*, 31.
[1532] Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.,* ***2004***, *126,* 1592.
[1533] Falciola, C.A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2006***, *45,* 5995.
[1534] Krafft, M.E.; Sugiura, M.; Abboud, K.A. *J. Am. Chem. Soc.* ***2001***, *123*, 9174.
[1535] **Ir**: Kinoshita, N.; Marx, K.H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* ***2004***, *69*, 7960. **Pt**: Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* ***2000***, *6*, 353. **Ru**: Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* ***2003***, 408.
[1536] See Boaz, N.W.; Ponaskik Jr., J.A.; Large, S.E.; Debenham, S.D. *Tetrahedron Asymmetry* ***2004***, *15*, 2151.
[1537] Molander, G.A.; Burke, J.P.; Carroll, P.J. *J. Org. Chem.* ***2004***, *69*, 8062; Kloetzing, R.J.; Lotz, M.; Knochel, P. *Tetrahedron Asymmetry* ***2003***, *14*, 255; Nakano, H.; Yokayama, J.-i.; Koiyama, Y.; Fjita, R.; Hongo, H. *Tetrahedron Asymmetry* ***2003***, *14*, 2361; Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron Asymmetry* ***2003***, *14*, 3137.
[1538] See Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89,* 257.
[1539] See Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 284.
[1540] Hamada, Y.; Sakaguchi, K.-e.; Hatano, K.; Hara, O. *Tetrahedron Lett.* ***2001***, *42*, 1297.
[1541] Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12104; Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* ***2004***, *45*, 7613.

methylene compounds can be used as nucleophiles,[1542] including enolate anions.[1543] Other nucleophiles can be used to displace allylic carbonates,[1544] often in conjunction with chiral ligands to give the product with enantioselectivity. Polymer-supported phosphine ligands have been used successfully,[1545] and catalyst systems other than Pd have been used for this reaction with allylic carbonates.[1546]. Potassium vinyltrifluoroborates (Reaction **10-73**) have also been used in Pd catalyzed coupling reactions with allylic acetates.[1547]

Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.[1548] Propargylic esters have been used in Pd catalyzed coupling reactions, including a reaction with trialkylindium reagents.[1549]

10-61 Coupling of Organometallic Reagents with Sulfate Esters, Sulfoxides, Sulfones, Nitro, and Acetals

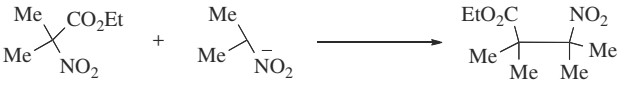
Alkyl-de-sulfonyl and de-sulfonyloxy-substitution, and so on; **Alkyl-de-alkoxy-substitution**, and so on; **Alkyl-de-nitration**, and so on

$$RSO_2X + R'M \longrightarrow R{-}R'$$

Leaving groups other than halide, esters or carbonate, or sulfonate esters are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. The reactions of sodium sulfonates and alkyl halides in ionic liquids have been reported.[1550] The SO_2Ph group of allylic sulfones can be a leaving group if a Pd complex is present.[1551] The NR_2 group from *Mannich bases* (e.g., $RCOCH_2CH_2NR_2$), can also act as a leaving group

[1542] **Amide esters:** Kazmaieer, U.; Zumpe, F.L. *Angew. Chem. Int. Ed.* ***1999***, *38,* 1468.
[1543] Evans, P.A.; Lawler, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8642. For a reaction is a silyl enol ether see Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2000***, *41*, 8807.
[1544] **Aryllithium reagents:** Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* ***2003***, *125*, 7158. **Alkoxides**: Evans, P.A.; Leahy, D.K.; Slieker, L.M. *Tetrahedron Asymmetry* ***2003***, *14*, 3613. **Phenoxide anions**: Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2000***, *122*, 5012; López, F.; Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3426. **Secondary amines**: Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10405. **Primary amines**: Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 15164. ***N*** **-Lithiosulfonamides**: Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. *J. Am. Chem. Soc.* ***2002***, *124*, 8782. ***C*****-Alkylation with an indole**: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* ***2004***, *6*, 3199. **Michael addition of conjugated esters**: Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* ***2000***, *12*, 9552.
[1545] Uozumi, Y.; Shibatmoi, K. *J. Am. Chem. Soc.* ***2001***, *123*, 2919.
[1546] **Ru**: Trost, B.M.; Fraisse, P.L.; Ball, Z.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1059. **Mo**: Glorius, F.; Pfaltz, A. *Org. Lett.* ***1999***, *1,* 141; Malkov, A.V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* ***2001***, *42*, 509. **Ir**: Alexakis, A.; Polet, D. *Org. Lett.* ***2004***, *6*, 3529; Lee, P.H.; Sung, S.-y.; Lee, K.; Chang, S. *Synlett* ***2002***, 146.
[1547] Kabalka, G.W.; Al-Masum, M. *Org. Lett.* ***2006***, *8,* 11.
[1548] Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. *J. Org. Chem.* ***2001***, *66,* 589. See also, Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* ***2001***, *66,* 7676.
[1549] Riveiros, R.; Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *Org. Lett.* ***2006***, *8,* 1403.
[1550] Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.G. *Synth. Commun.* ***2004***, *34*, 4031.
[1551] Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5979.

in this reaction (elimination–addition mechanism, Sec. 10.F). A nitro group can be displaced[1552] from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,[1553] and even from simple tertiary nitro compounds of the form R_3CNO_2[1554] or ArR_2CNO_2[1555] by salts of nitroalkanes, for example,



These reactions take place by SET mechanisms.[1556] However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.[1557] The SO_2R group of allylic sulfones can be replaced by CHZZ′ (C=CCH$_2$—SO_2R → C=CCH$_2$—CHZZ′) if a $Mo(CO)_6$ catalyst is used.[1558]

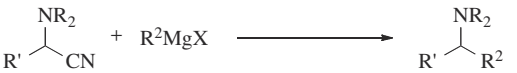
tert-Butylsulfones react with organolithium reagents, in the presence of a catalytic amount of an iron complex, to give coupling.[1559] In this case the *t*-BuSO_2 unit becomes a "leaving group". A sulfoxide was a "leaving group" in the cyclization of a carboxylic acid that contains a sulfoxide unit at C-4. Treatment with phenyliodonium bis(trifluoroacetate) gave the five-membered ring lactone.[1560] Similar displacement of TolSO_2 was observed with tolylsulfones and diethylzinc.[1561]

Phosphonic esters, $ROPO(OR)_2$, react with allylic *Grignard reagents* to give the coupling product.[1562]

OS **I**, 471; **II**, 47, 360; **VII**, 351; **VIII**, 97, 471.

10-62 The Bruylants Reaction

Alkyl-de-cyanation



The *Bruylants reaction* is the reaction of an aminonitrile with a *Grignard reagen*t to give a substituted amine.[1563] This reaction is most often used for the preparation of aliphatic amines via aliphatic *Grignard reagents*. In a few cases, vinylic *Grignard reagents* can be used to prepare allylic amines.[1564] The use of $AgBF_4$ to convert amino nitriles to the

[1552] See Kornblum, N. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 361–393; Kornblum, N. *Angew. Chem. Int. Ed.* ***1975***, *14*, 734; Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* ***1991***, 423; Kornblum, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemisry*, VCH, NY, ***1990***, pp. 46–85.

[1553] Kornblum, N.; Kelly, W.J.; Kestner, M.M. *J. Org. Chem.* ***1985***, *50*, 4720.

[1554] Kornblum, N.; Erickson, A.S. *J. Org. Chem.* ***1981***, *46*, 1037.

[1555] Kornblum, N.; Carlson, S.C.; Widmer, J.; Fifolt, M.J.; Newton, B.N.; Smith, R.G. *J. Org. Chem.* ***1978***, *43,* 1394.

[1556] For a review of the mechanism, see Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431. See also, Kornblum, N.; Wade, P.A. *J. Org. Chem.* ***1987***, *52*, 5301; Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17,* 283; Ref. 1479.

[1557] Kornblum, N.; Boyd, S.D.; Ono, N. *J. Am. Chem. Soc.* ***1974***, *96,* 2580.

[1558] Trost, B.M.; Merlic, C.A. *J. Org. Chem.* ***1990***, *55*, 1127.

[1559] Jin, L.; Julia, M.; Verpeaux, J.N. *Synlett* ***1994***, 215.

[1560] Casey, M.; Manage, A.C.; Murphy, P.J. *Tetrahedron Lett.* ***1992***, *33,* 965.

[1561] Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* ***2002***, *124,* 5940.

[1562] Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 5879.

[1563] Bruylants, P. *Bull. Soc. Chem. Belg.* ***1924***, *33,* 467.

[1564] Trost, B.M.; Spagnol, M.D. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2083.

corresponding iminium ion facilitates the *Bruylants reaction* with vinylic *Grignard reagents*.[1565] Replacement of the cyano group in a tertiary nitrile is also possible.[1566]

Displacement of a cyano group in α-cyanoketones is possible. Treatment of the α-cyanoketone with SmI_2 followed by addition of an excess of allyl bromide gave the α-allyl ketone derivative.[1567] α-Cyano amines react with allyl bromide and then zinc metal to give homoallylic amines after treatment with dilute acetic acid in THF.[1568]

10-63 Coupling Involving Alcohols

De-hydroxyl-coupling

$$\mathrm{ROH + R'M \longrightarrow R{-}R'}$$

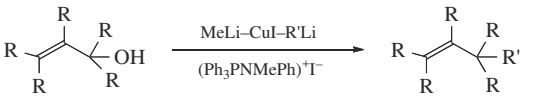
In some cases, it is possible to couple an alcohol in the presence of an organometallic compound.[1569] Allylic alcohols are coupled with alkylmagnesium bromides in the presence of $Ti(OiPr)_4$, for example.[1570] Allylic alcohols can be coupled with arylboronic acids in an ionic liquid solvent and a Rh catalyst.[1571] The Pd catalyzed reaction of active methylene compounds with allylic alcohols[1572] or benzylic alcohols[1573] is also known. The coupling of an alcohol to the α carbon of a ketone ($RCOMe + R'OH$) to give a β-substituted alcohol [$RCH(OH)CH_2R'$] is possible in the presence of a Ru catalyst.[1574] Alcohols are coupled to allenes in the presence of an Ir catalyst.[1575] Allylic carbonates are coupled to allylic alcohols with a Ni catalyst.[1576]

$$2 \quad \mathrm{ROH} \xrightarrow[-78\,^\circ\mathrm{C}]{\mathrm{MeLi{-}TiCl_3}} \mathrm{R{-}R}$$

Allylic or benzylic alcohols can be symmetrically coupled[1577] by treatment with methyllithium and titanium trichloride at −78 °C[1578] or by refluxing with $TiCl_3$ and $LiAlH_4$ (as shown).[1579] When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylic-rearranged products is found. A free radical mechanism is involved.[1580] The $TiCl_3$—$LiAlH_4$ reagent can also convert 1,3-diols to cyclopropanes, provided that at least one phenyl group is present.[1581]

[1565] Agami, C.; Couty, F.; Evano, G. *Org. Lett.* ***2000***, *2,* 2085.
[1566] Katritzky, A.R.; Yang, H.; Singh, S.K. *J. Org. Chem.* ***2005***, *70,* 286.
[1567] Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Tetrahedron Lett.* ***1999***, *40*, 7055.
[1568] Bernardi, L.; Bonini, B.F.; Capitò, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* ***2003***, 1778.
[1569] For a review of Pd catalyzed reactions, see Muzart, J. *Tetrahedron* ***2005***, *61*, 4179.
[1570] Kulinkovich, O.G.; Epstein, O.L.; Isakov, V.E.; Khmel'nitskaya, E.A. *Synlett* ***2001***, 49.
[1571] Kabalka, G.W.; Dong, G.; Venkataiah, B. *Org. Lett.* ***2003***, *5*, 893.
[1572] Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4085.
[1573] Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* ***2002***, 1823.
[1574] Cho, C.S.; Kim, B.T.; Kim. T.-J.; Shim. S.C. *J. Org. Chem.* ***2001***, *66*, 9020. See also, Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* ***2007***, 2850.
[1575] Bower, J.F.; Skucas, E.; Patman, R.L.; Krische, M.J. *J. Am. Chem. Soc.* ***2007***, *129*, 15134.
[1576] Sumida, Y.; Hayashi, S.; Hirano, K.; Hideki, H.; Oshima, K. *Org. Lett.* ***2008***, *10,* 1629.
[1577] See Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12,* 363, pp. 377–388.
[1578] Sharpless, K.B.; Hanzlik, R.P.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1968***, *90*, 209.
[1579] McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* ***1978***, *43*, 3249. For another method, see Nakanishi, S.; Shundo, T.; Nishibuchi, T.; Otsuji, Y. *Chem. Lett.* ***1979***, 955.
[1580] van Tamelen, E.E.; Åkermark, B.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1969***, *91*, 1552.
[1581] Walborsky, H.M.; Murati, M.P. *J. Am. Chem. Soc.* ***1980***, *102,* 426.

Tertiary alcohols ($R_3C—OH$) react with trimethylaluminum at 80–200 °C to give methylation ($R_3C—Me$).[1582] The presence of side products from elimination and rearrangement, as well as the lack of stereospecificity,[1583] indicate an S_N1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the α position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation [see also, reactions of Me_3Al with ketones (**16-24**) and with carboxylic acids (**16-82**)]. The Me_2TiCl_2 compound reacts with tertiary alcohols in the same way.[1584] β-Alkylation of secondary alcohols has been reported using alcohol substrates in the presence of an Ir complex.[1585]



147

Allylic alcohols couple with a reagent prepared from MeLi, CuI, or R′Li in the presence of $(Ph_3PNMePh)^+ I^-$ to give alkenes (e.g., **147**) that are products of allylic rearrangement.[1586]

The reaction gives good yields with primary, secondary, and tertiary alcohols, and with alkyl and aryllithium reagents.[1587] Allylic alcohols also couple with certain *Grignard reagents*[1588] in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.

Allenic alcohols couple with allyl indium reagents at 140 °C to give allylic alcohol products.[1589] Similarly, ω-hydroxy lactones couple with organoindium reagents.[1590] Phenols react with vinyl boronates and a copper catalyst to give aryl vinyl ethers.[1591]

Alcohols react with allylsilanes, in the presence of an $InCl_3$[1592] or $InBr_3$[1593] catalyst to give the corresponding coupling product ($R_2CHOH \rightarrow R_2CH—CH_2CH=CH_2$). Silyl ethers are also coupled to allylsilanes in the presence of $InCl_3$.[1594] Proparygylic alcohols have been coupled to allylic silanes using an Au catalyst[1595] or a Rh catalyst.[1596]

[1582] Harney, D.W.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27,* 1639.
[1583] Salomon, R.G.; Kochi, J.K. *J. Org. Chem.* ***1973***, *38*, 3715.
[1584] Reetz, M.T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* ***1981***, 237.
[1585] Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* ***2005***, *7,* 4017.
[1586] Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1985***, *50*, 1597. For another procedure, see Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* ***1978***, *156*, C9.
[1587] See Cella, J.A. *J. Org. Chem.* ***1982***, *47*, 2125.
[1588] Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* ***1981***, *103,* 1846, and references cited therein. See Felkin, H.; Swierczewski, G. *Tetrahedron* ***1975***, *31*, 2735; Fujisawa, T.; Iida, S.; Yukizaki, H.; Sato, T. *Tetrahedron Lett.* ***1983***, *24,* 5745.
[1589] Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc,* ***1996***, *118*, 4699.
[1590] Bernardelli, P.; Paquette, L.A. *J. Org. Chem.* ***1997***, *62*, 8284.
[1591] McKinley, N.F.; O'Shea, D.F. *J. Org. Chem.* ***2004***, *69*, 5087.
[1592] Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2006***, *71,* 8516; Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem. Int. Ed.* ***2006***, *45,* 793.
[1593] Kim, S.H.; Shin, C.; Pae, A.N.; Koh, H.Y.; Chang, M.H.; Chung, B.Y.; Cho, Y.S. *Synthesis* ***2004***, 1581.
[1594] Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2007***, *72,* 8588.
[1595] Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* ***2005***, *127,* 14180.
[1596] Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* ***2005***, *127*, 15354.

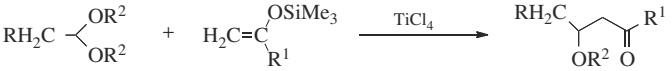
10-64 Coupling of Organometallic Reagents with Compounds Containing the Ether Linkage[1597]

Alkyl-de-alkoxy-substitution

$$R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX$$

$$RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX$$

Acetals,[1598] ketals, and ortho esters[1599] react with *Grignard reagents* to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (Reaction **10-6**). This procedure is a way of converting a halide (R″X, which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde (R″CHO), increasing the length of the carbon chain by one carbon (see also, Reaction **10-76**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3.[1600] Dihydropyrans react with *Grignard reagents* in the presence of a Ni catalyst.[1601] Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,[1602] for example,



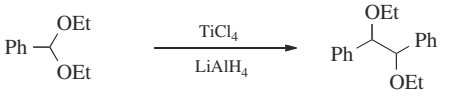
ω-Ethoxy lactams react with *Grignard regents* to give ω-substituted lactams.[1603] Tertiary amines can be prepared by the reaction of amino ethers with *Grignard reagents*,[1604] ($R_2NCH_2—OR' + R^2MgX \rightarrow R_2NCH_2—R^2$) or with lithium dialkylcopper reagents.[1605]

Ordinary ethers are not cleaved by *Grignard reagents* (in fact, diethyl ether and THF are the most common solvents for *Grignard reagents*), although more active organometallic compounds often do cleave them.[1606] However, methyl ethers have been replaced with a methyl group ($MeMgX + ROMe \rightarrow R—Me$) via a Ni catalyzed coupling reaction with MeMgBr.[1607] Oxetanes have been opened with organolithium reagents and $BF_3{\bullet}OEt_2$[1608] and also with excess Li metal with a biphenyl catalyst.[1609] Allylic ethers can be cleaved by

[1597] See Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* ***1975***, *44,* 41.
[1598] See Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043; Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1985***, *38,* 1031. For a list of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 934–942.
[1599] See DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 44–45, 224–230.
[1600] Normant, J.F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* ***1989***, *45,* 507; Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J.F. *Pure Appl. Chem.* ***1988***, *60,* 49.
[1601] Ducoux, J.-P.; LeMénez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* ***1993***, *58*, 1290.
[1602] See Mori, I.; Ishihara, K.; Flippin, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55,* 6107, and references cited therein.
[1603] Wei, Z.Y.; Knaus, E.E. *Org. Prep. Proceed. Int.* ***1993***, *25*, 255.
[1604] See Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* ***1989***, *373*, 1. See also, Bourhis, M.; Bosc, J.; Golse, R. *J. Organomet. Chem.* ***1983***, *256*, 193.
[1605] Germon, C.; Alexakis, A.; Normant, J.F. *Bull. Soc. Chim. Fr.* ***1984***, II-377.
[1606] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1013–1045.
[1607] Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. J. *Am. Chem. Soc.* ***2008,*** *130,* 3268.
[1608] Bach, T.; Eilers, F. *Eur. J. Org. Chem.* ***1998***, 2161.
[1609] Rama, K.; Pasha, M.A. *Tetrahedron Lett.* ***2000***, *41*, 1073.

Grignard reagents in THF if CuBr is present.[1610] The reaction can take place either with or without allylic rearrangement.[1611] Propargylic ethers give allenes.[1612] Vinylic ethers can also be cleaved by *Grignard reagents* in the presence of a catalyst, in this case, a Ni complex.[1613] Silyl enol ethers $R_2C{=}CROSiMe_3$ behave similarly.[1614] Bicyclic benzofurans can be opened by dialkylzinc reagents in the presence of a Pd catalyst.[1615]

Certain acetals and ketals can be dimerized in a reaction similar to Reaction **10-56** by treatment with $TiCl_4$—$LiAlH_4$, for example,[1616]



85%

Also see, Reaction **10-65**.

OS **II**, 323; **III**, 701. Also see, OS **V**, 431.

10-65 The Reaction of Organometallic Reagents with Epoxides

3*(OC)-seco*-Alkyl-de-alkoxy-substitution



The reaction between *Grignard reagents* or organolithium reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[1617] The *Grignard reagent* may be aromatic or aliphatic, although tertiary *Grignard reagents* give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. With allylic *Grignard reagents*, the addition of a catalytic amount of $Yb(OTf)_3$ facilitated alkylation.[1618] Organolithium reagents,[1619] in the presence of chiral additives, lead to the 2-substituted alcohol with good enantioselectivity. Similar reaction with a chiral *Schiff base* gave the same type of product, with excellent enantioselectivity.[1620]

[1610] Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J.F.; Villieras, J. *Tetrahedron Lett.* ***1975***, 3837; Claesson, A.; Olsson, L. *J. Chem. Soc., Chem. Commun.* ***1987***, 621.

[1611] Calo, V.; Lopez, L.; Pesce, G. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1301. See also, Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A.M. *J. Org. Chem.* ***1990***, *55*, 2294.

[1612] Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* ***1990***, *112,* 8042.

[1613] Kocienski, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* ***1988***, *29*, 2353.

[1614] Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* ***1980***, *21*, 3915.

[1615] Lauens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* ***200***, *122*, 1804.

[1616] Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 2059.

[1617] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 961–1012; Schaap, A.; Arens, J.F. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87,* 1249. Also see Schrumpf, G.; Grätz, W.; Meinecke, A.; Fellenberger, K. *J. Chem. Res. (S)* ***1982***, 162.

[1618] Likhar, P.R.; Kumar, M.P.; Bandyopadhyay, A.K. *Tetrahedron Lett.* ***2002***, *43*, 3333.

[1619] Hodgson, D.M.; Stent, M.A.H.; Stefane, B.; Wilson, F.X. *Org. Biomol. Chem.* ***2003***, *1*, 1139; Hodgson, D.M.; Maxwell, C.R.; Miles, T.J.; Paruch, E.; Stent, M.A.H.; Matthews, I.R.; Wilson, F.X.; Witherington, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4313.

[1620] Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* ***1998***, *39*, 9023.

Lithium dialkylcopper reagents also give the reaction,[1621] as do higher order cuprates,[1622] often producing higher yields. They have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often in a regioselective manner.[1623] The use of BF_3 increases the reactivity of R_2CuLi, enabling it to be used with thermally unstable epoxides.[1624] Lithium diaminocyano cuprates have also been used.[1625]

The reaction has also been performed with other organometallic compounds.[1626] Trialkylaluminum reagents open epoxides with delivery of the alkyl group to carbon.[1627] In the presence of a Lewis acid catalyst (e.g., BF_3), alkylation can occur at the more substituted carbon.[1628] *Friedel–Crafts type alk*ylation (see Reaction **11-11**) is possible when an aromatic compound reacts with an epoxide and $AlCl_3$.[1629] Epoxides react with allyl bromide in the presence of In metal, with the expected delivery of allyl to the less substituted carbon.[1630] When a substituted epoxide was treated with CO, $BF_3{\bullet}OEt_2$, and a Co catalyst, carbonylation occurred and the final product was a β-lactone.[1631] Similar β-lactone forming reactions were reported using substituted epoxides, CO, and a metal compound–BF_3 complex.[1632] A double carbonylation reaction was reported in the presence of an Al complex, generating an anhydride.[1633] Five-membered ring lactams were formed from substituted epoxides using $BF_3{\bullet}OEt_2$ followed by treatment with KHF_2.[1634] Ring opening of epoxides with Ti compounds has been shown to be selective for the more substituted carbon.[1635] Epoxides react with Ag salts of alkynes, in the

[1621] See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents,* Wiley, NY, ***1980***, pp. 103–113. See also, Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* ***1982***, *104,* 2305; Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* ***1992***, *33*, 8087.

[1622] Chauret, D.C.; Chong, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3695.

[1623] Chong, J.M.; Cyr, D.R.; Mar, E.K. *Tetrahedron Lett.* ***1987***, *28*, 5009; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* ***1987***, *28*, 1993.

[1624] See Alexakis, A.; Jachiet, D.; Normant, J.F. *Tetrahedron* ***1986***, *42,* 5607.

[1625] Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* ***1993***, 1201.

[1626] See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 307–310; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1045–1063. **Ba**: Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 493. **Mn**: Tang, J.; Yorimitsu, H.; Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***1997***, *38*, 9019. **Sn**: Yadav, J.S.; Reddy, B.V.S.; Satheesh, G. *Tetahedron Lett.* ***2003***, *44*, 6501. **Zn**: Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* ***2004***, 2151

[1627] Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* ***2001***, 4445; Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* ***2001***, *66,* 5388; Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* ***2001***, *3*, 1765; Shanmugam, P.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 3265 (formation of *O*-silyl ether product). For the reaction in an ionic liquid see Zhou, H.; Campbell, E.J.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2229.

[1628] See Zhao, H.; Pagenkopf, B.L. *Chem. Commun.* ***2003***, 2592.

[1629] Lin, J.; Kanazaki, S.; Kashino, S.; Tsuboi, S. *Synlett* ***2002***, 899.

[1630] Hirashita, T.; Mitsui, K.; Hayashi, Y.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 9189. For a reaction using Pd nanoparticles, see Jiang, N.; Hu, Q.; Reid, C.S.; Ou, Y.; Li, C.J. *Chem. Commun.* ***2003***, 2318.

[1631] Lee, J.T.; Thomas, P.J.; Apler, H. *J. Org. Chem.* ***2001***, *66*, 5424.

[1632] Schmidt, J.A.R.; Mahadevan, V.; Getzler, Y.D.Y.L.; Coates, G.W. *Org. Lett.* ***2004***, *6*, 373.

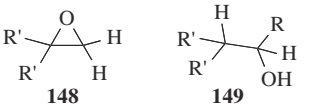
[1633] Rowley, J.M.; Lobkovsky, E.B.; Coates, G.W. *J. Am. Chem. Soc.* ***2007***, *129*, 4948.

[1634] Movassaghi, M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2456.

[1635] Tanaka, T.; Hiramatsu, K.; Kobayashi, Y.; Ohno, H. *Tetrahedron* ***2005***, *61,* 6726.

presence of Zr compounds, to give the rearrangement product, a propargylic alcohol.[1636] A Ga/Sm induced ring opening with alkyl halides has been reported.[1637]

In the presence of a Sc catalyst, chiral allylic boranes open epoxides at the less substituted position to generate chiral, homoallylic alcohols.[1638]



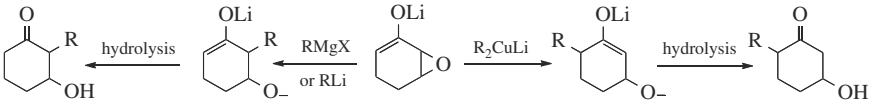
148 **149**

When *gem*-disubstituted epoxides (**148**), and sometimes other epoxides, are treated with *Grignard reagents*, the product may be **149**, that is, the new alkyl group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the *Grignard reagent*. Halohydrins are often side products.



150

When the substrate is a vinylic epoxide,[1639] *Grignard reagents* generally give a mixture of the normal product and the product of allylic rearrangement (**150**).[1640] Butyllithium reacted with a *gem*-difluoroalkylidene epoxide ($F_2C{=}CR$–epoxide) and S_N2' displacement gave alkylation at the difluoro carbon and opened the epoxide.[1641] The latter often predominates. In the case of R_2CuLi,[1642] acyclic substrates give mostly allylic rearrangement (S_N2').[1639] The double bond of the "vinylic" epoxide can be part of an enolate anion. In this case, R_2CuLi give exclusive allylic rearrangement (S_N2') to **151** after hydrolysis, while *Grignard* and organolithium reagents opened the epoxide directly (S_N2) to give **152** after hydrolysis.[1643]



152 **151**

An organometallic equivalent that opens epoxides is a hydrosilane, for example, Me_3SiH, and CO, catalyzed by dicobalt octacarbonyl:[1644] See Reaction **10-55** for other coupling reactions with organosilanes. Silyl enol ethers react with epoxides in a related reaction, but a Lewis acid (e.g., $TiCl_4$) is required.[1645]

OS **I**, 306; **VII**, 501; **VIII**, 33, 516; **X**, 297.

[1636] Albert, B.J.; Koide, K. *J. Org. Chem.* ***2008***, *73,* 1093.
[1637] Gohain, M.; Prajapati, D. *Chem. Lett.* ***2005***, *34*, 90.
[1638] Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Oullet, S.G. *Org. Lett.* ***2002***, *4*, 83.
[1639] For a list of organometallic reagents that react with vinylic epoxides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 244–250.
[1640] Marshall, J.A.; Trometer, J.D.; Cleary, D.G. *Tetrahedron* ***1989***, *45,* 391.
[1641] Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* ***2004***, *69*, 7616.
[1642] See Marshall, J.A. *Chem. Rev.* ***1989***, *89,* 1503.
[1643] Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc.* ***1981***, *103,* 2114.
[1644] Murai, T.; Kato, S.; Murai, T.; Toki, T.; Suzuki, S.; Sonoda, N. *J. Am. Chem. Soc.* ***1984***, *106*, 6093.
[1645] Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R.N. *Tetrahedron* ***2001***, *57*, 583.

10-66 Reaction of Organometallics with Aziridines



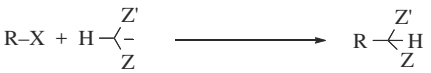
Aziridines have been opened by organometallic reagents to give amines.[1646] It is also possible to open aziridines, although they are less reactive than epoxides,[1647] with organometallic reagents particularly when there is an *N*-sulfonyl group (e.g., tosyl, formally making it a sulfonamide). *Grignard reagents* react with *N*-tosyl 2-phenylaziridine to give the corresponding *N*-tosylamine.[1648] Organocuprates (**10-58**) reaction with *N*-alkylaziridines to give the corresponding amine.[1649] In a *Friedel–Crafts type reaction* (**11-11**), aziridines react with benzene, in the presence of $In(OTf)_3$, to give the β-aryl amine.[1650]

N-Tosyl aziridines have also been opened with enolate anions, which led to a pyrroline derivative,[1651] and with $Me_2S{=}CHCO_2Et$ (see Reaction **16-46**) to generate a *N*-tosyl azetidine.[1652] Allylic alcohols open *N*-tosylaziridines with KSF–Montmorillonite clay.[1653] C-Arylation is possible with a Ag(I) catalyst.[1654] *N*-Sulfonyl aziridines react with the enolate anions of β-keto esters under phase-transfer conditions.[1655] *N*-Tosylaziridines react with $InCl_3$ to give the chloro *N*-tosylamine.[1656]

Aziridines react with nucleophiles other than carbon nucleophiles. In the presence of tetrabutylammonium fluoride (TBAF), trimethylsilyl azide reacts with *N*-tosylaziridines to give the azido *N*-tosylamine.[1657] *N*-Benzylic aziridines are opened by trimethylsilyl azide in the presence of a Cr catalyst.[1658] Acetic anhydride reacts with *N*-tosylaziridines, in the presence of PBu_3, to give the *N*-tosylamino acetate.[1659] Mediated by Lewis bases, aziridines react with silylated nucleophiles.[1660]

10-67 Alkylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



The metal-catalyzed displacement of allylic acetates and carbonates (Reaction **10-60**) clearly falls into this category. However, this section will focus on the more general reaction of active methylene compounds with substrates bearing a leaving group, not

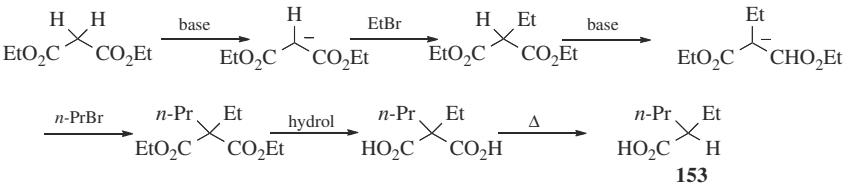
[1646] See Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* ***1987***, *43*, 565.
[1647] Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* ***1995***, *60*, 2514.
[1648] Müller, P.; Nury, P. *Org. Lett.* ***1999***, *1,* 439; Müller, P.; Nury, P. *Helv. Chim. Acta* ***2001***, *84*, 662.
[1649] Penkett, C.S.; Simpson, I.D. *Tetrahedron Lett.* ***2001***, *42*, 1179.
[1650] Saidi, M.R.; Azizi, N.; Naimi-Jamal, M.R. *Tetrahedron Lett.* ***2001***, *42*, 8111.
[1651] Lygo, B. *Synlett* ***1993***, 764.
[1652] Nadir, U.K.; Arora, A. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2605.
[1653] Yadav, J.S.; Reddy, B.V.S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* ***2002***, *43,* 5105.
[1654] Bera, M.; Roy, S. *Tetrahedron Lett.* ***2007***, *48,* 7144.
[1655] Moss, T.A.; Fenwick, D.R.; Dixon, D.J. *J. Am. Chem. Soc.* ***2008***, *130*, 10076.
[1656] Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M. *Synlett* ***2001***, 1417.
[1657] Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2000***, *65*, 1344.
[1658] Li, Z.; Fernández, M.; Jacobsen, E.N. *Org. Lett.* ***1999***, *1*, 1611.
[1659] Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* ***2003***, *44*, 4411.
[1660] Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2005***, *7,* 3509. See also Matsukawa, S.; Tsukamoto, K. *Org. Biomol. Chem.* ***2009***, ***7***, 3792.

necessarily allylic substrates or metal catalyzed. When compounds contain two or three strong electron-withdrawing groups on a carbon atom bearing a proton (the so-called α-proton), that proton is more acidic than compounds without such groups (Sec. 5.B.i, category 1). Treatment with a suitable base (a base that has a conjugate acid with a pK_a greater than the α-proton) removes the α-proton and generates the corresponding enolate anion (Reaction **10-68**). These enolate anions react as carbon nucleophiles and attack alkyl halides, resulting in their alkylation.[1661] Both Z and Z′ may be COOR′, CHO, COR′,[1662] CONR'$_2$, COO^-, CN,[1663] NO_2, SOR′, SO_2R',[1664] SO_2OR', $SO_2NR'_2$ or similar groups.[1665] Some commonly used bases are sodium ethoxide and potassium *tert*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones–Z, Z′ = COR′), sodium hydroxide in water or aq alcohol or acetone, or even sodium carbonate,[1666] is a strong enough base for the reaction. If at least one Z group is COOR′, saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane with $NaNH_2$ as the base.[1667] If the solvent used in the reaction is acidic enough to protonate either the enolate anion or the base, an equilibrium will be established leading to only small amounts of the enolate anion (thermodynamic conditions). Such protic solvents include water, alcohols, or amines. To avoid this reaction, solvents that do not contain an acidic proton (aprotic solvents) are used, but protic solvents can be used in some cases. The use of polar aprotic solvents (e.g., DMF or DMSO), markedly increases the rate of alkylation[1668] but also increases the extent of alkylation at the oxygen rather than the carbon with highly reactive species (e.g., iodomethane, Sec. 10. G.viii). In general, enolate anions, such as those described here, react with alkyl halides via C-alkylation, although trialkylsilyl halides and anhydrides tend to react via O-alkylation. Phase-transfer catalysis has also been used,[1669] and the use of chiral phase-transfer catalysts led to enantioselectivity in the alkylated product.[1670] The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however, Reaction **10-67**). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing O-alkylation, elimination (if the enolate anion is a strong enough base), and dialkylation.

With substrates (e.g., ZCH_2Z') it is possible to alkylate twice. Initial removal of the proton with a base followed by alkylation of the resulting enolate anion with RX, can be

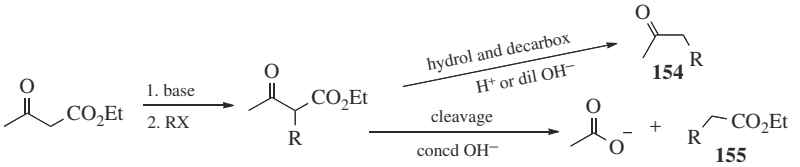
[1661] For dicussions of Reactions **10-67** and **10-68**, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, ***1972***, pp. 492–570, 586–595; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 1–26.
[1662] See Christoffers, J. *Synth. Commun.* ***1999***, *29,* 117.
[1663] See Fatiadi, A.J. *Synthesis* ***1978***, 165, 241; Freeman, F. *Chem. Rev.* ***1969***, *69*, 591.
[1664] See Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *Russ. Chem. Rev.* ***1986***, *55,* 883.
[1665] For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1522–1527 *ff*, 1765–1769.
[1666] See Fedorynski, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* ***1978***, *43,* 4682.
[1667] Murphy, W.S.; Hamrick, Jr., P.J.; Hauser, C.R. *Org. Synth.* ***V***. 523.
[1668] Zaugg, H.E.; Dunnigan, D.A.; Michaels, R.J.; Swett, L.R.; Wang, T.S.; Sommers, A.H.; DeNet, R.W. *J. Org. Chem.* ***1961***, *26*, 644; Johnstone, R.A.W.; Tuli, D.; Rose, M.E. *J. Chem. Res. (S)* ***1980***, 283.
[1669] See Tundo, P.; Venturello, P.; Angeletti, E. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2159.
[1670] Park, E.J.; Kim, M.H.; Kim, D.Y. *J. Org. Chem.* ***2004***, *69*, 6897.

followed by subsequent removal of the proton from ZCHRZ′ and then alkylation with the same or a different RX. An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (Reaction **12-40**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid (**153**) from malonic ester. A variation of this alkylation sequence employs 1,2-dibromoethane as the alkylating agent, and subsequent treatment with 1, 8-diazabicycl [5.4.0]undec-7-ene (DBU) leads to incorporation of a vinyl group on the α carbon.[1671] Another variation involved coupling of a dimalonate with an allylic carbonate (see Reaction **10-60**), using a polymer-supported Pd catalyst.[1672]



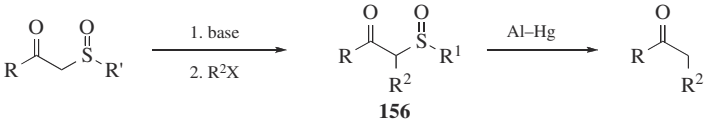
153

It is obvious that many carboxylic acids of the formulas RCH_2CO_2H and $RR'CHCO_2H$ can be synthesized by this method [for some other ways of preparing such acids (see Reactions **10-70**–**10-73**)]. Another important example is the *acetoacetic ester synthesis*, in which Z is CO_2Et and Z′ is $COCH_3$. In this case, the product can be decarboxylated with acid or dilute base (Reaction **12-40**) to give a ketone (**154**) or cleaved with concentrated base (Reaction **12-43**) to give a carboxylic ester (**155**) and a salt of acetic acid. This reaction has been done in *tert*-butanol in the presence of alumina, *in vacuo*, to give the alkylated keto acid directly from the keto ester.[1673]



154 **155**

Another way of preparing ketones involves alkylation[1674] of β-keto sulfoxides[1675] or sulfones,[1676] to give **156**.



156

The sulfoxide group in the product (**156**) is easily reduced (desulfurized, see Reaction **19-70**) to give the ketone in high yields using aluminum amalgam or by electrolysis.[1677]

[1671] Bunce, R.A.; Burns, S.E. *Org. Prep. Proceed. Int.* ***1999***, *31*, 99.
[1672] Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3412.
[1673] Bhar, S.; Chaudhuri, S.K.; Sahu, S.G.; Panja, C. *Tetrahedron* ***2001***, *57*, 9011.
[1674] See Trost, B.M. *Chem. Rev.* ***1978***, *78*, 363; Solladié, G. *Synthesis* ***1981***, 185.
[1675] Gassman, P.G.; Richmond, G.D. *J. Org. Chem.* ***1966***, *31*, 2355; Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107.
[1676] Kurth, M.J.; O'Brien, M.J. *J. Org. Chem.* ***1985***, 3846.
[1677] Lamm, B.; Samuelsson, B. *Acta Chem. Scand.* ***1969***, *23,* 691.

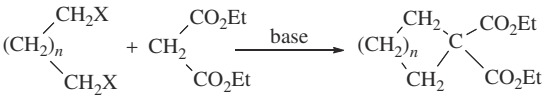
β-Keto sulfoxides [e.g., **156** or sulfones (—SO_2—)] are easily prepared (Reaction **16-86**). When one group attached to the sulfur atom is chiral, the alkylation proceeds with reasonable enantioselectivity.[1678]

Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is CO_2Et and Z′ is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, using *N*-acetylaminomalonic esters, $(EtO_2C)_2CHNHCOCH_3$. Hydrolysis and decarboxylation of the product in this case gives an α-amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

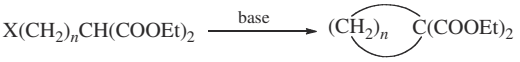
The reaction is not limited to Z—CH_2—Z′ compounds. Other compounds have acidic CH hydrogens. Some examples are the methyl hydrogens of α-aminopyridines, the methyl hydrogens of ynamines of the form $CH_3C\cdots CNR_2$[1679] (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (Sec. 2.I.ii), hydrogens connected to a triple-bond carbon (Reaction **10-74**), and the hydrogen of HCN (Reaction **10-75**) can also be removed with a base and the resulting ion alkylated (see also, Reactions **10-68**–**10-72**). α-Imino esters have been used since treatment with a strong base with a titanium catalyst followed by an aldehyde leads to hydroxy amino esters.[1680]

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter, and hence gives up its proton to the base. However, if 2 molar equivalents of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion (a dianion) occurs at the less acidic position, in this case the second most acidic position[1681] (see Sec. 10.G.vii). The first and second ion pair acidities of β-diketones has been studied.[1682]

When ω,ω′-dihalides are used, ring closures can be effected:[1683]



This method has been used to close rings of three ($n = 0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.[1684]



[1678] Enders, D.; Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* ***2003***, 3939.
[1679] Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1970***, *35*, 3405.
[1680] Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* ***1993***, *34*, 677. See Kotha, S.; Kuki, A. *Tetrahedron Lett.* ***1992***, *33*, 1565 for a related reaction.
[1681] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1540–1541. Also see, Lu, Y.-Q.; Li, C.-J. *Tetrahedron Lett.* ***1996***, *37*, 471.
[1682] Facchetti, A.; Streitwieser, A. *J. Org. Chem.* ***2004***, *69*, 8345.
[1683] Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR* ***1983***, *19,* 474.
[1684] See Walborsky, H.M.; Murari, M.P. *Can. J. Chem.* ***1984***, *62,* 2464; Bose, A.K.; Manhas, M.S.; Chatterjee, B.G.; Abdulla, R.F. *Synth. Commun.* ***1971***, *1*, 51. For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 156–157, 165–166.

This method has been shown to be applicable to medium rings (10–14 members) without the use of high-dilution techniques.[1685]

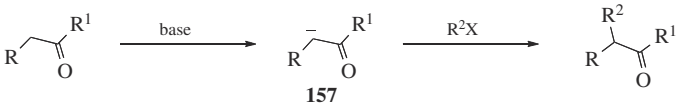
The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, although an SET[1686] mechanism may be involved in certain cases,[1687] especially where the nucleophile is an α-nitro carbanion[1688] and/or the substrate contains a nitro or cyano[1689] group. Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate anion) is treated with a tertiary carbocation generated *in situ* from an alcohol or alkyl halide and BF_3 or $AlCl_3$,[1690] or with a tertiary alkyl perchlorate.[1691]

Alkylation α to a nitro group can be achieved with the *Katritzky pyrylium–pyridinium reagents*.[1692] This reaction probably has a free radical mechanism.[1693]

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **VIII**, 5, 312, 381. See also, OS **VIII**, 235.

10-68 Alkylation of Ketones, Aldehydes, Nitriles, and Carboxylic Esters

α-Acylalkyl-de-halogenation, and so on



157

Ketones,[1694] nitriles,[1695] and carboxylic esters[1696] can be alkylated in the α position in a reaction similar to **10-67**.[1652] The pK_a of the proton α to the carbonyl or CN is in the range of 19–25 depending on the number of substituents (see Table 8.1), and a base that has a conjugate acid with a pK_a greater than that proton must be employed. Note that since only one activating group is present, compared with two activating groups for the substrates in Reaction **10-67**, the pK_a of the α-proton is higher (a weaker acid) and a stronger base is required. Reaction of the α-proton with the base generates the key nucleophilic

[1685] Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* ***1987***, *65*, 1298; Brillon, D.; Deslongchamps, P. *Can. J. Chem.* ***1987***, *65,* 43, 56.

[1686] These SET mechanisms are often called $S_{RN}1$ mechanisms. See also, Ref. 107.

[1687] Bordwell, F.G.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* ***1989***, *111,* 1052.

[1688] For a review of mechanisms with these nucleophiles, see Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283.

[1689] Kornblum, N.; Fifolt, M. *Tetrahedron* ***1989***, *45*, 1311.

[1690] See Crimmins, T.F.; Hauser, C.R. *J. Org. Chem.* ***1967***, *32,* 2615; Boldt, P.; Militzer, H.; Thielecke, W.; Schulz, L. *Liebigs Ann. Chem.* ***1968***, *718,* 101.

[1691] Boldt, P.; Ludwieg, A.; Militzer, H. *Chem. Ber.* ***1970***, *103*, 1312.

[1692] Katritzky, A.R.; Kashmiri, M.A.; Wittmann, D.K. *Tetrahedron* ***1984***, *40*, 1501.

[1693] Katritzky, A.R.; Chen, J.; Marson, C.M.; Maia, A.; Kashmiri, M.A. *Tetrahedron* ***1986***, *42,* 101.

[1694] See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, ***1979***, pp. 85–352.

[1695] See Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* ***1984***, *31*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1801–1808. See Taber, D.F.; Kong, S. *J. Org. Chem.* ***1997***, *62*, 8575; Rojas, G.; Baughman, T.W.; Wagener, K.B. *Synth. Commun.* ***2007***, *37,* 3923.

[1696] See Petragnani, N.; Yonashiro, M. *Synthesis* ***1982***, 521. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1724–1758*ff*.

intermediate, an enolate anion (**157**). The most common bases[1697] are lithium diethylamide (Et_2NLi), lithium diisopropylamide[$(Me_2CH)_2NLi$, LDA],[1698] lithium hexamethyldisilazide [$LiN(SiMe_3)_2$], *t*-BuOK, $NaNH_2$, and KH. The base lithium *N*-isopropyl-*N*-cyclohexylamide (LICA) is particularly successful for carboxylic esters[1699] and nitriles.[1700] Enolate anion formation with lithium amides can also be regioselective (see Reaction **12-22**).[1701] Lithium enolate anions exist as aggregates in solution.[1702] The mechanism for this deprotonation reaction has been studied,[1703] as has the rate of deprotonation.[1704]

Solid KOH in Me_2SO has been used to methylate ketones, in high yields.[1705] Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate anion conjugate base; others (especially *t*-BuOK) convert a significant fraction of the molecules. In the latter case, the *aldol reaction* (**16-34**) or *Claisen condensation* (**16-85**) may be side reactions, since under the thermodynamic conditions associated with this base both the free molecule and its conjugate base are present at the same time. Both lactones[1706] and lactams are similarly alkylated.[1707] Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, e.g., *t*-BuOK in *t*-BuOH). Some common solvents are DME, THF, DMF, and liquid NH_3. Phase-transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.[1708] Amino acid surrogates (**158**, R = N derivative) can be alkylated, often under phase-transfer conditions.[1709]

Direct alkylation of aldehydes is difficult when bases (e.g., KOH and NaOMe) are used, due to rapid aldol reaction (**16-34**), but aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields using the base KH to prepare the potassium enolate,[1710] or in moderate yields, by the use of a phase-transfer catalyst.[1711]

[1697] For a list of some bases, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1476–1479.

[1698] See Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P.v.R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed.* ***1986***, *25*, 465.

[1699] Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93,* 2319; Bos, W.; Pabon, H.J.J. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99,* 141. See also, Cregge, R.J.; Herrmann, J.L.; Lee, C.S.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 2425.

[1700] Watt, D.S. Tetrahedron Lett. **1974**, 707.

[1701] See Comins, D.L.; Killpack, M.O. *J. Org. Chem.* ***1987***, *52,* 104. See Xie, L.; Isenberger, K.M.; Held, G.; Dahl, M. *J. Org. Chem.* ***1997***, *62*, 7516 for steric versus electronic effects in kinetic enolate formation.

[1702] Liou, L.R.; McNeil, A.J.; Toombes, G.E.S.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130,* 17334; Khartabil, H.K.; Gros, P.C.; Fort, Y.; Ruiz-López, M.F. *J. Org. Chem.* ***2008***, *73,* 9393; Pratt, L.M.; Mu, R.; Carter, C.; Woodford, B. *Tetrahedron* ***2007***, *63,* 1331. See also Pratt, L.M.; Nguyen, S.C.; Thanh, B.T. *J. Org. Chem.* ***2008***, *73,* 6086.

[1703] Sun, X.; Kenkre, S.L.; Remenar, J.F.; Gilchrist, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 4765.

[1704] Majewski, M.; Nowak, P. *Tetrahedron Lett.* ***1998***, *39*, 1661.

[1705] Langhals, E.; Langhals, H. *Tetrahedron Lett.* ***1990***, *31*, 859.

[1706] See Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 467. Enolate anions of β-lactones are subject to ring opening: see Mori, S.; Shindo, M. *Org. Lett.* ***2004***, *6*, 3945.

[1707] Matsuo, J.-i.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* ***1998***, *39*, 9723.

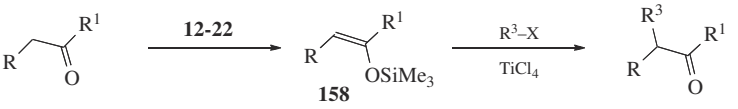
[1708] See Makosza, M. *Russ. Chem. Rev.* ***1977***, *46,* 1151; *Pure Appl. Chem.* ***1975***, *43,* 439; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 170–217; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 136–204.

[1709] Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* ***2005***, *127,* 5073.

[1710] Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* ***1985***, *41*, 5031.

[1711] Purohit, V.G.; Subramanian, R. *Chem. Ind. (London)* ***1978***, 731; Buschmann, E.; Zeeh, B. *Liebigs Ann. Chem.* ***1979***, 1585.

Even the use of amide bases (e.g., lithium diisopropylamide, LDA), lithium hexamethyl disilazide (LHMDS), or lithium tetramethylpiperidide (LTMP) to generate the enolate anion in an aprotic solvent (e.g., ether or THF) cannot completely suppress rapid aldol side reactions.

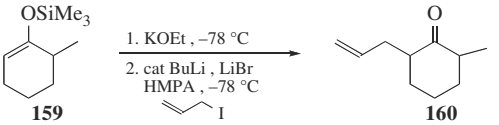


As in Reaction **10-67**, the alkyl halide that reacts with the enolate anion may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides may give predominant elimination if the enolate anion is a strong enough base (e.g., the enolate anion from Me_3CCOMe).[1712] Tertiary alkyl groups, as well as other groups that normally give S_N1 reactions, can be introduced if the reaction is performed on a silyl enol ether[1713] of a ketone, aldehyde, or ester (see **158**) with a Lewis acid catalyst.[1714] Tertiary alkyl fluorides were coupled to silyl enol ethers with BF_3•etherate.[1715] Note that tin enolates ($C{=}C{-}OSnR_3$) react with halides in the presence of a Zn catalyst.[1716] A chiral variation of this latter reaction was reported involving generation of the enolate anion in the presence of Me_3SnCl, a Pd catalyst, and a chiral ligand.[1717]

Metal-catalyzed alkylations that are related to this reaction are known. 1,3-Diketones are benzylated or allylated using Bi catalysts.[1718] Monoalkylation is possible using Pd catalysts,[1719] and Pd catalyzed asymmetric allylic alkylation is known[1720] α-Alkylation of ketones with alcohols uses a Ru catalyst,[1721] or Ni nanoparticles.[1722] A recyclable Pd catalyst is available.[1723] Zinc enolate anions have been used in enantioselective Pd catalyzed alkylation reactions.[1724]

Silyl enol ethers can be converted to the enolate anion, which can then be alkylated in the usual manner. The reaction of silyl enol ether (**159**) with KOEt followed by LiBr and a catalytic amount of *n*-butyllithium with allyl iodide gave **160**.[1725] Metal-catalyzed alkylation reactions are known with silyl enol ethers, including an In catalyzed[1726] reaction. An Ir catalyzed regioselective and enantioselective alkylation of silyl enol ethers using allylic carbonates as a substrate has been reported.[1727]

[1712] Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* ***1968***, *33*, 3477.
[1713] For a list of alkylations of silyl enol ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1494–1505.
[1714] Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3350. For a review, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1982***, *21*, 96.
[1715] Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2004***, *45*, 2555.
[1716] Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem Soc.* ***2002***, *124*, 7440.
[1717] Trost, B.M.; Schroeder, G.M. *J. Am. Chem. Soc.* ***1999***, *121,* 6759.
[1718] Rueping, M.; Nachtsheim, B.J.; Kuenkel, A. *Org. Lett.* ***2007***, *9,* 825.
[1719] Ranu, B.C.; Chattopadhyay, K.; Adak, L. *Org. Lett.* ***2007***, *9*, 4595. See Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* ***2007***, *129,* 7718.
[1720] Trost, B.M.; Schroeder, G.M. *Chemistry: European J.* ***2005***, *11,* 174.
[1721] Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron* ***2006***, *62,* 8988.
[1722] Alonso, F.; Riente, P.; Yus, M. *Synlett* ***2007***, 1872.
[1723] Kwon, M.S.; Kim, N.; Seo, S.H.; Park, I.S.; Cheedrala, R.K.; Park, J. *Angew. Chem. Int. Ed.* ***2005***, *44,* 6913.
[1724] Kinoshita, N.; Kawabata, T.; Tsubaki, K.; Bando, M.; Fuji, K. *Tetrahedron* ***2006***, *62,* 1756.
[1725] Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 369.
[1726] Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* ***2009***, *65*, 5462.
[1727] Graening, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2005***, *127*, 17192.



159 **160**

The metal-catalyzed (usually Ni) coupling reaction of an alkyl halide or an electrophilic substrate with a silane[1728] is known as *Hiyama coupling*.[1729] A Ni catalyzed Hiyama cross-coupling with a chiral additive leads to a chiral alkylated ketone.[1730] The nature of the ligand has an important impact on the reaction.[1731] There is a Pd catalyzed Hiyama cross-coupling.[1732] Aryl siloxanes have been used in this reaction.[1733]

Enol carbonates react with alkylating agents in the presence of a Pd catalyst. The decarboxylative alkylation of allyl enol carbonates to the corresponding allylcyclohexanone derivatives is known.[1734] An asymmetric version of this reaction has been reported.[1735] The same reaction can be done using enolate anion and allylic acetates with a Pd catalyst.[1736]

Vinylic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of $NiBr_2$ as a catalyst.[1737] Ketones have been vinylated by treating their enol acetates with vinylic bromides in the presence of a Pd catalyst,[1738] but direct reaction of a ketone, a vinyl halide, sodium *tert*-butoxide and a Pd catalyst also give the α-vinyl ketone.[1739] Also as in Reaction **10-67**, this reaction can be used to close rings.[1740] Rings have been closed by treating a dianion of a dialkyl succinate with a 1,ω-dihalide or ditosylate.[1741] This was applied to the synthesis of three-, four-, five-, and six-membered rings. When the attached groups were chiral (e.g., menthyl) the product was formed with > 90% ee.[1740]

[1728] For a reaction with a vinyl silane substrate, see Wang, Z.; Pitteloud, J.-P.; Montes, L.; Rapp, M.; Derane, D.; Wnuk, S.F. *Tetrahedron* ***2008***, *64,* 5322.
[1729] Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* ***2002***, *219*, 61; Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A.; Diederich, F., Eds., Wiley–VCH, New York, **2004**; Chap. 4.
[1730] Dai, X.; Strotman, N.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2008,*** *130*, 3302.
[1731] Raders, S.M.; Kingston, J.V.; Verkade, J.G. *J. Org. Chem.* ***2010***, *75,* 1744.
[1732] Zhang, L.; Wu, J. *J. Am. Chem. Soc.* ***2008***, *130*, 12250; Zhang, L.; Qing, J.; Yang, P.; Wu, J. *Org. Lett.* ***2008***, *10,* 4971; Ranu, B.C.; Dey, R.; Chattopadhyay, K. *Tetrahedron Lett.* ***2008***, *49,* 3430; Li, J.-H.; Deng, C.-L.; Liu, W.-J.; Xie, Y.-X. *Synthesis* ***2005***, 3039; Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synthesis* ***2006***, 969.
[1733] Chen, S.-N.; Wu, W.-Y.; Tsai, F.-Y. *Tetrahedron* ***2008***, *64,* 8164.
[1734] Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20,* 140. See also, Nicolaou, K.C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* ***2001***, *40,* 2482.
[1735] Behenna, D.C.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2004***, *126*, 15044.
[1736] Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3492.
[1737] Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* ***1977***, *99,* 4833.
[1738] Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* ***1983***, 839. For other methods, see Negishi, E.; Akiyoshi, K. *Chem. Lett.* ***1987***, 1007; Chang, T.C.T.; Rosenblum, M.; Simms, N. *Org. Synth. 66*, 95.
[1739] Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J.M.; Buchwald, S.L *Org. Lett.* ***2001***, *3*, 1897.
[1740] See Stork, G.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2016; Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 5270. In the last case, the substrate moiety is an epoxide function.
[1741] Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1985***, *107,* 3343; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Org. Synth. 67*, 76.

Efficient enantioselective alkylations are known,[1742] including the use a chiral base to form the enolate anion.[1743] Alternatively, a chiral auxiliary can be attached. Many auxiliaries are based on the use of chiral amides[1744] or esters.[1745] Subsequent formation of the enolate anion allows alkylation to proceed with high enantioselectivity. A subsequent step is required to convert the chiral amide or ester to the corresponding carboxylic acid. Chiral additives can also be used,[1746] and the influence of chelating ligands and hydrocarbon cosolvents has been studied for $LiN(TMS)_2$ mediated enolization reactions.[1747] The addition of triethylamine influences the (*E/Z*) selectivity of the enolate anion.[1748] Dynamic kinetic resolution has been used for the asymmetric alkylation of malonate derivatives using allenyl acetates.[1749]

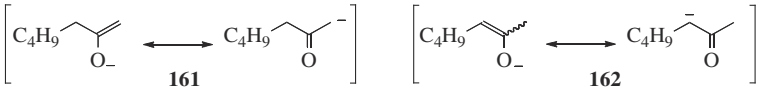
When the compound to be alkylated is an unsymmetrical ketone, the question arises as to which side will be alkylated (regioselectivity). If a phenyl or a vinylic group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regioselective; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the base,[1750] the cation, and the solvent. In any case, di- and trisubstitution are frequent[1751] and it is often difficult to stop with the introduction of just one alkyl group.[1752]

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.[1753] Among these are the following:

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side; the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (Reaction **16-86**). This generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (Reaction **12-43**).
2. Introduce an activating group on one side. Alkylation then takes place on that side (Reaction **10-67**). The activating group is then removed.

[1742] See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 236–245; Evans, D.A. in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, ***1984***, pp. 1–110.
[1743] See Murakata, M.; Nakajima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* ***1990***, 1657. For a review, see Cox. P.J.; Simpkins, N.S. *Tetrahedron: Asymmetry* ***1991***, *2*, 1, pp. 6–13.
[1744] See Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. *J. Org. Chem.* ***2003***, *68*, 4215. See Evans, D. A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071; Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1984***, *106*, 4261; Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* ***1985***, *68,* 2100; Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem. Int. Ed.* ***1981***, *20,* 207.
[1745] Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* ***1985***, *68,* 212.
[1746] Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* ***2000***, *33*, 432; Machajewski, T.D.; Wong, C.–H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1352.
[1747] Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2007***, *129,* 12023.
[1748] Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130,* 8726.
[1749] Trost, B.M.; Fandrick, D.R.; Dinh, D.C. *J. Am. Chem. Soc.* ***2005***, *127,* 14186.
[1750] See, for example, Prieto, J.A.; Suarez, J.; Larson, G.L. *Synth. Commun.* ***1988***, *18,* 253; Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* ***1989***, *30,* 2779.
[1751] See Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* ***1987***, 263.
[1752] See Morita, J.; Suzuki, M.; Noyori, R. *J. Org. Chem.* ***1989***, *54,* 1785.
[1753] See House, H.O. *Rec. Chem. Prog.* ***1968***, *28,* 99; Podraza, K.F. *Org. Prep. Proced. Int.* ***1991***, *23,* 217.

3. Prepare the desired one of the two possible enolate anions.[1754] The two ions (e.g., **161** and **162**) for

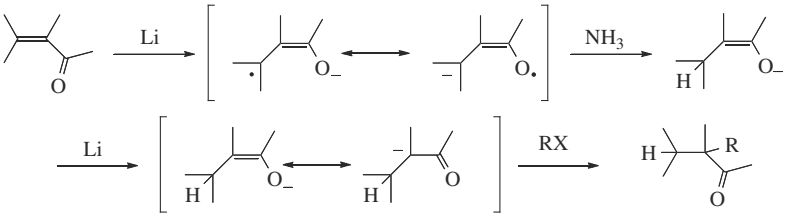


2-heptanone, interconvert rapidly only in the presence of the parent ketone or any stronger acid.[1755] In the absence of such acids, it is possible to prepare either **161** or **162** and thus achieve selective alkylation on either side of the ketone.[1756] The desired enolate anion can be obtained by treatment of the corresponding enol acetate with 2 equiv of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, for example,



The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.[1745] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.[1755] An alternate procedure involves conversion of a silyl enol ether[1757] (see Reaction **12-17**) or a dialkylboron enol ether[1758] (an enol borinate, see Reaction **10-73**) to the corresponding enolate anion. If the less hindered enolate anion is desired (e.g., **161**), it can be prepared directly from the ketone by treatment with LDA in THF or DME at $-78\,^{\circ}C$.[1759]

4. Begin not with the ketone itself, but with an α,β-unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3, such a ketone is reduced to an enolate anion. When the alkyl halide is added, it must react with the enolate anion on the side where the double bond was.[1760] Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, although the product is the same as if the saturated ketone had been alkylated on the desired side.

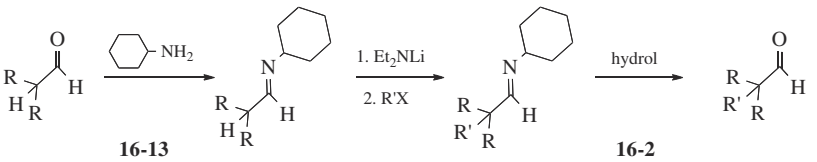


[1754] See d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979; Stork, G. *Pure Appl. Chem.* ***1975***, *43,* 553.
[1755] House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30,* 1341.
[1756] House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36,* 2361. For an improved procedure, see Liotta, C.L.; Caruso, T.C. *Tetrahedron Lett.* ***1985***, *26,* 1599.
[1757] See Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* ***1985***, *18*, 181; Rasmussen, J.K. *Synthesis* ***1977***, 91. See Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* ***2007***, *129,* 1034.
[1758] Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36,* 1790.
[1759] House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495.
[1760] See Caine, D. *Org. React.* ***1976***, *23,* 1. Also see Näf, F.; Decorzant, R. *Helv. Chim. Acta* ***1974***, *57*, 1317; Wender, P.A.; Eissenstat, M.A. *J. Am. Chem. Soc.* ***1978***, *100*, 292.

Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N,N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.[1761] Alkylation of an unsymmetrical ketone at the more substituted position was reported using an alkyl bromide, NaOH, and a calix[*n*]arene catalyst (see Sec. 4.H. category 2 for calixarenes).[1762]

Among other methods for the preparation of alkylated ketones are (1) Alkylation of silyl enol ethers using various reagents as noted above, (2) the *Stork enamine reaction* (Reaction **10-69**), (3) the acetoacetic ester synthesis (Reaction **10-67**), (4) alkylation of β-keto sulfones or sulfoxides (Reaction **10-67**), (5) acylation of $CH_3SOCH_2^-$ followed by reductive cleavage (Reaction **16-86**), (6) treatment of α-halo ketones with lithium dialkylcopper reagents (Reaction **10-57**), and (7) treatment of α-halo ketones with trialkylboranes (Reaction **10-73**).

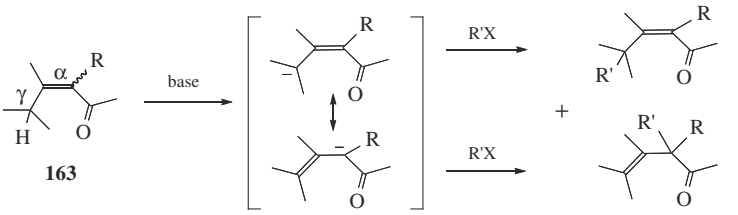
Aldehydes can be indirectly alkylated via an imine derivative of the aldehyde.[1763] The derivative is easily prepared (Reaction **16-13**) and the product easily hydrolyzed to the aldehyde (Reaction **16-2**). Either or both R groups may be hydrogen, so that mono-, di-, and trisubstituted acetaldehydes can be prepared by this method. The R′ group may be primary alkyl, allylic, or benzylic. Imine alkylation can also be applied to the preparation of substituted amine derivatives. An amino acid surrogate (e.g., $Ph_2C{=}NCH_2CO_2R$), when treated with KOH and an alkyl halide gives the C-alkylated product.[1764] When a chiral additive is used, good enantioselectivity was observed. This reaction has also been done in the ionic liquid Bmim tetrafluoroborate (see Sec. 9.D.iii).[1765] It is possible to alkylate α-amino amides directly.[1766]



Hydrazones and other compounds with C=N bonds can be similarly alkylated.[1743] The use of chiral amines or hydrazines[1767] [followed by hydrolysis (Reaction **16-2**) of the alkylated imine] can lead to chiral alkylated ketones in high optical yields[1768] (for an example, see Sec. 4.J). Lithiated imines are generated by the treatment of an imine with a

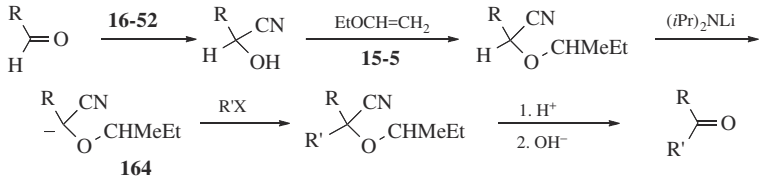
[1761] Yamashita, M.; Matsuyama, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1985***, *58,* 407.
[1762] Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* ***2000***, 1664.
[1763] See Fraser, R.R. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 65–105; Whitesell, J.K.; Whitesell, M.A. *Synthesis* ***1983***, 517. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1513–1518. Also see Goering, H. L.; Tseng, C.C. *J. Org. Chem.* ***1981***, *46*, 5250.
[1764] Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* ***2001***, *42*, 4645; Jew, S.-s.; Jeong, B.-s.; Yoo, M.-s.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.
[1765] Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59,* 701.
[1766] Myers, A.G.; Schnider, P.; Kwon, S.; Kung, D.W. *J. Org. Chem.* ***1999***, *64*, 3322.
[1767] See Enders, D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 275–339.
[1768] Meyers, A.I.; Williams, D.R.; White, S.; Erickson, G.W. *J. Am. Chem. Soc.* ***1981***, *103,* 3088; Enders, D.; Bockstiegel, B. *Synthesis* ***1989***, 493; Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth. 65,* 183.

suitable base, and reaction with an alkyl halide gives the alkylated imine.[1769] α-Magnesio imines also react with alkyl halides.[1770]



163

In α,β-unsaturated ketones, nitriles, and esters (e.g., **163**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylogy* (see Sec. 6.B), operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.



164

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (Reaction **15-5**), can be easily alkylated with primary or secondary alkyl or allylic halides.[1771] The R group can be aryl or a saturated or unsaturated alkyl. Since the cyanohydrins[1772] are easily formed from aldehydes (Reaction **16-52**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde (RCHO) to a ketone (RCOR′)[1773] (for other methods, see Reactions **10-71**, **16-82**, and **18-9**).[1774] In this procedure, the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.[1775] The German word *Umpolung*[1776] is used to describe this kind of reversal (another example is found in Reaction **10-71**). Since the ion **164** serves as a substitute for the unavailable $R(C{=}O)^-$ anion, it is often called a "masked" $R(C{=}O)^-$ ion.

[1769] Zuend, S.J.; Ramirez, A.; Lobkovsky, E.; Collum, D.B. *J. Am. Chem. Soc.* ***2006***, *128*, 5939.
[1770] Hatakeyama, T.; Ito, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2005***, *127*, 14192.
[1771] Stork, G.; Depezay, J.C.; D'Angelo, J. *Tetrahedron Lett.* ***1975***, 389. See also, Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H.G. *Chem. Ber.* ***1989***, *122*, 2131, and other papers in this series.
[1772] For a review of **164**, see Albright, J.D. *Tetrahedron* ***1983***, *39,* 3207.
[1773] Also see Stetter, H.; Schmitz, P.H.; Schreckenberg, M. *Chem. Ber.* ***1977***, *110,* 1971; Hünig, S. *Chimia*, ***1982***, *36,* 1.
[1774] See Martin, S.F. *Synthesis* ***1979***, 633.
[1775] See Block, E. *Reactions of Organosulfur Compounds,* Academic Press, NY, ***1978***, pp. 56–67; Gröbel, B.; Seebach, D. *Synthesis* **1977**, 357; Lever, Jr., O.W. *Tetrahedron* ***1976***, *32*, 1943; Seebach, D. *Angew. Chem. Int. Ed.* ***1969***, *8*, 639. Also see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1981***, *14,* 73; Hase, T.A. Umpoled Synthons, Wiley, NY, ***1987***, pp. xiii-xiv, 7-18, 219-317. For lists of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1435–1438.
[1776] See Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***; Seebach, D. *Angew. Chem. Int. Ed.* ***1979***, *18,* 239.

This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.[1777] In an interesting variation of nitrile alkylation, a quaternary bromide [PhC(Br)(Me)CN] reacted with allyl bromide, in the presence of a *Grignard reagent*, to give the alkylated product [$PhC(CN)(Me)CH_2CH{=}CH_2$].[1778]

A coupling reaction of two ketones to form a 1,4-diketone has been reported, using $ZnCl_2/Et_2NH$.[1779] An interesting allylic substitution at a 3° center involves the reaction of 3° 2-bromonitriles with *i*PrMgBr and allyl bromide to give the 2-allyl nitrile.[1780]

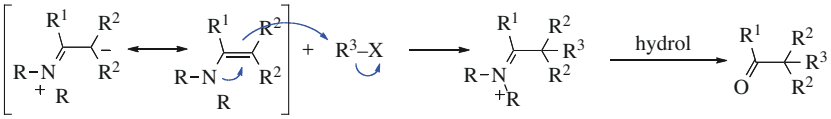
α-Alkylation of ketones with primary alcohols is possible using polymer-associated nanoparticulate Pd.[1781]

Protonation of enolate anions is discussed in Reaction **16-34**, in connection with the aldol condensation.

OS **III**, 44, 219, 221, 223, 397; **IV**, 278, 597, 641, 962; **V**, 187, 514, 559, 848; **VI**, 51, 115, 121, 401, 818, 897, 958, 991; **VII**, 153, 208, 241, 424; **VIII**, 141, 173, 241, 403, 460, 479, 486; **X**, 59, 460; **80**, 31.

10-69 The Stork Enamine Reaction

α-Acylalkyl-de-halogenation[1782]



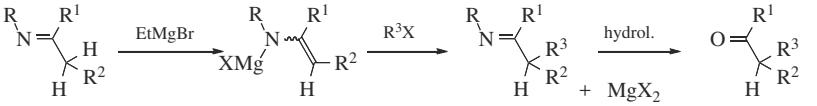
When enamines are treated with alkyl halides, an alkylation occurs to give an iminium salt via electron transfer from the electron pair on nitrogen, through the C=C to the electrophilic carbon of the alkyl halide.[1783] In effect, an enamine behaves as a "nitrogen enolate anion" and generally reacts as carbon nucleophiles.[1784] Hydrolysis of the iminium salt gives a ketone. Since the enamine is normally formed from a ketone (Reaction **16-13**), the net result is alkylation of the ketone at the α position. The method, known as the *Stork enamine reaction*,[1785] is an alternative to the ketone alkylation considered in Reaction **10-68**, generally giving monoalkylation of the ketone. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine. There are metal-catalyzed enamine alkylation reactions, including the use of Ir catalysts.[1786] There are reactions that are catalyzed by enamines, including asymmetric reactions.[1787]

[1777] Stork, G.; Ozorio, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* ***1978***, 5175.
[1778] Fleming, F.F.; Zhang, Z.; Knochel, P. *Org. Lett.* ***2004***, *6*, 501.
[1779] Nevar, N.M.; Kel'in, A.V.; Kulinkovich, O.G. *Synthesis* ***2000***, 1259.
[1780] Fleming, F.F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* ***2005***, *70,* 2200.
[1781] Yamada, Y.M.A.; Uozumi, Y. *Org. Lett.* ***2006***, *8,* 1375.
[1782] This is the IUPAC name with respect to the halide as substrate.
[1783] See Adams, J.P. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 125.
[1784] See Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209.
[1785] See Hickmott, P.W. *Tetrahedron,* ***1984***, *40,* 2989; ***1982***, *38*, 1975, 3363; Granik, V.G. *Russ. Chem. Rev.,* ***1984***, *53*, 383. Also see in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, the articles by Alt, G.H.; Cook, A. G. pp. 181–246, and Gadamasetti, G.; Kuehne, M.E. pp. 531–689; Whitesell, J.K.; Whitesell, M.A. *Synthesis,* ***1983***, 517; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 570–582, 766–772; Bláha, K.; Cervinka, O. *Adv. Heterocycl. Chem.,* ***1966***, *6*, 147, p. 186.
[1786] Weix, D.J.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129,* 7720.
[1787] Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chem. Rev.* ***2007***, *107*, 5471.

The method is quite useful for particularly active alkyl halides, (e.g., allylic, benzylic, and propargylic halides), and for α-halo ethers and esters. Other primary and secondary halides can show sluggish reactivity. The reaction of enamines with benzotriazole derivatives has been reported.[1788] Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction can also be applied to activated aryl halides (e.g., 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[1789] and to activated alkenes (e.g., acrylonitrile). The latter is a *Michael-type reaction* (**15-24**) with respect to the alkene.

Acylation[1790] can be accomplished with acyl halides or with anhydrides. Hydrolysis of the resulting iminium salt leads to a 1,3-diketone. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate (ClCOOEt;[1791] a CN group with cyanogen chloride[1792] (not cyanogen bromide or iodide, which leads to halogenation of the enamine); a CHO group with the mixed anhydride of formic and acetic acids[1791] or with DMF and phosgene;[1793] and a C(R)=NR′ group with a nitrilium salt RC≡N$^+$R′.[1794] The acylation of the enamine can take place by the same mechanism as alkylation, but another mechanism is also possible, if the acyl halide has an α hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (Reaction **17-14**), which adds to the enamine to give a cyclobutanone (Reaction **15-63**). This compound can be cleaved in the solution to form the same acylated imine salt (that would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.[1795]

N-Alkylation can be a problem, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF:[1796]



The imines are prepared by the reaction of secondary amines with aldehydes or ketones, mainly ketones (**16-13**). The enamine salt method has also been used to give good yields of mono α alkylation of α,β-unsaturated ketones.[1797] Enamines prepared from aldehydes and

[1788] Katritzky, A.R.; Fang, Y.; Silina, A. *J. Org. Chem.* ***1999***, *64*, 7622; Katritzky, A.R.; Huang, Z.; Fang, Y. *J. Org. Chem.* ***1999***, *64*, 7625.
[1789] Britten, A.Z.; Owen, W.S.; Went, C.W. *Tetrahedron* ***1969***, *25,* 3157.
[1790] See Hickmott, P.W. *Chem. Ind. (London)* ***1974***, 731; Hünig, S.; Hoch, H. *Fortschr. Chem. Forsch.* ***1970***, *14,* 235.
[1791] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* ***1963***, *85*, 207.
[1792] Kuehne, M.E. *J. Am. Chem. Soc*., ***1959***, *81,* 5400.
[1793] Ziegenbein, W. *Angew. Chem. Int. Ed. Engl.* ***1965***, *4,* 358.
[1794] Baudoux, D.; Fuks, R. *Bull. Soc. Chim. Belg.* ***1984***, *93,* 1009.
[1795] See Alt, G.H.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 204–215.
[1796] Stork, G.; Dowd, S.R. *J. Am. Chem. Soc*., ***1963***, *85,* 2178.
[1797] Stork, G.; Benaim, J. *J. Am. Chem. Soc*., ***1971***, *93,* 5938.

butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[1798] N-Alkylation in this case is presumably prevented by steric hindrance.

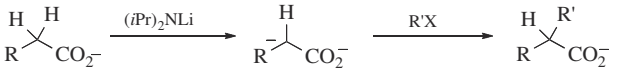
When the nitrogen of the substrate contains a chiral R group, both the *Stork enamine synthesis* and the enamine salt method can be used to perform enantioselective syntheses.[1799] The use of *S*-proline can generate a chiral enamine *in situ*, thus allowing alkylation to occur, giving alkylated product with good enantioselectivity. The reaction has been done intramolecularly.[1800]

Conjugate addition (*Michael addition*) occurs when enamines react with conjugated ketones. This reaction is discussed in Reaction **15-24**.

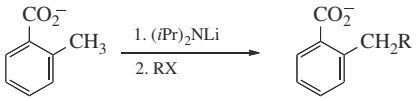
OS **V**, 533, 869; **VI**, 242, 496, 526; **VII**, 473.

10-70 Alkylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-halogenation



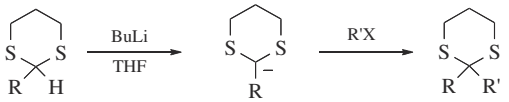
Carboxylic acids can be alkylated in the α position by conversion of their salts to dianions, which have resonance contributors,[1801] by treatment with a strong base (e.g., LDA).[1802] The use of Li^+ as the counterion increases the solubility of the dianionic salt. The reaction has been applied[1803] to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2CO_2H and RR^2CHCO_2H.[1695] Allkylation occurs at carbon, the more nucleophilic site relative to the carboxylate oxygen anion (see Sec. 10.G.vii). This procedure is an alternative to the malonic ester synthesis (Reaction **10-67**) as a means of preparing carboxylic acids and has the advantage that acids of the form $RR'R^2CCO_2H$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.[1804]



OS **V**, 526; **VI**, 517; **VII**, 249. See also, OS **VII**, 164.

10-71 Alkylation at a Position α to a Heteroatom

2-(2-Alkyl-thio) de-halogenation



[1798] Curphey, T.J.; Hung, J.C.; Chu, C.C.C. *J. Org. Chem.*, ***1975***, *40*, 607. See also, Ho, T.; Wong, C.M. *Synth. Commun.*, ***1974***, *4,* 147.

[1799] See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 248–255; Whitesell, J.K. *Acc. Chem. Res.* ***1985***, *18*, 280; Bergbreiter, D.E.; Newcomb, M. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 243–273.

[1800] Vignola, N.; List, B. *J. Am. Chem. Soc.* ***2004***, *126*, 450.

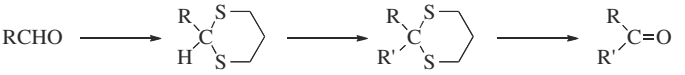
[1801] Mladenova, M.; Blagoev, B.; Gaudemar, M.; Dardoize, F.; Lallemand, J.Y. *Tetrahedron* ***1981***, *37,* 2153.

[1802] Pfeffer, P.E.; Silbert, L.S.; Chirinko, Jr., J.M. *J. Org. Chem.* ***1972***, *37*, 451.

[1803] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1717–1720*ff*.

[1804] Cregar, P.L. *J. Am. Chem. Soc.* **1970**, 92, 1396.

The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton $RSCH_2SR$ is even more acidic. 1,3-Dithianes can be alkylated[1805] if a proton is first removed by treatment with butyllithium in THF.[1806] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol (Reaction **16-11**) and can be hydrolyzed (Reaction **10-7**), this is a method for the conversion of an aldehyde to a ketone[1807] (see also, Reactions **10-68** and **18-9**):



This is another example of Umpolung (see Reaction **10-68**);[1773] the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane (R = H) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.[1808] The R′ group may be a primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.[1809] A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide ($EtSOCH_2SEt$).[1810]



Group **A** may be regarded as a structural equivalent for carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is convenient to have a word for units within molecules. Such a word is *synthon*, introduced by Corey,[1811] which is defined as a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B** (e.g., **C**; by Reactions **19-36** and **19-3**) and **D** (by Reactions **10-2** and **16-23**).[1812]

Carbanions generated from 1,3-dithianes also react with epoxides[1813] to give the expected products. Reaction with epoxides leads to intermediates that undergo the *Brook rearrangement* (Reaction **18-44**), which is synthetically useful in what is known as *anion relay chemistry*.

[1805] Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40,* 231. See Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* ***1989***, *45,* 7643; Ager, D.J. in Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. 19–37; Seebach, D. *Synthesis* ***1969***, 17, especially pp. 24–27; Olsen, R.K.; Curriev, Jr., Y.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 536–547.

[1806] See Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* ***1990***, *31*, 7261.

[1807] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1451–1454.

[1808] For a direct conversion of RX to RCHO, see Reaction **10-76**.

[1809] See Seebach, D.; Jones, N.R.; Corey, E.J. *J. Org. Chem.* ***1968***, *33,* 300; Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* ***1974***, 3653.

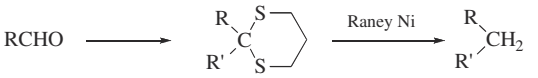
[1810] Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3267. See also, Schill, G.; Jones, P.R. *Synthesis* ***1974***, 117; Hori, I.; Hayashi, T.; Midorikawa, H. *Synthesis* ***1974***, 705.

[1811] Corey, E.J. *Pure Appl. Chem.* ***1967***, *14*, 19, pp. 20-23.

[1812] See Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1982***, *15,* 35.

[1813] See Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40,* 231.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with *Raney nickel* (Reaction **14-27**). Aldehydes can therefore be converted to chain-extended hydrocarbons:[1814]

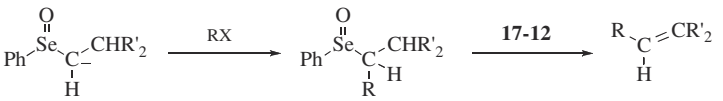


Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[1815]

If a stabilizing group other than sulfur is attached to the S—CH_2 unit of a thioether ($RSCH_2X$, where X is a stabilizing group), formation of the anion and alkylation can be facile. For example, benzylic and allylic thioethers ($RSCH_2Ar$ and $RSCH_2CH{=}CH_2$)[1816] and thioethers of the form $RSCH_3$ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)[1817] have been successfully alkylated at the carbon adjacent to the sulfur atom.[1818] Stabilization by one thioether group has also been used in a method for the homologation of primary halides.[1819] Thioanisole is treated with BuLi to give the corresponding anion,[1820] which reacts with the halide to give the thioether, which is then refluxed with a mixture of methyl iodide and sodium iodide in DMF to give the alkyl iodide as the final product (via an intermediate sulfonium salt). By this sequence, an alkyl halide (RX) is converted to its homologue RCH_2X by a pathway involving two laboratory steps (see also, Reaction **10-64**).

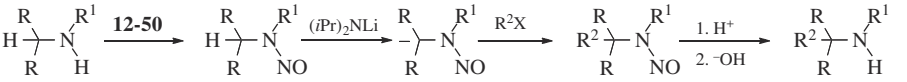
Vinylic sulfides containing an α hydrogen can also be alkylated[1821] by alkyl halides or epoxides. This method is for converting an alkyl halide (RX) to an α,β-unsaturated aldehyde, which is the synthetic equivalent of the unknown $^{-}HC{=}CH{-}CHO$ ion.[1822] Even simple alkyl aryl sulfides (RCH_2SAr and $RR'CHSAr$) have been alkylated α to the sulfur.[1823]

Sulfones[1824] and sulfonic esters can also be alkylated in the α position if strong enough bases are used.[1825] Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (Reaction **17-12**).[1826]

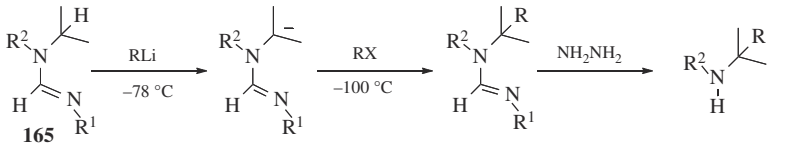


[1814] See Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Jones, J.B.; Grayshan, R. *Chem. Commun.* ***1970***, 141, 741.
[1815] See Lissel, M. *Liebigs Ann. Chem.* ***1982***, 1589.
[1816] Uemoto, K.; Kawahito, A.; Matsushita, N.; Skamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* ***2001***, *42*, 905.
[1817] Block, E.; Aslam, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6729.
[1818] Biellmann, J.F.; Ducep, J.B. *Tetrahedron* ***1971***, *27*, 5861. See also, Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* ***1972***, 259.
[1819] Corey, E.J.; Jautelat, M. *Tetrahedron Lett.* ***1968***, 5787.
[1820] Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1966***, *31*, 4097.
[1821] Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1973***, *95*, 2694.
[1822] See Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290.
[1823] Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* ***1977***, 1961.
[1824] See Magnus, P.D. *Tetrahedron* ***1977***, *33,* 2019, pp. 2022–2025; Hendrickson, J.B.; Sternbach, D.D.; Bair, K. W. *Acc. Chem. Res.* ***1977***, *10,* 306.
[1825] See Truce, W.E.; Hollister, K.R.; Lindy, L.B.; Parr, J.E. *J. Org. Chem.* ***1968***, *33*, 43; Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* ***1973***, 743, 746.
[1826] Reich, H.J.; Shah, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3250.

Alkylation can also be carried out, in certain compounds, at positions α to other heteroatoms,[1827] for example, at a position α to the nitrogen of tertiary amines.[1828] Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH hydrogen.

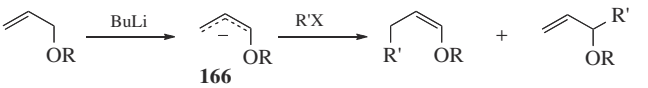


α-Lithiation of *N*-Boc amines has been accomplished and these react with halides in the presence of a Pd catalyst.[1829] Alkylation α to the nitrogen atom of a carbamate occurs when the carbamate is treated with a *Grignard reagent* under electrolysis conditions.[1830] α-Methoxy amides also react with allyl halides and zinc metal to give alkylation via replacement of the OMe unit.[1831] It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.[1832] In one example, a secondary amine is converted to its *N*-nitroso derivative (Reaction **12-50**).[1833] The *N*-nitroso product is easily hydrolyzed to the product amine (Reaction **19-51**).[1834] Alkylation of secondary and primary amines has also been accomplished with > 10 other protecting groups, involving conversion of amines to amides, carbamates,[1835] formamidines,[1836] and phosphoramides.[1831] In the case of formamidines (**165**), use of a chiral R′ leads to a chiral amine, in high ee, even when R is not chiral.[1837] The reaction of hydrazones with aryl halides, in the presence of a Pd catalyst leads to replacement of H with an aryl group (R'NH—N=CRH → R'NHC=NRR").[1838]



165

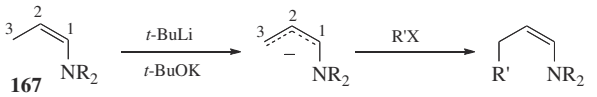
A proton can be removed from an allylic ether by treatment with an alkyllithium at about −70 °C (at higher temperatures the *Wittig rearrangement*, **18-22**, takes place) to give the ion **166**, which reacts with alkyl halides



166

[1827] See Krief, A. *Top. Curr. Chem.* ***1987***, *135*, 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 336–341.
[1828] Lepley, A.R.; Khan, W.A. *Chem. Commun.* ***1967***, 1198; Lepley, A.R.; Giumanini, A.G. *J. Org. Chem.* ***1966***, *31*, 2055; Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* ***1984***, *25,* 1353.
[1829] Dieter, R.K.; Li, S. *Tetrahedron Lett.* ***1995***, *36*, 3613.
[1830] Suga, S.; Okajima, M.; Yoshida, J.-i. *Tetrahedron Lett.* ***2001***, *42*, 2173.
[1831] Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* ***1994***, *35*, 1561.
[1832] For a review, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* ***1984***, *84*, 471.
[1833] Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* ***1977***, *110,* 1852; Renger, B.; Kalinowski, H.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 1866. For a review, see Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* ***1975***, *14,* 15.
[1834] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40,* 34, pp. 41–42.
[1835] For the use of *tert*-butyl carbamates, see Beak, P.; Lee, W. *Tetrahedron Lett.* ***1989***, *30,* 1197.
[1836] For a review, see Meyers, A.I. *Aldrichimica Acta* ***1985***, *18,* 59.
[1837] Meyers, A.I.; Miller, D.B.; White, F. *J. Am. Chem. Soc.* ***1988***, *110*, 4778; Gonzalez, M.A.; Meyers, A.I. *Tetrahedron Lett.* ***1989***, *30*, 43, 47 and references cited therein.
[1838] Takemiya, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128,* 14800.

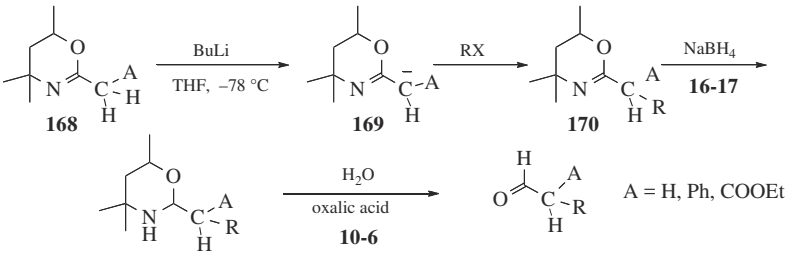
to give the two products shown.[1839] Similar reactions[1840] have been reported for allylic[1841] and vinylic tertiary amines. In the latter case, enamines (**167**), treated with a strong base, are converted to anions that are then alkylated, generally at C-3.[1842] (For direct alkylation of enamines at C-2, see Reaction **10-69**.)



It is also possible to alkylate a methyl, ethyl, or other primary group of an aryl ester ($ArCO_2R$), where Ar is a 2,4,6-trialkylphenyl group.[1843] Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to $^{-}CH_2O^{-}$.[1844]

OS **VI**, 316, 364, 542, 704, 869; **VIII**, 573.

10-72 Alkylation of Dihydro-1,3-Oxazine. The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids

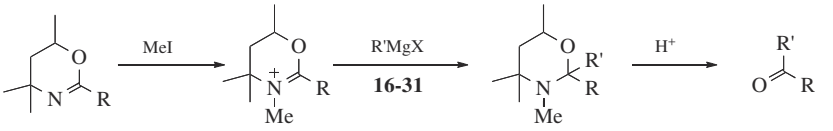


A synthesis of aldehydes[1845] developed by Meyers et al.[1846] begins with the commercially available dihydro-1,3-oxazine derivatives (**168**; A = H, Ph, or COOEt).[1847] Removal of a proton from the indicated carbon in **168** leads to the resonance stabilized and bidentate anion (**169**). Alkylation occurs regioselectively at carbon using many alkyl bromides and iodides. The R group of RX can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.[1848] The alkylated oxazine (**170**) is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements Reaction **10-71**, which converts RX to an aldehyde containing

[1839] Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290. See Hommes, H.; Verkruijsse, H.D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 113, and references cited therein.
[1840] See Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27,* 1.
[1841] Martin, S.F.; DuPriest, M.T. *Tetrahedron Lett.* ***1977***, 3925 and references cited therein.
[1842] For a review, see Ahlbrecht, H. *Chimia* ***1977***, *31*, 391.
[1843] Beak, P.; Carter. L.G. *J. Org. Chem.* ***1981***, *46*, 2363.
[1844] Seebach, D.; Meyer, N. *Angew. Chem. Int. Ed.* ***1976***, *15*, 438.
[1845] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1461–1465.
[1846] Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* ***1973***, *38*, 36.
[1847] See Schmidt, R.R. *Synthesis* ***1972***, 333; Collington, E.W. *Chem. Ind. (London)* ***1973***, 987.
[1848] Meyers, A.I.; Malone, G.R.; Adickes, H.W. *Tetrahedron Lett.* ***1970***, 3715.

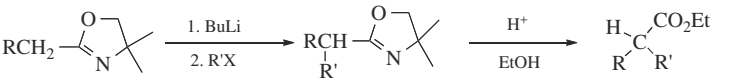
one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

The ion **169** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[1849] and with aldehydes and ketones (Reaction **16-38**). Similar aldehyde synthesis has also been carried out with thiazoles[1850] and thiazolines[1851] (five-membered rings containing N and S in the 1 and 3 positions).



171 **172**

The reaction has been extended to the preparation of ketones:[1852] Treatment of a dihydro-1,3-oxazine (**171**) with iodomethane forms the iminium salt (Reaction **10-31**) which, when treated with a *Grignard reagent* or organolithium compound (**16-31**), produces **172**, which can be hydrolyzed to a ketone. The R group can be alkyl, cycloalkyl, aryl, benzylic, and so on, and R′ of the *Grignard reagent* can be alkyl, aryl, benzylic, or allylic. Note that the heterocycles **168**, **170**, or **171** do not react directly with *Grignard reagents*. In another procedure, 2-oxazolines[1853] (**173**) can be alkylated to give **174**,[1854] which are easily converted directly to the esters **175** by heating in 5–7% ethanolic sulfuric acid.



173 **174** **175**

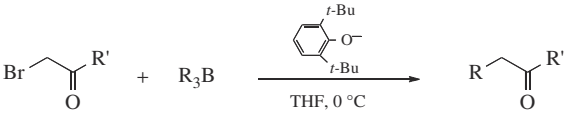
2-Oxazolines (**173** and **174**) are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,[1855] representing an alternative to the malonic ester synthesis (**10-67**) and to Reactions **10-70** and **10-73**. The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.[1856] Note that, unlike **168**, **173** can be alkylated even if R is alkyl. However, the C=N bond of **173** and **174** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[1857]

OS **VI**, 905.

[1849] Adickes, H.W.; Politzer, I.R.; Meyers, A.I. *J. Am. Chem. Soc.* ***1969***, *91,* 2155.
[1850] Altman, L.J.; Richheimer, S.L. *Tetrahedron Lett.* ***1971***, 4709.
[1851] Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* ***1975***, *40,* 2021.
[1852] Meyers, A.I.; Smith, E.M. *J. Org. Chem.* ***1972***, *37*, 4289.
[1853] For a review, see Meyers, A.I.; Mihelich, E.D. *Angew. Chem. Int. Ed.* ***1976***, *15,* 270.
[1854] Meyers, A.I.; Temple, Jr., D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* ***1974***, *39*, 2778; Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* ***1974***, *39*, 2783; Meyers, A.I.; Mihelich, E.D.; Kamata, K. *J. Chem. Soc., Chem. Commun.* ***1974***, 768.
[1855] See Meyers, A.I. *Pure Appl. Chem.* ***1979***, *51,* 1255; *Acc. Chem. Res.* ***1978***, *11*, 375. See also, Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. *J. Am. Chem. Soc.* ***1978***, *100,* 8182; Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.* ***1978***, *100,* 8186.
[1856] See Lutomski, K.A.; Meyers, A.I. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 213–274.
[1857] Meyers, A.I.; Temple Jr., D.L. *J. Am. Chem. Soc.* ***1970***, *92,* 6644, 6646.

10-73 Alkylation with Boranes, Boronic Acids, and Boronates

Alkyl-de-halogenation



Trialkylboranes react rapidly and in high yields with α-halo ketones,[1858] α-halo esters,[1859] α-halo nitriles,[1860] and α-halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[1861] in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.[1862] Potassium *tert*-butoxide is often a suitable base, but potassium 2,6-di-*tert*-butylphenoxide at 0 °C in THF gives better results in most cases, possibly because the large bulk of the two *tert*-butyl groups prevents the base from coordinating with the R_3B.[1863] The trialkylboranes are prepared by treatment of 3 equiv of an alkene with 1 equiv of BH_3 (Reaction **15-16**).[1864] With appropriate boranes, the R group transferred to α-halo ketones, nitriles, and esters can be vinylic,[1865] or (for α-halo ketones and esters) aryl.[1866]

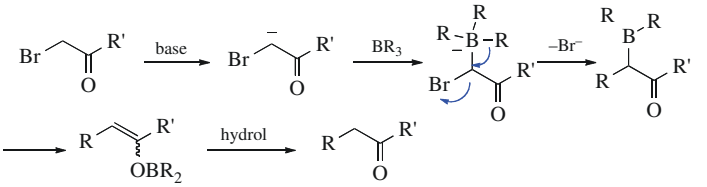
The reaction can be extended to α,α-dihalo esters[1867] and α,α-dihalo nitriles.[1868] It is possible to replace just one halogen or both. In the latter case, the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes (BR_3) with γ-halo-α,β-unsaturated esters.[1869] Alkylation takes place in the γ position, but the double bond migrates out of conjugation with the CO_2Et unit [$BrCH_2CH{=}CHCO_2Et \rightarrow RCH{=}CHCH_2CO_2Et$]. In this case, however, double-bond migration is an advantage, because nonconjugated β,γ-unsaturated esters are usually much more difficult to prepare than their α,β-unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H.C. Brown[1870] (see also, Reactions **15-16**, **15-27**, **18-31–18-40**, etc.). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (via the BR_3) can be coupled to a ketone, a nitrile, a carboxylic ester, or a sulfonyl derivative. Note that this is still

[1858] Brown, H.C.; Rogic, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1968***, *90*, 6218.
[1859] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90,* 818.
[1860] Brown, H.C.; Nambu, H.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6854.
[1861] Truce, W.E.; Mura, L.A.; Smith, P.J.; Young, F. *J. Org. Chem.* ***1974***, *39*, 1449.
[1862] See Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1, pp. 42–43, 143–150; Weill-Raynal, J. *Synthesis* ***1976***, 633; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 372–391, 404–409; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 275–278, 283–287.
[1863] Brown, H.C.; Nambu, H.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6852, 6854, 6855.
[1864] For an improved procedure, with 9-BBN (see Reaction **15-16**), see Brown, H.C.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91,* 2146; Brown, H.C.; Rogic, M.M.; Nambu, H.; Rathke, M.W. *J. Am. Chem. Soc.* ***1969***, *91,* 2147; Katz, J.; Dubois, J.E.; Lion, C. *Bull. Soc. Chim. Fr.* ***1977***, 683.
[1865] Brown, H.C.; Bhat, N.G.; Campbell, Jr., J.B. *J. Org. Chem.* ***1986***, *51,* 3398.
[1866] Brown, H.C.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91,* 4304.
[1867] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90,* 1911.
[1868] Nambu, H.; Brown, H.C. *J. Am. Chem. Soc.* ***1970***, *92,* 5790.
[1869] Brown, H.C.; Nambu, H. *J. Am. Chem. Soc.* ***1970***, *92,* 1761.
[1870] Brown, H.C. *Organic Syntheses via Boranes*, Wiley, NY, ***1975***; *Hydroboration*, W.A. Benjamin, NY, ***1962***; *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***.

another indirect way to alkylate a ketone (see Reaction **10-68**) or a carboxylic acid (see Reaction **10-70**), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (Reaction **10-67**).

Although superficially this reaction resembles Reaction **10-57**, it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also, Reactions **18-23**–**18-26**). The mechanism is not known with certainty,[1871] but it may be tentatively shown as (illustrated for an α-halo ketone):

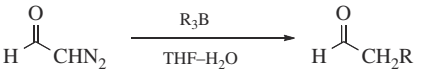


176

The first step is removal of the acidic proton by the base to give an enolate anion that combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group.[1872] Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate (**176**),[1873] which is hydrolyzed. Configuration at the alkyl group R is retained.[1874]

Alkenylboranes ($R'_2C{=}CHBZ_2$; Z = various groups) couple in high yields with vinylic,[1875] alkynyl, aryl, benzylic, and allylic halides or triflates in the presence of a Pd catalyst and a base to give $R'_2C{=}CHR$.[1876] 9-Alkyl-9-BBN compounds (Reaction **15-16**) also couple with vinylic and aryl halides,[1877] as well as with α-halo ketones, nitriles, and esters.[1878]

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes (**177**)[1879] react with trialkylboranes in a similar manner.

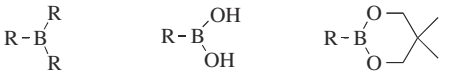


177

The mechanism is probably also similar. In this case, a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes[1880] is

[1871] See Prager, R.H.; Reece, P.A. *Aust. J. Chem.* ***1975***, *28,* 1775.
[1872] See Midland, M.M.; Zolopa, A.R.; Halterman, R.I. *J. Am. Chem. Soc.* ***1979***, *101*, 248. See also, Midland, M.M.; Preston, S.B. *J. Org. Chem.* ***1980***, *45,* 747.
[1873] Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.
[1874] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2150.
[1875] Occhiato, E.G.; Trabocchi, A.; Guarna, A. *Org. Lett.* ***2000***, *2*, 1241.
[1876] Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1989***, 1405; Rivera, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1991***, *32,* 2311; and references cited therein. For a review, see Matteson, D.S. *Tetrahedron* ***1989***, *45,* 1859.
[1877] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* ***1989***, *111*, 314. See also, Soderquist, J.A.; Santiago, B. *Tetrahedron Lett.* ***1990***, *31*, 5541.
[1878] Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1992***, 691; Brown, H.C.; Joshi, N.N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* ***1989***, *111,* 1754. For another such coupling, see Matteson, D.S.; Tripathy, P.B.; Sarkar, A.; Sadhu, K.M. *J. Am. Chem. Soc.* ***1989***, *111*, 4399.
[1879] Mikhailov, B.M.; Gurskii, M.E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1973***, *22,* 2588.
[1880] Hooz, J.; Morrison, G.F. *Can J. Chem.* ***1970***, *48,* 868.

especially notable, since successful reactions cannot be obtained with α-halo aldehydes.[1881]



Boranes **Boronic acids** **Boronates**

Alkyl[1882] and aryl[1883] boronic acids [$RB(OH)_2$] react with allylic acetates to give the alkylated product in the presence of a Pd catalyst.[1884] A cyclopropylboronic acid was coupled to an allylic bromide with silver oxide/KOH and a Pd catalyst.[1885] Arylboronic acids undergo a coupling reaction with epoxides in the presence of a Pd catalyst.[1886] Alkylboronic acids can also be coupled to aromatic compounds in the presence of $Cu(OAc)_2$ and a Pd catalyst.[1887] The Pd catalyzed coupling of vinyl halides and alkylboronic acids,[1888] which gives substituted alkenes, is related to the *Suzuki coupling* (Reaction **13-12**). Vinyl zirconium reagents were coupled to alkyl halides with a Pd catalyst.[1889] Arylation of sp^3 C—H positions can be done using arylboronates and a Rh catalyst.[1890] In a related but metal-free reaction, activated epoxides and aziridines are opened by borates.[1891]

Potassium aryl- and 1-alkenyltrifluoroborates ($ArBF_3K$ and RBF_3K) are easily prepared from organoboronic acids or esters. In general, the trifluoroborates have greater air stability and greater nucleophilicity[1892] when compared to the corresponding organoboranes and organoboronic acid derivatives. Potassium alkyltrifluoroborates undergo the Pd catalyzed coupling reaction with arenediazonium tetrafluoroborates,[1893] diaryliodonium salts,[1894] aryl halides,[1895] as well as with aryl triflates. An example of the latter reaction converted **178** to diphenylmethane via coupling with phenyl triflate.[1896] Alkenyltrifluoroborates can be coupled to aryl halides.[1897]

$$\underset{\mathbf{178}}{PhCH_2BF_3K} + PhOTf \xrightarrow[9\%\ PdCl_2(dppf)\cdot CH_2Cl_2]{3\ equv\ Cs_2CO_3,\ aq\ THF} PhCH_2Ph$$

where dppf = bis(diphenylphosphino)ferrocene.

OS **VI**, 919; **IX**, 107.

[1881] See Hooz, J.; Bridson, J.N.; Calzada, J.G.; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Org. Chem.* ***1973***, *38,* 2574.

[1882] Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* ***2004***, *60,* 3813. For a variation involving a borate complex, see Zou, G.; Falck, J.R. *Tetrahedron Lett.* ***2001***, *42*, 5817.

[1883] Nobre, S.M.; Monteiro, A.L. *Tetrahedron Lett.* ***2004***, *45,* 8225; Langle, S.; Abarbri, M.; Duchêne, A. *Tetrahedron Lett.* ***2003***, *44*, 9255.

[1884] Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* ***2008***, *130,* 17276.

[1885] Chen, H.; Deng, M.-Z. *J. Org. Chem.* ***2000,*** *65*, 4444.

[1886] Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* ***2005***, *46,* 6705.

[1887] Chen, X.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2006***, *128,* 12634.

[1888] Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* ***2001***, *42*, 3851. See also, Yoshida, H.; Yamaryo, Y.; Oshita, J.; Kunai, A. *Tetrahedron Lett.* ***2003***, *44,* 1541.

[1889] Wiskur, S.L.; Lorte, A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 82.

[1890] Pastine, S.J.; Gribkov, D.V.; Sames, D. *J. Am. Chem. Soc.* ***2006***, *128,* 14220.

[1891] Pineschi, M.; Bertolini, F.; Haak, R.M.; Crotti, P.; Macchia, F. *Chem. Commun.* ***2005***, 1426.

[1892] Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.

[1893] Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875.

[1894] Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29,* 2457.

[1895] Molander, G.A.; Gormisky, P.E. *J. Org. Chem.* ***2008***, *73,* 7481.

[1896] Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393.

[1897] Molander, G.A.; Rivero, M.R. *Org. Lett.* ***2002***, *4*, 107.

10-74 Alkylation at an Alkynyl Carbon

Alkynyl-de-halogenation

$$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$$

The reaction between alkyl halides and acetylide ions is useful, but of limited scope.[1898] Only primary halides unbranched in the β-position give good yields, although allylic halides can be used if CuI is present.[1899] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[1900] are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base (e.g., $NaNH_2$). Magnesium acetylides (prepared as in Reaction **12-22**) are also frequently used, although they react only with active substrates (e.g., allylic, benzylic, and propargylic halides) and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide–ethylenediamine complex.[1901] If 2 equiv of a very strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $RCH_2C{\equiv}CH + 2BuLi \rightarrow RCHC(C:^- + R'Br \rightarrow RR'CHC{\equiv}C:^-$.[1902] For another method of alkylating at an alkynyl carbon, see Reaction **18-26**. An alternative method for generating an alkyne anion treated a trialkylsilyl alkyne with potassium carbonate in methanol, and then methyllithium/LiBr.[1903] In the presence of an alkyl iodide, alkylation at the alkynyl carbon occurred. Terminal alkynes react with alkylzinc reagents in the presence of a Pd catalyst.[1904]

Other metalated terminal alkynes can be coupled to substrates with a leaving group, and even with other organometallics. In the presence of a Pd catalysts, an alkynyltin reagent reacts with an alkylzinc compound to give the corresponding alkyne.[1905] Terminal alkynes react with allylic bromides in the presence of a Ni catalyst.[1906] The reaction of a terminal alkyne with Zn(II) compounds allows reaction with silanes to give the 1-silylalkyne.[1907] A Re catalyzed C—H insertion reaction is known using terminal alkynes and an active methylene compound.[1908] Alkynylzinc compounds undergo Pd catalyzed cross-coupling reactions.[1909]

1-Haloalkynes react with various substrates in the presence of a metal catalyst. 1-Haloalkynes (e.g., R—C≡C—X react with $ArSnBu_3$ and CuI to give R—C≡C—Ar.[1910] Organozirconium compounds react in a similar manner.[1911] Acetylene reacts with 2 equiv of iodobenzene, in the presence of a Pd catalyst and CuI, to give 1,2-diphenylethyne.[1912]

[1898] See Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 790–800; Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 185–206, 241–244. Also see Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res. (S)* ***1978***, 106; ***1979***, 190.

[1899] Jeffery, T. *Tetrahedron Lett.* ***1989***, *30*, 2225.

[1900] See Krause, N.; Seebach, D. *Chem. Ber.* ***1988***, *121*, 1315.

[1901] Smith, W.N.; Beumel Jr., O.F. *Synthesis* ***1974***, 441.

[1902] Bhanu, S.; Scheinmann, F. *J. Chem. Soc. Perkin Trans.1,* ***1979***, 1218; Quillinan, A.J.; Scheinmann, F. *Org. Synth.* ***VI***, 595.

[1903] Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* ***2003***, *44*, 9087.

[1904] Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* ***2010***, *132,* 4101.

[1905] Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* ***2006***, *128,* 15048.

[1906] Nadal, M.L.; Bosch, J.; Vila, J.M.; Klein, G.; Ricart, S.; Moretó, J.M. *J. Am. Chem. Soc.* ***2005***, *127,* 10476.

[1907] Rahaim, Jr., R.J.; Shaw, J.T. *J. Org. Chem.* ***2008***, *73,* 2912.

[1908] Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* ***2005***, *7,* 4823.

[1909] Qian, M.; Negishi, E. *Tetrahedron Lett.* ***2005***, *46,* 2927.

[1910] Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* ***1998***, 1252.

[1911] Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* ***2000***, *65*, 6951.

[1912] Pal, M.; Kundu, N.G. *J. Chem. Soc. Perkin Trans 1,* ***1996***, 449. Also see, Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett,* ***1996***, *37*, 5527.

1-Trialkylsilyl alkynes react with 1-haloalkynes, in the presence of a CuCl catalyst, to give diynes[1913] and with aryl triflates to give 1-aryl alkynes.[1914] The enolate anion derived from a β-keto ester couples with 1-bromoalkynes to give the corresponding substitution product.[1915] 1-Bromoalkynes react with nitrogen compounds (e.g., imidazole) in the presence of a Cu catalyst to give the corresponding alkyne.[1916] 1-Bromoalkynes react with *Grignard* derived reagents in the presence of an Fe catalyst.[1917]

Alkynes couple with alkyl halides in the presence of SmI_2/Sm,[1918] or a copper catalyst.[1919] Alkynes react with hypervalent iodine compounds[1920] and with reactive alkanes (e.g., adamantane) in the presence of AIBN.[1921] The reaction of benzylic amines with terminal alkynes, in the presence of copper triflate and *tert*-butylhydroperoxide, leads to incorporation of the alkyne group α to the nitrogen.[1922] A similar reaction occurs at a methyl group of *N,N*-dimethylaniline.[1923] α-Methoxycarbamates ($MeO—CHR—NR^1—CO_2R^2$) react with terminal alkynes and CuBr to give the alkynylamine.[1924] In the presence of $GaCl_3$, $ClC{\equiv}CSiMe_3$ reacts with silyl enol ethers to give, after treatment with methanolic acid, an α-ethynyl ketone.[1925]

In a related reaction, terminal alkynes react with silanes (R_3SiH) in the presence of an Ir catalyst[1926] or zinc triflate[1927] to give the 1-trialkylsilyl alkyne. Similar products are obtained when terminal alkynes react with *N*-trialkylsilylamines and $ZnCl_2$.[1928]

OS **IV**, 117; **VI**, 273, 564, 595; **VIII**, 415; **IX**, 117, 477, 688; **76**, 263. Also see, OS **IV**, 801; **VI**, 925.

10-75 Preparation of Nitriles

Cyano-de-halogenation

$$RX + {}^{-}CN \longrightarrow RCN$$

The reaction between cyanide ion and alkyl halides is a convenient method for the preparation of nitriles,[1929] The reaction proceeds by a S_N2 mechanism,[1930] so primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give

[1913] Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39,* 4075.
[1914] See Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* ***1997***, 1233.
[1915] Poulsen, T.B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2007***, *129,* 441.
[1916] Laroche, C.; Li, J.; Freyer, M.W.; Kerwin, S.M. *J. Org. Chem.* ***2008***, *73,* 6462.
[1917] Castagnolo, D.; Botta, M. *Eur. J. Org. Chem.* ***2010***, 3224.
[1918] Murakami, M.; Hayashi, M.; Ito, Y. *Synlett,* ***1994***, 179.
[1919] Bieber, L.W.; da Silva, M.F. *Tetrahedron Lett.* ***2007***, *48,* 7088.
[1920] Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* ***1997***, 874.
[1921] Xiang, J.; Jiang, W.; Fuchs, P.L. *Tetrahedron Lett.* ***1997***, *38*, 6635.
[1922] Li, Z.; Li, C.-J. *Org. Lett.* ***2004***, *6*, 4997.
[1923] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2004***, *126*, 11810.
[1924] Zhang, J.; Wei, C.; Lei, C.-J. *Tetrahedron Lett.* ***2002***, *43,* 5731.
[1925] Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2002***, *4*, 2209.
[1926] Shimizu, R; Fuchikami, T. *Tetrahedron Lett.* ***2000***, *41*, 907.
[1927] Jiang, H.; Zhu, S. *Tetrahedron Lett.* ***2005***, *46,* 517.
[1928] Andreev, A.A.; Konshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.* ***2004***, *6,* 421.
[1929] See in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, the articles by Fatiadi, A.J. pt. 2, pp. 1057–1303, and Friedrich, K. pt. 2, pp. 1343–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 77–86.
[1930] For a discusion about the influence of solvent on this transition state, see Fang, Y.-r.; MacMillar, S.; Eriksson, J.; Kołodziejska-Huben, M.; Dybała-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K.C. *J. Org. Chem.* ***2006***, *71,* 4742.

moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. A number of solvents have been used, but the high yields and short reaction times observed with DMSO make it a very good solvent for this reaction.[1931] In general, polar aprotic solvents are the best choice. Other ways to obtain high yields under mild conditions are to use a phase-transfer catalyst,[1932] in alternative solvents (e.g., PEG 400 (a polyethylene glycol)],[1933] or with ultrasound.[1934] This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (Reaction **16-4**).

The cyanide ion is an ambident nucleophile (it can react via N or via C) and isonitriles (also called isocyanides, R—N≡C) may be side products.[1935] If the preparation of isocyanides is desired (see Reaction **10-40**), they can be made the main products by the use of reagents with more covalent metal–carbon bonds [e.g., silver or copper(I) cyanide,[1936] Sec. 10.G.vii, category 3]. However, the use of an excess of LiCN in acetone/THF gave the nitrile as the major product.[1937] Tosyl cyanide ($TolSO_2CN$) has been used in some cases.[1938] A radical cyanation of alkyl iodides has been reported using diethylphosphoryl cyanide[1939] (see Chap. 14).

Vinylic bromides can be converted to vinylic cyanides with CuCN,[1940] with KCN, a crown ether, and a Pd complex,[1941] or with KCN and a Ni(0) catalyst.[1942] Halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$: $R_3CCl + Me_3SiCN \rightarrow R_3CCN$.[1943] Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with NaCN, Me_3SiCl, and a catalytic amount of NaI in DMF—MeCN.[1944] Lewis acids have been used in conjunction with NaCN or KCN.[1945] α,β-Epoxy amides were opened to the β-cyano-α-hydroxyamide with Et_2AlCN.[1946] Cyanohydrins react with alkyl halides in some cases to give the nitrile.[1947]

Substrates that react with cyanide may contain leaving groups other than halides (e.g., esters of sulfuric and sulfonic acids, sulfates and sulfonates, respectively). Vinylic triflates

[1931] Smiley, R.A.; Arnold, C. *J. Org. Chem.* ***1960***, *25,* 257; Friedman, L.; Shechter, H. *J. Org. Chem.* ***1960***, *25*, 877.
[1932] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 94–112; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 96–108. See also, Bram, G.; Loupy, A.; Pedoussaut, M. *Tetrahedron Lett.* ***1986***, *27,* 4171; *Bull. Soc. Chim. Fr.* ***1986***, 124.
[1933] Cao, Y.-Q.; Che, B.-H.; Pei, B.-G. *Synth. Commun.* ***2001***, *31,* 2203.
[1934] Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* ***1984***, 725.
[1935] See Luanay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* ***2002***, *43*, 7201.
[1936] See Jackson, H.L.; McKusick, B.C. *Org. Synth.* ***IV***, 438.
[1937] Ciaccio, J.A.; Smrtka, M.; Maio, W.A.; Rucando, D. *Tetrahedron Lett.* ***2004***, *45*, 7201.
[1938] Kim, S.; Song, H.-J. *Synlett* ***2002***, 2110.
[1939] Cho, C.H.; Lee, J.Y.; Kim, S. *Synlett* ***2009***, 81.
[1940] See Lapouyade, R.; Daney, M.; Lapenue, M.; Bouas-Laurent, H. *Bull. Soc. Chim. Fr.* ***1973***, 720.
[1941] Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* ***1977***, 4429.
[1942] Procházka, M.; Siroky, M. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 1765.
[1943] Zieger, H.E.; Wo, S. *J. Org. Chem.* ***1994***, *59*, 3838. See Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* ***1993***, *58*, 16 for a similar reaction with allylic acetates. See Hayashi, M.; Tamura, M.; Oguni, N. *Synlett,* ***1992***, 663 for a similar reaction with epoxides using a Ti catalyst.
[1944] Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* ***1988***, *18,* 445.
[1945] See Iranpoor, N.; Shekarriz, M. *Synth. Commun.* ***1999***, *29,* 2249.
[1946] Ruano, J.L.G.; Fernández-Ibáñez, M.Á.; Castro, A.M.M.; Ramos, J.H.R.; Flamarique, A.C.R. *Tetrahedron Asymmetry* ***2002***, *13,* 1321.
[1947] Dowd, P.; Wilk, B.K.; Wlostowski, M. *Synth. Commun.* ***1993***, *23*, 2323; Wilk, B.K. *Synth. Commun.* ***1993***, *23*, 2481 and see Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* ***1993***, 975 for similar reactions with epoxides.

give vinylic cyanides when treated with LiCN, a crown ether, and a Pd catalyst.[1948] Epoxides give β-hydroxy nitriles. The C-2-Selectivity was observed when NaCN and $B(OMe)_3$ were reacted with a disubstituted epoxide.[1949] The use of trimethylsilyl cyanide (Me_3SiCN) and a Lewis acid generates the *O*-TMS β-hydroxy nitrile, and the use of $YbCl_3$ and a salen complex gave good enantioselectivity.[1950] Tetrabutylammonium cyanide converted a primary alcohol to the corresponding nitrile in the presence of PPh_3/DDQ.[1951] Alcohols are converted to cyanides by reaction with triphenylphosphine and cyanogen bromide.[1952]

Sodium cyanide in HMPA selectively cleaves methyl esters in the presence of ethyl esters:[1953]

$$RCOOMe + CN^- \longrightarrow MeCN + RCOO^-$$

OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

10-76 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

Formyl-de-halogenation

$$RX + Na_2Fe(CO)_4 \xrightarrow{PPh_3} \underset{\mathbf{179}}{RCOFe(CO)_3PPh_3^-} \xrightarrow{HOAc} RCHO$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[1954] by treatment with sodium tetracarbonylferrate(-2)[1955] (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **179** with acetic acid. The reagent $Na_2Fe(CO)_4$ can be prepared by treatment of iron pentacarbonyl [$Fe(CO)_5$] with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is generally not satisfactory for benzylic bromides, but a good yield of the ketone was obtained using benzyl chloride and aryl iodides.[1956] The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$, which can be isolated;[1957] it then reacts with Ph_3P to give **179**.[1958]

The synthesis can be extended to the preparation of ketones in six distinct ways.[1959] These include quenching **179** with a second alkyl halide (R′X) rather than acetic acid; omitting PPh_3 with first RX and then adding the second, R′X; treatment with RX in the presence of CO,[1955] followed by treatment with R′X′; treatment with an acyl halide followed by treatment with an alkyl halide or an epoxide, gives an α,β-unsaturated

[1948] Piers, E.; Fleming, F.F. *J. Chem. Soc., Chem. Commun.* ***1989***, 756.
[1949] Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* ***2003***, *5,* 1789.
[1950] Schaus, S.E.; Jacobsen, E.N. *Org. Lett.* ***2000***, *2,* 1001.
[1951] Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *J. Org. Chem.* ***2004***, *69,* 2562.
[1952] Tarrade-Matha, A.; Pillon, F.; Doris, E. *Synth. Commun.* ***2010***, *40,* 1646.
[1953] Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.
[1954] Cooke, Jr., M.P. *J. Am. Chem. Soc.* ***1970***, *92*, 6080.
[1955] See Collman, J.P. *Acc. Chem. Res.* ***1975***, *8,* 342. Also see Brunet, J. *Chem. Rev.* ***1990***, *90,* 1041.
[1956] Dolhem, E.; Barhdadi, R.; Folest, J.C.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***2001***, *57*, 525.
[1957] Siegl, W.O.; Collman, J.P. *J. Am. Chem. Soc.* ***1972***, *94,* 2516.
[1958] See Collman, J.P.; Finke, R.G.; Cawse, J.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1978***, *100,* 4766.
[1959] See Collman, J.P.; Hoffman, N.W. *J. Am. Chem. Soc.* ***1973***, *95,* 2689.

ketone.[1960] The final variations involve reaction of alkyl halides or tosylates with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones;[1961] when 1,4-dihalides are used, five-membered cyclic ketones are prepared.[1962]

Yet another approach uses electrolysis conditions with the alkyl chloride, $Fe(CO)_5$, and a Ni catalyst, which gives the ketone directly, in one step.[1963] In the first stage of methods 1, 2, and 3, primary bromides, iodides, and tosylates and secondary tosylates can be used. The second stage of the first-four methods requires more active substrates (e.g., primary iodides or tosylates or benzylic halides). Method 5 has been applied to primary and secondary substrates.

Other acyl organometallic reagents are known. An acyl zirconium reagent [e.g., RCOZr(Cl)Cp_2] reacted with allylic bromide in the presence of CuI to give the corresponding ketone, but with allylic rearrangement.[1964]

Symmetrical ketones (R_2CO) can be prepared by treatment of a primary alkyl or benzylic halide with $Fe(CO)_5$ and a phase-transfer catalyst,[1965] or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.[1966] Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH, with a Pd catalyst.[1967] Various other groups do not interfere. Several procedures for the preparation of ketones are catalyzed by Pd complexes. Alkyl aryl ketones are formed in good yields by treatment of a mixture of an aryl iodide, an alkyl iodide, and a Zn—Cu couple with CO ($ArI + RI + CO \rightarrow RCOAr$).[1968] Vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones.[1969] Aryl, vinylic, and benzylic halides can be converted to methyl ketones ($RX \rightarrow RCOMe$) by reaction with (α-ethoxyvinyl)tributyltin [$Bu_3SnC(OEt)=CH_2$].[1970] In addition, SmI_2 can be used to convert alkyl chlorides to ketones, in the presence of 50 atm of CO.[1971]

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (Reaction **10-71**). See also, Reaction **12-33**.

OS **VI**, 807.

10-77 Carbonylation of Alkyl Halides, Alcohols, or Alkanes

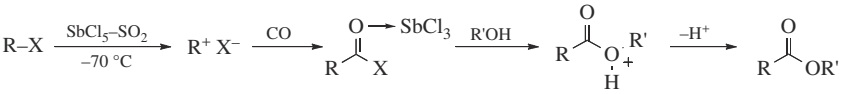
Alkoxycarbonyl-de-halogenation

$$RX + CO + R'OH \xrightarrow[-70\ ^\circ C]{SbCl_5-SO_2} RCOOR'$$

[1960] Yamashita, M.; Yamamura, S.; Kurimoto, M.; Suemitsu, R. *Chem. Lett.* ***1979***, 1067.
[1961] Cooke Jr., M.P.; Parlman, R.M. *J. Am. Chem. Soc.* ***1975***, *97*, 6863. However, see McMurry, J.E.; Andrus, A. *Tetrahedron Lett.* ***1980***, *21*, 4687, and references cited therein.
[1962] Yamashita, M.; Uchida, M.; Tashika, H.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2728.
[1963] Dolhem, E.; Ocafrain, M.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***1997***, *53*, 17089.
[1964] Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* ***2000***, *41*, 109.
[1965] des Abbayes, H.; Clément, J.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* ***1988***, *7,* 2293.
[1966] Garnier, L.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* ***1989***, *367,* 347.
[1967] Baillargeon, V.P.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108,* 452. See also, Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* ***1989***, 1816.
[1968] Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* ***1983***, *24*, 3869.
[1969] Goure, W.F.; Wright, M.E.; Davis, P.D.; Labadie, S.S.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 6417. See Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* ***1984***, *3,* 1108.
[1970] Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60,* 767.
[1971] Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.,* ***1997***, *119*, 2745.

A direct method for preparing a carboxylic acid treats an alkyl halide with $NaNO_2$ in acetic acid and DMSO.[1972] Reaction of an alkyl halide with $ClCOCO_2Me$ and $(Bu_3Sn)_2$ under photochemical conditions leads to the corresponding methyl ester.[1973]

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon.[1974] When an alkyl halide is treated with $SbCl_5—SO_2$ at $-70\,^{\circ}C$, it dissociates into the corresponding carbocation (Sec. 5.A.ii). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:[1975]



This has also been accomplished with concentrated H_2SO_4 saturated with CO.[1976] Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, using $HF—SbF_5—CO$.[1977]

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than seven carbons are cleaved into smaller fragments by this procedure.[1978] Similarly, tertiary alcohols[1979] react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch–Haaf reaction* (see also, **15-35**).[1980] If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO. Better results are obtained if trifluoromethanesulfonic acid (F_3CSO_2OH) is used instead of H_2SO_4.[1981] Iodo alcohols were transformed into lactones under radical conditions (AIBN, $allylSnBu_3$) and 45 atm of CO.[1982]

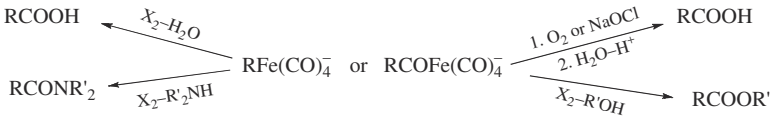
Another method[1983] for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl [$Ni(CO)_4$] in the presence of an alcohol and its conjugate base.[1984] When R′ is primary, RX may only be a vinylic or an aryl halide; retention of

[1972] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1997***, *62*, 234.
[1973] Kim, S.; Jon, S.Y. *Tetrahedron Lett.* ***1998***, *39*, 7317.
[1974] See Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 199–204, 212–220, 234–235. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1684–1685, 1694–1698, 1702–1704.
[1975] Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Myshenkova, T.N.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23,* 192.
[1976] Takahashi, Y.; Yoneda, N. *Synth. Commun.* ***1989***, *19*, 1945.
[1977] Paatz, R.; Weisgerber, G. *Chem. Ber.* ***1967***, *100*, 984. See Akhrem, I.; Afanas'eva, L.; Petrovskii, P.; Vitt, S.; Orlinkov, A. *Tetrahedron Lett.* ***2000***, *41*, 9903.
[1978] Yoneda, N.; Takahashi, Y.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2819.
[1979] See Bahrmann, H.; Cornils, B. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 226–241; Piacenti, F.; Bianchi, M. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 1–42.
[1980] See Bahrmann, H. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 372–413.
[1981] Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2441.
[1982] Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* ***2000***, *2*, 389.
[1983] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, ***1987***, pp. 749–768; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, pp. 335–359, pp. 348–356; Heck, R.F. *Adv. Catal.,* ***1977***, *26,* 323, p. 323; Cassar, L.; Chiusoli, G.P.; Guerrieri, F. *Synthesis* ***1973***, 509.

configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R′ is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

$$RX + Ni(CO)_4 \xrightarrow[R'OH]{R'O^-} RCOOR'$$

Still another method for the conversion of halides to acid derivatives makes use of $Na_2Fe(CO)_4$. As described in Reaction **10-76**, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $RFe(CO)_4^-$ or, if CO is present, the ion $RCOFe(CO)_4^-$. Treatment of $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[1985] Alternatively, $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ reacts with a halogen (e.g., I_2) in the presence of an alcohol to give a carboxylic ester,[1986] or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. Both $RFe(CO)_4^-$ and $RCOFe(CO)_4^-$, which are prepared from primary R, give high yields. With secondary R, the best results are obtained in the solvent THF by the use of $RCOFe(CO)_4^-$ prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters (RCO_2R') have also been prepared by treating primary alkyl halides RX with alkoxides $R'O^-$ in the presence of $Fe(CO)_5$.[1987] Here $RCOFe(CO)_4^-$ is presumably an intermediate.



Palladium complexes also catalyze the carbonylation of halides.[1988] Aryl (see Reaction **13-15**),[1989] vinylic,[1990] benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO, an alcohol or alkoxide, and a Pd complex.[1991] The Pd catalyzed carbonylation of organoindium compounds in the presence of methanol gives methyl esters.[1992] Similar reactivity was reported with vinyl triflates.[1993] α-Halo ketones are converted to β-keto esters with CO, an alcohol, NBu_3 and a palladium catalyst at

[1985] Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249.
[1986] Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249.
[1987] Yamashita, M.; Mizushima, K.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Chem. Lett.* ***1977***, 1355. See also, Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* ***1983***, *24,* 4005.
[1988] See Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57,* 299, pp. 303–309; Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–356, 366–370. See Kormos, C. M.; Leadbeater, N.E. *Synlett* ***2007***, 2006.
[1989] See Bessard, Y; Crettaz, R. *Heterocycles* ***1999***, *51*, 2589.
[1990] See Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1985***, *26,* 1109.
[1991] Kiji, J.; Okano, T.; Higashimae, Y.; Kukui, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1029.
[1992] Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* ***2008***, *130,* 9429.
[1993] Jutand, A.; Négri, S. *Synlett,* ***1997***, 719.

110 °C.[1994] Use of an amine instead of the alcohol or alkoxide leads to an amide.[1995] Reaction with an amine, AIBN, CO, and a tetraalkyltin catalyst also leads to an amide.[1996] Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a Co–imine complex.[1997] Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.[1998] Allylic *O*-phosphates were converted to allylic amides with CO and ClTi=NTMS, in the presence of a Pd catalyst.[1999] Terminal alkynes were converted to the alkynyl ester using CO, $PdBr_2$, $CuBr_2$ in methanol, and sodium bicarbonate.[2000]

Other organometallic reagents can be used to convert alkyl halides to carboxylic acid derivatives. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex.[2001] Variations introduce the R′ group via an ether (R'_2O),[2002] or an Al, Ti, or Zr alkoxide.[2003] The reaction of an alkene, a primary alcohol, and CO, in the presence of a Rh catalyst, led to carbonylation of the alkene and formation of the corresponding ester.[2004] Vinyl triflates were converted to the conjugated carboxylic acid with CO_2 and a Ni catalyst.[2005] Reaction with an α,ω-diiodide, Bu_4NF, and Mo $(CO)_6$ gave the corresponding lactone.[2006]

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α-keto acids or their derivatives.[2007] When the catalyst is a Pd complex, best results are obtained in the formation of α-keto amides.[2008] The R group is usually aryl or vinylic.[2009] The formation of α-keto acids[2010] or esters[2011] requires more severe conditions. α-Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.[2012] Cobalt catalysts have also been used and require lower CO pressures.[2007]

OS **V**, 20, 739.

[1994] Lapidus, A.L.; Eliseev, O.L.; Bondarenko, T.N.; Sizan, O.E.; Ostapenko, A.G.; Beletskaya, I.P. *Synthesis* ***2002***, 317.
[1995] Schoenberg, A.; Heck, R.F. *J. Org. Chem.* ***1974***, *39*, 3327. See also, Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* ***1997***, *27*, 361; Screttas, C.G.; Steele, B.R. *Org. Prep. Proceed. Int.* ***1990***, *22,* 271, pp. 288–314; Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 2662.
[1996] Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* ***1998***, 1953.
[1997] Isse, A.A.; Gennaro, A. *Chem. Commun.* ***2002***, 2798.
[1998] Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett.* ***1989***, *30,* 2615. See also, Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1989***, *111*, 927.
[1999] Ueda, K.; Mori, M. *Tetrahedron Lett.* ***2004***, *45,* 2907. For an intramolecular carbonylation to generate a cyclic amide, see Trost, B.M.; Ameriks, M.K. *Org. Lett.* ***2004***, *6*, 1745.
[2000] Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001***, *31*, 199.
[2001] For an example, see Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* ***2000***, *41*, 7601.
[2002] Buchan, C.; Hamel, N.; Woell, J.B.; Alper, H. *Tetrahedron Lett.* ***1985***, *26,* 5743.
[2003] Woell, J.B.; Fergusson, S.B.; Alper, H. *J. Org. Chem.* ***1985***, *50*, 2134.
[2004] Yokoa, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* ***2003***, *5*, 4329.
[2005] Senboku, H.; Kanaya, H.; Tokuda, M. *Synlett* ***2002***, 140.
[2006] Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Rolando, C. *J. Chem. Soc., Chem. Commun.* ***1992***, 1678.
[2007] For a review, see Collin, J. *Bull. Soc. Chim. Fr.* ***1988***, 976.
[2008] Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1982***, *233,* C64; Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1984***, *3*, 683.
[2009] Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1988***, *61,* 1251.
[2010] Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 837.
[2011] See Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1987***, *6,* 1640.
[2012] Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* ***1987***, *28*, 2721.

CHAPTER 11

Aromatic Substitution, Electrophilic

Most substitutions at an aliphatic carbon are by nucleophiles. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring leads to its reactivity as a Lewis base or a Brønsted–Lowry base, depending on the positive species. In electrophilic substitutions, a positive ion or the positive end of a dipole or induced dipole is attacked by the aromatic ring. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitution reactions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, OTs^-, and so on (i.e., the weakest bases). In electrophilic substitution reactions, the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell; that is, the weakest Lewis acids. The influence of solvents will vary with the reaction in many cases, and such details are discussed where appropriate in the reactions section (Sec. 11.F).[1]

11.A. MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceeds by just one mechanism with respect to the substrate.[2] In this mechanism, called the *arenium ion mechanism*, the electrophile, which can be viewed as a Lewis acid, is attacked by the π electrons of the aromatic ring, which can be viewed as a Lewis base, in the first step. This reaction leads to formation of a new C—X bond and a new sp^3 carbon in a positively charged intermediate called an arenium ion, where X is the electrophile. The positively charged intermediate (the arenium ion) is resonance stabilized, but not aromatic. Loss of a proton from the sp^3 carbon that is "adjacent" to the positive carbon in the arenium ion, in what is effectively an E1 process (see Sec. 17.A.ii) is driven by rearomatization of the ring from the arenium ion to give the aromatic substitution product. A proton therefore becomes the leaving group in this overall transformation, where X replaces H. The IUPAC designation for this mechanism is $A_E + D_E$. Another mechanism, much less common, consists of the opposite behavior: a leaving group departs *before* the electrophile arrives.

[1] For a review of electrophilic aromatic reactions in ionic liquids, see Borodkin, G.I.; Shubin, V.G. *Russ. J. Org. Chem.* ***2006****, 42,* 1745.

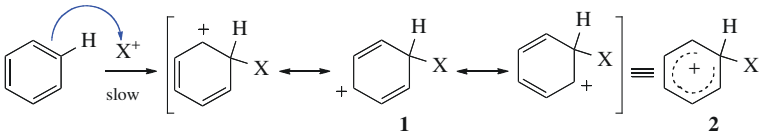
[2] See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***; Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 1–406.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

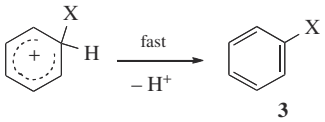
In this case, a substituent (*not* H) is attached to the aromatic ring, and the substituent is lost prior to incorporation of the electrophile. This mechanism, the S_E1 mechanism, corresponds to the S_N1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition–elimination mechanism has been postulated in one case (see Reaction **11-6**).

11.A.i. The Arenium Ion Mechanism[3]

In the arenium ion mechanism, the electrophilic species may be produced in various ways, but when H is replaced by X conversion of the aromatic ring to an arenium ion it is basically the same in all cases. For this reason, most attention in the study of this mechanism centers on the identity of the electrophilic entity and how it is produced.



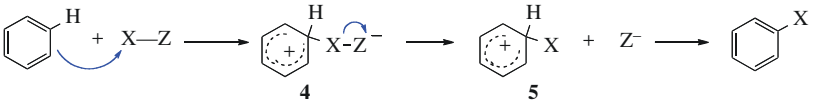
The electrophile may be a positive ion (X^+) or be a molecule that has a positive dipole. If it is a positive ion, it is attacked by the ring (a pair of electrons from the aromatic sextet is donated to the electrophile) and the product is a carbocation. This intermediate is a resonance hybrid, as shown in **1**, but is often represented as in **2**. The H atom to be replaced by X is shown in **1** for convenience. Ions of this type have been called[4] *Wheland intermediates*, σ *complexes*, but nowadays they are called *arenium ions*.[5] The inherent stability associated with aromaticity is no longer present in **1**, but the ion is stabilized by resonance. For this reason, the arenium ion is generally a highly reactive intermediate, although there are cases in which it has been isolated (see below).



Carbocations can react in various ways (see Sec. 5.A.iii), but for this type of ion the most likely pathway[6] is loss of either X^+ or H^+. In the second step of the mechanism, the reaction proceeds with loss of the proton and the aromatic sextet is restored in the final product (**3**). The second step is nearly always faster than the first, making the first rate determining, and the reaction is second order. If formation of the attacking species is slower still, the aromatic compound does not take part in the rate expression at all. If X^+ is lost, there is no net reaction, but if H^+ is lost, an aromatic substitution has taken place and a base (generally the counterion of the electrophilic species although solvents can also serve this purpose) is necessary to help remove it.

[3] This mechanism is sometimes called the S_E2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chap 12).
[4] See Olah, G.A. *J. Am. Chem. Soc.* ***1971****, 94,* 808.
[5] See Brouwer, D.M.; Mackor, E.L.; MacLean, C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 837–897; Perkampus, H. *Adv. Phys. Org. Chem.* ***1966****, 4,* 195.
[6] Also see de la Mare, P.B.D. *Acc. Chem. Res.* ***1974****, 7,* 361.

If the electrophilic species is not an ion but a molecule with a polarized covalent bond, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, as in the conversion of **4** to **5**. Note that when the aromatic ring attacks X, Z may be lost directly to give **5**.

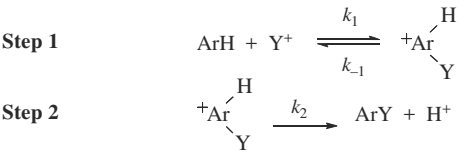


The electrophilic entities and how they are formed are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

1. *Isotope Effects*. If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than non-deuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[7] This result is incompatible with either the S_E1 or the simultaneous mechanism.

   However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1–3 for k_H/k_D instead of 6–7), there must be another explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:

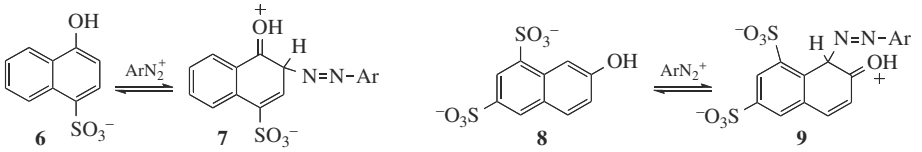


   The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.[8] The rate at which $ArHY^+$ reverts to ArH should be essentially the same as that at which $ArDY^+$ (or $ArTY^+$) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, $ArHY^+$ should go to ArY faster than either $ArDY^+$ or $ArTY^+$, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_2 1[ArH][Y^+]$) and no isotope effect is predicted. However, if $k_2 \leq k_{-1}$, reversion to starting materials is important. If k_2 for $ArDY^+$ (or $ArTY^+$) is $< k_2$ for $ArHY^+$, but k_{-1} is the same, then a larger proportion of $ArDY^+$ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor)* for

[7] Berglund-Larsson, U.; Melander, L. *Ark. Kemi* ***1953****, 6,* 219. See also, Zollinger, H. *Adv. Phys. Org. Chem.* ***1964****, 2,* 163.

[8] See Hammett, L.P. *Physical Organi Chemistry*, 2nd ed.; McGraw-Hill, NY, ***1970***, pp. 172–182.

$ArDY^+$ is less than that for $ArHY^+$. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.



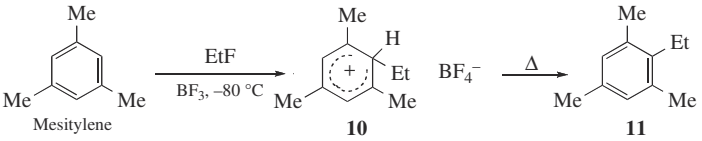
One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **6** gave no isotope effect, while coupling of **8** gave a k_H/k_D ratio of 6.55.[9] For steric reasons, it is much more difficult for **9** to lose a proton (it is harder for a base to approach) than it is for **7**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+, k_{-1} does not depend on steric factors[10] and is about the same for each. Thus the partition factor k_2/k_{-1} is sufficiently different for **7** and **9** that **8** exhibits a large isotope effect and **6** exhibits none.[11] Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

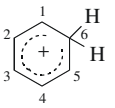
where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions, the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55–0.05 were obtained,[12] in accord with the arenium ion mechanism.

2. *Isolation of Arenium Ion Intermediates*. Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.[13] For example, **7** was isolated as a solid with a

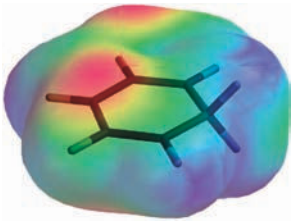


[9] Zollinger, H. *Helv. Chim. Acta* ***1955****, 38,* 1597, 1617, 1623.
[10] Snyckers, F.; Zollinger, H. *Helv. Chim. Acta* ***1970****, 53,* 1294.
[11] See Myhre, P.C.; Beug, M.; James, L.L. *J. Am. Chem. Soc.* ***1968****, 90*, 2105; Márton, J. *Acta Chem. Scand.* ***1969****, 23,* 3321, 3329.
[12] Bott, R.W.; Eaborn, C.; Greasley. P.M. *J. Chem. Soc.* ***1964***, 4803.
[13] See Koptyug, V.A. *Top. Curr. Chem.* ***1984****, 122,* 1; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974****, 23,* 1031; Shteingarts, V.D. *Russ. Chem. Rev.* ***1981****, 50,* 735; Farcasiu, D. *Acc. Chem. Res.* ***1982****, 15,* 46.

melting point of −15 °C from treatment of mesitylene with ethyl fluoride and the catalyst BF_3 at −80 °C. When **10** was heated, the normal substitution product (**11**) was obtained.[14] Even the simplest such ion, the benzenonium ion (**12**) has been prepared in $HF—SbF_5—SO_2ClF—SO_2F_2$ at −134 °C, where it could be studied



12



13

spectrally.[15] The ^{13}C NMR spectra of the benzenonium ion[16] and the pentamethylbenzenonium ion[17] give graphic evidence for the charge distribution shown in **12** (see the electron density map for the arenium ion, **13**). According to this, the 1, 3, and 5 carbons, each of which bears a positive charge of about +1/3 [note that C-1,-3,-5 (numbering from **12**) are lighter, indicating less electron density in **13**, whereas C-2,-4 are darker for higher electron density], should have a greater chemical shift in the NMR than the 2 and 4 carbon atoms, which are uncharged. The spectra bear this out. For example, ^{13}C NMR chemical shifts for **12** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.[16]

In Chapter 3, it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack of a positive ion by an aromatic ring, it has been suggested[18] that such a complex, called a π-*complex* (represented as **14**), is formed first, and then is converted to the arenium ion (**15**).[19] Stable solutions of arenium ions or π complexes (e.g., with Br_2, I_2, picric acid, Ag^+, or HCl) can be formed.[20] For example, π-complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity, which shows that positive and negative ions are present, while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were

[14] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1958****, 80,* 6541. See Effenberger, F. *Acc. Chem. Res.* ***1989****, 22*, 27.
[15] Olah, G.A.; Schlosberg, R.H.; Porter, R.D.; Mo, Y.K.; Kelly, D.P.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1972****, 94*, 2034.
[16] Olah, G.A.; Staral, J.S.; Asencio, G.; Liang, G.; Forsyth, D.A.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1978****, 100*, 6299.
[17] Lyerla, J.R.; Yannoni, C.S.; Bruck, D.; Fyfe, C.A. *J. Am. Chem. Soc.* ***1979****, 101*, 4770.
[18] Dewar, M.J.S. *Electronic Theory of Organic Chemistry;* Clarendon Press: Oxford, ***1949***.
[19] See Hubig, S.M.; Kochi, J.K. *J. Org. Chem.* ***2000****, 65,* 6807.
[20] See Gallivan, J.P.; Dougherty, D.A. *Org. Lett.* ***1999****, 1*, 103; Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2002****, 67*, 1727.

TABLE 11.1 Relative Stabilities of Arenium Ions, π-Complexes, and Relative Rates of Chlorination and Nitration[a]

Substituents	Relative Arenium Ion Stability[b]	Relative π-Complex Stability[b]	Rate of Chlorination[c]	Rate of Nitration[d]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-di-Me_3	1.00	1.00	1.00	1.00
o-di-Me_3	1.1	1.13	2.1	0.89
m-di-Me_3	26	1.26	200	0.84
1,2,4-Tri-Me_3	63	1.36	340	
1,2,3-Tri-Me_3	69	1.46	400	
1,2,3,4-tetra-Me_3	400	1.63	2,000	
1,2,3,5-tetra-Me_3	16,000	1.67	240,000	
Penta-Me_3	29,900		360,000	

Reprinted with permission Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* ***1953***, *75*, 577. Copyright © 1953 American Chemical Society.

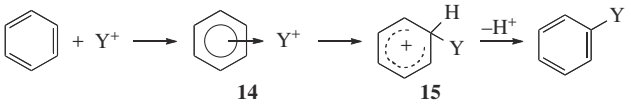
[a]In each case, *p*-xylene = 1.00.

[b]See Ref. 21.

[c]See Ref. 22.

[d]See Ref. 27.

determined by the relative basicity of the substrate toward HF.[21] The π-complex stabilities are relative equilibrium constants for the reaction[22] between the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: The π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal. Note that stable arenium ions have been obtained from large methylene-bridged polycyclic aromatic hydrocarbons.[23]



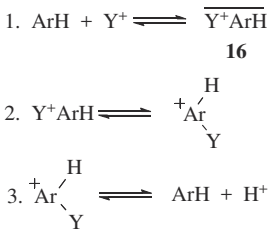
14 **15**

How can we tell if **14** is present on the reaction path? If it is present, there are two possibilities: (1) The formation of **14** is rate determining (the conversion of **14** to **15** is much faster), or (2) the formation of **14** is rapid, and the conversion **14** to **15** is rate determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the π

[21] Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* ***1953***, *75*, 577.
[22] Brown, H.C.; Brady, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 3570.
[23] Laali, K.K.; Okazaki, T.; Harvey, R.G. *J. Org. Chem.* ***2001***, *66*, 3977.

complexes, the latter are formed in the slow step.[24] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the π complex stabilities. For example, Table 11.1 lists chlorination rates.[22] Similar results were obtained in room temperature bromination with Br_2 in acetic acid[25] and in acetylation with CH_3CO^+ SbF_6^-.[26] It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of NO_2^+ BF_4^-), the relative rates resembled π complex stabilities much more than arenium ion stabilities (Table 11.1).[27] Similar results were obtained for bromination with Br_2 and $FeCl_3$ in nitromethane. These results were taken to mean[28] that in these cases π complex formation is rate determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π-complex stability,[29] which casts doubt on the rate-determining formation of a π complex in this case.[30] There is other evidence, from positional selectivities (discussed in Sec. 11.D), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **16**. The arenium complex mechanism is therefore written as:[31]

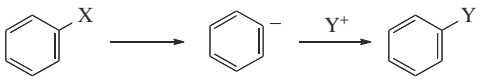


For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also, Sec. 11.D). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas-phase protonation of alkylbenzenes.[32]

[24] Condon, F.E. *J. Am. Chem. Soc.* ***1952****, 74,* 2528.
[25] Brown, H.C.; Stock, L.M. *J. Am. Chem. Soc.* ***1957****, 79,* 1421.
[26] Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964****, 86,* 2203.
[27] Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961****, 83,* 4571, 4581.
[28] Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964****, 86,* 1039, 1044.
[29] Rys, P.; Skrabal, P.; Zollinger, H. *Angew. Chem. Int. Ed.* ***1972****, 11,* 874. See also, DeHaan, F.P.; Covey, W.D.; Delker, G.L.; Baker, N.J.; Feigon, J.F.; Miller, K.D.; Stelter, E.D. *J. Am. Chem. Soc.* ***1979****, 101,* 1336; Santiago, C.; Houk, K.N.; Perrin, C.L. *J. Am. Chem. Soc.* ***1979****, 101*, 1337.
[30] See Ridd, J.H. *Acc. Chem. Res.* ***1971****, 4,* 248; Taylor, R.; Tewson, T.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 836; Naidenov, S.V.; Guk, Yu.V.; Golod, E.L. *J. Org. Chem. USSR* ***1982****, 18,* 1731. Also see Olah, G.A. *Acc. Chem. Res.* ***1971****, 4,* 240; Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974****, 96,* 2892; Sedaghat-Herati, M.R.; Sharifi, T. *J. Organomet. Chem.* ***1989****, 363,* 39; Banthorpe, D.V. *Chem. Rev.* ***1970****, 70,* 295, especially Sections VI and IX.
[31] See Stock, L.M. *Prog. Phys. Org. Chem.* ***1976****, 12*, 21; Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978****, 16,* 1.
[32] Holman, R.W.; Gross, M.L. *J. Am. Chem. Soc.* ***1989****, 111,* 3560.

11.A.ii. The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see Reactions **11-33** and **11-35**) or when a very strong base is present (see Reactions **11-1**, **11-10**, and **11-39**).[33] It consists of two steps with an intermediate carbanion. The IUPAC designation is $D_E + A_E$.



Reactions **12-41**, **12-45**, and **12-46** also take place by this mechanism when applied to aryl substrates.

11.B. ORIENTATION AND REACTIVITY

11.B.i. Orientation and Reactivity in Monosubstituted Benzene Rings[34]

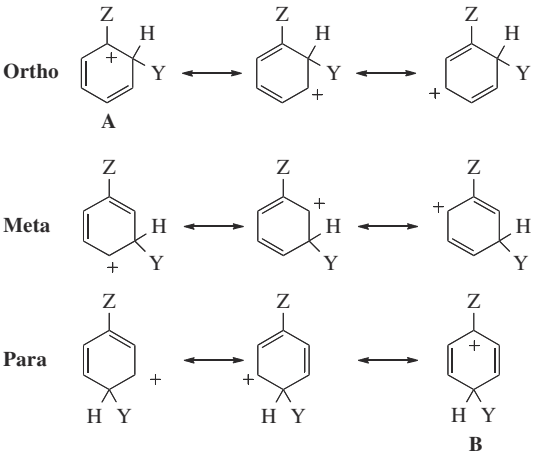
When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself.[35] The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it are *deactivating*. Some groups are predominantly meta directing; all of these are deactivating. Others are mostly ortho–para directing; while some of these (e.g., halogens) are deactivating too, most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects are explained on the basis of resonance and field effects of each group on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see Sec. 6.F). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. *Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates.* It is not easy to predict which of the three activation energies is lowest, but it is necessary to make the assumption that the free energy profile resembles either Fig. 6.2*a* or *b*. In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the *Hammond postulate* (Sec. 6.G), assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will

[33] Also see Eaborn, C.; Hornfeld, H.L.; Walton, D.R.M. *cgqtBunnett, J.F.; Miles J.H.; Nahabedian, K* ***1967***, 1036.
[34] See Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 122–145, 163–220.
[35] For a computational approach to evaluate substituent constants, see Galabov, B.; Ilieva, S.; Schaefer III, H.F. *J. Org. Chem.* ***2006****, 71,* 6382.

also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, the relative stabilities of the three intermediates can be used as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, product ratios that are quite different may be obtained. For example, the sulfonation of naphthalene at 80 °C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[36] while at 160 °C, where equilibrium is attained, the β isomer predominates[37] (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

The three possible ions from incorporation of Y at the ortho, meta, and para positions are shown below, and each arenium ion obviously has a positive charge in the ring. It is therefore possible to predict that any group Z that has an electron-donating field effect (+*I*, Z will have a − charge or a δ− dipole in most cases) should stabilize all three ions (relative to **1**), since electron donation to a positive center is stabilizing. On the other hand, electron-withdrawing groups (−*I*, Z will have a + charge or a δ+ dipole in most cases) will increase the positive charge on the ring (like charges repel), and destabilize the arenium ion. Formation of a stabilized ion should be faster than benzene, which generates **1**, or activating, but formation of a destabilized ion should be slower, or deactivating. Such field effects should taper off with distance and are thus strongest at the carbon connected to the group Z (known as the ipso carbon). Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge at the ipso carbon. Therefore, +*I* groups should stabilize all three ions, but mostly the ortho and para, so they should be not only activating but ortho–para-directing as well. On the other hand, −*I* groups, by removing electron density, should destabilize all three ions, but mostly the ortho and para, and should be not only deactivating but also meta directing.

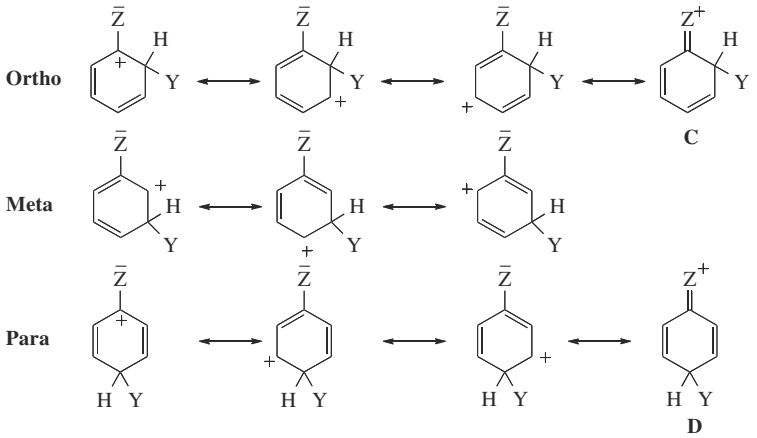


These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases, there is *resonance interaction* between Z and the ring; this also

[36] Fierz, H.E.; Weissenbach, P. *Helv. Chim. Acta* ***1920****, 3,* 312.
[37] Witt, O.N. *Ber.* ***1915****, 48,* 743.

affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. Two of the three (ortho and para) arenium ions would then have a fourth resonance contributor as shown. For each ion, the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but also because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except, of course, hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (Sec. 2.E), but also because it spreads the positive charge over a larger area, out onto group Z. Groups with a pair of electrons (e.g., the halogens) to contribute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.



On the basis of these discussions, we can distinguish three types of groups.

1. *Groups that Contain an Unshared Pair of Electrons on the Atom Connected to the Ring*. In this category are O^-, NR_2, NHR, NH_2,[38] OH, OR, NHCOR, OCOR, SR, and the four halogens.[39] The halogens deactivate the aromatic ring to substitution (the rate of reaction is slower than that of benzene), and this effect may arise from the unique energy level of the halogen lone-pair orbital, which is higher than the

[38] It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta directing (type 2). However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho–para direction is often found even under acidic conditions.

[39] See Chuchani, G. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 250–265; for ether groups see Kohnstam, G.; Williams, D.L.H. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 132–150.

adjacent π molecular orbital of benzene (π_1).[40] The widely held explanation for this, however, is that the halogens have a $-I$ effect. The SH group would probably belong here too, except that in the case of thiophenols, electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.[41] The resonance explanation predicts that all these groups should be ortho–para directing, and they are, though all except O^- are electron withdrawing by the field effect (Sec. 1.I). Therefore, for these groups, resonance is more important than the field effect. This result is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine[42] is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho–para, assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta or the unsubstituted ion. For most of the groups in this category, the meta ion is more stable than **1**, so that groups, such as NH_2 and OH, activate the meta positions too, but not as much as the ortho and para positions (see also, the discussion in Sec. 11.C).

2. *Groups that Lack an Unshared Pair on the Atom Connected to the Ring and that Are $-I$.* In this category are, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CF_3,[43] CN, SO_3H, CHO, COR, CO_2H, CO_2R, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[44] (SR_2^+, PR_3^+, etc.) and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.[45] The NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.[46]

[40] Tomoda, S.; Takamatsu, K.; Iwaoka, M. *Chem. Lett.* ***1998***, 581.

[41] Tarbell, D.S.; Herz, A.H.*J. Am. Chem. Soc.* ***1953****, 75,* 4657. Ring substitution *is* possible if the SH group is protected. See Walker, D. *J. Org. Chem.* ***1966****, 31,* 835.

[42] Carroll, T.X.; Thomas, T.D.; Bergersen, H.; Børve, K.J.; Sæthre, L.J. *J. Org. Chem.* ***2006****, 71,* 1961.

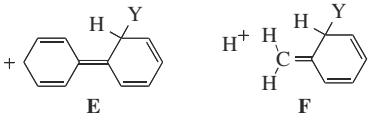
[43] See Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* ***2002****, 8*, 799.

[44] See Gilow, H.M.; De Shazo, M.; Van Cleave, W.C. *J. Org. Chem.* ***1971****, 36*, 1745; Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 167–176.

[45] Hartshorn, S.R.; Ridd, J.H. *J. Chem. Soc. B* ***1968***, 1063. Also see Ridd, J.H. in *Aromaticity, Chem. Soc. Spec. Publ., no. 21,* ***1967***, pp. 149–162.

[46] Brickman, M.; Utley, J.H.P.; Ridd, J.H. *J. Chem. Soc.* ***1965***, 6851.

3. *Groups that Lack an Unshared pair on the Atom connected to the Ring and that Are ortho–para Directing*. In this category are alkyl groups,[47] aryl groups, and the COO^- group,[48] all of which activate the ring. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho–para directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that forms like **E** are generated The effect of negatively charged groups like CO_2^- is easily explained by the field effect (negatively charged groups are of course electron donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, canonical forms can be drawn, even though there is no unshared pair. These, of course, are hyperconjugation forms like **F** (see above). This effect, like the field effect, predicts activation and ortho–para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups, which sums up both field and hyperconjugation effects, is that (for Z = R) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the *Baker–Nathan order* (Sec. 2.M), but not always.[49]



E **F**

11.B.ii. The Ortho/Para Ratio[50]

When an ortho–para directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much is the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.[51] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion (**12**), which arises from protonation of benzene, has the approximate charge distribution shown[52] (see **13** as well). If this model were accepted for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that >33% para and <67% ortho substitution would be found. In hydrogen exchange (Reaction **11-1**), where other effects are absent, it has been found for a number of

[47] For a discussion of the substituents effect of the methyl group, see Myrseth, V.; Sæthre, L.J.; Børve, K.J.; Thomas, T.D. *J. Org. Chem.* ***2007****, 72,* 5715.

[48] Spryskov, A.A.; Golubkin, L.N. *J. Gen. Chem. USSR* ***1961****, 31*, 833. Since the CO_2^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom encountered.

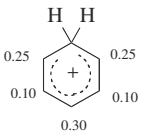
[49] See, however, Schubert, W.M.; Gurka, D.F. *J. Am. Chem. Soc.* ***1969****, 91,* 1443; Himoe, A.; Stock, L.M. *J. Am. Chem. Soc.* ***1969****, 91,* 1452.

[50] See Effenberger, F.; Maier, A.J. *J. Am. Chem. Soc.* ***2001****, 123*, 3429.

[51] Stock, L.M.; Himoe, A. *J. Am. Chem. Soc.* ***1961****, 83,* 4605.

[52] Olah, G.A. *Acc. Chem. Res.* ***1970****, 4,* 240, p. 248.

substituents that the average ratio of the logarithms of the partial rate factors for these positions (see Sec. 11.C for a definition of partial rate factor) was close to 0.865,[53] which is not far from the value predicted from the ratio of charge densities in **12**. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios >67:33[54] (of course, the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally >67:33). Another important factor is the steric effect. If either the group on the attacking ring or the group on the electrophile is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *tert*-butyl group gave 16% of the ortho product and 73% of the para.[55] Some groups are so large that they direct almost entirely para.



12

When the ortho–para directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (see above) shows that **C** is a canonical form with an *ortho*-quinoid structure, while **D** has a *para*-quinoid structure. *para*-Quinones are more stable than the ortho isomers, so it seems reasonable to assume that **D** is more stable than **C**, and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6[56] (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

11.B.iii. Ipso Attack

Orientation has been discussed previously in the case of monosubstituted benzenes entirely in terms of attachment at the ortho, meta, and para positions, but attachment at

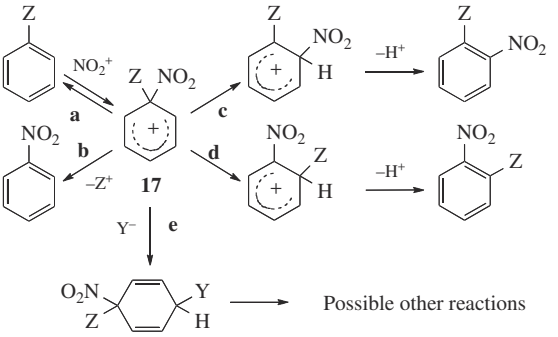
[53] Ansell, H.V.; Le Guen, J.; Taylor, R. *Tetrahedron Lett.* ***1973***, 13.

[54] Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 176–180.

[55] Nelson, K.L.; Brown, H.C. *J. Am. Chem. Soc.* ***1951***, *73,* 5605. See Baas, J.M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 285, 517, 831.

[56] Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* ***1969***, *91,* 3085; *Bioorg. Chem.* ***1971***, *1*, 140. See also, Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* ***1983***, *105,* 2018; ***1984***, *106,* 174; Chênevert, R.; Ampleman, G. *Can. J. Chem.* ***1987***, *65,* 307; Komiyama, M. *Polym. J. (Tokyo)* ***1988***, *20,* 439.

the position bearing the substituent (called the *ipso position*[57]) can also be important. Ipso attack has mostly been studied for nitration.[58] When attack of NO_2^+ leads to incorporation at the ipso position there are at least five possible fates for the resulting arenium ion (**17**).



Path a. The arenium ion can lose NO_2^+ and revert to the starting compounds. This results in no net reaction and is often undetectable.

Path b. The arenium ion can lose Z^+, in which case this is simply aromatic substitution with a leaving group other than H (see Reactions **11-33–11-41**).

Path c. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attachment of NO_2^+ at the ortho position of PhZ. It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,[59] though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relative reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attachment at the ortho position, but from attachment at the ipso position followed by rearrangement.[60]

Path d. The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (although the rearrangement would become apparent if there were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+.[61]

Path e. Attack of a nucleophile on **17**. In some cases, the products of such an attack (cyclohexadienes) have been isolated[62] (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

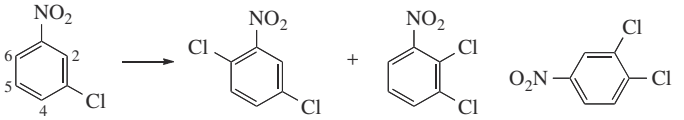
[57] Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* ***1971****, 93,* 3389; Traynham, J.G. *J. Chem. Educ.* ***1983****, 60,* 937.
[58] See Moodie, R.B.; Schofield, K. *Acc. Chem. Res.* ***1976****, 9,* 287. See also, Fischer, A.; Henderson, G.N.; RayMahasay, S. *Can. J. Chem.* ***1987****, 65*, 1233, and other papers in this series.
[59] See Gibbs, H.W.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1145.
[60] This was first pointed out by Myhre, P.C. *J. Am. Chem. Soc.* ***1972****, 94,* 7921.
[61] See Hartshorn, M.P.; Readman, J.M.; Robinson, W.T.; Sies, C.W.; Wright, G.J. *Aust. J. Chem.* ***1988****, 41,* 373.
[62] See Banwell, T.; Morse, C.S.; Myhre, P.C.; Vollmar, A. *J. Am. Chem. Soc.* ***1977****, 99*, 3042; Fischer, A.; Greig, C. C. *Can. J. Chem.* ***1978****, 56*, 1063.

11.B.iv. Orientation in Benzene Rings with More Than One Substituent[63]

It is often possible in these cases to predict the correct isomer. In many cases, the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise, the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult, as in *N*-acetyl-2-methoxyaniline. In a case such as where two groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxyl* group and not to the methyl. For this purpose, we can arrange the groups in the following order: NH_2, OH, NR_2, $O^- >$ OR, OCOR, NHCOR > R, Ar > halogen > meta-directing groups.
2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.[64]
3. When a meta-directing group is meta to an ortho–para directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **18** gives mostly **19**. The importance of this effect is underscored by the fact that **20**, which is in violation of the preceding rule, is formed in smaller amounts, but **21** is not formed at all. This is called the *ortho effect*,[65] and many such examples are known.[66] Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.



18 **19** **20** **21**

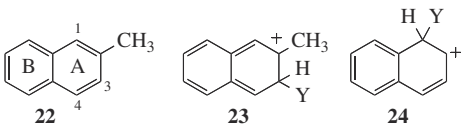
[63] For a quantitative discussion, see Section 11.C.
[64] See Kruse, L.I.; Cha, J.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 1333.
[65] This is not the same as the ortho effect mentioned at the end of Section 9.C.
[66] See Hammond, G.S.; Hawthorne, M.F. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 164–200, 178–182.

It is interesting that chlorination of **18** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attachment is therefore at position 6.

11.B.v. Orientation in Other Ring Systems[67]

In fused ring systems, the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when attack by naphthalene leads to attachment of the electrophile at the α position than when attack by naphthalene leads to attachment of the electrophile at the β position. Therefore, the α position is the preferred site of attachment,[68] although, as previously mentioned (Sec. 11.B.i), the isomer formed by substitution at the β-position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly, anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar,[69] in terms of mechanism, and rate data is available.[70] Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[71] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine,[72] it is not the free base that must attack the electrophile but the conjugate acid (the pyridinium ion),[73] making the reactivity much less than that of benzene, being similar to that of nitrobenzene. The 3 position is most reactive in electrophilic substitution reactions of pyridine. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine *N*-oxide.[74] Note that calculations show that the 2-pyridyl and 2-pyrimidyl cations are best represented as *ortho*-hetarynium ions, being more stable than their positional, nonconjugated isomers by as much as 18–28 kcal mol^{-1} (75–117 kJ mol^{-1}).[75]



22 **23** **24**

[67] See Hafner, H.; Moritz, K.L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 127–183; Bublitz, D.E.; Rinehart, Jr., K.L. *Org. React.* ***1969****, 17*, 1.

[68] See de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 169–209.

[69] See Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***.

[70] Katritzky, A.R.; Fan, W.-Q. *Heterocycles* ***1992****, 34*, 2179.

[71] See Marino, G. *Adv. Heterocycl. Chem.* ***1971****, 13,* 235.

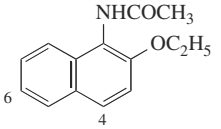
[72] See Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988****, 44,* 199; Katritzky, A.R.; Johnson, C.D. *Angew. Chem. Int. Ed.* ***1967****, 6,* 608; Abramovitch, R.A.; Saha, J.G. *Adv. Heterocycl. Chem.* ***1966****, 6,* 229. Also see Anderson, H.J.; Loader, C.E. *Synthesis* ***1985***, 353.

[73] Katritzky, A.R.; Kingsland, M. *J. Chem. Soc. B* ***1968***, 862.

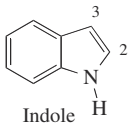
[74] Jaffé, H.H. *J. Am. Chem. Soc.* ***1954****, 76*, 3527.

[75] Gozzo, F. C.; Eberlin, M. N. *J. Org. Chem.* ***1999****, 64,* 2188.

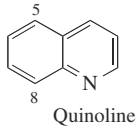
When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**22**) is activated by the methyl group; ring B is not (although the presence of a substituent in a fused ring system affects all the rings,[76] the effect is generally greatest on the ring to which it is attached). Substitution is therefore expected in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. Only forms like **23** are possible, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **24**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.[77] However, in some cases predictions are much harder to make. For example, chlorination or nitration of **25** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.[78]



25

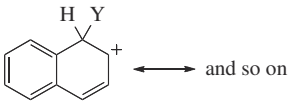


Indole

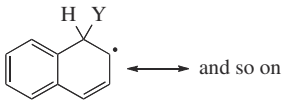


Quinoline

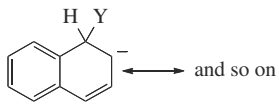
For fused heterocyclic systems too, predictions can be made based on the above principles, although many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.



24

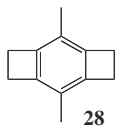


26



27

In alternant hydrocarbons (Sec. 2.J), the reactivity at a given position is similar for electrophilic, nucleophilic, and free radical substitution, because the same kind of resonance can be shown in all three types of intermediate (cf. **24**, **26**, and **27**). Attachment of the electrophile at the position that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+, NH_2^-, and $Ph^\bullet$, and always more readily than benzene.



28

[76] See Ansell, H.V.; Sheppard, P.J.; Simpson, C.F.; Stroud, M.A.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 381.

[77] See Kim, J.B.; Chen, C.; Krieger, J.K.; Judd, K.R.; Simpson, C.C.; Berliner, E. *J. Am. Chem. Soc.* ***1970,*** *92,* 910. Also see Gore, P.H.; Siddiquei, A.S.; Thorburn, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1781.

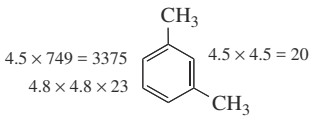
[78] Bell, F. *J. Chem. Soc.* ***1959***, 519.

When strain due to a ring fused on an aromatic ring deforms that ring out of planarity, the molecule is more reactive to electrophilic aromatic substitution.[79] This has been explained by the presence of a shortened bond for the sp^2 hybridized carbon, increasing the strain at that position. This finding is known as the *Mills–Nixon effect*.[80] There is EPR evidence (see Sec. 5.C.i) for 3,6-dimethyl-1,2,4,5-tetrahydrobenzo-bis-cyclobutene (**28**), which supports the *Mills–Nixon effect*,[81] and a theoretical study, which supports this.[82] However, *ab initio* studies of triannelated benzene rings shows *no evidence* for the *Mills–Nixon effect*, and a new motif for bond-alternating benzenes was proposed.[83] Indeed, it is argued that the *Mills–Nixon effect* is not real.[84]

11.C. QUANTITATIVE TREATMENTS OF REACTIVITY IN THE SUBSTRATE

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogen atoms that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. The *partial rate factor* may be defined for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors follow: for the ortho position $o_f^{Me} = 4.5$, for the meta $m_f^{Me} = 4.8$, and for the para $p_f^{Me} = 749$.[85] This means that toluene is acetylated at the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor >1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once the partial rate factors are known, the proportions of isomers to be obtained when two or more groups are present on a ring can be predicted, *if the assumption is made that the effect of substituents is independent*. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, the theoretical partial rate factors at each position can be calculated by multiplying those from toluene, so they should be as indicated.



[79] Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, ***1990***, p. 53.
[80] Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.
[81] Davies, A.G.; Ng, K.M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1857.
[82] Eckert-Maksić, M.; Maksić, Z.B.; Klessinger, M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 285.
[83] Baldridge, K.K.; Siegel, J.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.
[84] Siegel, J.S. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1721.
[85] Brown, H.C.; Marino, G.; Stock, L.M. *J. Am. Chem. Soc.* ***1959***, *81*, 3310.

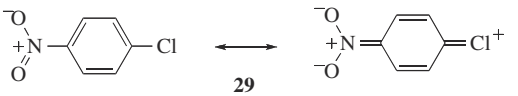
TABLE 11.2 Calculated and Experimental Isomer Distributions in the Acetylation of *m*-Xylene[a]

	Isomer Distribution (%)	
Position	Calculated	Observed
2	0.30	0
4	9.36	97.5
5	0.34	2.5

Reprinted with permission Marino G.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5929. Copyright © 1959 American Chemical Society.

[a]See Ref. 86.

From this, it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347[86] and the calculated and observed isomer distributions are listed in Table 11.2.[86] In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive (as in Sec. 11.B.ii).[87] For example, this treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects (e.g., those mentioned earlier, Sec. 11.B.iv), by products arising from ipso attack (Sec. 11.B.ii) and by resonance interaction *between* groups (e.g., **29**), which must make the results deviate from simple additivity of the effects of the groups.



29

Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means, overall rate ratios can be measured for specific positions.[88] Results obtained in this way[89] give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the HSAB concept (Sec. 8.E).[90] From MO theory, a quantity called *activation hardness* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attachment at that position; hence the treatment predicts the most likely orientations for incoming groups.

[86] Marino, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1959****, 81,* 5929.
[87] See Cook, R.S.; Phillips, R.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1166. For a theoretical treatment of why additivity fails, see Godfrey, M. *J. Chem. Soc. B* ***1971***, 1545.
[88] See Eaborn, C. *J. Organomet. Chem.* ***1975****, 100,* 43.
[89] See Eaborn, C.; Jackson, P.M. *J. Chem. Soc. B* **1969**, 21.
[90] Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1990****, 112*, 5720.

11.D. A QUANTITATIVE TREATMENT OF REACTIVITY OF THE ELECTROPHILE: THE SELECTIVITY RELATIONSHIP

Not all electrophiles are equally reactive. The nitronium ion is attacked not only by benzene but also by aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the reactivity of the group being attacked. The most obvious way to do this is with the *Hammett equation* (Sec. 8.G):

$$\log(k, k_0) = \rho\,\sigma$$

For aromatic substitution,[91] k_0 is divided by 6 and, for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a para position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4 for a list of σ^+ values).[92] Groups with a negative value of $\sigma_p{}^+$ or $\sigma_m{}^+$ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile, but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,[93] is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (1) their selectivity in attacking toluene rather than benzene, and (2) their selectivity between the meta and para positions in toluene.[93] As the table shows, an

TABLE 11.3 Relative Rates and Product Distributions in Some Electrophilic Substitutions on Toluene and Benzene[a]

	Relative Rate	Product Distribution, (%)	
Reaction	$k_{\text{toluene}}/k_{\text{benzene}}$	*m*	*p*
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

[a]See Ref. 93.

[91] See Exner, O.; Böhm, S. *J. Org. Chem.* ***2002****, 67,* 6320.
[92] See Koptyug, V.A.; Salakhutdinov, N.F.; Detsina, A.N. *J. Org. Chem. USSR* ***1984****, 20*, 1039.
[93] Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963****, 1*, 35.

electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable and more selective than the isopropyl (Sec. 5.A.ii), and Br_2 is more selective than Br^+. However, deviations from the relationship are known.[94] Selectivity depends not only on the nature of the electrophile, but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity S_f of a reaction as:

$$S_f = \log\left(\frac{p_f^{\mathrm{Me}}}{m_f^{\mathrm{Me}}}\right)$$

That is, the more reactive the reactive species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+\rho$ relationship with the linearity between log S_f and log p_f^{Me} and between log S_f and log m_f^{Me}, it is possible to derive the following expressions:

$$\log p_f^{\mathrm{Me}} = \left(\frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+}\right) S_f$$

$$\log m_f^{\mathrm{Me}} = \left(\frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+}\right) S_f$$

S_f is related to ρ by $S_f = \rho(\sigma_p^+ - \sigma_m^+)$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.[95] For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles. This is the reason why it is necessary to postulate the encounter complex mentioned in Section 11.A.i. For example, relative rates of nitration of *p*-xylene,

TABLE 11.4 Values of m_f^{Me}, p_f^{Me}, S_f, and ρ for Three Reactions of Toluene[a]

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
PhMe + EtBr $\xrightarrow[\text{benzene,25 °C}]{\text{GaBr}_3}$	1.56	6.02	0.587	−2.66
PhMe + HNO_3 $\xrightarrow[45\,^\circ\text{C}]{90\%\ \text{HOAc}}$	2.5	58	1.366	−6.04
PhMe + Br_2 $\xrightarrow[25\,^\circ\text{C}]{85\%\ \text{HOAc}}$	5.5	2420	2.644	−11.40

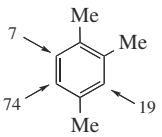
[a]See Ref. 95.

[94] See Olah, G.A.; Olah, J.A.; Ohyama, T. *J. Am. Chem. Soc.* ***1984****, 106*, 5284.

[95] Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963****, 1*, 35 presents many tables of these kinds of data. See also, DeHaan, F.P.; Chan, W.H.; Chang, J.; Ferrara, D.M.; Wainschel, L.A. *J. Org. Chem.* ***1986****, 51*, 1591, and other papers in this series.

1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,[96] though the extra methyl groups should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter[97] between an electrophile and substrate molecule)[98] that the presence of additional activating groups can no longer increase the rate.[99]

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.[100] Although steric effects are about the same at both positions, >10 times as much 5-nitro product was formed as 6-nitro product. It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, Sec. 11.B.ii).[101] Since the position of attachment is not determined in the rate-determining step, the 5:6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier[102] and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and we have seen (Sec. 11.B.ii) that there is evidence against this.

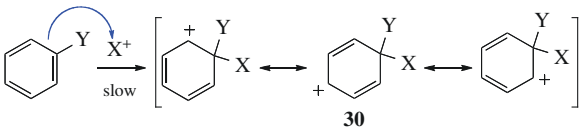


Relative rate ratios

One interesting proposal[103] is that the encounter pair is a radical pair $NO_2^{\bullet}$ $ArH^{\bullet+}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical pair subsequently collapses to the arenium ion. There is evidence[104] both for and against this proposal.[105]

[96] Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974****, 96*, 2892.
[97] See Moodie, R.B.; Schofield, K.; Thomas, P.N. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 318.
[98] See Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978****, 16*, 1.
[99] Manglik, A.K.; Moodie, R.B.; Schofield, K.; Dedeoglu, E.; Dutly, A.; Rys, P. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1358.
[100] Barnett, J.W.; Moodie, R.B.; Schofield, K.; Taylor, P.G.; Weston, J.B. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 747.
[101] See Sheats, G.F.; Strachan, A.N. *Can. J. Chem.* ***1978****, 56*, 1280. Also see Attinà, M.; Cacace, F.; de Petris, G. *Angew. Chem. Int. Ed.* ***1987****, 26,* 1177.
[102] Olah, G.A. *Acc. Chem. Res.* ***1971****, 4,* 240.
[103] Perrin, C.L. *J. Am. Chem. Soc.* ***1977****, 99,* 5516.
[104] See Sankararaman, S.; Haney, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1987****, 109,* 5235; Keumi, T.; Hamanaka, K.; Hasegawa, K.; Minamide, N.; Inoue, Y.; Kitajima, H. *Chem. Lett*. ***1988***, 1285; Johnston, J.F.; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1989***, 244. For evidence against it, see Eberson, L.; Radner, F. *Acc. Chem. Res.* ***1987****, 20,* 53; Baciocchi, E.; Mandolini, L. *Tetrahedron* ***1987****, 43*, 4035.
[105] See Morkovnik, A.S. *Russ. Chem. Rev.* ***1988****, 57,* 144.

11.E. THE EFFECT OF THE LEAVING GROUP



30

In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+ as indicated above, and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested[106]: (1) for leaving groups that depart without assistance (S_N1 process with respect to the leaving group), $NO_2{}^{+}$[107] $< i\text{Pr}^+ \sim SO_3 < t\text{-Bu}^+ \sim \text{ArN}_2{}^+ < \text{ArCHOH}^+ < NO^+ < CO_2$; (2) for leaving groups that depart with assistance from an outside nucleophile (S_N2 process), $Me^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Me_3Si^+$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **30** (see **1**, where Y = H) once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which attack of the original electrophile leads to attachment directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (i_f^X).[57] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo, *p*-bromo-, and *p*-chloroanisole, respectively.[108] This means, for example, that attack at the electrophile in this case leads to attachment at the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than attachment at the 4 position resulting from attack of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso attack at the methyl position was 6.8 times slower than attack of phenol leading to attachment at the para position.[109] Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.[110]

11.F. REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, and then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

[106] Perrin, C.L. *J. Org. Chem.* ***1971****, 36*, 420.
[107] See Bullen, J.V.; Ridd, J.H.; Sabek, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1681, and other papers in this series.
[108] Perrin, C.L.; Skinner, G.A. *J. Am.Chem. Soc.* ***1971***, *93*, 3389. See also, Fischer, P.B.; Zollinger, H. *Helv. Chim. Acta* ***1972****, 55*, 2139.
[109] Tee, O.; Iyengar, N.R.; Bennett, J.M. *J. Org. Chem.* ***1986****, 51*, 2585.
[110] See Clemens, A.H.; Hartshorn, M.P.; Richards, K.E.; Wright, G.J. *Aust. J. Chem.* ***1977****, 30,* 103, 113.

11.F.i. Hydrogen as the Leaving Group in Simple Substitution Reactions

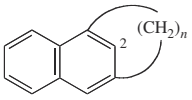
A. Hydrogen as the Electrophile

11-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation

$$ArH + D^+ \rightleftharpoons ArD + H^+$$

Aromatic compounds can exchange hydrogen atoms when treated with acids. The reaction is used chiefly to study mechanistic questions[111] (including substituent effects), but can also be useful to deuterate (add ^2H) or tritiate (add ^3H) aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D_2O gives slow exchange on heating, with only ortho and para hydrogen atoms being exchanged.[112] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general acid catalyzed, which means that a proton is transferred in the slow step[113] (Sec. 8.D). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[5] Simple aromatic compounds can be extensively deuterated in a convenient fashion by treatment with D_2O and BF_3.[114] It has been shown that tritium exchange takes place readily at the 2 position of **31**, despite the fact that this position is hindered by the bridge. The rates were not very different from the comparison compound 1,3-dimethylnaphthalene.[115]



n = 7, 8, 10

31

Hydrogen exchange can also be effected with strong bases[116] (e.g., NH_2^-). In these cases, the slow step is the proton transfer:[117]

$$ArH + B \longrightarrow Ar^- + BH^+$$

so the S_E1 mechanism and not the usual arenium ion mechanism is operating.[118] Aromatic rings can also be deuterated by treatment with D_2O and a Rh(III) chloride[119] or Pt[120] catalyst

[111] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 194–277.
[112] Small, P.A.; Wolfenden, J.H. *J. Chem. Soc.* ***1936***, 1811.
[113] See Kresge, A.J.; Chiang, Y.; Sato, Y. *J. Am. Chem. Soc.* ***1967***, *89,* 4418; Gruen, L.C.; Long, F.A. *J. Am. Chem. Soc.* ***1967***, *89,* 1287; Butler, A.B.; Hendry, J.B. *J. Chem. Soc. B* ***1970***, 852.
[114] Larsen, J.W.; Chang, L.W. *J. Org. Chem.* ***1978***, *43,* 3602.
[115] Laws, A.P.; Neary, A.P.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1033.
[116] See Elvidge, J.A.; Jones, J.R.; O'Brien, C.; Evans, E.A.; Sheppard, H.C. *Adv. Heterocycl. Chem.* ***1974***, *16,* 1.
[117] For a discussion of the aromatic character of this transition state, see Bernasconi, C.F. *Pure Appl. Chem.* ***2009***, *81,* 649.
[118] Shatenshtein, A.I. *Tetrahedron* ***1962***, *18,* 95.
[119] Lockley, W.J.S. *Tetrahedron Lett.* ***1982***, *23*, 3819; *J. Chem. Res. (S)* ***1985***, 178.
[120] See Blake, M.R.; Garnett, J.L.; Gregor, I.K.; Hannan, W.; Hoa, K.; Long, M.A. *J. Chem. Soc., Chem. Commun.* ***1975***, 930. See also, Parshall, G.W. *Acc. Chem. Res.* ***1975***, *8,* 113.

or with C_6D_6 and an alkylaluminum dichloride catalyst,[121] though rearrangements may take place during the latter procedure. Tritium (^3H, abbreviated T) can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.[121] Tritiation at specific sites (e.g., >90% para in toluene) has been achieved with T_2 gas and a microporous aluminophosphate catalyst.[122]

B. Nitrogen Electrophiles

11-2 Nitration or Nitro-de-hydrogenation

$$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2$$

Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.[123] For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids,[124] but for active substrates, the reaction can be carried out with nitric acid alone,[125] or in water, acetic acid, acetic anhydride, or chloroform.[126] Milder conditions are necessary for active compounds (e.g., amines, phenols, and pyrroles), since reaction with mixed nitric and sulfuric acids would oxidize these substrates. With active substrates, (e.g., anilines[127] and phenols,[128] nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.[129] Trimethoxybenzenes were nitrated easily with ceric ammonium nitrate on silica gel,[130] and mesitylene was nitrated in an ionic liquid using nitric acid–acetic anhydride.[131] Phenol can also be nitrated in an ionic liquid.[132] An alternative route for the nitration of activated aromatic compounds (e.g., anisole), used a nitrate ester ($RONO_2$) with triflic acid in an ionic liquid for ortho-selective nitration.[133]

[121] Long, M.A.; Garnett, J.L.; West, J.C. *Tetrahedron Lett.* ***1978***, 4171.
[122] Garnett, J.L.; Kennedy, E.M.; Long, M.A.; Than, C.; Watson, A.J. *J. Chem. Soc., Chem. Commun.* ***1988***, 763.
[123] See Esteves, P.M.; de M. Carneiro, J.W.; Cardoso, S.P.; Barbosa, A.G.H.; Laali, K.K.; Rasul, G.; Prakash, G.K.S.; Olah, G.A. J. *Am. Chem. Soc.* ***2003****, 125,* 4836; Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: Methods and Mechanisms*, VCH, NY, ***1989***; Schofield, K. *Aromatic Nitration*, Cambridge University Press, Cambridge, ***1980***; Hoggett, J.H.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitraton and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***; Weaver, W.M. in Feuer, H. *Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 1–48; de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 48–93. For a review of side reactions, see Suzuki, H. *Synthesis* ***1977***, 217. Also see, Bosch, E.; Kochi, J.K. *J. Org. Chem.* ***1994****, 59*, 3314; Olah, G.A.; Wang, Q.; Li, X.; Bucsi, I. *Synthesis* ***1992***, 1085; Olah, G.A.; Reddy, V.P.; Prakash, G.K.S. *Synthesis* ***1992***, 1087.
[124] Ramana, M.M.V.; Malik, S.S.; Parihar, J.A. *Tetrahedron Lett.* ***2004****, 45*, 8681.
[125] See Parac-Vogt, T.N.; Binnemans, K. *Tetrahedron Lett.* ***2004****, 45*, 3137.
[126] See Tasneem, Ali, M.M.; Rajanna, K.C.; Saiparakash, P.K. *Synth. Commun.* ***2001****, 31,* 1123.
[127] See Yang, X.; Xi, C. *Synth. Commun.* ***2007****, 37*, 3381.
[128] Calcium nitrate can be used for the microwave nitration of phenolic compounds. See Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Rao, S.; Speck, J.; Pekelny, U.; Pombo-Villars, E. *Tetrahedron Lett.* ***2006****, 47,* 1885. Also see Anuradha, V.; Srinivas, P.V.; Aparna, P.; Rao, J.M. *Tetrahedron Lett.* ***2006****, 47,* 4933; Shi, M.; Cui, S.-C.; Yin, W.-P. *Eur. J. Org. Chem.* ***2005***, 2379.
[129] See Ridd, J.H. *Chem. Soc. Rev.* ***1991****, 20,* 149.
[130] Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999****, 29*, 1195.
[131] Lancaster, N.L.; Llopis-Mestre, V. *Chem. Commun.* ***2003***, 2812.
[132] Rajogopal, R.; Srinivasan, K.V. *Synth. Commun.* ***2004****, 34*, 961.
[133] Laali, K.K.; Gettwert, V.J. *J. Org. Chem.* ***2001****, 66*, 35.

For nitration reactions of "normal" aromatic compounds, representative nitrating agents are $NaNO_2$ and trifluoroacetic acid,[134] N_2O_4/O_2 and a catalytic amount of zeolite Hβ,[135] $Yb(OTf)_3$,[136] $Bi(NO_3)_3{\cdot}5H_2O$,[137] ceric ammonium nitrate,[138] urea nitrate and nitrourea,[139] and nitronium salts.[140] A mixture of NO_2 and ozone has also been used.[141] Nitric acid, in the presence of P_2O_5 supported on SiO_2, is useful for the nitration of aromatic compounds under solvent-free conditions.[142] Nitration of styrene poses a problem since addition occurs at the C=C unit to give a 1-nitroethyl aryl.[143] Deactivated aromatic rings, as in acetophenone, were nitrated with N_2O_5 and $Fe(acac)_2$ (acac=acetylacetone).[144] Heterocycles (e.g., pyridine) are nitrated with N_2O_5 and SO_2.[145]

When anilines are nitrated under strong acid conditions, meta orientation is generally observed, because the ammonium salt is the species undergoing nitration, which is the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho–para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also, Sec. 11.B.i). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (Reaction **16-72**) or acetic anhydride (Reaction **16-73**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an *N*-nitro compound (Ar—NH—NO_2), which rapidly undergoes rearrangement (see Reaction **11-28**) to give the product.[146]

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $NO_2^+ BF_4^-$ in FSO_3H at 150 °C.[147]

[134] Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 1076; Zolfigol, M.A.; Ghaemi, E.; Madrakian, E. *Synth. Commun.* ***2000****, 30* , 1689; Zolfigol, M.A.; Bagherzadeh, M.; Madrakian, E.; Gaemi, E.; Taqian-Nasab, A. *J .Chem. Res. (S)* ***2001***, 140.

[135] Smith, K.; Almeer, S.; Black, S.J. *Chem. Commun.* ***2000***, 1571. See also, Smith, K.; Musson, A.; DeBoos, G. A. *J. Org. Chem.* ***1998****, 63*, 8448.

[136] Barrett, A.G.M.; Braddock, D.C.; Ducray, R.; McKinnell, R.M.; Waller, F.J. *Synlett* ***2000***, 57.

[137] Sun, H.-B.; Hua, R.; Yin, Y. *J. Org. Chem.* ***2005****, 70,* 9071.

[138] Yang, X.; Xi, C.; Jiang, Y. *Tetrahedron Lett.* ***2005****, 46,* 8781.

[139] Almog, J.; Klein, A.; Sokol, A.; Sasson, Y.; Sonenfeld, D.; Tamiri, T. *Tetrahedron Lett.* ***2006****, 47,* 8651.

[140] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1962****, 84,* 3684. Also see Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* ***1999****, 29*, 3295; Guk,Yu. V.; Ilyushin, M.A.; Golod, E.L.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1983****, 52,* 284.

[141] Nose, M.; Suzuki, H.; Suzuki, H. *J. Org. Chem.* ***2001****, 66*, 4356; Peng, X.; Suzuki, H. *Org. Lett.* ***2001****, 3*, 3431.

[142] Hajipour, A.R.; Ruoho, A.E. *Tetrahedron Lett.* ***2005****, 46*, 8307.

[143] Lewis, R.J.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 563.

[144] Bak, R.R.; Smallridge, A.J. *Tetrahedron Lett.* ***2001****, 42*, 6767.

[145] Arnestad, B.; Bakke, J.M.; Hegbom, I.; Ranes, E. *Acta Chem. Scand. B* ***1996****, 50*, 556.

[146] Ridd, J.H.; Scriven, E.F.V. *J. Chem. Soc., Chem. Commun.* ***1972***, 641. See also, Helsby, P.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1191.

[147] Olah, G.A.; Lin, H.C. *Synthesis* ***1974***, 444.

With most of the reagents mentioned, the attacking species is the nitronium ion (NO_2^+). Among the ways in which this ion is formed are

1. In concentrated sulfuric acid, by an acid–base reaction in which nitric acid is the base:

$$HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-$$

   This ionization is essentially complete.
2. In concentrated nitric acid alone,[148] by a similar acid–base reaction in which one molecule of nitric acid is the acid and another the base:

$$2\,HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

   This equilibrium lies to the left ($\sim 4\%$ ionization), but enough NO_2^+ is formed for nitration to occur.
3. The equilibrium just mentioned occurs to a small extent even in organic solvents.
4. With N_2O_5 in CCl_4, there is spontaneous dissociation:

$$N_2O_5 \rightleftharpoons NO_2^+ + NO_3^-$$

   but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.
5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form NO_2^+.

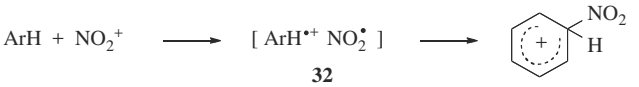
There is a great deal of evidence that NO_2^+ is present in most nitration reactions and that it is the attacking entity,[149] for example,

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at $1400\,cm^{-1}$ attributable to NO_2^+ and one at $1050\,cm^{-1}$ due to HSO_4^-.[150]
2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.[151] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.
3. The fact that nitronium salts in which nitronium ion is known to be present (by X-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.
4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+, not to that of other species.[152] When the reagent produces this ion in small

[148] See Belson, D.J.; Strachan, A.N. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 15.
[149] Hughes, E.D.; Ingold, C.K.in a series of several papers with several different coworkers, see *J. Chem. Soc.* ***1950***, 2400.
[150] Ingold, C.K.; Millen, D.J.; Poole, H.G. *J. Chem. Soc.* ***1950***, 2576.
[151] Gillespie, R.J.; Graham, J.; Hughes, E.D.; Ingold, C.K.; Peeling, E.R.A. *J. Chem. Soc.* ***1950***, 2504.
[152] See Ross, D.S.; Kuhlmann, K.F.; Malhotra, R. *J. Am. Chem. Soc.* ***1983****, 105,* 4299.

amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids, the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents (e.g., nitromethane, acetic acid, and CCl_4), the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see Sec. 11.D), such as **32**.[153]

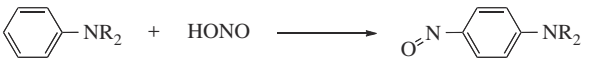


32

Arylboronic acids have been shown to react with ammonium nitrate and trifluoroacetic acid to give the corresponding nitrobenzene.[154]

OS **I**, 372, 396, 408 (see also, OS **53**, 129); **II**, 254, 434, 438, 447, 449, 459, 466; **III**, 337, 644, 653, 658, 661, 837; **IV**, 42, 364, 654, 711, 722, 735; **V**, 346, 480, 829, 1029, 1067.

11-3 Nitrosation or Nitroso-de-hydrogenation



Ring nitrosation[155] with nitrous acid is normally carried out only with active substrates (e.g., amines and phenols). However, primary aromatic amines give diazonium ions (Reaction **13-19**) when treated with nitrous acid,[156] and secondary amines tend to give *N*-nitroso rather than *C*-nitroso compounds (Reaction **12-50**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless, secondary aromatic amines can be *C*-nitrosated in two ways. The *N*-nitroso compound first obtained can be isomerized to a *C*-nitroso compound (Reaction **11-29**), or it can be treated with another equivalent of nitrous acid to give an *N,C*-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $CF_3COOH—CH_2Cl_2$.[157]

Much less work has been done on the mechanism of this reaction than on Reaction **11-2**.[158] In some cases, the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, N_2O_3, and so on, in each of which there is a carrier of NO^+. Both NOCl and NOBr are formed during the normal process of making nitrous acid (the treatment of sodium nitrite with HCl or HBr). Nitrosation requires active substrates because NO^+ is much

[153] See Ridd, J.H. *Chem. Soc. Rev.* **1991**, 20, 149; Kochi, J.K. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 53.
[154] Prakash, G.K.S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N.A.; Olah, G.A. *Org. Lett.* ***2004****, 6*, 2205.
[155] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76. Also see, Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.
[156] See Hoefnagel, M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1989****, 108*, 97.
[157] Radner, F.; Wall, A.; Loncar, M. *Acta Chem. Scand.* ***1990****, 44,* 152.
[158] See Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983****, 19,* 381. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.

less reactive than NO_2^+. Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+.[159] A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (Sec. 11.A.i) and isotope effects are found.[160] With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the *C*-nitroso product.[161] Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (Sec. 2.F).

OS **I**, 214, 411, 511; **II**, 223; **IV**, 247.

11-4 Diazonium Coupling

Arylazo-de-hydrogenation

$$ArH + Ar'N_2^+ \longrightarrow Ar{-}N{\equiv}N{-}Ar'$$

Aromatic diazonium ions normally couple only with active substrates (e.g., amines and phenols).[162] Many of the products of this reaction are used as dyes (*azo dyes*).[163] Presumably because of the size of the species attacked by the aromatic ring, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide (Ar—N=N—OH). Primary and secondary amines face competition from attack at the nitrogen.[164] However, the resulting *N*-azo compounds (aryl triazenes) can be isomerized to *C*-azo compounds (Reaction **11-30**). In at least some cases, even when the *C*-azo compound is isolated, it is the result of initial *N*-azo compound formation followed by isomerization. It is therefore possible to synthesize the *C*-azo compound directly in one laboratory step.[165] Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+. Some coupling reactions that are otherwise very slow

[159] Challis, B.C.; Higgins, R.J.; Lawson, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1831; Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2365.
[160] Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1597.
[161] Gosney, A.P.; Page, M.I. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1783.
[162] See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983****, 112*, 1; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, ***1978***, pp. 545–551.
[163] See Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***, pp. 85–148; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***, pp. 95–162.
[164] See Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1981****, 64,* 1717, 1728.
[165] Kelly, R.P.; Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1982****, 65*, 122.

(in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed in Section 11.A.i. Phase-transfer catalysis has also been used.[166]

Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N_2 would lead to very unstable carbocations.[167] Azobenzenes have been prepared by Pd catalyzed coupling of aryl hydrazides with aryl halides, followed by direct oxidation.[168]

The mechanism of (*Z*/*E*) isomerization in Ar—N=NAr systems has been studied.[169]

OS **I**, 49, 374; **II**, 35, 39, 145.

11-5 Direct Introduction of the Diazonium Group

Diazoniation or Diazonio-de-hydrogenation

$$\mathrm{ArH} \xrightarrow[\mathrm{HX}]{2\ \mathrm{HONO}} \mathrm{ArN_2{}^+X^-}$$

Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.[170] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in Reaction **11-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[171] The reagent (azidochloromethylene)dimethylammonium chloride [$Me_2N{=}C(Cl)N_3\ Cl^-$] can also introduce the diazonium group directly into a phenol.[172] A synthesis of solid aryldiazonium chlorides is now available.[173]

11-6 Amination or Amino-de-hydrogenation[174]

$$\mathrm{ArH} + \mathrm{HN_3} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArNH_2}$$

Aromatic compounds can be converted to primary aromatic amines in 10–65% yields, by treatment with hydrazoic acid (HN_3) in the presence of $AlCl_3$ or H_2SO_4.[175] Higher yields (>90%) have been reported with trimethylsilyl azide (Me_3SiN_3) and triflic acid (F_3CSO_2OH).[176] Treatment of an aromatic compound with tetramethylhydrazonium iodide and then ammonium also gives the aryl amine.[177] Tertiary amines have been prepared in ~50–90% yields by treatment of aromatic hydrocarbons with *N*-chlorodialkylamines; by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or

[166] Hashida, Y.; Kubota, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* ***1988****, 61*, 905.
[167] See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983****, 112*, 1, see pp. 3–6.
[168] Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* ***2003****, 5,* 979.
[169] Asano, T.; Furuta, H.; Hofmann, H.-J.; Cimiraglia, R.; Tsuno, Y.; Fujio, M. *J. Org. Chem.* ***1993****, 58*, 4418.
[170] Tedder, J.M. *J. Chem. Soc.* ***1957***, 4003.
[171] Kamalova, F.R.; Nazarova, N.E.; Solodova, K.V.; Yaskova, M.S. *J. Org. Chem. USSR* ***1988****, 24,* 1004.
[172] Kokel, B.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1980****, 19,* 716.
[173] Mohamed, S.K.; Gomaa, M.A.-M.; El-Din, A.M.N. *J. Chem. Res. (S)* ***1997***, 166.
[174] See Kovacic, P. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1493–1506.
[175] Kovacic, P.; Russell, R.L.; Bennett, R.P. *J. Am. Chem. Soc.* ***1964****, 86*, 1588.
[176] Olah, G.A.; Ernst, T.D. *J. Org. Chem.* ***1989****, 54*, 1203.
[177] Rozhkov, V.V.; Shevelev, S.A.; Chervin, I.T.; Mitchel, A.R.; Schmidt, R.D. *J. Org. Chem.* ***2003****, 68*, 2498.

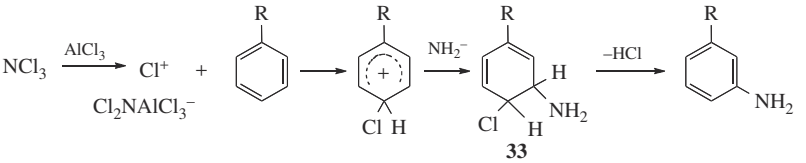
by irradiation.[178] Treatment of an aryl halide with an amine and a Pd catalyst leads to the aniline derivative.[179]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate-to-high yields by amination with an *N*-chlorodialkylamine (or an *N*-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^{+}, Cr^{2+}) in the presence of sulfuric acid.[180] The attacking species in this case is the aminium radical ion ($R_2NH^{\bullet}$) formed by[181]

$$R_2\overset{+}{N}HCl + M^{+} \longrightarrow R_2\overset{+}{N}H^{\bullet} + M^{2+} + Cl^{-}$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused-ring systems react well.[182]

Unusual orientation has been reported for amination with haloamines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominately meta amination.[183] It has been suggested that initial attack in this case is by Cl^{+} and that a nitrogen nucleophile (whose structure is not known but is represented here as NH_2^{-} for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon–carbon double bond followed by elimination of HCl from **33**.[184]



33

According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the σ-*substitution mechanism*.

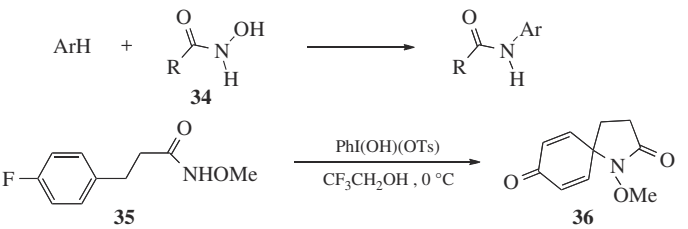
Diphenyliodonium salts react with amines in the presence of a Cu catalyst. Diphenyliodonium tetrafluoroborate, (Ph_2I^{+} BF_4^{-}), reacts with indole in DMF at 150 °C with a Cu $(OAc)_2$ catalyst (e.g., to give *N*-phenylindole).[185]

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60 °C: $ArH + Ar'N_3 \rightarrow ArNHAr'$.[186] Diarylamines are also obtained by the reaction of

[178] Bock, H.; Kompa, K. *Angew. Chem. Int. Ed.* ***1965****, 4,* 783; *Chem. Ber.* ***1966****, 99,* 1347, 1357, 1361.
[179] Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed. Engl.* ***1995****, 34*, 1348.
[180] See Minisci, F. *Top. Curr. Chem.* ***1976****, 62,* 1, see pp. 6–16, *Synthesis* ***1973***, 1, see pp. 2–12, Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972****, 4*, 203, pp. see 213–238.
[181] See Chow, Y.L. *React. Intermed. (Plenum)* ***1980****, 1,* 151.
[182] See Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* ***1984****, 49*, 4479.
[183] See Strand, J.W.; Kovacic, P. *J. Am. Chem. Soc.* ***1973****, 95,* 2977 and references cited therein.
[184] Kovacic, P.; Levisky, J.A. *J. Am. Chem. Soc.* ***1966****, 88,* 1000.
[185] Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002****, 32*, 903.
[186] Nakamura, K.; Ohno, A.; Oka, S. *Synthesis* ***1974***, 882. See also, Takeuchi, H.; Takano, K. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 611.

N-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCO_2H: $ArH + Ar'NHOH \rightarrow ArNHAr'$.[187]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid (**34**) in polyphosphoric acid, but the scope is essentially limited to phenolic ethers.[188] Naphthol reacted with a substituted hydrazine to give the 1-amino derivative.[189] The formation of hydroindole derivatives was accomplished by reaction of a *N*-carbamoyl phenylethylamine derivative with phenyliodine (**III**) diacetate, followed by Bu_4NF.[190] Direct amidation via ipso substitution by nitrogen was accomplished when a *N*-methoxy arylethylamide (**35**) was treated with [hydroxyl(tosyloxy)iodo]benzene (HTIB) in 2,2,2-trifluoroethanol, giving a *N*-methoxy spirocylcic amide (**36**).[191]



Aromatic compounds add to DEAD, in the presence of $InCl_3—SiO_2$ and microwave irradiation, to give the *N*-aryldiamino compound [$ArN(CO_2Et)—NHCO_2Et$].[192] An interesting variation in the alkylation reaction used 5 equiv of aluminum chloride in a reaction of *N*-methyl-*N*-phenylhydrazine and benzene to give *N*-methyl-4-phenylaniline.[193]

Also see, Reactions **13-5** and **13-16**.

C. Sulfur Electrophiles

11-7 Sulfonation or Sulfo-de-hydrogenation

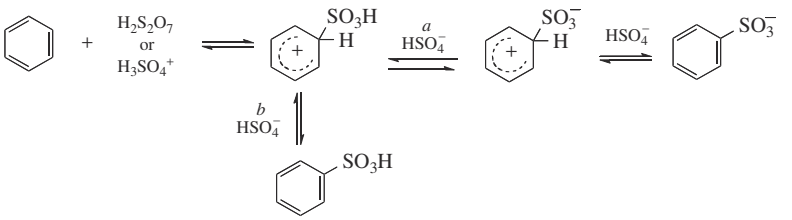
$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused-ring systems), aryl halides, ethers, carboxylic acids, amines,[194] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[195] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[196] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming H_2SO_4,

[187] Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* ***1981****, 103,* 645.
[188] March, J.; Engenito, Jr., J.S. *J. Org. Chem.* ***1981****, 46,* 4304. Also see, Cablewski, T.; Gurr, P.A.; Rander, K.D.; Strauss, C.R. *J. Org. Chem.* ***1994****, 59*, 5814.
[189] Tang, Q.; Zhang, C.; Luo, M. *J. Am. Chem. Soc.* ***2008****, 130*, 5840.
[190] Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* ***2002****, 67*, 3425.
[191] Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* ***2003****, 68*, 5429.
[192] Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M.; Madan, C. *Synlett* ***2001***, 1781.
[193] Ohwada, A.; Nara, S.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc, Perkin Trans. 1* ***2001***, 3064.
[194] See Khelevin, R.N. *J. Org. Chem. USSR* ***1987****, 23,* 1709; ***1988****, 24,* 535 and references cited therein.
[195] See Nelson, K.L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1355–1392; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 62–83, 87–124.
[196] See de Wit, P.; Woldhuis, A.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1988****, 107,* 668.

SO_3, $ClSO_2OH$, $ClSO_2NMe_2/In(OTf)_3$,[197] or other reagents.[198] A $FeCl_3$ based ionic liquid has been used for the sulfonation of aromatic compounds.[199] As with nitration (Reaction **11-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this reaction is reversible (see Reaction **11-38**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[200] Sulfur trioxide reacts much more rapidly than sulfuric acid with benzene (it is nearly instantaneous). Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see Reaction **11-36**).

A great deal of work has been done on the mechanism, chiefly by Cerfontain and coworkers.[201] Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aq H_2SO_4 solutions, the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below ~80–85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[202] (the changeover point varies with the substrate[203]). Evidence for a change in electrophile is that in both the dilute and the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as[202]:



The other product of the first step is HSO_4^- or H_2O from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to ~96% H_2SO_4, when a subsequent proton transfer becomes partially rate determining.[204] The $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is

[197] Frost, C.G.; Hartley, J.P.; Griffin, D. *Synlett* ***2002***, 1928.
[198] See Hajipour, A.R.; Mirjalili, B.B.F.; Zarei, A.; Khazdooz, L.; Ruoho, A.E. *Tetrahedron Lett.* ***2004****, 45*, 6607.
[199] Bahrami, K.; Khodei, M.M.; Shahbazi, F. *Tetrahedron Lett.* ***2008****, 49,* 3931.
[200] Spryskov, A.A. *J. Gen. Chem. USSR* ***1960****, 30,* 2433.
[201] See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***. For reviews, see Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1985***, 104, 153; Cerfontain, H.; Kort, C.W.F. *Int. J. Sulfur Chem. C 1971*, 6, 123; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 56–77.
[202] Cerfontain, H.; Lambrechts, H.J.A.; Schaasberg-Nienhuis, Z.R.H.; Coombes, R.G.; Hadjigeorgiou, P.; Tucker, G.P. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 659 and references cited therein.
[203] See Kaandorp, A.W.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1969****, 88,* 725.
[204] Kort, C.W.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1967****, 86*, 865.

thought to be $H_3S_2O_7^+$ (protonated $H_2S_2O_7$) up to ~104% H_2SO_4 and $H_2S_4O_{13}$ (H_2SO_4 + 3 SO_3) beyond this concentration.[205] Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.[206] Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate determining, at least in some solvents.

OS **II**, 42, 97, 482, 539; **III**, 288, 824; **IV**, 364; **VI**, 976.

11-8 Halosulfonation or Halosulfo-de-hydrogenation

$$ArH + ClSO_2OH \longrightarrow ArSO_2Cl$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[207] Since sulfonic acids can also be prepared by the same reagent (Reaction **11-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.[208] The reaction has also been effected with bromo- and fluorosulfuric acids. Sulfinyl chlorides (ArSOCl) have been prepared by the reaction of thionyl chloride and an aromatic compound on Montmorillonite K-10 clay.[209]

OS **I**, 8, 85.

11-9 Sulfonylation

Alkylsulfonylation or **Alkylsulfo-de-hydrogenation**

$$ArH + SOCl_2 \xrightarrow{TfOH} ArSOAr \qquad ArH + Ar'SO_2Cl \xrightarrow{AlCl_3} ArSO_2Ar'$$

Diaryl sulfoxides can be prepared by the reaction of aromatic compounds with thionyl chloride and triflic acid.[210] Diaryl sulfones have also been prepared using thionyl chloride with the ionic liquid [bmim]Cl·$AlCl_3$.[211] Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a *Friedel–Crafts catalyst*.[212] This reaction is analogous to *Friedel–Crafts acylation* with carboxylic acid halides (Reaction **11-17**). In a better procedure, the aromatic compound is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.[213] Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride ($ArSO_2OSO_2CF_3$) (generated *in situ* from $ArSO_2Br$ and CF_3SO_3Ag) without a catalyst.[214] Indium tris(triflate)[215] and indium trichloride[216] leads to sulfonation of aromatic compounds with sulfonyl chlorides. Indium bromide was used

[205] Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 633.
[206] Lammertsma, K.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 28 and references cited therein.
[207] For a review, see Gilbert, E.E. *Sulfonaton and Related Reactions*, Wiley, NY, ***1965***, pp. 84–87.
[208] See van Albada, M.P.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1548, 1557.
[209] Karade, N.N.; Kate, S.S.; Adude, R.N. *Synlett* ***2001***, 1573.
[210] Olah, G.A.; Marinez, E.R.; Prakash, G.K.S. *Synlett* ***1999***, 1397.
[211] See Mohile, S.S.; Potdar, M.K.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003****, 44*, 1255.
[212] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 77–83; Jensen, F.R.; Goldman, G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1319–1347.
[213] Sipe, Jr., H.J.; Clary, D.W.; White, S.B. *Synthesis* ***1984***, 283. See also, Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* ***1984***, 323.
[214] Effenberger, F.; Huthmacher, K. *Chem. Ber.* ***1976****, 109,* 2315. For similar methods, see Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* ***1988***, 395.
[215] Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Synlett* ***2001***, 830.
[216] Garzya, V.; Forbes, I.T.; Lauru, S.; Maragni, P. *Tetahedron Lett.* ***2004****, 45*, 1499.

with indoles.[217] A ferric chloride catalyzed reaction with microwave irradiation has also been reported,[218] as has the use of zinc metal with microwave irradiation.[219] The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.[220]

Direct formation of diaryl sulfones from benzenesulfonic acid and benzene was accomplished using Nafion-H.[221] Aryl halides react with sulfinic acid salts, via a proline-promoted CuI catalyzed coupling reaction.[222] Arylboronic acids (see Reaction **10-73**) are sulfonated in ionic liquids, using a Cu catalyst.[223]

OS **X**, 147.

D. Halogen Electrophiles

11-10 Halogenation[224]

Halo-de-hydrogenation

$$\mathrm{ArH} + \mathrm{Br_2} \xrightarrow{\text{catalyst}} \mathrm{ArBr}$$

1. *Chlorine[225] and Bromine.[226]* Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst.[227] For amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature, or with aqueous HBr in DMSO.[228] Typically, it is not possible to stop the reaction with anilines before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.[229] For this reason, the corresponding anilides are used if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[230] The rapid room temperature reaction with amines and phenols is often used as a test for these compounds. In general, for active substrates including anilines, phenols, naphthalene, and polyalkylbenzenes[231] (e.g., mesitylene and isodurene), no catalyst is needed. The overall effectiveness of reagents in aromatic substitution is $Cl_2 >$

[217] Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Swamy, T. *Tetahedron Lett.* ***2003****, 44*, 6055.
[218] Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J.-R. *J. Org. Chem.* ***2001****, 66*, 421.
[219] Bandgar, B.P.; Kasture, S.P. *Synth. Commun.* ***2001****, 31*, 1065.
[220] Hyatt, J.A.; White, A.W. *Synthesis* ***1984***, 214.
[221] Olah, G.A.; Mathew, T.; Prakash, G.K.S. *Chem. Commun.* ***2001***, 1696.
[222] Zhu, W.; Ma, D. *J. Org. Chem.* ***2005****, 70,* 2696.
[223] Kantam, M.L.; Neelima, B.; Sreedhar, B.; Chakravarti, R. *Synlett* ***2008***, 1455.
[224] See de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; Buehler, C.A.; Pearson, D.E. *Survey of Organic Synthesis*, Wiley, NY, ***1970***, pp. 392–404; Braendlin, H.P.; McBee, E.T. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1517–1593; Eisch, J.J. *Adv. Heterocycl. Chem.* ***1966****, 7*, 1. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 619–628.
[225] For electrophilicities of chlorinating agents, see Duan, X.-H.; Mayr, H. *Org. Lett.* ***2010****, 12,* 2238.
[226] For a computational study of the electrophilie affinity for the bromination of arenas, see Galabov, B.; Koleva, G.; Schaefer, III H.F.; Schleyer, P.v.R. *J. Org. Chem.* ***2010****, 75,* 2813.
[227] For a site-directed bromination using an electrochemical method, see Raju, T.; Kulangiappar, K.; Kulandainathan, M.A.; Malini, U.U.R.; Muthukumaran, A *Tetrahedron Lett.* ***2006****, 47,* 4581.
[228] Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Chem. Commun.* ***1996***, 2679.
[229] See Berthelot, J.; Guette, C.; Desbène, P.; Basselier, J.; Chaquin, P.; Masure, D. *Can. J. Chem.* ***1989****, 67*, 2061. For another procedure, see Onaka, M.; Izumi, Y. *Chem. Lett.* ***1984***, 2007.
[230] See Brittain, J.M.; de la Mare, P.B.D. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 522–532.
[231] See Baciocchi, E.; Illuminati, G. *Prog. Phys. Org. Chem.* ***1967****, 5,* 1.

$BrCl > Br_2 > ICl > I_2$. A mixture of $ZnBr_2$/diazene has been suggested for the regioselective para-bromination of activated aromatic substrates.[232]

When chlorination or bromination is carried out at high temperatures (e.g., 300–400 °C), ortho–para directing groups direct meta and vice versa.[233] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the S_E1 mechanism, for example, in the *t*-BuOK catalyzed bromination of 1,3,5-tribromobenzene.[234]

For less activated aromatic rings, iron was commonly used at one time for halogenation, but the real catalyst was shown not to be the iron itself, but rather the ferric bromide or chloride formed in small amounts from the reaction between iron and the reagent. Indeed, ferric chloride and other Lewis acids are typically directly used as catalysts, as is iodine. Many Lewis acids can be used, including thallium(III) acetate, which promotes bromination with high regioselectivity para to an ortho–para directing group.[235] A mixture of $Mn(OAc)_3$ and acetyl chloride, with ultrasound, chlorinates anisole with high selectivity.[236]

Other reagents can be used to promote chlorination or bromination. copper(II)-catalyzed chlorination has been reported using dioxygen as an oxidant.[237] *N*-Bromosuccinimide under photochemical conditions[238] brominates aromatic compounds, as does pyridinium bromide perbromide,[239] and NBS in acetic acid with ultrasound is effective.[240] Both NCS and NBS with aq BF_3 gave the respective chloride or bromide.[241] The NBS in an ionic liquid[242] gave the brominated aromatic, and para-bromination of aniline was reported by mixing aniline with the ionic liquid, bmim Br_2.[243] Similarly, hmim Br_3[244] without another reagent is a brominating agent. Bromine on silica gel[245] or with SO_2Cl_2[246] gave good yields of the brominated aromatic compound. Majetich et al.[247] reported the use of HBr/DMSO for the remarkably selective bromination of aniline. Highly para-selective bromination was accomplished using dioxane dibromide, under solvent free conditions.[248]

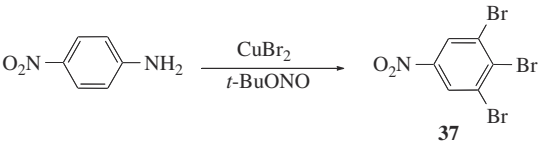
[232] Stropnik, T.; Bombek, S.; Kočevar, M.; Polanc, S. *Tetrahedron Lett.* ***2008****, 49*, 1729.
[233] See Kooyman, E.C. *Pure. Appl. Chem.* ***1963****, 7,* 193.
[234] Mach, M.H.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1974****, 96,* 936.
[235] McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1972****, 37*, 88.
[236] Prokes, I.; Toma, S.; Luche, J.-L. *J. Chem. Res. (S)* ***1996***, 164.
[237] Chen, X.; Hao, X.-S.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2006****, 128,* 6790.
[238] Chhattise, P.K.; Ramaswamy, A.V.; Waghmode, S.B. *Tetrahedron Lett.* ***2008****, 49,* 189.
[239] Reeves, W.P.; Lu, C.V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* ***1998****, 28*, 499. Also see, Bisarya, S.C.; Rao, R. *Synth. Commun.* ***1993****, 23*, 779.
[240] Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Synth. Commun.* ***1995****, 25*, 2401.
[241] Prakash, G.K.S.; Mathew, T.; Hoole, D.; Esteves, P.M.; Wang, Q.; Rasul, G.; Olah, G.A. *J. Am. Chem. Soc.* ***2004****, 126*, 15770. Also see Andersh, B.; Murphy, D.L.; Olson, R.J. *Synth. Commun.* ***2000****, 30*, 2091. For an Au catalyzed halogenation see Mo, F.; Yan, J.M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* ***2010****, 49,* 2028.
[242] See Rajagopal R.; Jarikote, D.V.; Lahoti, R.J.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***2003****, 44*, 1815. For a reaction in Bu_4NBr, see Ganguly, N.C.; De, P.; Dutta, S. *Synthesis* ***2005***, 1103.
[243] See Lei, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 2809.
[244] See Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* ***2004***, 2536.
[245] Ghiaci, M.; Asghari, J. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1151.
[246] Gnaim, J.M.; Sheldon, R.A. *Tetrahedron Lett.* ***2005****, 46,* 4465.
[247] Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* ***1997****, 62*, 4321.
[248] Chaudhuri, S.K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* ***2007****, 37,* 581.

Other reagents have been used for chlorination and bromination. If the substrate contains alkyl groups, side-chain halogenation (Reaction **14-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible. Sulfuryl chloride (SO_2Cl_2) in acetic acid chlorinates anisole derivatives,[249] and acetyl chloride with a catalytic amount of ceric ammonium nitrate also converted aromatic compounds to the corresponding chlorinated derivative.[250] A mixture of KCl and Oxone® chlorinated activated aromatic compounds.[251] Oxone and KBr gave good para-bromination of anisole,[252] as does NH_4Br/Oxone.[253] Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent[254] for substrates with strongly deactivating substituents.[255] *N*-Chlorosuccinimide in isopropyl alcohol[256] chlorinates aniline derivatives, and $KBr/NaBO_3 \cdot 4\ H_2O$ has been used for the bromination of aniline derivatives.[257] Conversion of aniline to the *N*-$SnMe_3$ derivative allowed *in situ* bromination with bromine, with high para selectivity after conversion to the free amine with aq KF.[258] Pyridinium bromochromate converted phenolic derivatives to brominated phenols.[259]

Predominant ortho chlorination[260] of phenols has been achieved with chlorinated cyclohexadienes,[261] while para chlorination of phenols, phenolic ethers, and amines can be accomplished with *N*-chloroamines[262] and with *N*-chlorodimethylsulfonium chloride ($Me_3S^+Cl\ Cl^-$).[263] The last method is also successful for bromination when *N*-bromodimethylsufonium bromide is used. Highly selective ortho chlorination of acetanilides has been reported, using a combination of P and Cu catalysts.[264] Iridium-catalyzed borylation of arenes leads to meta-halogenation.[265] Certain alkylated phenols can be brominated in the meta positions with Br_2 in the superacid solution SbF_5—HF.[266] It is likely that meta orientation is the result of conversion by the superacid of the OH group to the OH_2^+ group, which should be meta-directing because of its positive charge. Bromination and the *Sandmeyer reaction* (**14-20**) can be carried out in one laboratory step to give **37**

[249] Yu, G.; Mason, H.J.; Wu, X.; Endo, M.; Douglas, J.; Macor, J.E. *Tetrahedron Lett.* ***2001****, 42*, 3247.
[250] Roy, S.C.; Rana, K.K.; Guin, C.; Banerjee, B. *Synlett* ***2003***, 221.
[251] Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2002****, 32,* 279.
[252] Tamhankar, B.V.; Desai, U.V.; Mane, R.B.; Wadgaonkar, P.P.; Bedekar, A.V. *Synth. Commun.* ***2001****, 31,* 2021.
[253] Arun Kumar, M.; Rohitha, C.N.; Kulkarni, S.J.; Narender, N. *Synthesis* ***2010***, 1629.
[254] Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.
[255] Gottardi, W. *Monatsh. Chem.* ***1968****, 99*, 815; ***1969****, 100,* 42.
[256] Zanka, A.; Kubota, A. *Synlett* ***1999***, 1984.
[257] Roche, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***2000****, 41,* 2083.
[258] Smith, M.B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; La Chapelle, E. *Org. Lett.* ***2002****, 4*, 2321. A polymeric Sn reagent has been devloepd for this purpose, see Chrétien, J.-M.; Zammattio, F.; Le Grognec, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J.-P. *J. Org. Chem.* ***2005****, 70*, 2870.
[259] Patwari, S.B.; Baseer, M.A.; Vibhute, Y.B.; Bhusare, S.R. *Tetrahedron Lett.* ***2003****, 44,* 4893.
[260] See Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn.* ***1988****, 61*, 2226; de la Vega, F.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 653.
[261] Lemaire, M.; Guy, A.; Guette, J. *Bull. Soc. Chim. Fr.* ***1985***, 477.
[262] Lindsay Smith, J.R.; McKeer, L.C.; Taylor, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1529, 1537. See also, Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 123.
[263] Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* ***1986***, 868.
[264] Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* ***2006****, 128*, 7416.
[265] Murphy, J.M.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007****, 129*, 15434.
[266] Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem. Soc., Chem. Commun.* ***1980***, 110.

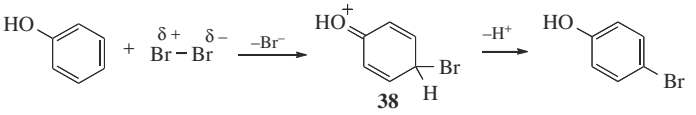
by treatment of an aromatic primary amine with $CuBr_2$ and *tert*-butyl nitrite, for example,[267]



37
94%

With deactivated aromatic derivatives, NBS and H_2SO_4 is an effective reagent, giving the meta-brominated product.[268] Bromination at C-6 of 2-aminopyridine was accomplished with NBS.[269] An alternative route reacted pyridine *N*-oxide with $POCl_3$ and triethylamine to give 2-chloropyridine.[270]

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.[271]



38

Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and the addition of acids should increase it. Intermediate **38** has been detected spectrally in the aqueous bromination of phenol.[272]

When a Lewis acid catalyst[273] is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be Cl_2 or Br_2, polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species (e.g., H_2OBr^+, the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[274] With HOCl in water the electrophile may be Cl_2O, Cl_2, or H_2OCl^+; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself.[275] It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.[275] It has been demonstrated in the reaction between *N*-methylaniline and calcium hypochlorite that the chlorine entity is

[267] Doyle, M.P.; Van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* ***1980****, 45*, 2570.
[268] Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K.K. *J. Org. Chem.* ***2007****, 72,* 5867.
[269] Cañibano, V.; Rodríguez, J.F.; Santos, M.; Sanz-Tejedor, A.; Carreño, M.C.; González, G.; García-Ruano, J.L. *Synthesis* ***2001***, 2175.
[270] Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* ***2001****, 31,* 2507.
[271] See de la Mare, P.B.D., *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; de la Mare, P.B.D.; Swedlund, B.E. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***; pp. 490–536; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 83–139. See also, Keefer, R.M.; Andrews, L.J. *J. Am. Chem. Soc.* ***1977****, 99*, 5693; Tee, O.S.; Paventi, M.; Bennett, J.M. *J. Am. Chem. Soc.* ***1989****, 111*, 2233.
[272] Tee, O.S.; Iyengar, N.R.; Paventi, M. *J. Org. Chem.* ***1983****, 48,* 759. See also, Tee, O.S.; Iyengar, N.R. *Can. J. Chem.* ***1990****, 68,* 1769.
[273] See also, Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* ***2005***, 2837.
[274] See Rao, T.S.; Mali, S.I.; Dangat, V.T. *Tetrahedron* ***1978****, 34,* 205.
[275] Swain, C.G.; Crist, D.R. *J. Am. Chem. Soc.* ***1972****, 94,* 3195.

attacked by the *nitrogen* to give *N*-chloro-*N*-methylaniline, which rearranges (as in Reaction **11-31**) to give a mixture of ring-chlorinated *N*-methylanilines in which the ortho isomer predominates.[276] In addition to hypohalous acids and metal hypohalites, organic hypohalites are reactive. An example is *tert*-butylhypobromite (*t*-BuOBr), which brominated toluene in the presence of zeolite (HNaX).[277]

Furan and thiophene are known to polymerize in the presence of strong acid, both Brønsted–Lowry and Lewis. For such highly reactive heteroaromatic systems, alternative halogenating reagents are commonly used. Furan was converted to 2-bromofuran with a bromine•dioxane complex (e.g., at $<0\,^{\circ}C$.[278] 3-Butylthiophene reacted with NBS/acetic acid to give 2-bromo-3-butylthiophene.[279] *N*-Methylpyrrole reacted with NBS and a catalytic amount of PBr_3, at $-78\,^{\circ}C \rightarrow -10\,^{\circ}C$, to give *N*-methyl-3-bromopyrrole.[280]

2. *Iodine*. Iodine is the least reactive of the halogens in aromatic substitution.[281] Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[282] Examples of such oxidizing agents used with I_2 are HNO_3, SO_3, hypervalent iodine compounds [e.g., $PhI(OTf)_2$,[283] $NaIO_4$,[284] ammonium iodide and H_2O_2,[285] ceric ammonium nitrate,[286] peroxydisulfates,[287] and a mixture of $NaIO_4$/KI/NaCl].[288] A solvent-free iodination used I_2 and $AgNO_3$.[289] The reagent ICl is a better iodinating agent than iodine itself.[290] A mixture of $ICl/In(OTf)_3$ has also been used.[291] Iodination can also be accomplished by treatment of the substrate with NCI and H_2SO_4,[292] *N*-Iodosuccinamide and trifluoroacetic acid,[293] KI/KIO_3 in aq methanol,[294] KI and H_2O_2,[295] and NaI with an iron catalyst.[296] Sodium periodate and iodine was used to iodinate β-carbolines.[297] A solvent-free iodination was accomplished using $NaICl_2$ and

[276] Paul, D.F.; Haberfield, P. *J. Org. Chem.* ***1976****, 41,* 3170.
[277] Smith, K.; El-Hiti, G.A.; Hammond, M.E.W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2745.
[278] See Baciocchi, E.; Clementi, S.; Sebastiani, G.V. *J. Chem. Soc., Chem. Commun.* ***1975***, 875.
[279] Hoffmann, K.J.; Carlsen, P.H.J. *Synth. Commun.* ***1999****, 29,* 1607.
[280] Dvornikova, E.; Kamienska-Trela, K. *Synlett* ***2002***, 1152.
[281] See Pizey, J.S. in Pizey, J.S. *Synthetic Reagents,* Vol. 3, Wiley, NY, ***1977***, pp. 227–276. For a review of aromatic iodination, see Merkushev, E.B. *Synthesis* ***1988***, 923.
[282] Butler, A.R. *J. Chem. Educ.* ***1971****, 48*, 508.
[283] Panunzi, B.; Rotiroti, L.; Tingoli, M. *Tetrahedron Lett.* ***2003****, 44*, 8753.
[284] Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***2000****, 73*, 951.
[285] Narender, N.; Reddy, K.S.R.; Krishna Mohan, K.V.V.; Kulkarni, S.J. *Tetrahedron Lett.* ***2007****, 48,* 6124.
[286] Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V.S. *Tetrahedron Lett.* ***2007****, 48,* 81.
[287] Tajik, H.; Esmaeili, A.A.; Mohammadpoor-Baltork, I.; Ershadi, A.; Tajmehri, H. *Synth. Commun.* ***2003****, 33*, 1319.
[288] Emmanuvel, L.; Shukla, R.K.; Sudalai, A.; Gurunath, S.; Sivaram, S. *Tetrahedron Lett.* ***2006****, 47,* 4793.
[289] Yusubov, M.S.; Tveryakova, E.N.; Krasnokutskaya, E.A.; Perederyna, I.A.; Zhdankin, V.V. *Synth. Commun.* ***2007****, 37,* 1259.
[290] See McCleland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164; Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-i. *Tetrahedron Lett.* ***2000****, 41*, 9383.
[291] Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* ***2005****, 61,* 11657.
[292] Chaikovskii, V.K.; Shorokhodov, V.I.; Filimonov, V.D. *Russ. J. Org. Chem.* ***2001***, *37,* 1503.
[293] Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* ***2002****, 43*, 5047.
[294] Adimurthy, S.; Ramachandraiah, G.; Ghosh, P.K.; Bedekar, A.V. *Tetrahedron Lett.* ***2003****, 44*, 5099.
[295] Reddy, K.S.K.; Narender, N.; Rohitha, C.N.; Kulkarni, S.J. *Synth. Commun.* ***2008****, 38,* 3894.
[296] Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* ***2003****, 44*, 8781.
[297] Bonesi, S.M.; Erra-Balsells, R. *J. Heterocyclic Chem.* ***2001****, 38*, 77.

an *N*-bromoammonium salt.[298] Another solvent-free iodination used I_2 with $Bi(NO_3)_3$ on silica gel.[299] A mixture of iodine/pyridine/dioxane leads to selective para-iodination of aniline derivatives.[300] Selective ortho cyanation allows the reaction with iodine to give the corresponding aryl iodide.[301] Iodination of activated aromatics has been reported using KI and ammonium peroxodisulfate.[302] *N*-Iodosuccinimide and *p*-toluenesulfonic acid give regioselective iodination of phenol and related compounds.[303]

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species (e.g., phenols), where there is good evidence that I_2 is the attacking entity.[304] There is evidence that AcOI may be the reactive entity when peroxyacetic acid is the oxidizing agent,[305] and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.[306] The I^+ ion has been implicated in several procedures.[307] For an indirect method for accomplishing aromatic iodination see (Reaction **12-31**).

3. *Fluorine*. Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2.[308] It has been accomplished at low temperatures (e.g., -70 to $-20\,^{\circ}C$, depending on the substrate),[309] but the reaction is not yet of preparative significance. Fluorination has also been reported with acetyl hypofluorite (CH_3CO_2F, generated from F_2 and sodium acetate),[310] and with an *N*-fluoroperfluoroalkyl sulfonamide [e.g., $(CF_3SO_2)_2NF$].[311] Pyridine has been converted to 2-fluoropyridine with $F_2/I_2/NEt_3$ in 1,1,2-trichloro-1,2,2-trifluoroethane.[312] However, none of these methods seems likely to displace the *Schiemann reaction* (**13-23**; heating diazonium tetrafluoroborates) as the most common method for introducing fluorine into aromatic rings.

OS **I**, 111, 121, 123, 128, 207, 323; **II**, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III**, 132, 134, 138, 262, 267, 575, 796; **IV**, 114, 166, 256, 545, 547, 872, 947; **V**, 117, 147, 206, 346; **VI**, 181, 700; **VIII**, 167; **IX**, 121, 356. Also see, OS **II**, 128.

[298] Hajipour, A.R.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2002****, 34*, 647.
[299] Alexander, V.M.; Khandekar, A.C.; Samant, S.D. *Synlett* ***2003***, 1895.
[300] Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron Lett.* ***2005****, 46,* 5421.
[301] Usui, S.; Hashimoto, Y.; Morey, J.V.; Wheatley, A.E.H.; Uchiyama, M. *J. Am. Chem. Soc.* ***2007****, 129,* 15102.
[302] Ganguly, N.C.; Barik, S.K.; Dutta, S. *Synthesis* ***2010***, 1467.
[303] Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M.M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* ***2009****, 50*, 2664.
[304] Grovenstein, Jr., E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; McKelvey, Jr., J.M.; Sullivan, R.J. *J. Am. Chem. Soc.* ***1973****, 95,* 4261.
[305] Ogata, Y.; Urasaki, I. *J. Chem. Soc. C* ***1970***, 1689.
[306] Arotsky, J.; Butler, R.; Darby, A.C. *J. Chem. Soc. C* ***1970***, 1480.
[307] Galli, C. *J. Org. Chem.* ***1991****, 56*, 3238.
[308] See German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986****, 86*, 997. Also see Hewitt, C.D.; Silvester, M.J. *Aldrichimica Acta* ***1988****, 21*, 3.
[309] Stavber, S.; Zupan, M. *J. Org. Chem.* ***1983****, 48,* 2223. See also, Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1991****, 56*, 142.
[310] See Visser, G.W.M.; Bakker, C.N.M.; van Halteren, B.W.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.* ***1986****, 51,* 1886.
[311] Singh, S.; DesMarteau, D.D.; Zuberi, S.S.; Witz, M.; Huang, H. *J. Am. Chem. Soc.* ***1987****, 109,* 7194.
[312] Chambers, R.D.; Parsons, M.; Sandford, G.; Skinner, C.J.; Atherton, M.J.; Moilliet, J.S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 803.

E. Carbon Electrophiles

A new carbon–carbon bond is formed in the reactions in this section. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

11-11 Friedel–Crafts Alkylation

Alkylation or **Alkyl-de-hydrogenation**

$$\mathrm{ArH} + \mathrm{RCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{Ar{-}R}$$

The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.[313] Catalytic asymmetric Friedel–Crafts alkylation reactions are known.[314] The most important reagents are alkyl halides, alkenes, and alcohols, but other types of reagent have also been employed.[313] Tertiary halides are particularly good substrates since they form relatively stable tertiary carbocations. When alkyl halides are used, the reactivity order is F > Cl > Br > I.[315] This trend can be seen in reactions of dihalo compounds (e.g., $FCH_2CH_2CH_2Cl$), which react with benzene to give $PhCH_2CH_2CH_2Cl$[316] when the catalyst is BCl_3. By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also, Reaction **11-14**).[317] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of an aromatic compound; it is usually not possible to stop the reaction earlier.[318] Thus, benzene with CH_2Cl_2 gives not $PhCH_2Cl$, but Ph_2CH_2; benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted to give Ph_3CCl. Functionalized alkyl halides [e.g., $ClCH(SEt)CO_2Et$] undergo Friedel–Crafts alkylation.[319] Montmorillonite clay-(K10) is an effective medium for alkylation reactions.[320]

Alkenes are especially good alkylating agents, generally proceeding by formation of an intermediate carbocation that reacts with the electron-rich aromatic ring, and the final product (**39**) incorporates a H and Ar from ArH to a C=C double bond. Many variations are possible. This reaction has been accomplished in an ionic liquid, using $Sc(OTf)_3$ as the catalyst.[321] Other catalysts include $Sm(OTf)_3$.[322] Intramolecular versions lead to

[313] See Roberts, R.M.; Khalaf, A.A. *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, NY, ***1984***. For a treatise on Friedel–Crafts reactions in general, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1965***. See Olah, G.A. *Friedel–Crafts Chemistry*, Wiley, NY, ***1973***.

[314] Poulsen, T.B.; Jørgensen, K.A. *Chem. Rev.* ***2008****, 108,* 2903; Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* ***2006****, 128,* 8156; Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* ***2007****, 129,* 292; Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* ***2007****, 129,* 1484; Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre. P. *Org. Lett.* ***2007****, 9,* 1403; Adachi, S.; Tanaka, F.; Watanabe, K.; Watada, A.; Harada, T. *Synthesis* ***2010***, 2652; Faita, G.; Mella, M.; Toscanini, M.; Desimoni, G. *Tetrahedron* ***2010****, 66,* 3024.

[315] See Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955****, 77,* 5584.

[316] Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1964****, 29,* 2317.

[317] See Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 881–905. This review also covers the case of alkylation versus acylation.

[318] See Belen'kii, L.I.; Brokhovetsky, D.B.; Krayushkin, M.M. *Chem. Scr.,* ***1989****, 29,* 81.

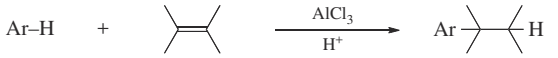
[319] See Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* ***2000****, 41*, 9109.

[320] Sieskind, O.; Albrecht, P. *Tetrahedron Lett.* ***1993****, 34*, 1197.

[321] See Song, C.E.; Shim, W.H.; Roh, E.J.; Choi, J.H. *Chem. Commun.* ***2000***, 1695.

[322] Hajra, S.; Maji, B.; Bar, S. *Org. Lett.* ***2007****, 9,* 2783.

polycyclic aromatic compounds.[323] Benzene reacted with 1,2,3,6-tetrahydropyridine in the presence of trifluoromethanesulfonic acid to give 4-phenylpiperidine.[324]



39

When 4-methoxyphenol reacted with isobutylene (electrolysis with 3 M $LiClO_4$ in nitromethane and acetic acid), initial reaction with the phenolic oxygen generated an ether moiety and the resulting carbocation was attacked by the aromatic ring to form a benzofuran.[325] Enantioselective alkylations have been reported for pyrroles and indoles, using a chiral Pybox–Cu complex.[326]

Acetylene reacts with 2 mol of aromatic compound to give 1,1-diarylethanes, and phenylacetylene reacted to give 1,1-diarylethenes with a $Sc(OTf)_3$ catalyst.[327] Variations are possible here as well. Phenol reacted with trimethylsilylethyne, in the presence of $SnCl_4$ and 50% BuLi, at 105 °C, to give the 2-vinyl phenolic derivative.[328] A Ru catalyzed intramolecular reaction with a pendant alkyne unit led to a dihydronapthalene derivative,[329] and a Rh catalyzed reaction led to indanone derivatives.[330] An acidic fluoroantimonate(V) ionic liquid has been used as a catalyst.[331]

Alcohols are more active than alkyl halides, but if a Lewis acid catalyst is used more catalyst is required, since the catalyst complexes with the OH group. However, proton acids (e.g., H_2SO_4) are often used to catalyze alkylation with alcohols. An intramolecular cyclization was reported from an allylic alcohol, using P_2O_5, to give indene derivatives.[332] Secondary alcohols are coupled to aromatic compounds using a heterobimetallic Ir—Sn complex.[333] Molecular iodine has been used to catalyze benzylation of arenes with benzylic alcohols.[334] A "contra Friedel–Crafts" *tert*-butylation has been reported.[335] Diastereoselective alkylation is possible from alcohol precursors. High facial diastereoselectivity was reported with "chiral benzylic cations", for example.[336]

[323] See Youn, S.W.; Pastine, S.J.; Sames, D. *Org. Lett.* ***2004****, 6,* 581.
[324] Klumpp, D.A.; Beauchamp, P.S.; Sanchez Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001****, 42*, 5821.
[325] Chiba, K.; Fukuda, M.; Kim, S.; Kitano, Y.; Toda, M. *J. Org. Chem.* ***1999****, 64*, 7654; Abe, H.; Koshiba, N.; Yamasaki, A.; Harayama, T. *Heterocycles* ***1999****, 51* 2301. See also, Shen, Y.; Atobe, M.; Fuchigami, T. *Org. Lett.* ***2004****, 6,* 2441.
[326] Palomo, C.; Oiarbide, M.; Kardak, B.G.; García, J.M.; Linden, A. *J. Am. Chem. Soc.* ***2005****, 127,* 4154.
[327] Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* ***2000***, 1573,
[328] Kobayashi, K.; Yamaguchi, M. *Org. Lett.* ***2001****, 3*, 241.
[329] Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* ***2000****, 65*, 4913; Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* ***2002****, 67*, 1414; Nishizawa, M.; Takao, H.; Yadav, V.K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003****, 5*, 4563; Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* ***2004****, 6*, 2361. See also, Fillion, E.; Carson, R.J.; Trépanier, V.E.; Goll, J.M.; Remorova, A.A. *J. Am. Chem. Soc.* ***2004****, 126*, 15354.
[330] Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* ***2005****, 127,* 2872; Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* ***2005****, 127,* 3248; Shintani, R.; Hayashi, T. *Org. Lett.* ***2005****, 7,* 2071.
[331] Choi, D.S.; Kim, J.H.; Shin, U.S.; Deshmukh, R.R.; Song, C.E. *Chem. Commun.* ***2007***, 3482.
[332] Basavaiah, D.; Bakthadoss, M.; Reddy, G.J. *Synthesis* ***2001***, 919; Nishibayashi, Y.; Joshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002****, 124*, 11846.
[333] Podder, S.; Choudhury, J.; Roy, S. *J. Org. Chem.* ***2007****, 72,* 3129.
[334] Sun, G.; Wang, Z. *Tetrahedron Lett.* ***2008****, 49,* 4929.
[335] Clayden, J.; Stimson, C.C.; Keenan, M. *Chem. Commun.* ***2006***, 1393.
[336] Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* ***2005****, 127,* 9348.

When carboxylic esters are the reagents, there is competition between alkylation and acylation (Reaction **11-17**). This competition can often be controlled by choice of catalyst, and alkylation is usually favored, but carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers,[337] thiols, sulfates, sulfonates, alkyl nitro compounds,[338] and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring,[339] and cyclopropyl[340] units. For all types of reagent, the reactivity order is allylic $\sim$ benzylic $>$ tertiary $>$ secondary $>$ primary. Alkyl mesylates undergo alkylation reaction with benzene rings in the presence of $Sc(OTf)_3$.[341] Allylic acetates undergo alkylation with $Mo(CO)_6$[342] and allylic chlorides react in the presence of $ZnCl_2/SiO_2$.[343]

Naphthalene and other fused ring compounds are so reactive that they react with the catalyst, and therefore tend to give poor yields in Friedel–Crafts alkylation. Heterocyclic rings also tend to be poor substrates for the reaction. Although some furans and thiophenes have been alkylated, polymerization is quite common, and a true alkylation of a pyridine or a quinoline has never been described.[344] *N*-Methylpyrrole reacted with the C=C unit of methacrolein in the presence of a chiral catalyst (a chiral Friedel–Crafts catalyst) to give the 2-alkylated pyrrole, with good enantioselectivity.[345] Alkylation at C-5 of 2-trimethylsilylfuran was accomplished using the carbocation [$(p\text{-}MeOC_6H_4)_2CH^+$ OTf] and Proton Sponge (see Sec. 8.F, category 6).[346] The reaction of isoquinoline with $ClCO_2Ph$ and AgOTf, followed by reaction with an allylic silane, led to a 2-allylic dihydroisoquinoline.[347]

Regardless of which reagent is used, a catalyst is nearly always required.[348] Lewis acid catalysts (e.g., aluminum chloride and boron trifluoride) are the most common, but many other Lewis acids have been used,[349] and also proton acids (e.g., HF and H_2SO_4).[350] Calcium has been used to catalyze Friedel–Crafts alkylation reactions, at room temperature.[351] For active halides, a trace of a less active catalyst (e.g., $ZnCl_2$) may be enough. For an unreactive halide (e.g., chloromethane), a more powerful catalyst (e.g., $AlCl_3$) is needed, and in larger amounts. In some cases, especially with alkenes, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3$

[337] See Podder, S.; Roy, S. *Tetrahedron* ***2007****, 63,* 9146.
[338] Bonvino, V.; Casini, G.; Ferappi, M.; Cingolani, G.M.; Pietroni, B.R. *Tetrahedron* ***1981****, 37*, 615.
[339] Taylor, S.K.; Dickinson, M.G.; May, S.A.; Pickering, D.A.; Sadek, P.C. *Synthesis* ***1998***, 1133. See also, Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2051.
[340] Patra, P.K.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* ***1993****, 34*, 3951.
[341] Singh, R.P.; Kamble, R.M.; Chandra, K.L.; Saravanani, P.; Singh, V.K. *Tetrahedron* ***2001***, *57*, 241.
[342] Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1997***, 137.
[343] Kodomari, M.; Nawa, S.; Miyoshi, T. *J. Chem. Soc. Chem.Commun.* ***1995***, 1895.
[344] Drahowzal, F.A. in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, p. 433.
[345] Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2001****, 123,* 4370.
[346] Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* ***2001****, 3*, 1629.
[347] Yamaguchi, R.; Nakayasu, T.; Hatano, B.; Nagura, T.; Kozima, S.; Fujita, K.-i. *Tetrahedron* ***2001****, 57*, 109.
[348] See Stang, P.J.; Anderson, A.G. *J. Am. Chem. Soc.* ***1978****, 100*, 1520.
[349] See Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2004****, 44,* 238.
[350] See Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 201–366, 853–881. A reusable catalyst derived from a heteropoly acid has been reported; see Okumura, K.; Yamashita, K.; Hirano, M.; Niwa, M. *Chem. Lett.* ***2005****, 34,* 716
[351] Niggemann, M.; Meel, M.J. *Angew. Chem. Int. Ed.* ***2010****, 49*, 3684.

$> FeCl_3 > SbCl_5$[352] $> ZrCl_4, SnCl_4 > BCl_3, BF_3, SbCl_3$[353]; but the reactivity order in each case depends on the substrate, reagent, and conditions. Other Lewis acids have been used, of course, including $SeCl_2$,[354] $InCl_3$,[355] and enantiopure cycloalkyldialkylsilyl triflimide catalysts.[356]

Friedel–Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating (the product is more reactive than the starting aromatic substrate), and di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl and isopropyl) is only ~1.5–3 times as fast as benzene for *Friedel–Crafts alkylations*,[357] so it is often possible to obtain high yields of monoalkyl product.[358] Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity, but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[359] This factor can be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

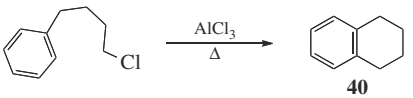
It is important to note that the OH, OR, NH_2, and so on, groups do not facilitate the reaction, since most Lewis acid catalysts coordinate with these basic groups. Although phenols give the usual *Friedel–Crafts reactions*, orienting ortho and para, the reaction is very poor for aniline derivatives. However, amines can undergo the reaction if alkenes are used as reagents and aluminum anilides as catalysts.[360] In this method, the catalyst is prepared by treating the amine to be alkylated with one-third equiv of $AlCl_3$. A similar reaction can be performed with phenols, though here the catalyst is $Al(OAr)_3$.[361] Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see Reaction **11-23**). For an indirect method for regioselective ortho methylation of phenols, see Reaction **15-65**.

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful *Friedel–Crafts alkylations* when electron-withdrawing groups are present.[362] This is not because the attacking species is not powerful enough; indeed we have seen (Sec. 11.D) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, *Friedel–Crafts alkylation* can be accomplished.[363] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (Reaction **13-17**).

[352] See Yakobson, G.G.; Furin, G.G. *Synthesis* ***1980***, 345.
[353] Russell, G.A. *J. Am. Chem. Soc.* ***1959****, 81*, 4834.
[354] Potapov, V.A.; Khuriganova, O.I.; Amosova, S.V. *Russ. J. Org. Chem.* ***2009****, 45,* 1569.
[355] Kaneko, M.; Hayashi, R.; Cook, G.R. *Tetrahedron Lett.* ***2007****, 48,* 7085.
[356] See Tang, Z.; Mathieu, B.; Tinant, B.; Dive, G.; Ghosez, L. *Tetrahedron* ***2007****, 63,* 8449.
[357] Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1962****, 84*, 1688.
[358] See Davister, M.; Laszlo, P. *Tetrahedron Lett.* ***1993****, 34*, 533 for examples of paradoxical selectivity in Friedel–Crafts alkylation.
[359] Francis, A.W. *Chem. Rev.* ***1948****, 43,* 257.
[360] See Stroh, R.; Ebersberger, J.; Haberland, H.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963****, 2*, 227.
[361] Koshchii, V.A.; Kozlikovskii, Ya.B.; Matyusha, A.A. *J. Org. Chem. USSR* ***1988****, 24,* 1358; Laan, J.A.M.; Giesen, F.L.L.; Ward, J.P. *Chem. Ind. (London)* ***1989***, 354. See Stroh, R.; Seydel, R.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963****, 2,* 337.
[362] Shen, Y.; Liu, H.; Chen, Y. *J. Org. Chem.* ***1990****, 55*, 3961.
[363] Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, p. 34.

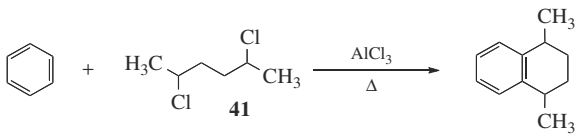
The intermediate for *Friedel–Crafts alkylation* is a carbocation, and rearrangement to a more stable cation can be quite facile. Therefore, rearrangement of the alkyl substrate occurs frequently and is an important synthetic limitation of *Friedel–Crafts alkylation*. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and usually occurs by migration of the smaller group on the adjacent carbon. Therefore, in the absence of special electronic or resonance influences on the migrating group (e.g., phenyl), H migrates before methyl, which migrates before ethyl, and so on (see discussion of rearrangement mechanisms in Chap 18). It is therefore not usually possible to put a primary alkyl group (other than methyl[364] and ethyl) onto an aromatic ring by *Friedel–Crafts alkylation*. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (Reaction **11-17**), followed by reduction (Reaction **19-61**).

An important use of the *Friedel–Crafts alkylation* reaction is to effect ring closure,[365] via an intramolecular process.[366] The most common method is to heat an aromatic compound with aluminum chloride having a halogen, hydroxy, or alkene group in the proper position, as, for example, in the preparation of tetralin (**40**).



40

Another way of effecting ring closure through *Friedel–Crafts alkylation* is to use a reagent containing two groups (e.g., **41**). These reactions are most successful for the preparation of six-membered rings,[367] though five- and seven-membered rings have also been closed in this manner. For other *Friedel–Crafts* ring-closure reactions, see Reactions **11-15**, **11-13**, and **11-17**. An interesting variation in this reaction showed that *N*-acyl aniline derivatives, upon treatment with $Et_2P(=O)H$ in water and a water soluble initiator (V-501) led to an intramolecular alkylation reaction to give an amide.[368]



41

As mentioned above, the electrophile in *Friedel–Crafts alkylation* is a carbocation, at least in most cases.[369] This is in accord with the knowledge that carbocations rearrange in the direction primary → secondary → tertiary (see Chap 18). In each case, the cation is

[364] See Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* ***2000****, 41*, 7555.
[365] See Barclay, L.R.C. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 785–977.
[366] See Stashenko, E.E.; Martínez, J.R.; Tafurt-García, G.; Palma, A.; Bofill, J.M. *Tetrahedron* ***2008****, 64,* 7407.
[367] See Khalaf, A.A.; Roberts, R.M. *J. Org. Chem.* ***1966****, 31,* 89.
[368] Khan, T.A.; Tripoli, R.; Crawford, J.T.; Martin, C.G.; Murphy, J.A. *Org. Lett.* ***2003****, 5*, 2971.
[369] See Taylor, R. *Electrophilic Aromatic Substitution*, *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 188–213.

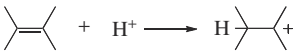
formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are

From alkyl halides $RCl + AlCl_3 \rightarrow R^+ + AlCl_4^-$

From alcohols[370] and Lewis acids $ROH + AlCl_3 \rightarrow ROAlCl_2 \rightarrow R^+ + {}^-OAlCl_2$

From alcohols and protonic acids $ROH + H^+ \rightarrow ROH_2^+ \rightarrow R^+ + H_2O$

From alkenes (a supply of protons is usually required)



There is direct evidence, from IR and NMR spectra, that the *tert*-butyl cation is quantitatively formed when *tert*-butyl chloride reacts with $AlCl_3$ in anhydrous liquid HCl.[371] In the case of alkenes, *Markovnikov's rule* (Sec. 15.B.ii) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride[372] and 1-chloroadamantane[373] alkylate activated aromatic rings (e.g., phenols and amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.[374] Note in Section 10.F that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.[375] Lewis acids (e.g., BF_3[376] or $AlEt_3$[377] can also be used for alkylation of aromatic rings with alkene units.

There is considerable evidence that many *Friedel–Crafts alkylations*, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, $AlCl_4^-$ as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,[378] although the same ratios are expected if the same species are attacked in each case. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[379] In these instances, a mechanism in which the carbocation is slowly formed and then rapidly attacked by the aromatic ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, are rapidly attacked by the ring (acting as a nucleophile), there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an S_N2 mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely S_N2 mechanism requires inversion of configuration. Most investigations of *Friedel–Crafts* stereochemistry, even where an S_N2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion.

[370] See Bijoy, P.; Subba Rao, G.S.R. *Tetrahedron Lett.* ***1994****, 35*, 3341.
[371] Kalchschmid, F.; Mayer, E. *Angew. Chem. Int. Ed.* ***1976****, 15,* 773.
[372] See Chuchani, G.; Zabicky, J. *J. Chem. Soc. C* ***1966***, 297.
[373] Takaku, M.; Taniguchi, M.; Inamoto, Y. *Synth. Commun.* ***1971****, 1,* 141.
[374] Bryce-Smith, D.; Perkins, N.A. *J. Chem. Soc.* ***1962***, 5295.
[375] Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* ***1982****, 47*, 5503.
[376] Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* ***1995****, 36*, 4749.
[377] Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* ***1994****, 35*, 4887.
[378] Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1956****, 78,* 2182.
[379] See Choi, S.U.; Brown, H.C. *J. Am. Chem. Soc.* ***1963****, 85,* 2596.

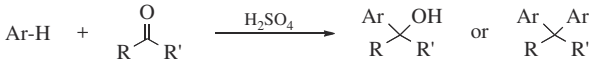
A few exceptions have been found,[380] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[381]

Rearrangement is possible even with a non-carbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ in the absence of any aromatic compound gave a mixture of the starting material and $^{14}CH_3CH_2Br$.[382] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below $-7°$.[383] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see Reaction **11-33**).[384]

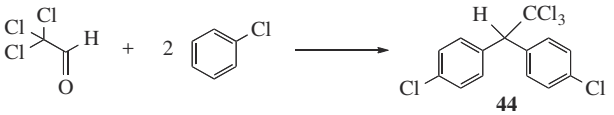
See Reaction **11-17** for *Friedel–Crafts acylation*. See Reaction **14-17** and **14-19** for free radical alkylation.

OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

11-12 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



When an aldehyde, ketone, or other carbonyl-containing substrate is treated with a protonic or Lewis acid, an oxygen-stabilized cation is generated. In the presence of an aromatic ring, *Friedel–Crafts type alkylation* occurs. The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[385] The reaction can be used to prepare alcohols,[386] though more often the alcohol initially produced reacts with another molecule of aromatic compound (Reaction **11-11**) to give diarylation. For this the reaction is quite useful, an example being the preparation of 1,1,1-trichloro-2,2′-bis (*p*-chlorophenyl)ethane DDT, **44**:



44

The diarylation reaction is especially common with phenols (the diaryl product here is called a bisphenol). The reaction is normally carried out in alkaline solution on the phenolate ion.[387] Another variation involved *Friedel–Crafts coupling* of an aldehyde to an activated aromatic compound (an aniline derivative) to give diaryl carbinols that exhibited

[380] Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Effenberger, F.; Weber, T. *Angew. Chem. Int. Ed.* ***1987****, 26,* 142.

[381] Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* ***1969****, 25*, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* ***1991****, 56*, 183.

[382] Adema, E.H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962****, 81*, 323, 336.

[383] See Roberts, R.M.; Gibson, T.L. *Isot. Org. Chem.* ***1980****, 5,* 103.

[384] See Lee, C.C.; Hamblin, M.C.; Uthe, J.F. *Can. J. Chem.* ***1964****, 42*, 1771.

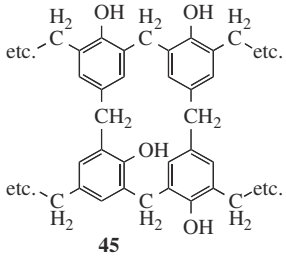
[385] See Hofmann, J.E.; Schriesheim, A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 597–640.

[386] See Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* ***1980***, 124.

[387] For a review, see Schnell, H.; Krimm, H. *Angew. Chem. Int. Ed.* ***1963****, 2,* 373.

atropisomerism (see Sec. 4.C, category 5).[388] When the reaction was done with a chiral aluminum complex, modest enantioselectivity was observed.

The hydroxymethylation of phenols with formaldehyde is called the *Lederer–Manasse reaction*. This reaction must be carefully controlled,[389] since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure (**45**) is produced. However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins, **45**), are of considerable commercial importance.



45

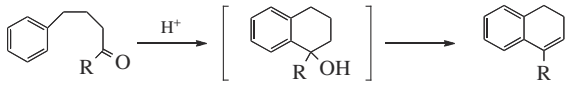
The attacking species is the carbocation ($R_2(OH)C^+$) formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution.

When an aromatic ring is treated with diethyl oxomalonate [$(EtOOC)_2C{=}O$)], the product is an arylmalonic acid derivative [$ArC(OH)(COOEt)_2$], which can be converted to an arylmalonic acid [$ArCH(COOEt)_2$].[390] This is therefore a way of applying the malonic ester synthesis (Reaction **10-67**) to an aryl group (see also, Reaction **13-14**). Of course, the opposite mechanism applies here: The aryl species is the nucleophile.

Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.[391] Conjugated aldehydes undergo *Friedel–Crafts alkylation* with aryltrifluoroborate salts, in the presence of a catalytic amount of an imidazolidinone.[392]

OS **III**, 326; **V**, 422; **VI**, 471, 856; **VIII**, 75, 77, 80. Also see, OS **I**, 214.

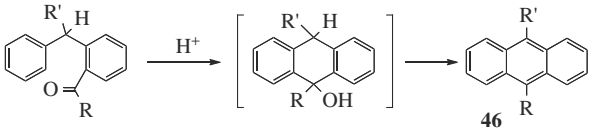
11-13 Cyclodehydration of Carbonyl-Containing Compounds



As described in Reaction **11-12**, the reaction of carbonyl-containing functional groups with protonic or Lewis acids lead to oxygen-stabilized carbocations. When generated in the presence of an aromatic ring, *Friedel–Crafts alkylation* occurs to give an alcohol or an alkene, if dehydration occurs under the reaction conditions. When an

[388] Gothelf, A.S.; Hansen, T.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 854.
[389] See Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* ***1981***, 143.
[390] Ghosh, S.; Pardo, S.N.; Salomon, R.G. *J. Org. Chem.* ***1982****, 47,* 4692.
[391] Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978****, 100*, 4842; Nagata, W.; Okada, K.; Aoki, T. *Synthesis* ***1979***, 365.
[392] Lee, S.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2007****, 129,* 15438.

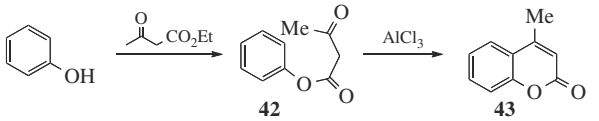
aromatic compound contains an aldehyde or ketone function in a position suitable for closing a suitably sized ring, treatment with acid results in cyclodehydration. The reaction is a special case of **11-12**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.[393] The method is very general and is widely used to close both carbocyclic and heterocyclic rings.[394] Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,[395] diarylmethanes, which contain a carbonyl group in the ortho position, can be cyclized to anthracene derivatives (**46**). In this case, 1,4-dehydration takes place, at least formally.



46

An intramolecular cyclization of an aryl ether to the carbonyl of a pendant aryl ketone, on clay with microwave irradiation, led to a benzofuran via *Friedel–Crafts cyclization* and elimination of water.[396]

A variation of this reaction involves acylation of a β-keto ester, followed by *Friedel–Crafts cyclization* of the ketone moiety. The product is a coumarin (**43**), in what is known as the *Pechmann condensation*.[397] Isolation of esters (e.g., **42**) is not always necessary, and protonic acids can be used rather than Lewis acids. The *Pechmann condensation* is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe_2), and alkyl groups meta to the hydroxyl of the phenol.[398] The reaction has been accomplished using microwave irradiation on graphite/Montmorillonite K-10.[399] *Pechmann condensation* in an ionic liquid using ethyl acetate has also been reported.[400]

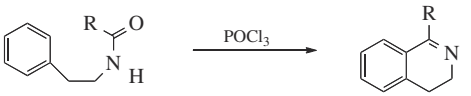


42 **43**

The carbonyl unit involved in the cyclization process is not restricted to aldehydes and ketones. The carbonyl of acid derivatives (e.g., amides) also can be utilized. One of the more important cyclodehydration reactions is applied to the formation of heterocyclic systems via cyclization of β-aryl amides, in what is called the *Bischler–Napieralski reaction*.[401] In this reaction, amides of the type **47** are cyclized with phosphorous oxychloride or other reagents, including polyphosphoric acid, sulfuric acid, or phosphorus

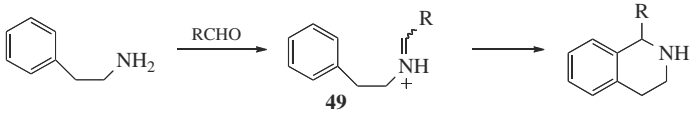
[393] See Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* ***1988****, 53,* 759.
[394] See Bradsher, C.K. *Chem. Rev.* ***1987****, 87,* 1277.
[395] Bradsher, C.K. *Chem. Rev.* ***1987****, 87*, 1277, see pp. 1287–1294.
[396] Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. *Synlett* ***2000***, 1273.
[397] von Pechmann, H.; Duisberg, C. *Ber.* ***1883****, 16,* 2119; Sethna, S.; Phadke, R. *Org. React.* ***1953****, 7,* 1. For a Pechmann condensation in ionic liquids, see Kumar, V.; Tomar, S.; Patel, R.; Yousaf, A.; Parmar, V.S.; Malhotra, S.V. *Synth. Commun.* ***2008****, 38,* 2646.
[398] Miyano, M.; Dorn, C.R. *J. Org. Chem.* ***1972****, 37*, 259.
[399] Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* ***2001****, 42*, 2791.
[400] See Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001****, 42,* 9285.
[401] See Fodor, G.; Nagubandi, S. *Tetrahedron* ***1980****, 36,* 1279.

pentoxide, to give a dihydroisoquinoline (**48**). The *Bischler–Napieralski reaction* has been done in ionic liquids using $POCl_3$.[402] The reaction has also been done using solid-phase (see Sec. 9.D.iv) techniques.[403]



47 **48**

If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline.[404] Higher yields can be obtained if the amide is treated with PCl_3 to give an imino chloride ($ArCH_2CH_2N{=}CR{-}Cl$), which is isolated and then cyclized by heating.[405] In this latter case, a nitrilium ion ($ArCH_2CH_2{}^{+}N{\equiv}CR$) is an intermediate.



49

Another useful variation is the *Pictet–Spengler isoquinoline synthesis*, also known as the *Pictet–Spengler reaction*.[406] The reactive intermediate is an iminium ion (**49**) rather than an oxygen-stabilized cation, but attack at the electrophilic carbon of the C=N unit (see Reaction **16-31**) leads to an isoquinoline derivative. When a β-arylamine reacts with an aldehyde, the product is an iminium salt, which cyclizes with an aromatic ring to complete the reaction and generate a tetrahydroisoquinoline.[407] Metal-catalyzed reactions are known, including the use of $AuCl_3/AgOTf$.[408] A variety of aldehydes can be used, and substitution on the aromatic ring leads to many derivatives. When the reaction is done in the presence of a chiral catalyst, good enantioselectivity was observed.[409]

Another variation in this basic procedure leads to tetrahydroisoquinolines. When phenethylamine was treated with *N*-hydroxymethylbenzotriazole and then $AlCl_3$ in chloroform, cyclization occurred, and reduction with sodium borohydride gave the 1,2,3,4-tetrahydro-*N*-methylisoquinoline.[410]

OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550; **VI**, 1. Also see, OS **I**, 54.

[402] See Judeh, Z.M.A.; Ching, C.B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* ***2002****, 43*, 5089.
[403] Chern, M.-S.; Li, W.R. *Tetrahedron Lett.* ***2004****, 45*, 8323.
[404] Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* ***1998****, 39*, 6609.
[405] Fodor, G.; Gal, G.; Phillips, B.A. *Angew. Chem. Int. Ed.* ***1972****, 11*, 919.
[406] Pictet, A.; Spengler, T. *Ber.* ***1911****, 44*, 2030; Cox, E.D.; Cook, J.M. *Chem. Rev.* ***1995****, 95*, 1797. See also, Whaley, W.M.; Govindachari, T.R. *Org. React.* ***1951****, 6*, 74; Youn, S.W. *Org. Prep. Proceed. Int.* ***2006****, 38,* 505.
[407] Ong, H.H.; May, E.L. *J. Heterocyclic Chem.* ***1971****, 8*, 1007.
[408] Youn, S.W. *J. Org. Chem.* ***2006****, 71,* 2521.
[409] Seayad, J.; Seayad, A.M.; List, B. *J. Am. Chem. Soc.* ***2006****, 128*, 1086; Raheem, I.T.; Thiara, P.S.; Peterson, E.A.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2007****, 129,* 13404; Sewgobind, N.V.; Wanner, M.J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J.H.; Hiemstra, H. *J. Org. Chem.* ***2008****, 73,* 6405.
[410] Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.

11-14 Haloalkylation or Haloalkyl-de-hydrogenation

$$\mathrm{ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl}$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[411] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether ($ClCH_2OMe$) or methoxyacetyl chloride ($MeOCH_2COCl$).[412] Zinc chloride is the most common catalyst, but other Friedel–Crafts catalysts are also employed. As with Reaction **11-12** and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in Reaction **11-12**, and then the HCl converts this to the chloroalkyl compound.[413] The acceleration of the reaction by $ZnCl_2$ has been attributed[414] to the raising of the acidity of the medium, causing an increase in the concentration of $HOCH_2^+$ ions.

OS **III**, 195, 197, 468, 557; **IV**, 980.

11-15 Friedel–Crafts Arylation: The Scholl Reaction

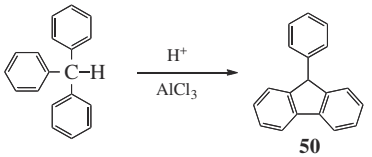
De-hydrogen-coupling

$$\mathrm{2\,ArH \xrightarrow[H^+]{AlCl_3} Ar{-}Ar + H_2}$$

The coupling of two aromatic molecules by treatment with a Lewis and a proton acid is called the *Scholl reaction*.[415] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. The reaction becomes important with large fused-ring systems, so ordinary *Friedel–Crafts reactions* (**11-11**) on these systems are rare. For example, naphthalene gives binaphthyl under *Friedel-Crafts conditions*. Yields can be

[411] See Belen'kii, L.I.; Vol'kenshtein, Yu.B.; Karmanova, I.B. *Russ. Chem. Rev.* ***1977****, 46*, 891; Olah, G.A.; Tolgyesi, W.S. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 659–784.
[412] McKillop, A.; Madjdabadi, F.A.; Long, D.A. *Tetrahedron Lett.* ***1983****, 24,* 1933.
[413] Ogata, Y.; Okano, M. *J. Am. Chem. Soc.* ***1956****, 78*, 5423. See also, Olah, G.A.; Yu, S.H. *J. Am. Chem. Soc.* ***1975****, 97,* 2293.
[414] Lyushin, M.M.; Mekhtiev, S.D.; Guseinova, S.N. *J. Org. Chem. USSR* ***1970****, 6,* 1445.
[415] See Kovacic, P.; Jones, M.B. *Chem. Rev.* ***1987****, 87*, 357; Balaban, A.T.; Nenitzescu, C.D. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 979–1047.

increased by the addition of a salt (e.g., $CuCl_2$ or $FeCl_3$), which acts as an oxidant.[416] Rhodium[417] and Ru catalysts[418] have also been used.



50

Intramolecular *Scholl reactions* (e.g., formation of **50** from triphenylmethane) are much more successful than the intermolecular reaction. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of type **12** (Sec. 11.A.i, category 2), which would be the electrophile that attacks the other ring.[419] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free radical arylations, see Reactions **12-15**, **13-26**, **13-27**, **13-10**, **14-17**, and **14-18**.

OS **IV**, 482; **X**, 359. Also see, OS **V**, 102, 952.

11-16 Arylation of Aromatic Compounds by Metalated Aryls

$$\mathrm{Ar}\text{—}M \xrightarrow{\mathrm{Ar'}\text{—H}} \mathrm{Ar}\text{—}\mathrm{Ar'}$$

Many metalated aryl compounds are known to couple with aromatic compounds. Aniline derivatives react with $ArPb(OAc)_3$, for example, to give the 2-arylaniline.[420] Phenolic anions also react to form biaryls, with modest enantioselectivity in the presence of brucine.[421] A Mn(III) mediated synthesis of biaryls used microwave irradiation for the coupling reaction.[422] The homocoupling reaction of aryl *Grignard reagents* in the presence of TEMPO is known.[423]

Phenylboronates [$ArB(OR)_2$] react with electron-deficient aromatic compounds (e.g., acetophenone) to give the biaryl.[424] Arylboronates also react with π-allyl Pd complexes to form the alkylated aromatic compound.[425] Arylboronic acids are also coupled in the presence of metal catalysts.[426] Organoborates can be coupled using an oxovanadium catalyst,[427] and potassium phenyltrifluoroborates can be coupled to aromatics using a combination of Pd and Cu catalysts.[428]

[416] For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 77–84; Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* ***1993****, 58,* 7271.
[417] Barrett, A.G.M.; Itoh, T.; Wallace, E.M. *Tetrahedron Lett.* ***1993****, 34*, 2233. For a microwave promoted reaction, see Lewis, J.C.; Wu, J.Y.; Bergman, R.G.; Ellman, J.A. *Angew. Chem. Int. Ed.* ***2006****, 45*, 1589.
[418] Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* ***2005****, 127,* 6632. For a coupling reaction of pyridines, see Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* ***2007****, 129,* 11006.
[419] See Clowes, G.A. *J. Chem. Soc. C* ***1968***, 2519.
[420] Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* ***2000***, 1676.
[421] Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***2002****, 124,* 5365.
[422] Demir, A.S.; Findik, H.; Saygili, N.; Subasi, N.T. Te*trahedron* ***2010****, 66,* 1308.
[423] Maji, M.S.; Studer, A. Synthesis **2009**, 2467.
[424] Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2003****, 125*, 1698.
[425] Ortar, G. *Tetrahedron Lett.* ***2003****, 44*, 4311.
[426] Basl, O.; Li, C.-J. *Org. Lett.* ***2008****, 10,* 3661.
[427] Mizuno, H.; Sakurai, H.; Amaya, T.; Hirao, T. *Chem. Commun.* ***2006***, 5042.
[428] Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* ***2008****, 73,* 7428.

A Cu catalyzed coupling reaction with hypervalent arylated iodine derivatives is known.[429]

See Reactions **13-9**, **13-11**, and **13-12**.

11-17 Friedel–Crafts Acylation

Acylation or Acyl-de-hydrogenation

$$\mathrm{ArH} + \mathrm{RCOCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCOR}$$

The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.[430] The reaction is of wide scope. Reagents other than acyl halides can be used,[431] including carboxylic acids,[432] anhydrides, and ketenes. Oxalyl chloride has been used to give diaryl 1,2-diketones.[433] Carboxylic esters usually give alkylation as the predominant product (see Reaction **11-11**).[434] *N*-Carbamoyl β-lactams reacted with naphthalene in the presence of trifluoromethanesulfonic acid to give the keto-amide.[435]

The alkyl group (R in RCOCl) may be aryl as well as alkyl.[436] The major disadvantages of *Friedel–Crafts alkylation*, polyalkylation, and rearrangement of the intermediate carbocation, are not a problem in *Friedel–Crafts acylation*. Rearrangement of the alkyl group (R in RCOCl) is never found because the intermediate is an acylium ion (an acyl cation, $RC{\equiv}O^+$, see below), which is stabilized by resonance. Because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, $I > Br > Cl > F$.[437] Catalysts are Lewis acids,[438] similar to those in Reaction **11-11**, but in acylation a little >1 equiv of catalyst is required per mole of reagent, because the first mole coordinates with the oxygen of the reagent [as in $R(Cl)C{=}O^{+-}AlCl_3$].[439] A reusable catalyst [$Ln(OTf)_3$—$LiClO_4$] has been developed.[440] Ferric chloride in an ionic liquid has

[429] Phipps, R.J.; Grimster, N.P.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2008****, 130,* 8172.

[430] See Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1964***, as follows: Vol. 1, Olah, G.A. pp. 91–115; Vol. 3, Gore, P.H. pp. 1–381; Peto, A.G. pp. 535–910; Sethna, S. pp. 911–1002; Jensen, F.R.; Goldman, G. pp. 1003–1032. Also see Gore, P.H. *Chem. Ind. (London)* ***1974***, 727; *Advances in Friedel–Crafts Acylation Reactions: Catalytic and Green Processes*, Sartori, G.; Maggi, R., CRC Press, Boca Raton, FL. ***2009***.

[431] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1423–1426.

[432] Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* ***2003****, 44*, 7715. See Kaur, J.; Kozhevnikov, I.V. *Chem.Commun.* ***2002***, 2508.

[433] Taber, D.F.; Sethuraman, M.R. *J. Org. Chem.* ***2000****, 65*, 254.

[434] See Hwang, J.P.; Prakash, G.K.S.; Olah, G.A. *Tetrahedron* ***2000****, 56*, 7199.

[435] Anderson, K.W.; Tepe, J. *Org. Lett.* ***2002****, 4,* 459.

[436] For a discussion of the relationship between electrophilicity of the substituting agents and substrate selectivity, see Meneses, L.; Fuentealba, P.; Contreras, R. *Tetrahedron* ***2005****, 61*, 831.

[437] Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961****, 34*, 480; Corriu, R. *Bull. Soc. Chim. Fr.* ***1965***, 821.

[438] See Pearson, D.E.; Buehler, C.A. *Synthesis* ***1972***, 533. Examples include, **Ga(ONf)$_3$**, where Nf = nonafluorobutanesulfonate: Matsu, J.-i.; Odashima, K.; Kobayashi, S. *Synlett* ***2000***, 403. **In(OTf)$_3$** with $LiClO_4$: Chapman, C.J.; Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Tetrahedron Lett.* ***2001****, 42*, 773. **InCl$_3$**: Choudhary, V.R.; Jana, S.K.; Patil, N.S. *Tetrahedron Lett.* ***2002****, 43*, 1105. **Sc(OTf)$_3$**: Kawada, A.; Mitamura, S.; Matsuo, J-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* ***2000****, 73*, 2325. **Yb[C(SO$_2$C$_4$F$_4$)$_3$]$_3$**: Barrett, A.G.M.; Bouloc, N.; Braddock, D.C.; Chadwick, D.; Henderson, D.A. *Synlett* ***2002***, 1653. **BiOCl$_3$**: Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* ***2003****, 44,* 2037. **ZnO**: Sarvari, M.H.; Sharghi, H. *J. Org. Chem.* ***2004****, 69*, 6953.

[439] See Chevrier, B.; Weiss, R. *Angew. Chem. Int. Ed.* ***1974****, 13,* 1.

[440] Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* ***1996***, 183. Kawada, A.; Mitamura, S.; Kobayashi, S. *SynLett,* ***1994***, 545; Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* ***1995****, 36,* 409.

also been used.[441] The HY-Zeolite has also been used to facilitate the reaction with acetic anhydride.[442] Catalyts include a Pd catalyst, which was used with acetic anhydride,[443] $TiCl_4$,[444] SmI_2,[445] In metal,[446] acetyl chloride, and zinc powder with microwave irradiation.[447] *Friedel–Crafts acylation* using a carboxylic acid with a catalyst called Envirocat-EPIC (an acid-treated clay-based material) was reported.[448] *Friedel–Crafts acylation* was reported in an ionic liquid.[449] An interesting acylation reaction was reported that coupled trichlorophenylmethane to benzene, giving benzophenone in the presence of the ionic liquid $AlCl_3$–BPC.[450] (butylpyridiniumchloroaluminate = BPC). Acylation has been accomplished in carbon disulfide.[451] An interesting variation couples a conjugated acid chloride with benzene, in the presence of $AlCl_3$ and microwave irradiation, to give an indanone.[452]

Protonic acids can be used as catalysts when the reagent is a carboxylic acid.[453] Triflic anhydride promotes dehydrative acylation of carboxylic acids,[454] as does P_2O_5/SiO_2.[455] An aryl carboxylic acid can be converted to the acid chloride *in situ* with cyanuric chloride and $AlCl_3$, leading to *Friedel–Crafts acylation*.[456] A solvent-free method is also available using tosic acid/graphite.[457]

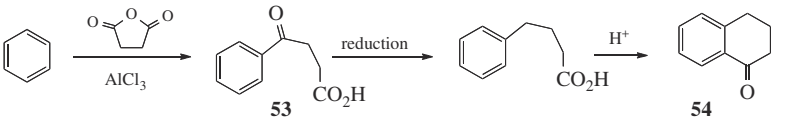
The mixed carboxylic sulfonic anhydrides ($RCOOSO_2CF_3$) are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[458] With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), *Friedel–Crafts acylation* can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all.

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in Reaction **11-11**. Compounds containing ortho–para directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from *N*- or *O*-acylation; however, *O*-acylated phenols can be converted to *C*-acylated phenols by the *Fries rearrangement* (Reaction **11-27**). *Friedel–Crafts acylation* is usually prevented by meta-directing (deactivating) groups.

[441] Khodaei, M.M.; Bahrami, K.; Shahbazi, F. *Chem. Lett.* ***2008****, 37,* 844.
[442] Sreekumar, R.; Padmukumar, R. *Synth. Commun.* ***1997****, 27*, 777. See Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***1994****, 35,* 2601.
[443] Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M.T. *Org. Lett.* ***2001****, 3*, 417.
[444] Bensari, A.; Zaveri, N.T. *Synthesis* ***2003***, 267.
[445] Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* ***2006****, 47*, 5467.
[446] Jang, D.O.; Moon, K.S.; Cho, D.H.; Kim, J.-G. *Tetrahedron Lett.* ***2006****, 47*, 6063.
[447] Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* ***2003***, 2877.
[448] Bandgar, B.P.; Sadavarte, V.S. *Synth. Commun.* ***1999****, 29*, 2587.
[449] See Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* ***2003****, 5*, 2219.
[450] See Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2000****, 30,* 1605.
[451] Georgakilas, V.; Perdikomatis, G.P.; Triantafyllou, A.S.; Siskos, M.G.; Zarkadis, A.K. *Tetrahedron* ***2002****, 58,* 2441.
[452] Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. *J. Org. Chem.* ***2006****, 71,* 4312.
[453] See Kawamura, M.; Cui, D.-M.; Shimada, S. *Tetrahedron* ***2006****, 62,* 9201. Also see Posternak, A.G.; Garlyauskayte, R.Yu.; Yagupolskii, L.M. *Tetrahedron Lett.* ***2009****, 50*, 446.
[454] Khodaei, M.M.; Alizadeh, A.; Nazari, E. *Tetrahedron Lett.* ***2007****, 48,* 4199.
[455] Zarei, A.; Hajipour, A.R.; Khazdooz, L. *Tetrahedron Lett.* ***2008****, 49,* 6715.
[456] Kangani, C.O.; Day, B.W. *Org. Lett.* ***2008****, 10*, 2645.
[457] Sarvari, M.H.; Sharghi, H. *Helv. Chim. Acta* ***2005****, 88,* 2282.
[458] Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* ***1983****, 116*, 1195. See also, Keumi, T.; Yoshimura, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1988****, 44*, 455.

Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles[459] but not pyridines or quinolines, can be acylated in good yield. Initial reaction of indole with Et_2AlCl[460] or $SnCl_4$,[461] followed by acetyl chloride leads to 3-acetylindole. By comparison, the reaction of *N*-acetylindole with acetic anhydride and $AlCl_3$ gave *N*,6-diacetylindole.[462] Acetylation at C-3 was also accomplished with acetyl chloride in the ionic liquid emimcl–$AlCl_3$.[463] Gore, in Ref. 430 (pp. 36–100; with tables, pp. 105–321), presents an extensive summary of the substrates to which this reaction has been applied.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,[464] in which case the product contains a carboxyl group in the side chain (**53**). When succinic anhydride is used, the product is $ArCOCH_2CH_2CO_2H$. This can be reduced (Reaction **19-61**) to $ArCH_2CH_2CH_2CO_2H$, and can then be cyclized by an internal *Friedel–Crafts acylation* to give **54**. The total process is called the *Haworth reaction*:[465]



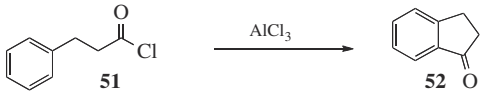
53 **54**

When a mixed-anhydride ($RCOOCOR'$) is the reagent, two products are possible: ArCOR and $ArCOR'$. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then $ArCOR'$ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[466] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid (HCOOCOR).

An important use of the *Friedel–Crafts acylation* is to effect ring closure.[467] This closure can be accomplished if an acyl halide, anhydride, or carboxylic acid[468] group is in the proper position. An example is the conversion of **51** to **52**. The reaction is used mostly to close six-membered rings, but has also been done for five- and seven-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.[469] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. Many fused-ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[470] One of the most

[459] Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Rao, R.S.; Kumar, S.P. *Tetrahedron Lett.* ***2002****, 43,* 8133.
[460] Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N.A.; Kadow, J.F.; Wang, T. *J. Org. Chem.* ***2002****, 67*, 6226.
[461] Ottoni, O.; de V.F. Neder, A.; Dias, A.K.B.; Cruz, R.P.A.; Aquino, L.B. *Org. Lett.* ***2001****, 3*, 1005.
[462] Cruz, R.P.A.; Ottoni, O.; Abella, C.A.M.; Aquino, L.B. *Tetrahedron Lett.* ***2001****, 42*, 1467. See Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* ***2004****, 69*, 2913.
[463] See Yeung, K.-S.; Farkas, M.E.; Qiu, Z.; Yang, Z. *Tetrahedron lett.* ***2002****, 43*, 5793.
[464] See Peto, A.G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 535.
[465] See Agranat, I.; Shih, Y. *J. Chem. Educ.* ***1976****, 53,* 488.
[466] Edwards, Jr., W.R.; Sibelle, E.C. *J. Org. Chem.* ***1963****, 28,* 674.
[467] See Sethna, S. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 911–1002. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1427–1431.
[468] See Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* ***2004****, 45,* 1741.
[469] See Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* ***1954****, 76,* 5462.
[470] See Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 325–332; Thomson, R.H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***; pp. 136–139.

common catalysts for intramolecular *Friedel–Crafts acylation* is polyphosphoric acid[471] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.



Thioesters are coupled to arylboronic acids in the presence of a Pd catalyst, in a *Friedel–Crafts acylation*-type coupling.[472] Acyl halides are coupled to arylboronic acids under microwave irradiation.[473]

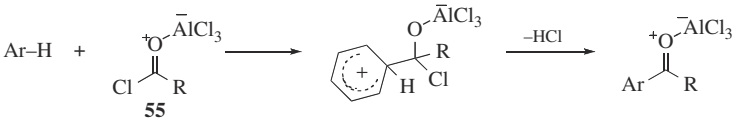
The mechanism of *Friedel–Crafts acylation* is not completely understood,[474] but at least two mechanisms probably operate, depending on conditions.[475] In most cases, the attacking species is the acyl cation, either free or as an ion pair, formed by[476]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, RCO^+ may lose CO to give R^+, so that the alkyl arene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride (Me_3CCOCl) gives the normal acyl product with anisole, but yields the alkyl product (Me_3CPh) with benzene. In the other mechanism, an acyl cation is not involved, but the 1:1 complex (**55**) attacks directly.[477] Free-ion attack is more likely for sterically hindered R.[478] The ion CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents (e.g., nitrobenzene); but in nonpolar solvents (e.g., as chloroform) only the complex and not the free ion is present.[479] In any event, 1 molar equivalent of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with RCO^+ SbF_6^-, no catalyst is required and the free ion[480] (or ion pair) is undoubtedly the attacking entity.[481] The use of $LiClO_4$ on the metal triflate catalyzed *Friedel–Crafts acylation* of methoxynaphthalene derivatives has been examined. The presence of the lithium salt leads to acylation in the ring containing the methoxy unit, whereas reaction occurs in the other ring in the absence of lithium salts.[482] Note that lithium perchlorate

[471] See Rowlands, D.A. in Pizey, J.S. *Synthetic Reagents,* Vol. 6, Wiley, NY, ***1985***, pp. 156–414.
[472] Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L.S. *J. Am. Chem. Soc.* ***2007****, 129,* 1132.
[473] Poláčková, V.; Toma, Š.; Augustínová, I. *Tetrahedron* ***2006****, 62*, 11675.
[474] See Effenberger, F.; Eberhard, J.K.; Maier, A.H. *J. Am. Chem. Soc.* ***1996****, 118*, 12572.
[475] See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 222–237.
[476] After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey, G.; Susz, P.B. *Helv. Chim. Acta* ***1964****, 47,* 1828.
[477] See Tan, L.K.; Brownstein, S. *J. Org. Chem.* ***1983****, 48,* 302.
[478] Gore, P.H. *Bull. Chem. Soc. Jpn.* ***1962****, 35,* 1627; Satchell, D.P.N. *J. Chem. Soc.* ***1961***, 5404.
[479] Cassimatis, D.; Bonnin, J.P.; Theophanides, T. *Can. J. Chem.* ***1970****, 48*, 3860.
[480] See Chevrier, B.; Le Carpentier, J.; Weiss, R. *Acta Crystallogr., Sect. B,* ***1972****, 28,* 2673; *J. Am. Chem. Soc.* ***1972****, 94*, 5718.
[481] Olah, G.A.; Lin, H.C.; Germain, A. *Synthesis* ***1974***, 895. Also see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990****, 22,* 1.
[482] Kobayashi, S.; Komoto, I. *Tetrahedron* ***2000****, 56*, 6463.

forms a complex with acetic anhydride, which can be used for the *Friedel–Crafts acetylation* of activated aromatic compounds.[483]



A related reaction couples an acid chloride with an aromatic compound in the presence of a Rh catalyst, but the coupling reaction involves a decarbonylation to give a biaryl.[484]

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **VI**, 34, 618, 625 **X**, 125.

Reaction **11-18** is a direct formylation of the ring.[485] Reaction **11-17** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 h at $-6°$,[486] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[487] Mixed anhydrides of formic and other acids are known[488] and can be used to formylate amines (see Reaction **16-73**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See Reaction **13-17** for a nucleophilic method for the formylation of aromatic rings.

A related reaction involves a biaryl, where one ring is a phenol. Treatment with BCl_3 and an $AlCl_3$ catalyst, followed by reaction with CO and $Pd(OAc)_2$, led to carbonylation and acylation to give the corresponding lactone.[489] Carbonylation of aromatic compounds can lead to aryl ketones. Heating an aromatic compound with $Ru(CO)_{12}$, ethylene and 20 atm. of CO gave the corresponding aryl ethyl ketone.[490]

11-18 Formylation

Formylation or **Formyl-de-hydrogenation**

$$\text{Ar—H} \longrightarrow \text{Ar—CHO}$$

The reaction with disubstituted formamides (R_2N—CHO) and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*,[491] is the most common method

[483] Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinalde, S.; Sambri, L. *Tetrahedron Lett.* ***2002*** *. 43,* 6331.

[484] Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* ***2008****, 130,* 8136.

[485] See Olah, G.A.; Kuhn, S.J.; Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1153–1256; Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* ***1987****, 87,* 671. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1423–1426.

[486] Staab, H.A.; Datta, A.P. *Angew. Chem. Int. Ed.* ***1964****, 3,* 132.

[487] Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Sommer, J. *Angew. Chem. Int. Ed.* ***1979****, 18,* 614.

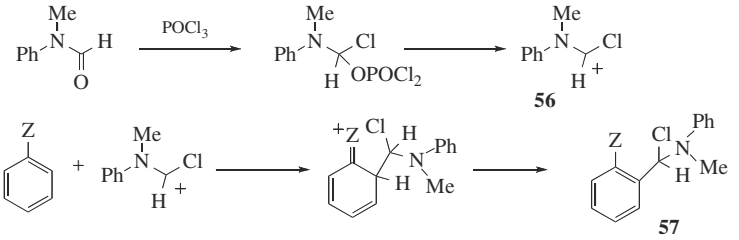
[488] Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964****, 83*, 863.

[489] Zhou, Q.J.; Worm, K.; Dolle, R.E. *J.Org. Chem.* ***2004****, 69,* 5147.

[490] Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* ***2000****, 65*, 1475.

[491] See Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proceed. Int.* ***1993****, 25*, 338 for improvements in this reaction.

for the formylation of aromatic rings.[492] However, it is applicable only to active substrates (e.g., amines and phenols). An intramolecular version is also known.[493] Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes and ferrocenes). Although *N*-phenyl-*N*-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used.[494] Phosgene ($COCl_2$) has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of Reaction **11-17**), but not often. The attacking species[495] is **56**,[496] and the mechanism is probably that shown to give **57**, which is unstable and easily hydrolyzes to the product. Either formation of **56** or the reaction of **56** with the substrate can be rate determining, depending on the reactivity of the substrate.[497]



When $(CF_3SO_2)_2O$ was used instead of $POCl_3$, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.[498]

In a related reaction, paraformaldehyde can be used, with $MgCl_2$-NEt_3, to convert phenol to phenol 2-carbaldehyde.[499] Another variation treated acetanilide with $POCl_3$—DMF and generated 2-chloroquinoline-3-carboxaldehyde.[500] Used in conjunction with conjugated hydroxylamines, a tandem *Vilsmeier–Beckman reaction* (see Reaction **18-17** for the *Beckman rearrangement*) leads to pyridines (2-chloro-3-carboxaldehyde).[501] A chain-extension variation has been reported in which an aryl alkyl ketone is treated with $POCl_3$/DMF on silica with microwave irradiation to give a conjugated aldehyde [ArC(=O)R → ArC(Cl)=CHCHO].[502]

OS **I**, 217; **III**, 98, **IV**, 331, 539, 831, 915.

$$\mathrm{ArH} + \mathrm{Zn(CN)_2} \xrightarrow{\mathrm{HCl}} \mathrm{ArCH{=}NH_2{}^+Cl^-} \xrightarrow{\mathrm{H_2O}} \mathrm{ArCHO}$$

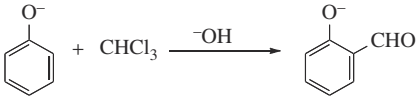
Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction*[503] and can be applied to alkylbenzenes, phenols and their ethers, as well as many heterocyclic

[492] SeeJutz, C. *Adv. Org. Chem.* ***1976****, 9*, pt. 1, 225.
[493] Meth-Cohn, O.; Goon, S. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 85.
[494] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 1–99.
[495] For a review of such species, see Kantlehner, W. *Adv. Org. Chem.* ***1979****, 9,* pt. 2, 5.
[496] See Jugie, G.; Smith, J.A.S.; Martin, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 925.
[497] Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2070.
[498] Martínez, A.G.; Alvarez, R.M.; Barcina, J.O.; Cerero, S. de la M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *J. Chem. Soc., Chem. Commun.* ***1990***, 1571.
[499] Hofsløkken, N.U.; Skattebøl, L. *Acta Chem. Scand.* ***1999****, 53*, 258.
[500] Ali, M.M.; Tasneem, Rajanna, K.C.; Prakash, P.K.S. *Synlett* ***2001***, 251. Also see Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* ***2001****, 57*, 3465.
[501] Amaresh, R.R.; Perumal, P.T. *Synth. Commun.* ***2000****, 30,* 2269.
[502] Paul, S.; Gupta, M.; Gupta, R. *Synlett* ***2000***, 1115.
[503] See Truce, W.E. *Org. React.* ***1957****, 9,* 37; Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* ***1995****, 60*, 2106 for rate studies.

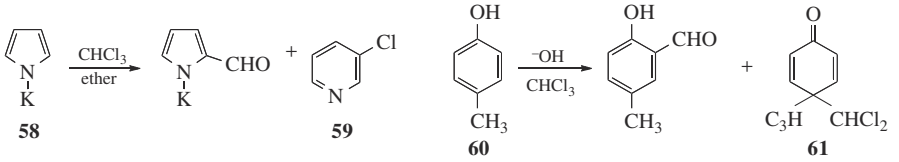
compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction, the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished. The mechanism of the *Gatterman reaction* has not been investigated very much, but it is known that an initially formed, but not isolated nitrogen-containing product, is hydrolyzed to aldehyde. This product is presumed to be $ArCH{=}NH_2^+Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions (F_3CSO_2OH–SbF_5, see Sec. 5.A.ii), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H){=}N^+H_2$.[504] The *Gatterman reaction* may be regarded as a special case of Reaction **11-24**.

Another method, formylation with CO and HCl in the presence of $AlCl_3$ and CuCl[505] (the *Gatterman–Koch reaction*), is limited to benzene and alkylbenzenes.[506] Aryl halides are converted to aryl aldehydes with CO/H_2 in the presence of a Pd catalyst.[507]

OS **II**, 583; **III**, 549.



In the *Reimer–Tiemann reaction*, aromatic rings are formylated by reaction with chloroform and hydroxide ion.[508] The method is useful only for phenols and certain heterocyclic compounds (e.g., pyrroles and indoles). Unlike the previous formylation methods (Reaction **11-18**), this one is conducted in basic solution. Yields are generally low, seldom rising >50%.[509] The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.[510] Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **58** and **60** gave, respectively, **59** and **61**, as well as the normal aldehyde products. From the nature of the reagents and

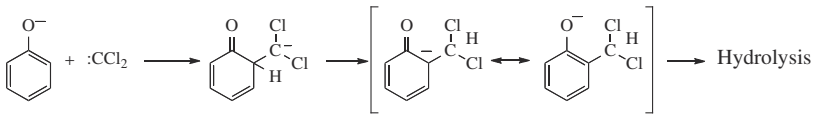


58 **59** **60** **61**

from the kind of abnormal products obtained, it is clear that the reactive entity in this reaction is dichlorocarbene (CCl_2).[511] This product is known to be produced by treatment of chloroform with bases (see Reaction **10-3**); it is an electrophilic reagent and is known to

[504] Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* ***1991****, 113,* 691.
[505] See, however, Toniolo, L.; Graziani, M. *J. Organomet. Chem.* ***1980****, 194,* 221.
[506] See Crounse, N.N. *Org. React.* ***1949****, 5,* 290.
[507] Sergeev, A.G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* ***2008****, 130*, 15549.
[508] See Wynberg, H.; Meijer, E.W. *Org. React.* ***1982****, 28*, 1.
[509] See Cochran, J.C.; Melville, M.G. *Synth. Commun.* ***1990****, 20*, 609.
[510] See, however, Neumann, R.; Sasson, Y. *Synthesis* ***1986***, 569.
[511] See Kulinkovich, O.G. *Russ. Chem. Rev.* ***1989****, 58,* 711.

give ring expansion of aromatic rings (see Reaction **15-64**), accounting for products like **58**. The mechanism of the normal reaction is thus something like[512]:



The formation of **61** in the case of **60** can be explained by attack of some of the CCl_2 ipso to the CH_3 group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the *Reimer–Tiemann reaction* is the *Duff reaction*, in which hexamethylenetetramine [$(CH_2)_6N_4$] is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism[513] has been proposed that involves initial aminoalkylation (Reaction **11-22**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with F_3CCO_2H, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.[514] In this case too, an imine seems to be an intermediate.

OS **III**, 463; **IV**, 866

$$ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO$$

Besides Reaction **11-18**, several other formylation methods are known.[515] In one of these, dichloromethyl methyl ether formylates aromatic rings with *Friedel–Crafts catalysts*.[516] The ArCHClOMe compound is probably an intermediate. Orthoformates have also been used.[517] In another method, aromatic rings are formylated with formyl fluoride (HCOF) and BF_3.[518] Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl, PhBr, and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with 2 molar equivalents of paraformaldehyde in aprotic solvents in the presence of $SnCl_4$ and a tertiary amine.[519] Phenols have also been formylated indirectly by conversion to the aryllithium reagent followed by treatment with *N*-formyl piperidine.[520] See also, the indirect method mentioned at Reaction **11-23**. Aryl halides are converted to the corresponding aldehyde in a related reaction.[521]

OS **V**, 49; **VII**, 162.

Reactions **11-19** and **11-20** are direct carboxylations[522] of aromatic rings.[523]

[512] Robinson, E.A. *J. Chem. Soc.* ***1961***, 1663; Hine, J.; van der Veen, J.M. *J. Am. Chem. Soc.* ***1959****, 81*, 6446. See also, Langlois, B.R. *Tetrahedron Lett.* ***1991****, 32,* 3691.
[513] Ogata, Y.; Kawasaki, A.; Sugiura, F. *Tetrahedron* ***1968****, 24,* 5001.
[514] Smith, W.E. *J. Org. Chem.* ***1972****, 37,* 3972.
[515] See Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 545.
[516] Lewin, A.H.; Parker, S.R.; Fleming, N.B.; Carroll, F.I. *Org. Prep. Proceed. Int.* ***1978****, 10*, 201.
[517] Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* ***1963****, 96,* 308.
[518] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960****, 82*, 2380.
[519] Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1862.
[520] Hardcastle, I.R.; Quayle, P.; Ward, E.L.M. *Tetrahedron Lett.* ***1994****, 35*, 1747.
[521] Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Groß, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2005****, 45*, 154.
[522] See Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1982***, 132.
[523] See Olah, G.A.; Olah, J.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1257–1273.

11-19 Carboxylation with Carbonyl Halides

Carboxylation or **Carboxy-de-hydrogenation**

$$ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH$$

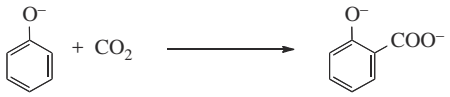
Phosgene, in the presence of *Friedel–Crafts catalysts*, can carboxylate the ring. This process is analogous to Reaction **11-17**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl is attacked by another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, including oxalyl chloride, urea hydrochloride, chloral (Cl_3CCHO),[524] carbamoyl chloride (H_2NCOCl), and *N*,*N*-diethylcarbamoyl chloride.[525] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.[526]

Although mechanistically different, other methods are available to convert aromatic compounds to aromatic carboxylic acids. The Pd catalyzed reaction of aromatic compounds and formic acid leads to benzoic acid derivatives.[527] Diphenyliodonium tetrafluoroborate ($Ph_2I^+ BF_4^-$) reacts with CO and In in DMF, with a Pd catalyst, to give benzophenone.[528]

OS **V**, 706; **VII**, 420.

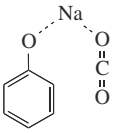
11-20 Carboxylation with Carbon Dioxide: The Kolbe–Schmitt Reaction

Carboxylation or **Carboxy-de-hydrogenation**



Sodium phenoxides can be carboxylated, mostly in the ortho position, by CO_2 (the *Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,[529] making the carbon of the CO_2 more positive and putting it in a good position to attack the ring. Potassium phenoxide, which is less likely to form such a complex, is chiefly attacked in the para position. There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2.[530] At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate (sodium salicylate does not rearrange).[531] Carbon tetrachloride can be used instead of CO_2 under *Reimer–Tiemann* (Reaction **11-18**) conditions.

[524] Menegheli, P.; Rezende, M.C.; Zucco, C. *Synth. Commun.* ***1987****, 17*, 457.
[525] Naumov, Yu.A.; Isakova, A.P.; Kost, A.N.; Zakharov, V.P.; Zvolinskii, V.P.; Moiseikina, N.F.; Nikeryasova, S.V. *J. Org. Chem. USSR* ***1975****, 11*, 362.
[526] See Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* ***1988***, 763.
[527] Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* ***2004****, 6*, 2437.
[528] Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002****, 32*, 3431.
[529] Hales J.L.; Jones, J.I.; Lindsey, A.S. *J. Chem. Soc.* ***1954***, 3145.
[530] See Hirao, I.; Kito, T. *Bull. Chem. Soc. Jpn.* ***1973****, 46,* 3470.
[531] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 344–348. See also, Ota, K. *Bull. Chem. Soc. Jpn.* ***1974****, 47*, 2343.



Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.[532] The ^{14}C labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.[533] The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with Pd compounds as catalysts.[534] In addition, a Pd catalyzed reaction has been used directly to prepare acyl fluorides $ArH \rightarrow ArCOF$.[535] Molybdovanadophosphates have been used for anisole in the presence of CO and O_2.[536] A Pd catalyzed carboxylation has been reported using Ag_2CO_3 and CO.[537]

An enzymatic carboxylation was reported, in supercritical CO_2 (see Sec. 9.D.ii), in which exposure of pyrrole to *Bacillus megaterium* PYR2910 and $KHCO_3$ gave the potassium salt of pyrrole 2-carboxylic acid.[538]

OS **II**, 557.

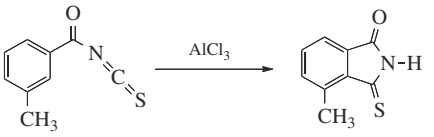
11-21 Amidation

N-Alkylcarbamoyl-de-hydrogenation

$$ArH + RNCO \xrightarrow{AlCl_3} ArCONHR$$

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[539] The R group may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.[540] The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[541] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way of putting a carboxyl group on a ring ortho to one already there (**62** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $ArCH_2CONCS$, where six-membered rings are formed. An intramolecular reaction of 2-amido biaryls leads to carbazoles in the presence of Pd and Cu catalysts.[542]

[532] Yasuhara, Y.; Nogi, T. *J. Org. Chem.* ***1968****, 33,* 4512, *Chem. Ind. (London)* ***1969***, 77.
[533] Yasuhara, Y.; Nogi, T.; Saisho, H. *Bull. Chem. Soc. Jpn.* ***1969****, 42,* 2070.
[534] See Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* ***1987***, 1159; Ugo, R.; Chiesa, A. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2625.
[535] Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1987****, 334,* 205.
[536] Ohashi, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2005***, 486.
[537] Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2008****, 130,* 14082. See also, Sakakibara, K.; Yamashita, M.; Nozaki, K. *Tetrahedron Lett.* ***2005****, 46,* 959.
[538] Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* ***2001***, 2194.
[539] Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* ***1986****, 42,* 885.
[540] Jagodzinski, T. *Synthesis* ***1988***, 717.
[541] Smith, P.A.S.; Kan, R.O. *J. Org. Chem.* ***1964****, 29,* 2261.
[542] Tsang, W.C.P.; Zheng, N.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2005****, 127*, 14560.



62

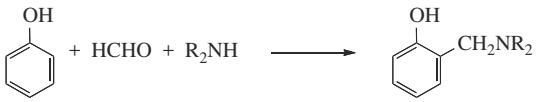
There are interesting transition metal catalyzed reactions that lead to aryl amides. The use of $POCl_3$ and DMF, with a Pd catalyst, converts aryl iodides to benzamides.[543] Carbonylation is another method that generates amides. When an aryl iodide was treated with a secondary amine and $Mo(CO)_6$, in the presence of 3 equiv of DBU, 10% $Pd(OAc)_2$, with microwave irradiation at 100 °C, the corresponding benzamide was obtained.[544] Aminocarbonylation is accomplished with microwave irradiation using hydroxylamine as an ammonia equivalent.[545]

OS **V**, 1051; **VI**, 465.

Reactions **11-12–11-23** involve the introduction of a CH_2Z group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all *Friedel–Crafts reactions* of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 16.

11-22 Aminoalkylation and Amidoalkylation

Dialkylaminoalkylation or **Dialkylamino-de-hydrogenation**



Phenols, secondary and tertiary aromatic amines,[546] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminoalkylation is a special case of the *Mannich reaction* (**16-19**). When phenols and other activated aromatic compounds are treated with *N*-hydroxymethylchloroacetamide, *amidomethylation* takes place[547] to give **63**, which is often hydrolyzed *in situ* to the aminoalkylated product. Other *N*-hydroxyalkyl and *N*-chlorinated compounds have also been used.[379] Nitroethane in polyphosphoric acid can be used for the acetamidation of aromatic compounds.[548]

[543] Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* ***2002****, 4*, 2849. Also see Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A.F. *J. Org. Chem.* ***2001****, 66*, 4311. See also, Schnyder, A.; Indolese, A.F. *J. Org. Chem.* ***2002****, 67*, 594.

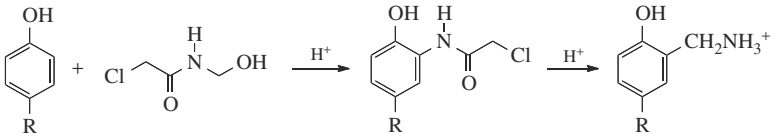
[544] Wannberg, J.; Larhed, M. *J. Org. Chem.* ***2003****, 68*, 5750.

[545] Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* ***2006****, 62,* 4665.

[546] Miocque, M.; Vierfond, J. *Bull. Soc. Chim. Fr.* ***1970***, 1896, 1901, 1907.

[547] For a review, see Zaugg, H.E. *Synthesis* ***1984***, 85.

[548] Aksenov, A.V.; Aksenov, N.A.; Nadein, O.N.; Aksenova, I.V. *Synlett* ***2010***, 2628.

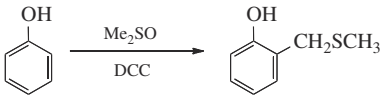


63

Aryl halides are aminomethylated with potassium organotrifluoroborates.[549]
OS **I**, 381; **IV**, 626; **V**, 434; **VI**, 965; **VII**, 162.

11-23 Thioalkylation

Alkylthioalkylation or **Alkylthioalkyl-de-hydrogenation**



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with DMSO and 1,3-dicyclohexylcarbodiimide (DCC).[550] Other reagents can be used instead of DCC, among them $SOCl_2$,[551] or acetic anhydride.[552] Alternatively, the phenol can be treated with DMS and NCS, followed by triethylamine.[553] The reaction can be applied to amines (to give *o*-$NH_2C_6H_4CH_2SMe$) by treatment with *t*-BuOCl, Me_2S, and NaOMe in CH_2Cl_2.[554] Aromatic hydrocarbons have been thioalkylated with ethyl α-(chloromethylthio) acetate ($ClCH_2SCH_2CO_2Et$) to give $ArCH_2SCH_2CO_2Et$,[555] and with methyl methylsulfinylmethyl sulfide ($MeSCH_2SOMe$) or methylthiomethyl *p*-tolyl sulfone ($MeSCH_2SO_2C_6H_4Me$) to give $ArCH_2SMe$,[556] in each case with a Lewis acid catalyst.

OS **VI**, 581, 601.

11-24 Acylation with Nitriles: The Hoesch Reaction

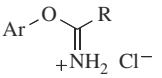
Acylation or **Acyl-de-hydrogenation**

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

Friedel–Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben–Hoesch reaction*.[557] In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds (e.g., pyrrole), but it can be extended to aromatic amines

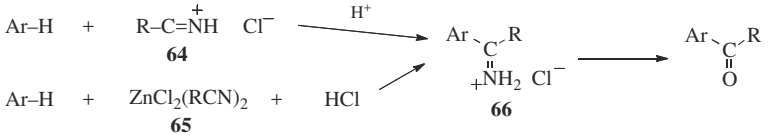
[549] Molander, G.A.; Sandrock, D.L. *Org. Lett.* ***2007****, 9,* 1597.
[550] Olofson, R.A.; Marino, J.P. *Tetrahedron* ***1971****, 27,* 4195.
[551] Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 2715.
[552] Hayashi, Y.; Oda, R. *J. Org. Chem.* ***1967****, 32*, 457; Pettit, G.H.; Brown, T.H. *Can. J. Chem.* ***1967****, 45,* 1306; Claus, P. *Monatsh. Chem.* ***1968****, 99,* 1034.
[553] Gassman, P.G.; Amick, D.R. *J. Am. Chem. Soc.* ***1978****, 100,* 7611.
[554] Gassman, P.G.; Gruetzmacher, G. *J. Am. Chem. Soc.* ***1973****, 95,* 588; Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* ***1973****, 95*, 590, 591.
[555] Tamura, Y.; Tsugoshi, T.; Annoura, H.; Ishibashi, H. *Synthesis* ***1984***, 326.
[556] Torisawa, Y.; Satoh, A.; Ikegami, S. *Tetrahedron Lett. 1988, 29*, 1729.
[557] See Ruske, W. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 383–497.

by the use of BCl_3.[558] Acylation in the case of aniline derivatives is regioselectively ortho. Monohydric phenols, however, generally do not give ketones[559] but are attacked at the oxygen to produce imino esters. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$, and then the substrate added at 0 °C.[560] In fact, this procedure increases yields with any nitrile. If thiocyanates (RSCN) are used, thiol esters (ArCOSR) can be obtained. The *Gatterman reaction* (Reaction **11-18**) is a special case of the *Hoesch synthesis*.



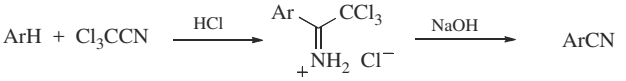
An imino ester

The reaction mechanism is complex and not completely settled.[561] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**66**). Among the possible reactive species are **64** and **65**. In the second stage, the salts are hydrolyzed to the products, first the iminium salt, and then the ketone. Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of F_3CSO_2OH.[562] The mechanism in this case is different.



OS **II**, 522.

11-25 Cyanation or Cyano-de-hydrogenation



Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate [$Hg(ONC)_2$].[563] In the case of Cl_3CCN, the actual attacking entity is probably $Cl_3C—C^+=NH$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines (ArNHR), as well as phenols, can be cyanated in the ortho position with Cl_3CCN and BCl_3.[564]

Note that aryl triflates are converted to the aryl nitrile by treatment with $Zn(CN)_2$ and a Pd catalyst.[565]

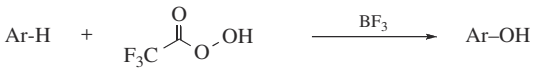
OS **III**, 293.

[558] Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* ***1979****, 44,* 578.
[559] For an exception, see Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* ***1981****, 46*, 189.
[560] Zil'berman, E.N.; Rybakova, N.A. *J. Gen. Chem. USSR* ***1960****, 30*, 1972.
[561] See Ruske, W. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 383; Jeffery, E.A.; Satchell, D.P.N. *J. Chem. Soc. B* ***1966***, 579.
[562] Amer, M.I.; Booth, B.L.; Noori, G.F.M.; Proença, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1075.
[563] Olah, G.A. in Olah, G.A. in Olah, *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 119–120.
[564] Adachi, M.; Sugasawa, T. *Synth. Commun.* ***1990****, 20,* 71.
[565] Kubota, H.; Rice, K.C. *Tetrahedron Lett.* ***1998****, 39,* 2907.

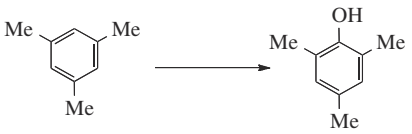
F. Oxygen Electrophiles

Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

11-26 Hydroxylation or Hydroxy-de-hydrogenation



There have been only a few reports of direct hydroxylation[566] by an electrophilic process (see, however, **14-5**).[567] In general, poor results are obtained, partly because the introduction of an OH group activates the ring, which suppresses further reaction. Quinone formation is common. However, alkyl-substituted benzenes (e.g., mesitylene or durene) can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[568] In the case of mesitylene, the product (**67**) is not subject to further attack.



67

In a related procedure, even benzene and substituted benzenes (e.g., PhMe, PhCl, and xylenes) can be converted to phenols in good yields with sodium perborate–F_3CSO_2OH.[569] Aromatic amines, *N*-acyl amines, and phenols were hydroxylated with H_2O_2 in SbF_5-HF.[570] Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite (AcOF) at $-75\,^{\circ}C$.[571]

Another hydroxylation reaction is the *Elbs reaction*.[572] In this method, phenols can be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution.[573] Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland–Sims oxidation*. Yields are low with either phenols or amines, generally $<50\%$. The mechanisms are not clear,[574] but for the *Boyland–Sims oxidation* there is evidence that the $S_2O_8^{2-}$ ion attacks at the ipso position, and then a migration follows.[575]

[566] For a list of hydroxylation reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 977–978.
[567] See Jacquesy, J.; Gesson, J.; Jouannetaud, M. *Rev. Chem. Intermed.* ***1988****, 9,* 1, see pp. 5–10; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 173–176, 347–350.
[568] Hart, H.; Buehler, C.A. *J. Org. Chem.* ***1964****, 29,* 2397. See also, Hart, H. *Acc. Chem. Res.* ***1971****, 4,* 337.
[569] Prakash, G.K.S.; Krass, N.; Wang, Q.; Olah, G.A. *Synlett* ***1991***, 39.
[570] Berrier, C.; Carreyre, H.; Jacquesy, J.; Joannetaud, M. *New J. Chem.* ***1990****, 14,* 283, and cited references.
[571] Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* ***1987****, 109,* 3789.
[572] See Behrman, E.J. *Org. React.* ***1988****, 35,* 421.
[573] See Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1982****, 23,* 1573, 1577.
[574] Walling, C.; Camaioni, D.M.; Kim, S.S. *J. Am. Chem. Soc.* ***1978****, 100,* 4814.
[575] Srinivasan, C.; Perumal, S.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1855.

Electrolysis of benzene, in the presence of trifluoroacetic acid and triethylamine, leads to a 73% yield of phenol.[576] Photolytic hydroxylation of benzene has been reported in the presence of mesoporous TiO_2.[577] Deactivated rings (e.g., nitrobenzene) are selectively ortho hydroxylated by molecular oxygen in the presence of $H_5PV_2Mo_{10}O_{40}$ polyoxometalate.[578] Nitrous oxide has been used as an oxidant, in the presence of FeAlPO catalysts.[579]

G. Metal Electrophiles

Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (Reactions **12-22** and **12-23**).

11.F.ii. Hydrogen as the Leaving Group in Rearrangement Reactions

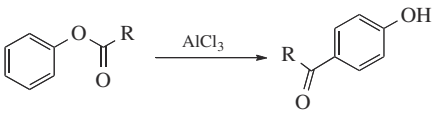
In these reactions, a group is detached from a *side chain* and then reattached the ring, but in other aspects they resemble the reactions already treated in this chapter.[580] Since a group moves from one position to another in a molecule, these are rearrangements (also see Chap 18). In all these reactions, the question arises as to whether the group that cleaves from a given molecule is attacked by the same molecule or another one; that is, Is the reaction intramolecular or intermolecular? For intermolecular reactions, the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases the migrating group could never be completely free, or else it would be able to react with another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.[581]

The *Claisen* (Reaction **18-33**) and *benzidine* (Reaction **18-36**) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups Cleaving from Oxygen

11-27 The Fries Rearrangement

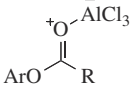
1/*C*-Hydro,5/*O*-acyl-interchange[582]



[576] Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* ***1996****, 52*, 3889.
[577] Shiraishi, Y.; Saito, N.; Hirai, T. *J. Am. Chem. Soc.* ***2005****, 127,* 12820. Also see Mita, S.; Sakamoto, T.; Yamada, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* ***2005****, 46,* 7729; Tani, M.; Sakamoto, T.; Mita, S.; Sakaguchi, S.; Ishii, Y. *Angew. Chem. Int. Ed.* ***2005****, 44,* 2586.
[578] Khenkin, A.M.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* ***2005****, 127,* 9988.
[579] Shiju, N.R.; Fiddy, S.; Sonntag, O.; Stockenhuber, M.; Sankar, G. *Chem. Commun.* ***2006***, 4955.
[580] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***; Williams, D.L.H.; Buncel, I.M. *Isot. Org. Chem.* ***1980****, 5,* 147; Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 433–486.
[581] See Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.
[582] This is the name for the para migration. For the ortho migration, the name is 1/*C*-hydro,3/*O*-acyl-interchange.

Phenolic esters can be rearranged by heating with *Friedel–Crafts catalyst*s in a synthetically useful reaction known as the *Fries rearrangement*.[583] Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. The ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Exceptions are known, but low temperatures generally favor the para product and high temperatures favor the ortho product. The R group may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a *Friedel–Crafts* process. In the case of aryl benzoates treated with F_3CSO_2OH, the *Fries rearrangement* was shown to be reversible and an equilibrium was established.[584] Transition metal catalyzed *Fries rearrangements* have been reported.[585]

Questions remain about the exact mechanism.[586] Opinions have been expressed that it is completely intermolecular,[587] completely intramolecular,[588] and partially inter- and intramolecular.[589] One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in Reaction **11-17**, an initial complex (**68**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required. In the presence of aluminum chloride, the *Fries rearrangement* can be induced with microwave irradiation.[590] Simply heating phenyl acetate with microwave irradiation gives the *Fries rearrangement*.[591] The *Fries rearrangement* has been carried out in ionic melts.[592]



68

[583] See Shine, H.J. *Aromatic Rearrangments*, Elsevier, NY, ***1967***, pp. 72–82, 365–368; Gerecs, A. in Olah, G.A. in Olah, G. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 499–533. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, p. 1310.

[584] Effenberger, F.; Gutmann, R. *Chem. Ber.* ***1982****, 115,* 1089.

[585] With **Hf(OTf)$_4$** see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996****, 37*, 2053. With **Sc(OTf)$_3$**, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996****, 37*, 4183; with **ZrCl$_4$** see Harrowven, D.C.; Dainty, R.F. *Tetrahedron Lett.* ***1996****, 37*, 7659.

[586] See Sharghi, H.; Eshghi, H. *Bull. Chem. Soc. Jpn.* ***1993****, 66*, 135.

[587] Martin, R.; Gavard, J.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* ***1986***, 659 and cited references.

[588] Ogata, Y.; Tabuchi, H. *Tetrahedron* ***1964****, 20,* 1661.

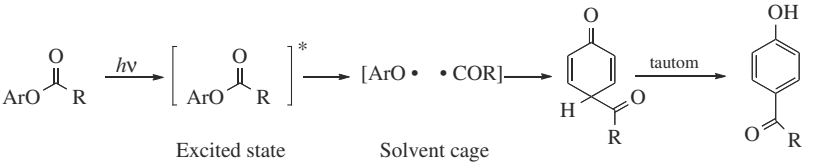
[589] Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.

[590] Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999****, 29*, 1195.

[591] Paul, S.; Gupta, M. *Synthesis* ***2004***, 1789.

[592] Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001****, 42*, 1979.

The *Fries rearrangement* can also be carried out with UV light, in the absence of a catalyst.[593] This reaction, called the *photo-Fries rearrangement*,[594] is predominantly an intramolecular free radical process. Both ortho and para migration are observed.[595] Unlike the Lewis acid catalyzed *Fries rearrangement*, the *photo-Fries reaction* can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following mechanism involving formation of the excited state ester followed by dissociation to a radical pair[596] for the *photo-Fries rearrangement*[597] (illustrated for para attack).



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogen atoms), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.[598] Other evidence[599] for the mechanism is that CIDNP has been observed during the course of the reaction[600] and that the ArO• radical has been detected by flash photolysis[601] and by nanosecond time-resolved Raman spectroscopy.[602]

A LDA-mediated *anionic Fries rearrangement* of aryl carbamates has been reported.[603] The so-called *anionic Snieckus–Fries rearrangement* has also been discussed.[604]

Treatment of *O*-arylsulfonate esters with $AlCl_3$—$ZnCl_2$, on silica with microwave irradiation, leads to 2-sulfonyl phenols in a *thia-Fries rearrangement*.[605] A similar reaction was reported with *O*-arylsulfonamides.[606]

OS **II**, 543; **III**, 280, 282.

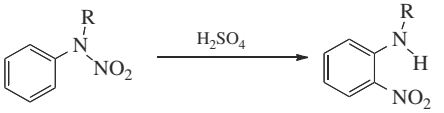
[593] Finnegan, R.A.; Matice, J.J. *Tetrahedron* ***1965****, 21*, 1015.
[594] See Bellus, D. *Adv. Photochem.* ***1971****, 8*, 109; Bellus, D.; Hrdlovic, P. *Chem. Rev.* ***1967****, 67,* 599. See Cui, C.; Wang, X.; Weiss, R.G. *J. Org. Chem.* ***1996****, 61*, 1962.
[595] The migration can be made almost entirely ortho by cyclodextrin encapsulation (see Sec. 3.C.iv): Syamala, M.S.; Rao, B.N.; Ramamurthy, V. *Tetrahedron* ***1988****, 44,* 7234. See also, Veglia, A.V.; Sanchez, A.M.; de Rossi, R.H. *J. Org. Chem.* ***1990****, 55,* 4083.
[596] Proposed by Kobsa, H. *J. Org. Chem.* ***1962****, 27*, 2293.
[597] It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Sander, M.R.; Hedaya, E.; Trecker, D.J. *J. Am. Chem. Soc.* ***1968****, 90*, 7249; Bellus, D. *Adv. Photochem.* ***1971****, 8*, 109.
[598] Meyer, J.W.; Hammond, G.S. *J. Am. Chem. Soc.* ***1972****, 94,* 2219.
[599] See Shine, H.J.; Subotkowski, W. *J. Org. Chem.* ***1987****, 52*, 3815.
[600] Adam, W. *J. Chem. Soc., Chem. Commun.* ***1974***, 289.
[601] Kalmus, C.E.; Hercules D.M. *J. Am. Chem. Soc.* ***1974****, 96,* 449.
[602] Beck, S.M.; Brus, L.E. *J. Am. Chem. Soc.* ***1982****, 104,* 1805.
[603] For a discussion of the role of aggregates and mixed aggregates in this reaction, see Singh, K.J.; Collum, D.B. *J. Am. Chem. Soc.* ***2006****, 128*, 13753.
[604] Riggs, J.C.; Singh, K.J.; Yun, M.; Collum, D.B. *J. Am. Chem. Soc.* ***2008****, 130,* 13709.
[605] Moghaddam, F.M.; Dakamin, M.G. *Tetrahedron Lett.* ***2000****, 41*, 3479.
[606] Benson, G.A.; Maughan, P.J.; Shelly, D.P.; Spillane, W.J. *Tetrahedron Lett.* ***2001****, 42*, 8729.

B. Groups Cleaving from Nitrogen[607]

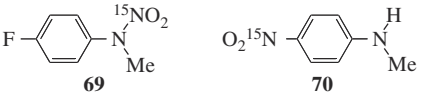
It has been shown that $PhNH_2D$ rearranges to *o*- and *p*-deuterioaniline.[608] The migration of OH, formally similar to Reactions **11-28**–**11-32**, is a nucleophilic substitution and is treated in Chapter 13 (**13-32**).

11-28 Migration of the Nitro Group

1/ *C*-Hydro,3/*N*-nitro-interchange

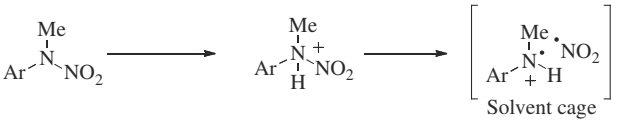


N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.[609] Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,[610] although direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring and then is attacked by another molecule must be ruled out. Further results indicating an intramolecular process include the observation that rearrangement of several substrates in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[611] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled *p*-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[612] On the other hand, rearrangement of



69 **70**

69 in the presence of unlabeled $PhNMeNO_2$ gave labeled **70**, which did not arise by displacement of F.[613] The R group may be hydrogen or alkyl. Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,[614] and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.[615] Among the evidence

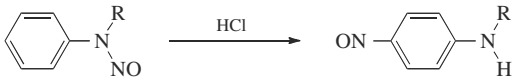


[607] See Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand–Reinhold, Princeton, NJ, ***1973***, pp. 192–199.
[608] Okazaki, N.; Okumura, A. *Bull. Chem. Soc. Jpn.* ***1961****, 34,* 989.
[609] See Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F,* pt. 1, Wiley, NY, ***1982***, pp. 127–153; White, W.N. *Mech. Mol. Migr.* ***1971****, 3,* 109–143; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 235–249.
[610] Hughes, E.D.; Jones, G.T. *J. Chem. Soc.* ***1950***, 2678.
[611] Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.
[612] Geller, B.A.; Dubrova, L.N. *J. Gen. Chem. USSR* ***1960****, 30,* 2627.
[613] White, W.N.; Golden, J.T. *J. Org. Chem.* ***1970****, 35,* 2759.
[614] Banthorpe, D.V.; Thomas, J.A. *J. Chem. Soc.* ***1965***, 7149, 7158. Also see, Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.
[615] White, W.N.; White, H.S.; Fentiman, A. *J. Org. Chem.* ***1976****, 41*, 3166.

for the latter view[616] are the effects of substituents on the rate of the reaction,[617] ^{15}N and ^{14}C kinetic isotope effects that show nonconcertedness,[618] and the fact that both *N*-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-*N*-methylaniline.[619] These side products are formed when the radicals escape from the solvent cage.

11-29 Migration of the Nitroso Group: The Fischer–Hepp Rearrangement

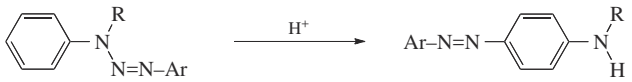
1/ *C*-Hydro-5/*N*-nitroso-interchange



The migration of a nitroso group, formally similar to Reaction **11-28**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct *C*-nitrosation of secondary aromatic amines (see Reaction **12-50**). The reaction, known as the *Fischer–Hepp rearrangement*,[620] is brought about by treatment of *N*-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems, the para product is usually formed exclusively.[621] The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea[622] shows that it is intramolecular[623] since, if NO^+, NOCl, or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

11-30 Migration of an Arylazo Group

1/*C*-Hydro-5/ *N*-arylazo-interchange

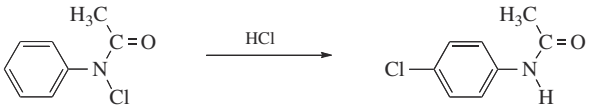


Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.[624] These are first diazotized at the amino group (see Reaction **11-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

[616] See White, W.N.; Klink, J.R. *J. Org. Chem.* ***1977****, 42,* 166; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1982***, 261.
[617] White, W.N.; Klink, J.R. *J. Org. Chem.* ***1970****, 35*, 965.
[618] Shine, H.J.; Zygmunt, J.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984****, 106*, 3610.
[619] White, W.N.; White, H.S. *J. Org. Chem.* ***1970****, 35*, 1803.
[620] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 113–128; Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 231–235.
[621] See Titova, S.P.; Arinich, A.K.; Gorelik, M.V. *J. Org. Chem. USSR* ***1986****, 22*, 1407.
[622] Morgan, T.D.B.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 74.
[623] See also, Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 801.
[624] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 212–221.

11-31 Migration of Halogen: The Orton Rearrangement

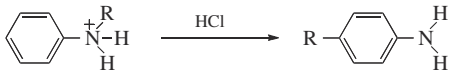
1/*C*-Hydro-5/*N*-halo-interchange



Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.[625] The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with *N*-chloro- and *N*-bromoamines and less often with *N*-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is considerable evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.[626] First, the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2; then the chlorine halogenates the ring as in Reaction **11-10**. Among the evidence is that chlorine has been isolated from the reaction mixture. The *Orton rearrangement* can also be brought about photochemically[627] and by heating in the presence of benzoyl peroxide.[628] These are free radical processes.

11-32 Migration of an Alkyl Group[629]

1/*C*-Hydro-5/*N*-alkyl-interchange



When HCl salts of arylalkylamines are heated at ~200–00 °C, migration occurs in what is called the *Hofmann–Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine, but also aniline and di- and trimethylanilines.[630] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:

$$R\overset{+}{N}H_2Ar + Cl^- \longrightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^-, Cl^-, and I^- gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.[630] Further evidence is that the alkyl halides isolated are not rearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal *Friedel–Crafts alkylation* process (Reaction **11-11**), accounting

[625] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 221–230, 362–364: Bieron, J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 263–269.
[626] See Golding, P.D.; Reddy, S.; Scott, J.M.W.; White, V.A.; Winter, J.G. *Can. J. Chem.* ***1981,*** *59*, 839.
[627] See Hodges, F.W. *J. Chem. Soc.* ***1933***, 240.
[628] See Coulson, J.; Williams, G.H.; Johnston, K.M. *J. Chem. Soc. B* ***1967***, 174.
[629] See Grillot, G.F. *Mech. Mol. Migr.* ***1971,*** *3* 237; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 249–257.
[630] Ogata, Y.; Tabuchi, H.; Yoshida, K. *Tetrahedron* ***1964,*** *20,* 2717.

for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.[631]

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350 °C with a metal halide (e.g., $CoCl_2$, $CdCl_2$, or $ZnCl_2$). When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[632] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.

When acylated arylamines are photolyzed, migration of an acyl group takes place[633] in a process that resembles the photo-Fries reaction (**11-27**).

11.F.iii. Other Leaving Groups

Three types of reactions are considered in this section.

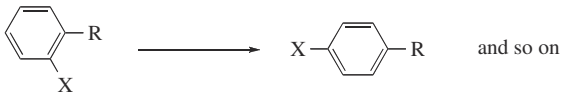
1. Reactions in which hydrogen replaces another leaving group:

$$ArX + H^+ \longrightarrow ArH$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$ArX + Y^+ \longrightarrow ArY$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:



The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

11-3 Reversal of Friedel–Crafts Alkylation

Hydro-de-alkylation or **Dealkylation**

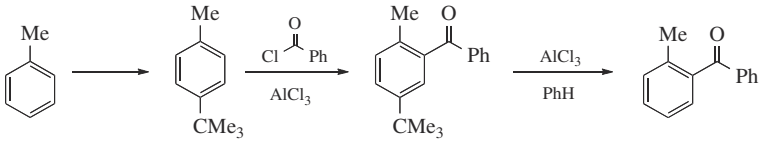
$$ArR + H^+ \xrightarrow{AlCl_3} ArH$$

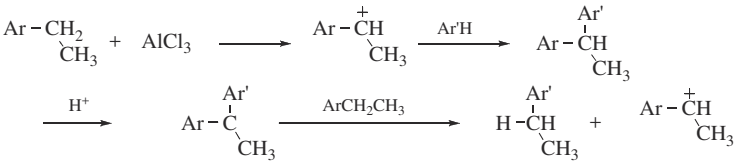
Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed.[634] For example, 4-*tert*-butyltoluene (**71**) reacted with benzoyl chloride and $AlCl_3$ to give the acylated product, and subsequent treatment with $AlCl_3$ led to loss of the *tert*-butyl group to give **72**.[635]

Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using *Friedel–Crafts catalysts* (Lewis or proton acids)

[631] Hart, H.; Kosak, J.R. *J. Org. Chem.* ***1962****, 27,* 116.
[632] See Birchal, J.M.; Clark, M.T.; Goldwhite, H.; Thorpe, D.H. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2579.
[633] See Nassetta, M.; de Rossi, R.H.; Cosa, J.J. *Can. J. Chem.* ***1988****, 66,* 2794.
[634] See Tashiro, M. *Synthesis* ***1979***, 921; Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* ***1976****, 8*, 51.
[635] Hofman, P.S.; Reiding, D.J.; Nauta, W.T. *Recl. Trav. Chim. Pays-Bas* ***1960****, 79,* 790.

on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an alkene, occurs only at high temperatures, >400 °C.[636] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5-product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes[637] (entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position[638] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*- but no *p*-xylene, while *p*-xylene gave *p*- and *m*- but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments[639] (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[640]



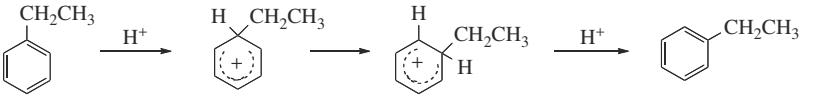


The mechanism[641] of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.[642]

Evidence for this mechanism is that optically active $PhCHDCH_3$ labeled in the ring with ^{14}C and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and two deuterium atoms and that the rate of loss of radioactivity was about equal

[636] Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 36–38.
[637] McCaulay, D.A.; Lien, A.P. *J. Am. Chem. Soc.* ***1953****, 75,* 2407. For similar results, see Bakoss, H.J.; Roberts, R. M.G.; Sadri, A.R. *J. Org. Chem.* ***1982****, 47*, 4053.
[638] Roberts, R.M.G.; Douglass, J.E. *J. Org. Chem.* ***1963****, 28,* 1225.
[639] Allen, R.H.; Yats, L.D. *J. Am. Chem. Soc.* ***1959****, 81,* 5289.
[640] Allen, R.H. *J. Am. Chem. Soc.* ***1960****, 82*, 4856.
[641] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 1–55.
[642] Streitwieser, Jr., A.; Reif, L. *J. Am. Chem. Soc.* ***1964****, 86,* 1988.

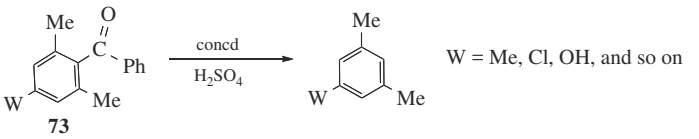
to the rate of loss of optical activity.[642] The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed:[643]



There is evidence from ^{14}C labeling that intramolecular migration occurs only through 1,2-shifts.[644] Any 1,3- or 1,4-migration takes place by a series of two or more 1,2-shifts.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3—H_2O$, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[645] Alkyl groups have also been replaced by groups other than hydrogen (nitro groups).

Unlike alkylation, *Friedel–Crafts acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,[646] especially where there are two ortho substituents (e.g., the hydro-de-benzoylation of **73**).[647]



73

OS **V**, 332. Also see, OS **III**, 282, 653; **V**, 598.

11-34 Decarbonylation of Aromatic Aldehydes

Hydro-de-formylation or **Deformylation**

$$ArCHO \xrightarrow{H_2SO_4} ArH + CO$$

The decarbonylation of aromatic aldehydes with sulfuric acid[648] is the reverse of the *Gatterman–Koch reaction* (**11-18**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: The attacking species is H^+ and the leaving group is HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[649] Aromatic aldehydes

[643] Olah, G.A.; Meyer, M.W.; Overchuk, N.A. *J. Org. Chem.* ***1964****, 29,* 2313.

[644] See Steinberg, H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962****, 81,* 185; Koptyug, V.A.; Isaev, I.S.; Vorozhtsov, Jr., N.N. *Doklad. Akad. Nauk SSSR,* ***1963****, 149*, 100.

[645] Olah, G.A.; Meyer, M.W. *J. Org. Chem.* ***1962****, 27,* 3682.

[646] See Keumi, T.; Morita, T.; Ozawa, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 599; Giordano, C.; Villa, M.; Annunziata, R. *Synth. Commun.* ***1990****, 20,* 383.

[647] Al-Ka'bi, J.; Farooqi, J.A.; Gore, P.H.; Moonga, B.S.; Waters, D.N. *J. Chem. Res. (S)* ***1989***, 80.

[648] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 316–323; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 695–760.

[649] Burkett, H.; Schubert, W.M.; Schultz, F.; Murphy, R.B.; Talbott, R. *J. Am. Chem. Soc.* ***1959****, 81,* 3923.

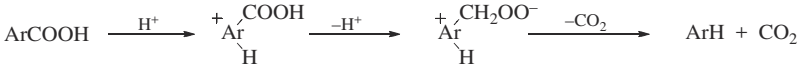
have also been decarbonylated with basic catalysts.[650] When basic catalysts are used, the mechanism is probably similar to the S_E1 process of Reaction **11-35** (see also, Reaction **14-32**).

11-35 Decarboxylation of Aromatic Acids

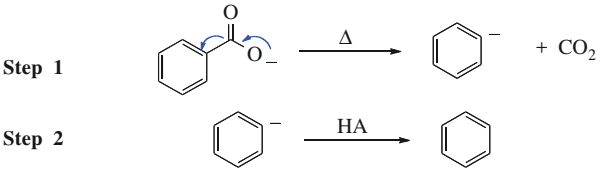
Hydro-de-carboxylation or **Decarboxylation**

$$\mathrm{ArCOOH} \xrightarrow[\text{quinoline}]{\text{Cu}} \mathrm{ArH} + \mathrm{CO_2}$$

The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method, the salt of the acid ($\mathrm{ArCOO^-}$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups. In this method, decarboxylation takes place by the arenium ion mechanism,[651] with H^+ as the electrophile and CO_2 as the leaving group.[652] Evidently, the order of electrofugal ability is $CO_2 > H^+ > COOH^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.



When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the S_E1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.[653]



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.[654] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.[654] It has been shown that cuprous salts of aromatic acids

[650] Bunnett, J.F.; Miles J.H.; Nahabedian, K.V. *J. Am. Chem. Soc.* ***1961****, 83*, 2512; Forbes, E.J.; Gregory, M.J. *J. Chem. Soc. B* ***1968***, 205.

[651] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 303–316; Willi, A.V. *Isot. Org. Chem.* ***1977****, 3,* 257.

[652] See Willi, A.V.; Cho, M.H.; Won, C.M. *Helv. Chim. Acta* ***1970****, 53*, 663.

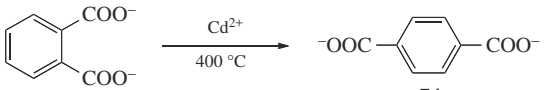
[653] See Segura, P.; Bunnett, J.F.; Villanova, L. *J. Org. Chem.* ***1985****, 50*, 1041.

[654] Cohen, T.; Schambach, R.A. *J. Am. Chem. Soc.* ***1970****, 92,* 3189. See also, Aalten, H.L.; van Koten, G.; Tromp, J.; Stam, C.H.; Goubitz, K.; Mak, A.N.S. *Recl. Trav. Chim. Pays-Bas* ***1989****, 108,* 295.

are easily decarboxylated by heating in quinoline[655] and that arylcopper compounds are intermediates that can be isolated in some cases.[656] Metallic silver has been used in place of copper, with higher yields.[657] Silver acetate has also been used to promote decarboxylation.[658] A photolytic decarboxylation also has been reported, under a dioxygen atmosphere in the presence of HgF_2.[659]

In certain cases, the carboxyl group can be replaced by electrophiles other than hydrogen (e.g., NO,[657] I,[660] Br,[661] or Hg).[662] Although closely related to reactions in Chapter 13 (Reactions **13-9**, **13-11**, and **13-12**), a decarboxylative coupling reaction of aryl halides and arylcarboxylic acids has been reported, using Pd and Cu catalysts, to give the corresponding biaryl.[663]

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**74**) is produced:[664]



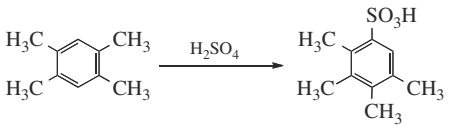
Phthalate ion **74**

In a similar process, potassium benzoate heated with Cd salts disproportionates to benzene and **74**. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.[665] An S_E1 mechanism has been suggested.[666] The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[667]

For aliphatic decarboxylation, see Reaction **12-40**.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see, OS **I**, 56.

11-36 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be

[655] Cohen, T.; Berninger, R.W.; Wood, J.T. *J. Org. Chem.* ***1978****, 43*, 37.
[656] See Ibne-Rasa, K.M. *J. Am. Chem. Soc.* ***1962****, 84,* 4962.
[657] Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* ***1970****, 24,* 3353.
[658] Gooßen, L.J.; Linder, C.; Rodríguez, N.; Lange, P.P.; Fromm, A. *Chem. Commun.* ***2009***, 7173.
[659] Farhadi, S.; Zaringhadam, P.; Sahamieh, R.Z. *Tetrahedron Lett.* ***2006****, 47,* 1965.
[660] Singh, R.; Just, G. *Synth. Commun.* ***1988****, 18*, 1327.
[661] See Grovenstein, Jr., E.; Ropp, G.A. *J. Am. Chem. Soc.* ***1956****, 78*, 2560.
[662] Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 101–105.
[663] Goossen, L.J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L.M. *J. Am. Chem. Soc.* ***2007****, 129,* 4824; Goossen, L.J.; Rodrguez, N.; Linder, C. *J. Am. Chem. Soc.* ***2008****, 130,* 15248.
[664] Ogata, Y.; Nakajima, K. *Tetrahedron* ***1965****, 21,* 2393; Ratusky, J.; Sorm, F. *Chem. Ind. (London)*, ***1966***, 1798.
[665] See Ratusky, J. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 915–944.
[666] See Ratusky, J. *Collect. Czech. Chem. Commun.* ***1973****, 38*, 74, 87, and references cited therein.
[667] Ratusky, J. *Collect. Czech. Chem. Commun.* ***1968****, 33,* 2346.

any combination of alkyl and halogen groups, where the alkyl groups can be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give alkenes. Since a sulfo group can later be removed (Reaction **11-38**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, and so on, indicating an intermolecular process, at least partially.

The mechanism of the *Jacobsen reaction* is not established,[668] but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.[669] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[670]

Isomerization of alkyl groups in substituted biphenyls has been observed[671] when the medium is a superacid (see Sec. 5.A.ii).

B. Oxygen Leaving Groups

11-37 Deoxygenation

$$\mathrm{ArOR} \longrightarrow \mathrm{ArH}$$

In a few cases, it is possible to remove an oxygen substituent directly from the aromatic ring. Treatment of an aryl mesylate (ArOMs) with a Ni catalyst in DMF, for example, leads to the deoxygenated product, Ar-H.[672]

C. Sulfur Leaving Groups

11-38 Desulfonation or Hydro-de-sulfonation

$$\mathrm{ArSO_3H} \xrightarrow[\text{dil. } \mathrm{H_2SO_4}]{135-200^\circ\mathrm{C}} \mathrm{ArH} + \mathrm{H_2SO_4}$$

The cleavage of sulfo groups from aromatic rings is the reverse of Reaction **11-7**.[673] By the principle of microscopic reversibility, the mechanism is also the reverse.[674] Dilution is generally used, as the reversibility of sulfonation decreases with increasing H_2SO_4 concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[675] In another catalytic process, aromatic

[668] See Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 717; Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 214–226; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 22–32, 48–55.

[669] Cerfontain, H.; Koeberg-Telder, A. *Can. J. Chem.* ***1988****, 66,* 162.

[670] Marvell, E.N.; Webb, D. *J. Org. Chem.* ***1962****, 27,* 4408.

[671] Sherman, S.C.; Iretskii, A.V.; White, M.G.; Gumienny, C.; Tolbert, L.M.; Schiraldi, D.A. *J. Org. Chem.* ***2002****, 67,* 2034.

[672] Sasaki, K.; Kubo, T.; Sakai, M.; Kuroda, Y. *Chem. Lett,* ***1997***, 617.

[673] See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 185–214; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 349–355; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 427–442. See also, Krylov, E.N. *J. Org. Chem. USSR* ***1988****, 24,* 709.

[674] See Kozlov, V.A.; Bagrovskaya, N.A. *J. Org. Chem. USSR* ***1989****, 25*, 1152.

[675] Feigl, F. *Angew. Chem.* ***1961****, 73*, 113.

sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with an Rh catalyst.[676] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in Reaction **14-32**.

$$ArSO_2Br \xrightarrow{RhCl(PPh_3)_3} ArBr$$

OS **I**, 388; **II**, 97; **III**, 262; **IV**, 364. Also see, OS **I**, 519; **II**, 128; **V**, 1070.

D. Halogen Leaving groups

11-39 Dehalogenation or Hydro-de-halogenation

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by *Friedel–Crafts catalysts*. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, Br^- or I^- is present to combine with the I^+ or Br^+ coming off.[677] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,[678] both intramolecular[679] and intermolecular.[680] The mechanism is probably the reverse of that of Reaction **11-10**.[681] Debromination of aromatic rings having two attached amino groups was accomplished by refluxing in aniline containing acetic acid/HBr.[682]

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases (e.g., 1,2,4-tribromobenzene) is converted to 1,3,5-tribromobenzene by treatment with PhNHK.[683] This reaction, which involves aryl carbanion intermediates (S_E1 mechanism), has been called the *halogen dance*.[684]

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Bu_3SnH,[685] catalytic-hydrogenolysis,[686] catalytic-transfer hydrogenolysis,[687] Na—Hg in liquid NH_3,[688] $LiAlH_4$,[689] $NaBH_4$ and a catalyst,[690] NaH,[691] HCO_2H[692] or

[676] Blum, J.; Scharf, G. *J. Org. Chem.* ***1970****, 35,* 1895.
[677] Pettit, G.R.; Piatak, D.M. *J. Org. Chem.* ***1960****, 25*, 721.
[678] Olah, G.A.; Meidar, D.; Olah, J.A. *Nouv. J. Chim.*, ***1979****, 3,* 275.
[679] Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* ***1982****, 23,* 1673.
[680] Augustijn, G.J.P.; Kooyman, E.C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* ***1963****, 82,* 965.
[681] Choguill, H.S.; Ridd, J.H. *J. Chem. Soc.* ***1961***, 822; Shine, H.J. *Aromatic Rearrangements, Elsevier, NY,* ***1967***, p. 1; Ref. 636.
[682] Choi, H.; Chi, D.Y. *J. Am. Chem. Soc.* ***2001****, 123,* 9202.
[683] Moyer, Jr., C.E.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1963****, 85,* 1891.
[684] Bunnett, J.F. *Acc. Chem. Res.* ***1972****, 5,* 139; Mach, M.H.; Bunnett, J.F. *J. Org. Chem.* ***1980****, 45,* 4660; Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* ***1989***, 771.
[685] Maitra, U.; Sarma, K.D. *Tetrahedron Lett.* ***1994****, 35*, 7861.
[686] See Subba Rao, Y.V.; Mukkanti, K.; Choudary, B.M. *J. Organomet. Chem.* ***1989****, 367,* C29. See also, Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* ***2002****, 43*, 7247.
[687] Anwer, M.K.; Spatola, A.F. *Tetrahedron Lett.* ***1985****, 26,* 1381.
[688] Austin, E.; Alonso, R.A.; Rossi, R.A. *J. Chem. Res. (S)* ***1990***, 190.
[689] Brown, H.C.; Chung, S.; Chung, F. *Tetrahedron Lett.* ***1979***, 2473. See Chung, F.; Filmore, K.L. *J. Chem. Soc., Chem. Commun.* ***1983***, 358; Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 905. See also, Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 907.
[690] Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* ***1989****, 54*, 5308.
[691] Nelson, R.B.; Gribble, G.W. *J. Org. Chem.* ***1974****, 39,* 1425.
[692] Barren, J.P.; Baghel, S.S.; McCloskey, P.J. *Synth. Commun.* ***1993****, 23,* 1601.

aq HCO_2^-[693] with Pd/C,[694] ammonium formate in aq isopropyl alcohol with a Pd catalyst,[695] and Raney nickel in alkaline solution,[696] the last method being effective for fluorine as well as for the other halogens. Aryl iodides are reduced with DMAP methiodide salt.[697] Carbon monoxide, with potassium tetracarbonylhydridoferrate [$KHFe(CO)_4$] as a catalyst, specifically reduces aryl iodides.[698] Not all of these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free radical processes. Photochemical[699] and electrochemical[700] reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to *Grignard reagents* (Reaction **12-38**) followed by hydrolysis (Reaction **11-41**).

OS **III**, 132, 475, 519; **V**, 149, 346, 998; **VI**, 82, 821.

11-40 Formation of Organometallic Compounds

$$\mathrm{ArBr + M \longrightarrow ArM}$$
$$\mathrm{ArBr + RM \longrightarrow ArM + RBr}$$

These reactions are considered along with their aliphatic counterparts at Reactions **12-38** and **12-39**.

E. Metal Leaving Groups

11-41 Hydrolysis of Organometallic Compounds

Hydro-de-metalation or **Demetalation**

$$\mathrm{ArM + H^+ \longrightarrow ArH + M^+}$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals (e.g., Mg, Li, etc.), water is sufficiently acidic. The most important example of this reaction is hydrolysis of *Grignard reagents*, but M may be many other metals or metalloids. Examples are SiR_3, HgR, Na, and $B(OH)_2$. Since aryl *Grignard* and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids (e.g., alkynes).

$$\mathrm{PhMgBr + H{-}C{\equiv}C{-}H \longrightarrow H{-}C{\equiv}C{:}^{-}{}^{+}MgBr + PhH}$$

Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.[701] Where the bonding is essentially ionic, this is a simple acid–base reaction. For the aliphatic counterpart of this reaction, see Reaction **12-24**.

Other reactions of aryl organometallic compounds are treated with their aliphatic analogues: Reactions **12-25**–**12-27** and **12-30**–**12-37**.

[693] Arcadi, A.; Cerichelli, G.; Chiarini, M.; Vico, R.; Zorzan, D. *Eur. J. Org. Chem.* ***2004***, 3404.
[694] See Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* ***2006****, 62,* 7926. Also see Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* ***2007****, 63,* 4266.
[695] Nakao, R.; Rhee, H.; Uozumi, Y. *Org. Lett.* ***2005****, 7,* 163.
[696] de Koning, A.J. *Org. Prep. Proced. Int.* ***1975****, 7,* 31.
[697] Garnier, J.; Murphy, J.A.; Zhou, S.-Z.; Turner, A.T. *Synlett* ***2008***, 2127.
[698] Brunet, J.; Taillefer, M. *J. Organomet. Chem.* ***1988****, 348,* C5.
[699] See Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* ***1973****, 95*, 5085.
[700] See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 142–143. Also see, Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992****, 33,* 1499.
[701] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 278–303, 324–349.

CHAPTER 12

Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic

Chapter 11 pointed out that the most important leaving groups in electrophilic substitution are those that can best exist with an outer shell that is deficient in a pair of electrons. For aromatic systems, the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions [e.g., α to a carbonyl group or at an alkynyl position (RC≡CH)]. Since metallic ions are easily able to bear positive charges, organometallic compounds should be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C—C bonds; in these reactions there are carbon leaving groups (Reactions **12-40–12-46**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is generated when an atom or group is removed as a positive species from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

[1] See Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, 5 Vols., Wiley, NY, ***1984–1990***; Haiduc, I.; Zuckerman, J.J. *Basic Organometallic Chemistry*, Walter de Gruyter, NY, ***1985***; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***; Aylett, B.J. *Organometallic Compounds*, 4th ed., Vol. 1, pt. 2; Chapman and Hall, NY, ***1979***; Maslowsky, Jr., E. *Chem. Soc. Rev.* ***1980***, *9*, 25, and in Tsutsui, M. *Characterization of Organometallic Compounds*, Wiley, NY, ***1969–1971***, the articles by Cartledge, F.K.; Gilman, H. pt. 1, pp. 1–33, and by Reichle, W.T. pt. 2, pp. 653–826.

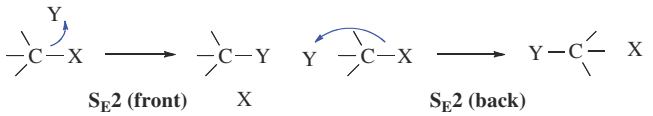
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

12.A. MECHANISMS

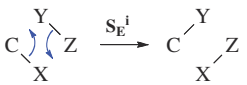
For aliphatic electrophilic substitution, at least four possible major mechanisms can be distinguished:[2] S_E1, S_E2 (front), S_E2 (back), and S_Ei. The S_E1 is unimolecular; the other three are bimolecular. Note that the term "S_EAr" has been proposed to represent electrophilic aromatic substitution, so that the term "S_E2" refers exclusively to electrophilic substitutions where a steric course is possible.[3] To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" were proposed, referring to retention and inversion of configuration, respectively.

12.A.i. Bimolecular Mechanisms: S_E2 and S_Ei

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this also means that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, it brings only a vacant orbital to the substrate. Predicting the direction of the attack is not as straightforward. Two main possibilities can be imagined: delivery of the electrophile to the front, which is S_E2 (front), or delivery of the electrophile to the rear, which is S_E2 (back). The possibilities can be pictured (charges not shown):



Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which these possibilities may be distinguished, the former mechanism should result in retention of configuration and the latter results in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the antiproduct via a S_E2' reaction.[4] When the electrophile reacts from the front, there is a third possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C—Y bond is formed:

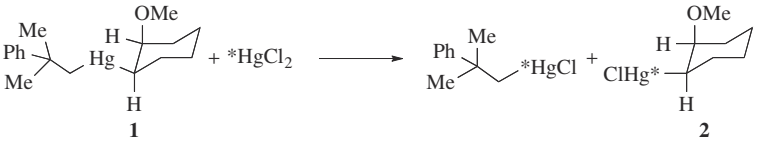


[2] See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North-Holland Publishing Company, Amsterdam, The Netherlands, ***1968***; Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149; Reutov, O.A. *Pure Appl. Chem.* ***1978***, *50*, 717; *Tetrahedron* ***1978***, *34*, 2827.

[3] Gawley, R.E. *Tetrahedron Lett.* ***1999***, *40,* 4297.

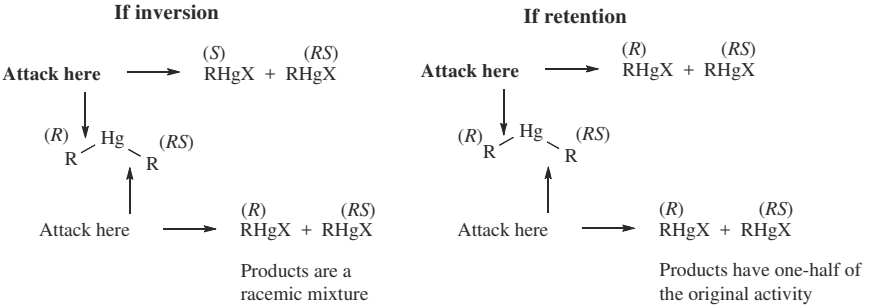
[4] Buckle, M.J.C.; Fleming, I.; Gil, S. *Tetrahedron Lett.* ***1992***, *33*, 4479.

This mechanism, which is called the S_Ei mechanism[5] (IUPAC designation: *cyclo*-$D_EA_ED_nA_n$), also results in retention of configuration.[6] Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.



1 **2**

It is evident that these three mechanisms are not easy to distinguish. All three mechanisms give second-order kinetics, and two mechanisms result in retention of configuration.[7] In fact, although much work has been done on this question, there are few cases in which one of these three can be unequivocally established to demonstrate that another is not actually taking place. Clearly, a study of the stereochemistry can distinguish between S_E2 (back) on the one hand and S_E2 (front) or S_Ei on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_E2 (front) or S_Ei mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg—C bond), since each of the products contained about one-half of the labeled mercury.[8] Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (see Sec. 10.A.i).[9] Still another indication is the behavior of neopentyl as a substrate. The S_N2 reactions at neopentyl are extremely slow (Sec. 10.G.i), because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[10] is further evidence for frontside attack. One final elegant experiment may be noted.



[5] The names for these mechanisms vary throughout the literature. For example, the S_Ei mechanism has also been called the S_E2, the S_E2 (closed), and the S_E2 (cyclic) mechanism. The original designations, S_E1, S_E2, and so on, were devised by the Hughes–Ingold school.

[6] It has been contended that the S_Ei mechanism violates the principle of conservation of orbital symmetry (sec Reaction **15-60, A**), and that the S_E2 (back) mechanism partially violates it: Slack, D.A.; Baird, M.C. *J. Am. Chem. Soc.* ***1976****, 98,* 5539.

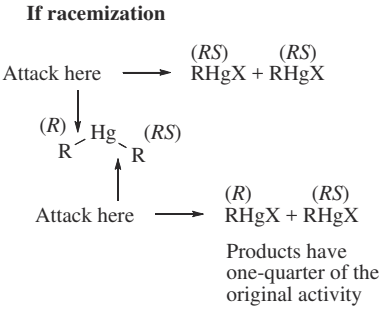
[7] See Flood, T.C. *Top. Stereochem.* ***1981****, 12*, 37. See also, Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971****, 93,* 4048.

[8] Winstein, S.; Traylor, T.G.; Garner, C.S. *J. Am. Chem. Soc.* ***1955****, 77,* 3741.

[9] Schöllkopf, U. *Angew. Chem.* ***1960****, 72*, 147. See Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966****, 1*, 283, pp. 353–370.

[10] Hughes, E.D.; Volger, H.C. *J. Chem. Soc.* ***1961***, 2359.

The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.[11] This compound was prepared by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 molar equivalents of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking. The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.



However, inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (Reaction **12-40**) gives inverted *sec*-butyl bromide.[12] A number of other organometallic compounds have also been shown to give inversion when treated with halogens,[13] although others do not.[14] So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside

$$\textit{sec}\text{-BuSnR}_3 + \text{Br}_2 \longrightarrow \textit{sec}\text{-BuBr} \qquad \text{R} = \text{Neopentyl}$$

attack exist[15] but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located[16] are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,[17] and most stereochemical investigations have therefore been made with these substrates. Only a few optically active *Grignard reagents* (see Sec. **12-38**) have been prepared[18] (i.e., in which the only stereogenic center is the

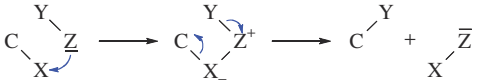
[11] Jensen, F.R. *J. Am. Chem. Soc.* ***1960****, 82*, 2469; Ingold, C.K. *Helv. Chim. Acta* ***1964****, 47,* 1191.
[12] Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971****, 93,* 4048. See Fukuto, J.M.; Jensen, F.R. *Acc. Chem. Res.* ***1983****, 16,* 177.
[13] See Magnuso, R.H.; Halpern, J.; Levitin, I.Ya.; Vol'pin, M.E. *J. Chem. Soc. Chem. Commun.* ***1978***, 44.
[14] See Rahm, A.; Pereyre, M. *J. Am. Chem. Soc.* ***1977****, 99*, 1672; McGahey, L.F.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979****, 101,* 4397; Olszowy, H.A.; Kitching, W. *Organometallics* ***1984****, 3,* 1676. Also see Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* ***1985****, 286,* 305.
[15] See Bergbreiter, D.E.; Rainville, D.P. *J. Organomet. Chem.* ***1976****, 121*, 19.
[16] See Sokolov, V.I. *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach, NY, ***1990***.
[17] See Jensen, F.R.; Whipple, L.D.; Wedegaertner, D.K.; Landgrebe, J.A. *J. Am. Chem. Soc.* ***1959****, 81,* 1262; Charman, H.B.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1959***, 2523, 2530.
[18] This was done first by Walborsky, H.M.; Young, A.E. *J. Am. Chem. Soc.* ***1964****, 86*, 3288.

carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C—Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl *Grignard reagent* with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.[19] It is likely that inversion takes place only when steric hindrance prevents reaction on the frontside and when the electrophile does not carry a Z group (see above).

The S_E2 (back) mechanism can be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the S_E2 (front) and the S_Ei mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the S_Ei mechanism on the one hand and the S_E2 pathways on the other, involves the study of salt effects on the rate. It may be recalled (Sec. 10.G.iv) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the S_Ei mechanism would be less influenced by salt effects than would either of the S_E2 mechanisms. On this basis, Abraham and Johnson[20] concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ (X = Cl or I) take place by S_E2 and not by S_Ei mechanisms. Similar investigations involve changes in solvent polarity[21] (see also, Sec. 12.C.i). In the case of the reaction (where R = R′ = *i*Pr and R = *i*Pr, R′ = neopentyl), the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.[22]

$$\textit{sec}\text{-BuSnR}_2\text{R}' + \text{Br}_2 \longrightarrow \textit{sec}\text{-BuBr}$$

On the basis of evidence from reactivity studies, it has been suggested[23] that a variation of the S_Ei mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



This process has been called the S_EC[22] or S_E2 (co-ord)[24] mechanism (IUPAC designation $A_n + \textit{cyclo}\text{-}D_EA_ED_n$).

It has been shown that in certain cases (e.g., $Me_4Sn + I_2$) the reactants in an S_E2 reaction, when mixed, give rise to an immediate charge-transfer spectrum (Sec. 3.C.i), showing that an EDA complex has been formed.[25] In these cases, it is likely that the EDA complex is an intermediate in the reaction.

[19] Jensen, F.R.; Nakamaye, K.L. *J. Am. Chem. Soc.* ***1966,*** *88*, 3437.
[20] Abraham, M.H.; Johnston, G.F. *J. Chem. Soc. A,* ***1970***, 188.
[21] See Abraham, M.H.; Dorrell, F.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 444.
[22] Fukuto, J.M.; Newman, D.A.; Jensen, F.R. *Organometallics* ***1987****, 6,* 415.
[23] Abraham, M.H.; Hill, J.A. *J. Organomet. Chem.* ***1967****, 7,* 11.
[24] Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, ***1973***, p. 15.
[25] Fukuzumi, S.; Kochi, J.K. *J. Am. Chem. Soc.* ***1980****, 102,* 2141, 7290.

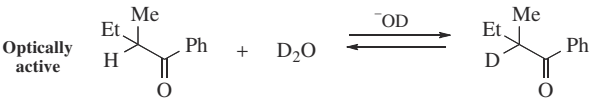
12.A.ii. The S_E1 Mechanism

The S_E1 mechanism is analogous to the S_N1. It involves two steps: A slow ionization and a fast combination.

Step 1 $R{-}X \xrightarrow{\text{slow}} R^- + X^+$

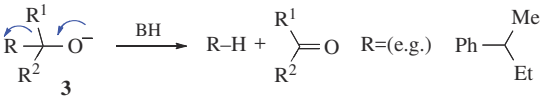
Step 2 $R^- + Y^+ \longrightarrow R{-}Y$

The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction, the rate of deuterium exchange was the same as the rate of racemization[26] and there was an isotope effect.[27]



It is known that S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1]bicyclic systems, Sec. 10.A.ii) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration, or at least partial retention. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure (this means that there is pyramidal inversion as with amines, Sec. 4.C, category 3). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (Sec. 5.B.i). For simple alkyl carbanions, the main approach to deduce the structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case, racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

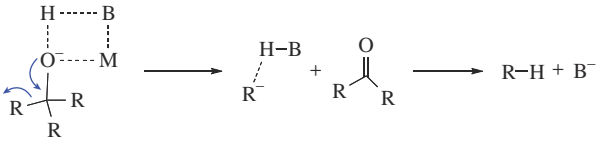
However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in an alkoxide (see **3**) cleavage Reaction (**12-41**):



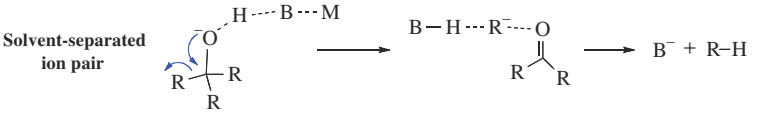
which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R^-).[28] By changing the solvent, Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free, but is solvated. In nondissociating,

[26] Hsu, S.K.; Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* ***1938***, 78.
[27] Wilson, C.L. *J. Chem. Soc.* ***1936***, 1550.
[28] See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969****, 91*, 1009. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 138–158.

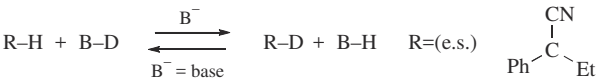
nonpolar solvents (e.g., benzene or dioxane), the alkoxide ion exists as an ion pair, solvated by the solvent BH:



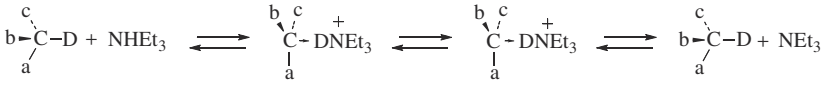
In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. This solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents (e.g., diethylene glycol), a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solvate it only from the opposite side:



When C—H bond formation occurs, the result is inversion. Racemization occurs in polar aprotic solvents (e.g., DMSO). In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and is solvated symmetrically.

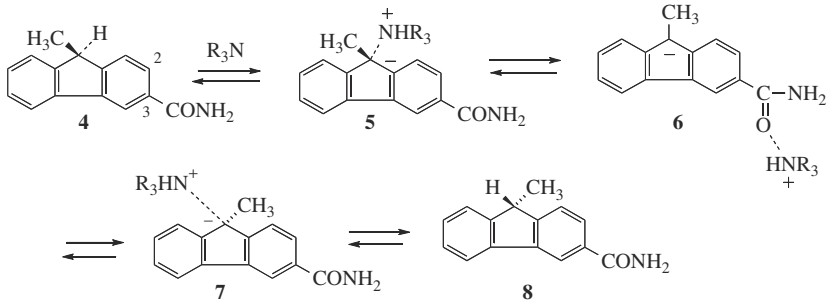


Similar behavior was found for carbanions generated by base-catalyzed hydrogen-exchange (Reaction **12-1**).[29] In this case, information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A $k_e k_a$ ratio substantially >1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A $k_e k_a$ ratio of ~ 1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (see Sec. 10.A.i). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be <0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

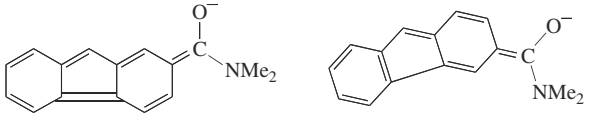


[29] See Roitman, J.N.; Cram, D.J. *J. Am. Chem. Soc.* ***1971****, 93*, 2225, 2231 and references cited therein; Cram, J.M.; Cram, D.J. *Intra-Sci. Chem. Rep.* ***1973****, 7(3)*, 1; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

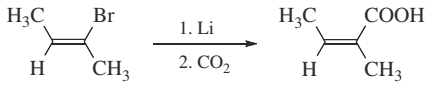
Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.



The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**4**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes a proton from the 9 position of **4** and conducts the proton out to the C=O oxygen (**6**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **7** gives the inverted product **8**. Of course, **6** could also go back to **4**, but a molecule that undergoes the total process **4** → **5** → **6** → **7** → **8** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*,[30] is that the 12-carboxamido isomer of **4** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**9**) results in disruption of the aromatic sextet in both benzene rings (cf. **10** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion–pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[31]



It is known that vinylic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention, which is the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:[32]



[30] Cram, D.J.; Ford, W.T.; Gosser, L. *J. Am. Chem. Soc.* ***1968****, 90*, 2598; Ford, W.T.; Cram, D.J. *J. Am. Chem. Soc.* ***1968****, 90,* 2606, 2612. See also, Buchholz, S.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem. Int. Ed.* ***1989****, 28,* 73.

[31] Almy, J.; Hoffman, D.H.; Chu, K.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1973****, 95*, 1185.

[32] Dreiding, A.S.; Pratt, R.J. *J. Am. Chem. Soc.* ***1954****, 76,* 1902. See also, Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972****, 94,* 2273.

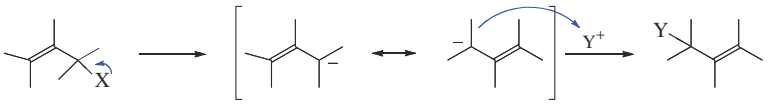
Only ~5% of the cis isomer (tiglic acid) was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (Sec. 5.B.ii) and S_E1 reactions involving them proceed with retention of configuration.

12.A.iii. Electrophilic Substitution Accompanied by Double-Bond Shifts

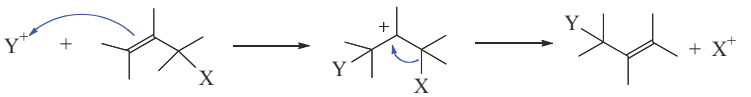


11 **12**

When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged (**11** → **12**). This type of process is analogous to the nucleophilic allylic rearrangements discussed in Section 10.D. There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, which then attacks the electrophile Y.

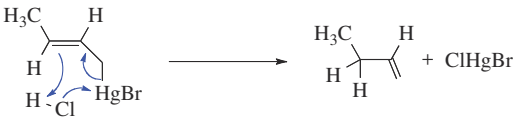


In the other pathway, the Y group is first attacked by the π-bond, giving a carbocation, which then loses X with formation of the alkene unit.

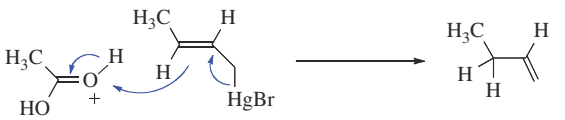


These mechanisms are more fully discussed under Reaction **12-2**.

Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups.[33] Sleezer et al.[34] found that crotylmercuric bromide reacted with HCl ~10^7 times faster than *n*-butylmercuric bromide and the product was >99% 1-butene. These facts point to an S_Ei' mechanism (IUPAC designation *cyclo*-$1/3/D_EA_ED_nA_n$):



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an S_E2' mechanism (IUPAC designation $1/3/D_EA_E$)[34]:



[33] See Courtois, G.; Miginiac, L. *J. Organomet. Chem.* ***1974****, 69*, 1.

[34] Sleezer, P.D.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* ***1963****, 85*, 1890. See also, Kashin, A.N.; Bakunin, V.N.; Khutoryanskii, V.A.; Beletskaya, I.P.; Reutov, O.A. *J. Organomet. Chem.* ***1979****, 171*, 309.

The geometry of electrophilic allylic rearrangement has not been studied very much (cf. the nucleophilic case, Sec. 10.E), but in most cases the rearrangement takes place with antistereoselectivity,[35] although syn stereoselectivity has also been demonstrated.[36] In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both syn and anti stereoselectivity, depending on whether the substrate was cis or trans.[37]

12.A.iv. Other Mechanisms

Addition–elimination (Reaction **12-16**) and cyclic mechanisms (Reaction **12-40**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions. The exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

12.B. REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Therefore, only a few conclusions can be drawn, most of them sketchy or tentative.[38]

1. *Effect of Substrate*. For S_E1 reactions, electron-donating groups decrease rates and electron-withdrawing groups increase them. This is expected for a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the S_E2 (back) mechanism, Jensen and Davis[12] showed that the reactivity of alkyl groups is similar to that for the S_N2 mechanism (i.e., Me > Et > Pr > *i*Pr > neopentyl), as is expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) mechanism in cases where stereochemical investigation is not feasible.[39] For S_E2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.[40] One such study, which examined the reaction $RHgBr + Br_2 \rightarrow RBr$ catalyzed by Br^-, gave the results shown in Table 12.1.[41] This data shows that branching increased the rates, while β branching decreased them. Sayre and Jensen[41]

[35] Matassa, V.G.; Jenkins, P.R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* ***1989****, 29*, 321.
[36] Young, D.; Kitching, W. *J. Org. Chem.* ***1983****, 48,* 614; *Tetrahedron Lett.* ***1983****, 24*, 5793.
[37] Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1982****, 18,* 1973. See also, Wickham, G.; Young, D.; Kitching, W. *Organometallics* ***1988****, 7*, 1187.
[38] See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, ***1973***, pp. 211–241.
[39] Also see Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett.* ***1984****, 25,* 2407.
[40] See Abraham, M.H.; Broadhurst, A.T.; Clark, I.D.; Koenigsberger, R.U.; Dadjour, D.F. *J. Organomet. Chem.* ***1981****, 209*, 37.
[41] Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979****, 101,* 6001.

TABLE 12.1 Relative Rates of the Reaction of RHgBr with Br_2 and Br[a]

R	Relative Rate	R	Relative Rate
Me	1	Et	10.8
Et	10.8	*i*-Bu	1.24
*i*Pr	780	Neopentyl	0.173
t-Bu	3370		

Reprinted with permission Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc. 1979, 101*, 6001. Copyright © 1979 American Chemical Society.

[a]See Ref. 41.

attributed the decreased rates to steric hindrance, although attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transition state.[42] Of course, steric hindrance should also be present with the a branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is a rather large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed[43] to an S_E2 mechanism involving ion pairs, analogous to Sneen's ion-pair mechanism for nucleophilic substitution (Sec. 10.A.iv). Solvolysis of 2-bromo-1,1,1-trifluoro-2-(*p*-methoxyphenyl)ethane in water proceeds via a free carbocation intermediate, but ion pairing influences the reaction in the presence of bromide ion.[44]

2. *Effect of Leaving Group*. For both S_E1 and second-order mechanisms, the more polar the C—X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence >1, the nature of the other group or groups attached to the metal thus has an effect on the reaction. For example, consider a series of organomercurials (RHgW). Because a more electronegative W decreases the polarity of the C—Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg—*t*-Bu > Hg—*i*Pr > HgEt > HgMe, reported for acetolysis of R_2Hg,[42] since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the reported results have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei. A number of reports of S_E1 reactions with metallic leaving groups have appeared,[45] but the mechanism is not easy to prove and many of

[42] Also see Nugent, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976****, 98,* 5979.
[43] Reutov, O.A. *J. Organomet. Chem.* ***1983****, 250,* 145. See also, Butin, K.P.; Magdesieva, T.V. *J. Organomet. Chem.* ***1985****, 292*, 47.
[44] Richard, J.P. *J. Org. Chem.* ***1992****, 57*, 625.
[45] See Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1980****, 29*, 1461. See also, Dembech, P.; Eaborn, C.; Seconi, G. *J. Chem. Soc. Chem. Commun.* ***1985***, 1289.

these reports have been challenged.[46] Reutov and co-workers[45] expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and refer to such processes as $S_E1(N)$ reactions.

3. *Effect of Solvent*.[47] In addition to the solvent effects on certain S_E1 reactions mentioned earlier (Sec. 12.A.ii), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (Sec. 10.G.iv), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1, in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (Sec. 12.A.ii), the solvent can also exert an influence between the S_E2 (front or back) and S_Ei mechanisms in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms are much less affected.

12.C. REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

12.C.i. Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

12-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with Reaction **11-1**, the exchange reaction is mostly used to study mechanistic questions (e.g., relative acidities), but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids (e.g., H_2SO_4) are used, only fairly acidic protons on carbon can exchange (e.g., acetylenic and allylic). However, primary, secondary, and tertiary hydrogen atoms of alkanes can be exchanged by treatment with superacids (Sec. 5.A.ii).[48] The order of hydrogen reactivity is tertiary > secondary > primary. Where C—C bonds are present, they may be cleaved also (Reaction **12-47**). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the C—H bond to give the pentavalent methanonium ion, which loses

$$H_3C{-}H + H^+ \rightleftharpoons \left[H_3C\begin{matrix}H\\H\end{matrix}\right]^+ \rightleftharpoons CH_3^+ + H^2$$

Methanonium ion

[46] See Kitching, W. *Rev. Pure Appl. Chem.* ***1969****, 19,* 1.
[47] See Petrosyan, V.S. *J. Organomet. Chem.* ***1983****, 250,* 157.
[48] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, ***1985***, pp. 244–249; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973****, 12,* 173.

H_2 to give a tervalent carbocation.[49] The methanonium ion (CH_5^+) has a three-center, two-electron bond.[50] It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion (CH_5^+) has been detected in the mass spectrum.[51] The IR spectrum of the ethanonium ion ($C_2H_7^+$) has been measured in the gas phase.[52] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogen atoms, leaving the CH_3^+ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogen atoms, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange), or it can react with additional CH_4 molecules (Reaction **12-20**) to eventually yield the *tert*-butyl cation, which is stable in these superacid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+.[53] Complete or almost complete perdeuteriation of cyclic alkenes has been achieved by treatment with dilute DCl/D_2O in sealed Pyrex tubes at 165–280 °C.[54]

Exchange with bases involves an S_E1 mechanism.

Step 1 $RH + B^- \longrightarrow R^- + BH$

Step 2 $R^- + BD \longrightarrow RD{-}B^-$

Of course, such exchange is most successful for relatively acidic protons (e.g., those α to a carbonyl group), but even weakly acidic protons can exchange with bases if the bases are strong enough (see Sec. 5.B.i).

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated treatment with D_2 gas and a catalyst (e.g., Rh, Pt, or Pd).[55]

OS **VI**, 432.

12-2 Migration of Double Bonds

3/Hydro-de-hydrogenation

$$C_5H_{11}{-}CH_2{-}CH=CH_2 \xrightarrow[Me_2SO]{KNH_2} C_5H_{11}{-}CH=CH{-}CH_3$$

The double bonds of many unsaturated compounds may be isomerized[56] upon treatment with strong bases.[57] In many cases, equilibrium mixtures are obtained and the

[49] See McMurry, J.E.; Lectka, T. *J. Am. Chem. Soc.* ***1990****, 112*, 869; Culmann, J.; Sommer, J. *J. Am. Chem. Soc.* ***1990****, 112,* 4057.

[50] See Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.

[51] See Sefcik, M.D.; Henis, J.M.S.; Gaspar, P.P. *J. Chem. Phys.* ***1974****, 61,* 4321.

[52] Yeh, L.I.; Pric, J.M.; Lee, Y.T. *J. Am. Chem. Soc.* ***1989****, 111*, 5597.

[53] Lukas, J.; Kramer, P.A.; Kouwenhoven, A.P. *Recl. Trav. Chim. Pays-Bas* ***1973****, 92,* 44.

[54] Werstiuk, N.H.; Timmins, G. *Can. J. Chem.* ***1985****, 63,* 530; ***1986****, 64*, 1564.

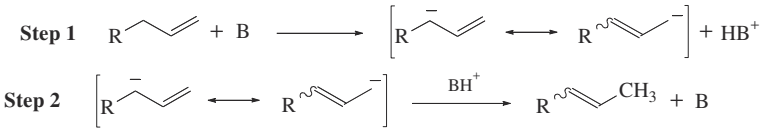
[55] See Atkinson, J.G.; Luke, M.O.; Stuart, R.S. *Can. J. Chem.* ***1967****, 45*, 1511.

[56] For a list of methods used to shift double and triple bonds, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 220–226, 567–568.

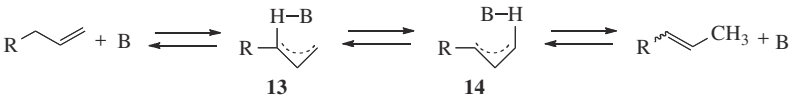
[57] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 25–123; DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 437–449; Hubert, A.J.; Reimlinger, H. ***1970***, 405; Mackenzie, K. in *The Chemistry of Alkenes*, Vol. 1, Patai, S., pp. 416–436, Vol. 2, Zabicky, J., pp. 132–148; Wiley, NY, 1964, ***1970***; Broaddus, C.D. *Acc. Chem. Res.* ***1968****, 1*, 231.

thermodynamically most stable isomer predominates.[58] If the new double bond can be in conjugation with one already present or with an aromatic ring, the conjugated compound is favored.[59] If the choice is between an exocyclic and an endocyclic double bond (particularly with six-membered rings), endocyclic is usually preferred. In the absence of such considerations, *Zaitsev's rule* (Sec. 17.B) applies and the double bond goes to the carbon with the fewest hydrogen atoms. All these considerations lead to predictions that terminal alkenes can be isomerized to internal ones, nonconjugated alkenes to conjugated, exo six-membered ring alkenes to endo, and so on, and not the other way around.

The term *prototropic rearrangement* is sometimes used as an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by a base to give a resonance-stabilized carbanion, and reaction with a proton is at the position that will give the more stable alkene:[60]



This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (Sec. 10.D). Ultraviolet spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^+ are identical, showing that the same carbanion is present in both cases, as required by this mechanism.[61] The acid BH^+ protonates the position that will give the more stable product, although the ratio of the two possible products can vary with the identity of BH^+.[62] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[63] The intramolecular nature has been ascribed to a *conducted tour mechanism* (Sec. 12.A.iii) in which the base leads the proton from one carbanionic site to the other (**13** → **14**).[64]



Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis[65] acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation and then another is lost:

Step 1 $CH_3—CH_2—CH=CH_2 + H^+ \longrightarrow CH_3—CH_2—\overset{+}{C}H—CH_3$

Step 2 $CH_3—CH_2—\overset{+}{C}H—CH_3 \longrightarrow CH_3—CH=CH—CH_3 + H^+$

[58] See Hine, J.; Skoglund, M.J. *J. Org. Chem.* ***1982****, 47,* 4766. See also, Hine, J.; Linden, S. *J. Org. Chem.* ***1983****, 48*, 584.

[59] For a review of conversions of β,γ enones to α,β enones, see Pollack, R.M.; Bounds, P.L.; Bevins, C.L. in Patai, S.; Rappoport, Z. *The Chemistry of Enones,* pt. 1, Wiley, NY, ***1989***, pp. 559–597.

[60] See Pollack, R.M.; Mack, J.P.G.; Eldin, S. *J. Am. Chem. Soc.* ***1987****, 109*, 5048.

[61] Rabinovich, E.A.; Astaf'ev, I.V.; Shatenshtein, A.I. *J. Gen. Chem. USSR* ***1962****, 32,* 746.

[62] Hünig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem. Int. Ed.* ***1987****, 26,* 1281.

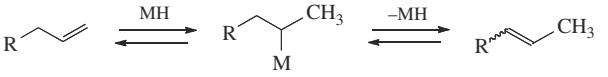
[63] See Cram, D.J.; Uyeda, R.T. *J. Am. Chem. Soc.* ***1964****, 86*, 5466; Ohlsson, L.; Wold, S.; Bergson, G. *Ark. Kemi.,* ***1968****, 29*, 351.

[64] Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 851.

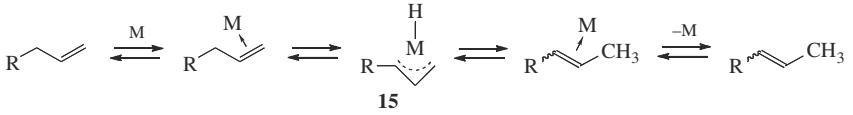
[65] See Cameron G.S.; Stimson, V.R. *Aust. J. Chem.* ***1977****, 30,* 923.

As in the case of the base-catalyzed reaction, the thermodynamically most stable alkene is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture that contains not only 1-decene and *cis*- and *trans*-2-decene, but also the cis and trans isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable alkenes predominate, but many of them have stabilities that are close together.

Double-bond isomerization can take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (Sec. 10.E). Electrocyclic and sigmatropic rearrangements are treated at Reactions **18-27** to **18-35**. Double-bond migrations have also been accomplished photochemically,[66] and by means of metallic ion (most often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.[67] With metal compounds there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition–elimination mechanism*:



The other mechanism, called the π-*allyl complex mechanism*, does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3-π-allyl complex **15** (see Sec. 3.C.i, category 1 and Reaction **10-60**). Another difference between the two mechanisms is that the former involves 1,2- and the latter 1,3-shifts. The isomerization of 1-butene Rh catalyzed reaction is an example that takes place by the metal hydride mechanism,[68] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$ catalyzed isomerization of 3-ethyl-1-pentene.[69] A Pd catalyst was used to convert alkynones ($RCOC{\equiv}CCH_2CH_2R'$) to 2,4-alkadien-1-ones ($RCOCH{=}CHCH{=}CHCHR'$).[70] The reaction of an en-yne with $HSiCl_3$ and a Pd catalyst generated an allene with moderate enantioselectivity (see Sec. 4.C, category 5 for chiral allenes).[71]



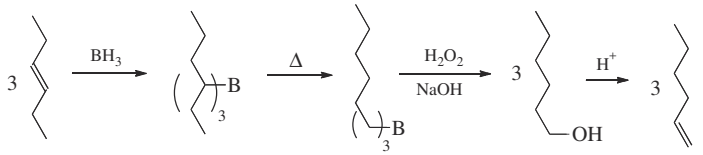
15

The metal-catalysis method has been used for the preparation of simple enols, by isomerization of allylic alcohols, for example.[72] Some enols are stable enough for isolation

[66] Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 22–24.
[67] See Rodriguez, J.; Brun, P.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1989***, 799–823; Otsuka, S.; Tani, K. in Morrison, J. D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 171–191 (enantioselective); Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 173–193; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Academic Press, NY, ***1974***, pp. 9–37; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 76–82; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3,* 1, pp. 133–149.
[68] Cramer, R. *J. Am. Chem. Soc.* ***1966***, *88,* 2272.
[69] Casey, C.P.; Cyr, C.R. *J. Am. Chem. Soc.* ***1973***, *95,* 2248.
[70] Trost, B.M.; Schmidt, T. *J. Am. Chem. Soc.* ***1988***, *110,* 2301.
[71] Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* ***2001***, *123*, 12915.
[72] Bergens, S.H.; Bosnich, B. *J. Am. Chem. Soc.* ***1991***, *113,* 958.

(see Sec. 4.Q.iv), but slowly tautomerize to the aldehyde or ketone, with half-lives ranging from 40 to 50 min to several days.[72]

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable alkene is usually formed in the largest amount, although a few anomalies are known. An indirect method of double-bond isomerization is known, leading to migration in the other direction. This involves conversion of the alkene to a borane (Reaction **15-16**), rearrangement of the borane (Reaction **18-11**), oxidation and hydrolysis of the newly formed borane to the alcohol (**17**) (see Reaction **12-31**), and dehydration of the alcohol (Reaction **17-1**) to the alkene. The reaction is driven by the fact that with heating the addition of borane is reversible, and the equilibrium favors formation of the less sterically hindered borane, **16** in this case.



16 **17**

Since the migration reaction is always toward the end of a chain, terminal alkenes can be produced from internal ones, so the migration is often opposite to that with the other methods. Alternatively, the rearranged borane can be converted directly to the alkene by heating with an alkene of molecular weight higher than that of the product (Reaction **17-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[73]

See Reaction **15-1** for related reactions in which double bonds migrate or isomerize.

$$R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3$$

Triple bonds can also migrate in the presence of bases,[74] but through an allene intermediate:[75] In general, strong bases (e.g., $NaNH_2$) convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide, $NH_2CH_2CH_2CH_2NHK$[76]), because the equilibrium is shifted by formation of the acetylide ion. With weaker bases (e.g., NaOH), which are not strong enough to remove the acetylenic proton, the internal alkynes are favored because of their greater thermodynamic stability. In some cases, the reaction can be stopped at the allene stage.[77] The reaction then becomes a method for the preparation of allenes.[78] The reaction of propargylic alcohols with tosylhydrazine (PPh_3) and DEAD also generates allenes.[79] In a related reaction, base

[73] See Duhaime, R.M.; Lombardo, D.A.; Skinner, I.A.; Weedon, A.C. *J. Org. Chem.* ***1985****, 50,* 873.

[74] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 124–204; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445; Bushby, R.J. *Q. Rev. Chem. Soc.* ***1970****, 24*, 585; Iwai, I. *Mech. Mol. Migr.* ***1969****, 2,* 73.

[75] See Huntsman, W.D. in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2, Wiley, NY, ***1980***, pp. 521–667.

[76] Macaulay, S.R. *J. Org. Chem.* ***1980****, 45,* 734; Abrams, S.R. *Can. J. Chem.* ***1984****, 62,* 1333.

[77] See Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* ***2000***, 493.

[78] See Cunico, R.F.; Zaporowski, L.F.; Rogers, M. *J. Org. Chem.* ***1999****, 64*, 9307.

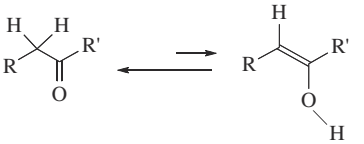
[79] Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* ***1996****, 118*, 4492. See Moghaddam, F.M.; Emami, R. *Synth. Commun.* ***1997****, 27*, 4073 for the formation of alkoxy allenes from propargyl ethers.

induced isomerization of propargylic alcohols leads to conjugated ketones in some cases.[80] Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., HF—PF_5) are used.[81] If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

OS **II**, 140; **III**, 207; **IV**, 189, 192, 195, 234, 398, 683; **VI**, 68, 87, 815, 925; **VII**, 249; **VIII**, 146, 196, 251, 396, 553; **X**, 156, 165; **81**, 147

12-3 Keto–Enol Tautomerization

3/*O*-Hydro-de-hydrogenation



The tautomeric equilibrium between enols and ketones or aldehydes (keto–enol tautomerism) is a form of prototropy,[82] but is not normally a preparative reaction. For some ketones, however, both forms can be prepared (see Sec. 2.N.i, category 3 for a discussion of this and other types of tautomerism). Keto–enol tautomerism occurs in systems containing one or more carbonyl groups linked to sp^3 carbons bearing one or more hydrogen atoms. *The keto is generally more stable than the enol tautomer for neutral systems,* and for most ketones and aldehydes only the keto form is detectable under ordinary conditions. The availability of additional intramolecular stabilization through hydrogen bonding or complete electron delocalization (as in phenol), may cause the enol tautomer to be favored.

Keto–enol tautomerism is usally a slow process, but it can be catalyzed by a trace of acid or base.[83] In this equilibrium, the heteroatom is the basic site and the proton is the acidic site. For tautomerism in general (see Sec. 2.N.i),[84] the presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphiprotic properties.[84] Polar protic solvents (e.g., water or alcohol) may participate in the proton transfer by forming a cyclic or a linear complex with the tautomers.[85] Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base,

[80] Sonye, J.P.; Koide, K. *J. Org. Chem.* ***2006****, 71,* 6254.

[81] Barry, B.J.; Beale, W.J.; Carr, M.D.; Hei, S.; Reid, I. *J. Chem. Soc. Chem. Commun.* ***1973***, 177.

[82] Patai, S. *The Chemistry of the Carbonyl Group,* Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols,* Wiley, NY, ***1990***; Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* ***1997****, 69*, 1933; Fontana, A.; De Maria, P.; Siani, G.; Pierini, M.; Cerritelli, S.; Ballini, R. *Eur. J. Org. Chem.* ***2000***, 1641; Iglesias, E. *Curr. Org. Chem.* ***2004****, 8,* 1.

[83] See Jones, J.R. *The Ionisation of Carbon Acids,* Academic Press, London, ***1973***; Toullec, J. *Adv. Phys. Org. Chem.* ***1982****, 18,* 1; Chiang, Y.; Kresge, A.J.; Santaballa, J.A.; Wirz, J. *J. Am. Chem. Soc.* ***1988****, 110*, 5506.

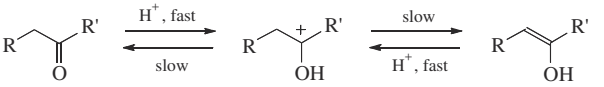
[84] See Raczynska, E.D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* ***2005****, 105,* 3561 for a general discussion of tautomerism. Also see Rappoport, Z. *The Chemistry of Enols,* Wiley, NY, ***1990***; Zabicky, J. *The Chemistry of Amides,* Wiley, London, ***1970***; Boyer, J.H. *The Chemistry of the Nitro and Nitroso Groups,* Interscience Publishers, NY, ***1969***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro Compounds and their Derivatives*, Wiley, NY, ***1982***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*, Wiley, Chichester, ***1996***; Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1998***.

[85] Gorb, L.; Leszczynski, J. *J. Am. Chem. Soc.* ***1998****, 120,* 5024; Guo, J. X.; Ho, J. J. *J. Phys. Chem. A* ***1999****, 103,* 6433.

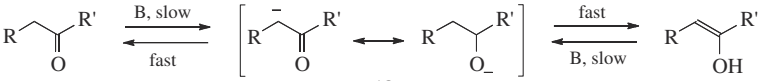
the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.[86] The structural features of the carbonyl compound influences the equilibrium.[87] Differing conjugative stabilization by CH-π orbital overlap does not directly influence stereoselectivity, and steric effects are generally not large enough to cause the several kilocalorie per mole (kcal mol^{-1}) energy difference seen between transition structures unless there is exceptional crowding.[88] Note that sterically stabilized enols are known,[89] including arylacetaldehydes.[90] Torsional strain involving vicinal bonds does contribute significantly to stereoselectivity in enolate formation.[88]

The acid base catalyzed mechanisms are identical to those in Reaction **12-2**.[91]

Acid catalyzed



Base catalyzed[92]



18

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of *microscopic reversibility*.[93] As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of ∼5) in both the basic-[94] and the acid[95]-catalyzed processes. The keto–enol/enolate anion equilibrium has been studied in terms of the influence of β-oxygen[96] or β-nitrogen[97] substituents. The stereochemistry of enol protonation can be controlled by varying the proximal group and by changing the acidity of the medium.[98]

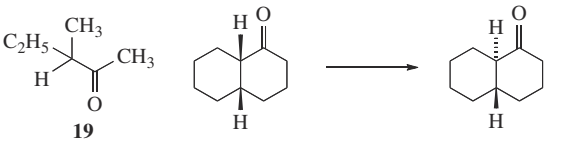
[86] Briegleb, G.; Strohmeier, W. *Angew. Chem.* ***1952****, 64,* 409; Baddar, F. G.; Iskander, Z. *J. Chem. Soc.* ***1954***, 203.
[87] Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998****, 120,* 2290.
[88] Behnam, S.M.; Behnam, S.E.; Ando, K.; Green, N.S.; Houk, K.N. *J. Org. Chem.* ***2000****, 65,* 8970.
[89] Miller, A.R. *J. Org. Chem.,* ***1976****, 41,*3599.
[90] Fuson, R.C.; Tan, T.-L. *J. Am. Chem. Soc.* ***1948****, 70,* 602.
[91] See Keeffe, J.R.; Kresge, A.J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 399–480; Toullec, J. *Adv. Phys. Org. Chem.* ***1982****, 18,* 1. Also see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell Univ. Press, Ithaca, NY, ***1973***, pp. 171–181; Shelly, K.P.; Venimadhavan, S.; Nagarajan, K.; Stewart, R. *Can. J. Chem.* ***1989****, 67*, 1274. Also see Pollack, R.M. *Tetrahedron* ***1989****, 45,* 4913.
[92] Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: See Bruice, P.Y. *J. Am. Chem. Soc.* ***1990****, 112*, 7361 and references cited therein.
[93] For a proposed concerrted mechanism, see Capon, B.; Siddhanta, A.K.; Zucco, C. *J. Org. Chem.* ***1985****, 50,* 3580. For evidence against it, see Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. ***1987****, 109,* 4000 and references cited therein.
[94] Xie, L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1991****, 113,* 3123.
[95] Lienhard, G.E.; Wang, T. *J. Am. Chem. Soc.* ***1969****, 91*, 1146. See also, Toullec, J.; Dubois, J.E. *J. Am. Chem. Soc.* ***1974****, 96,* 3524.
[96] Chiang, Y.; Kresge, A.J.; Meng, Q.; More O'Ferrall, R.A.; Zhu, Y. *J. Am. Chem. Soc.* ***2001****, 123*, 11562.
[97] Chiang, Y.; Griesbeck, A.G.; Heckroth, H.; Hellrung, B.; Kresge, A.J.; Meng, Q.; O'Donoghue, A.C.; Richard, J.P.; Wirz, J. *J. Am. Chem. Soc.* ***2001****, 123,* 8979.
[98] Zimmerman, H.E.; Cheng, J. *J. Org. Chem.* ***2006****, 71,* 873.

The base induced reaction generates an enolate anion rather than an enol, and the formation of and reactions of enolate anions are discussed further in Reactions **10-60**, **10-67**, **16-24**, and **16-34**. Note that ring strain plays no significant role on the rate of base-catalyzed enolization.[99] In certain cases (e.g., benzofuranones), base-induced enolate anion formation may give a transition state in which aromaticity can play a role. One study showed that aromatic stabilization of the transition state is ahead of proton transfer, and aromaticity appears to lower the intrinsic barrier to this reaction.[100] Enolizable hydrogen atoms can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O containing) gas-chromatography column.[101]



Benzofuranone

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. When enol ethers or esters are hydrolyzed, the initially formed enols immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to a stereogenic carbon α to a carbonyl group (as in **19**) is treated with acid or base, racemization results.[102] If there is another stereogenic center in the molecule, the less stable diastereomer can be converted to the more stable one in this manner. For example, *cis*-decalone can be equilibrated to the trans isomer. Isotopic exchange can similarly be accomplished at the α position of an aldehyde or ketone. In cyclic compounds, cis- to trans- isomerization can occur via the enol.[103] The role of additives (e.g., $ZnCl_2$) on the stereogenic enolization reactions using chiral cases has been discussed.[104]



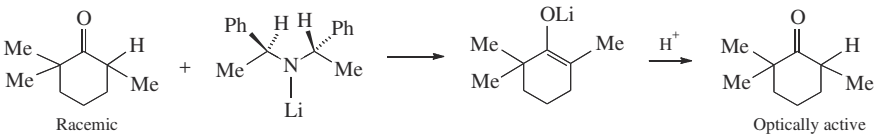
19 *cis*-Decalone *trans*-Decalone

If a full equivalent of base per equivalent of ketone is used, the enolate ion (**18**) is formed and can be isolated[105] (see, e.g., the alkylation reaction in Reaction **10-68**).[106]

[99] Cantlin, R.J.; Drake, J.; Nagorski, R.W. *Org. Lett.* ***2002****, 4,* 2433.
[100] Bernasconi, C.F.; Pérez-Lorenzo, M. *J. Am. Chem. Soc.* ***2007****, 129,* 2704.
[101] Senn, M.; Richter, W.J.; Burlingame, A.L. *J. Am. Chem. Soc.* ***1965****, 87,* 680; Richter, W.J.; Senn, M.; Burlingame, A.L. *Tetrahedron Lett.* ***1965***, 1235.
[102] For an exception, see Guthrie, R.D.; Nicolas, E.C. *J. Am. Chem. Soc.* ***1981****, 103,* 4637.
[103] Dechoux, L.; Doris, E. *Tetrahedron Lett.* ***1994****, 35*, 2017.
[104] Coggins, P.; Gaur, S.; Simpkins, N.S. *Tetrahedron Lett.* ***1995****, 36*, 1545.
[105] See Wen, J.Q.; Grutzner, J.B. *J. Org. Chem.* ***1986****, 51*, 4220.
[106] See d'Angelo, J. *Tetrahedron* ***1976****, 32*, 2979. Also see Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gran-Masse, H.; Melnyk, O. *J. Org. Chem.* ***2002****, 67*, 526.

Enantioselective enolate anion protonation reactions have been studied.[107] Enolate protonation is discussed in section Reaction **16-34**. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic. Aggregation behavior of stereoselective enolizations mediated by Mg and Ca bis(amides) have been studied.[108]

In the case of the ketone (**20**), a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral base (**21**).[109] This happened because **21** reacted with one enantiomer of **20** faster than with the other (an example of *kinetic resolution*). The enolate (**22**) must remain coordinated with the chiral amine, and it is the amine that reprotonate **22**, not an added proton donor.



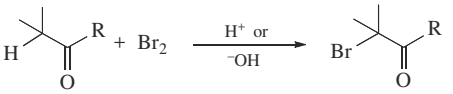
There are many enol–keto interconversions and acidification reactions of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

Halogenation of unactivated hydrocarbons is discussed in Reaction **14-1**.

12-4 Halogenation of Aldehydes and Ketones

Halogenation or **Halo-de-hydrogenation**



Aldehydes and ketones can be halogenated in the α position with bromine, chlorine, or iodine,[110] although the reaction is less successful with fluorine.[111] Sulfuryl chloride,[112] $Me_3SiCl—Me_2SO$,[113] and NCS[114] have been used as reagents for chlorination.

[107] Vedejs, E.; Kruger, A.W.; Suna, E. *J. Org. Chem.* ***1999****, 64*, 7863.
[108] He, X.; Allan, J.F.; Noll, B.C.; Kennedy, A.R.; Henderson, K.W. *J. Am. Chem. Soc.* ***2005****, 127,* 6920.
[109] Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* ***1986****, 27,* 631. See also, Cain, C.M.; Cousins, R.P.C.; Coumbarides, G.; Simpkins, N.S. *Tetrahedron* ***1990****, 46,* 523.
[110] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 459–478; De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, Wiley, NY, 1988. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp.709–719.
[111] See Rozen, S.; Filler, R. *Tetrahedron* ***1985****, 41,* 1111; German, L.; Zemskov, S. *New Fluorinating Agents in Organic Chemistry*; Springer, NY, ***1989***.
[112] Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4; Wiley, NY, ***1981***, pp. 336–396.
[113] Fraser, R.R.; Kong, F. *Synth. Commun.* ***1988****, 18*, 1071.
[114] See Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* ***2008****, 49*, 3802. Alse see Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* ***2008****, 64,* 5191.

α-Chloroaldehydes are formed with Cl_2 and a catalytic amount of tetraethylammonium chloride.[115] Bromination methods include NBS (see Reaction **14-3**),[116] Me_3SiBr—DMSO,[117] tetrabutylammonium tribromide,[118] *in situ* generated $ZnBr_2$ in water,[119] and bromine• dioxane on silica with microwave irradiation.[120] α-Chlorination[121] and also bromination[122] have been reported in ionic liquids. Enantioselective chlorination[123] and bromination[124] methods are known, including methods that use enolate anions as intermediates.[125] Organocatalyzed asymmetric α-halogenation methods are known that can be applied to incorporation of virtually any halogen.[126] β-Keto esters and 1,3-diketones are α-brominated using bromodimethylsulfonium bromide.[127] 1,3-Diketones, β-ketoesters, and malonates are chlorinated using sodium hypochlorite or brominated using sodium hypobromite.[128]

Iodination has been accomplished by the direct reaction of ketones with molecular iodine,[129] with I_2-cerium(IV) ammonium nitrate,[130] NCS/NaI,[131] ICl/NaI/$FeCl_3$,[132] and with iodine using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in methanol.[133] Methyl ketones react with NIS and tosic acid with microwave irradiation without solvent to give the α-iodoketone.[134] An asymmetric iodination of aldehydes used NIS, with a catalytic amount of benzoic acid and a chiral biaryl amine.[135]

Although less prevalent than those noted above, several methods have been reported for the preparation of α-fluoro aldehydes and ketones,[136] including enantioselective fluorination protocols.[137] Organocatalytic α-fluorination is known for aldehydes and ketones.[138]

[115] Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Pagnoni, U.M.; Parson, A.F.; Pinetti, A. *Synthesis* ***2003***, 2173.
[116] Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* ***2004***, 470. See Guha, S.K.; Wu, B.; Kim, B.S.; Baik, W.; Koo, S. *Tetrahedron Lett.* ***2006****, 47,* 291; Arbuj, S.S.; Waghmode, S.B.; Ramaswamy, A.V. *Tetrahedron Lett.* ***2007****, 48,* 1411. See also Sreedhar, B.; Reddy, P.S.; Madhavi, M. *Synth. Commun.* ***2007****, 37*, 4149.
[117] Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* ***1986***, 428.
[118] Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* ***1987****, 60,* 1159.
[119] Juneja, S.K. Choudhary, D.; Paul, S.; Gupta, R. *Synth. Commun.* ***2006****, 36 ,* 2877.
[120] Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* ***2003****, 44*, 439.
[121] Lee, J.C.; Park, H.J. *Synth. Commun.* ***2006****, 36* , 777.
[122] Pingali, S.R.K.; Madhav, M.; Jursic, B.S. *Tetrahedron Lett.* ***2010****, 51*, 1383.
[123] Brochu, M.P.; Brown, S.P.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2004****, 126*, 4108; Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K.A. *J. Am. Chem. Soc.* ***2004****, 126,* 4790. See Wang, L.; Cai, C.; Curran, D. P.; Zhang, W. *Synlett* ***2010***, 433.
[124] See Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K.A. *Chem. Commun.* ***2005***, 4821.
[125] See France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* ***2005***, 475.
[126] See Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* ***2009****, 7,* 2005.
[127] Khan, A.T.; Ali, Md.A.; Goswami, P.; Choudhury, L.H. *J. Org. Chem.* ***2006****, 71*, 8961.
[128] Meketa, M.L.; Mahajan, Y.R.; Weinreb, S.M. *Tetrahedron Lett.* ***2005****, 46,* 4749.
[129] Rao, M.L.N.; Jadhav, D.N. *Tetrahedron Lett.* ***2006****, 47,* 6883. Also see Yadav, J.S.; Kondaji, G.; Reddy, M.S.R.; Srihari, P. *Tetrahedron Lett.* ***2008****, 49,* 3810.
[130] Horiuchi, C.A.; Kiji, S. *Bull. Chem. Soc. Jpn.* ***1997****, 70,* 421. For another reagent, see Sket, B.; Zupet, P.; Zupan, M.; Dolenc, D. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 3406.
[131] Yamamoto, T.; Toyota, K.; Morita, N. *Tetrahedron Lett.* ***2010****, 51*, 1364.
[132] Mohanakrishnan, A.K.; Prakash, C.; Ramesh, N. *Tetrahedron* ***2006****, 62,* 3242.
[133] Jereb, M.; Stavber, S.; Zupan, M. *Tetrahedron* ***2003****, 59,* 5935.
[134] Lee, J.C.; Bae, Y.H. *Synlett* ***2003***, 507.
[135] Kano, T.; Ueda, M.; Maruoka, K. J. *Am. Chem. Soc.* ***2008****, 130,* 3728.
[136] Davis, F.A.; Kasu, P.V.N. *Org. Prep. Proceed. Int.* ***1999****, 31,* 125.
[137] See Pihko, P.M. *Angew. Chem. Int. Ed.* ***2006****, 45*, 544.
[138] Enders, D.; Hüttl, M.R.M. *Synlett* ***2005***, 991.

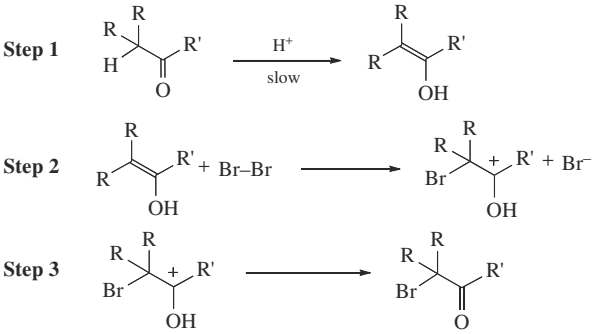
Selectfluor, [F–TEDA–BF_4. 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] has been used for the monofluorination of ketones,[139] as has a mixture of $KI—KIO_3—H_2SO_4$.[140] Active compounds (e.g., β-keto esters and β-diketones) have been fluorinated with an *N*-fluoro-*N*-alkylsulfonamide[141] (this can result in enantioselective fluorination, if an optically active *N*-fluorosulfonamide is used[142]), with $F_2/N_2—HCO_2H$,[143] and with NF_3O/Bu_4NOH.[144] Acetyl hypofluorite fluorinates simple ketones in the form of their lithium enolate anions.[145] Aldehydes have been α-fluorinated using *N*-fluorobenzenesulfonimide as an electrophilic source of fluorine and an imidazolidinone as an organocatalyst.[146] The enantioselective α-fluorination of oxindoles has been reported using *N*-fluorobenzenesulfonimide, a Pd catalyst, and a chiral ligand,[147] and also with an organocatalyst.[148]

For unsymmetrical ketones, the preferred position of halogenation is usually the more substituted: a CH group, then a CH_2 group, and then CH_3[149]; however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced, but only when there is no α-hydrogen and the reaction is generally not very useful (see Reaction **14-4**). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one α position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogen atoms of the first carbon have been replaced (see below). If one of the groups is methyl, the haloform reaction (**12-44**) takes place. With acid catalysts, it is usually possible to stop the reaction after only one halogen has been incorporated, although a second halogen can be introduced by the use of excess reagent. In chlorination, the second halogen generally appears on the same side as the first,[150] while in bromination the α,α′-dibromo product is found.[151] Actually, with both halogens it is the α,α-dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α′-isomer.[150] α,α′-Dichloro ketones are formed by reaction of a methyl ketone with an excess of $CuCl_2$ and LiCl in DMF[152] or with HCl and H_2O_2 in methanol.[153] Aryl methyl ketones can be dibrominated in high yields with benzyltrimethylammonium tribromide.[154] Active methylene compounds are chlorinated

[139] See Loghmani-Khouzani, H.; Poorheravi, M.R.; Sadeghi, M.M.M.; Caggiano, L.; Jackson, R.F.W. *Tetrahedron* ***2008****, 64,* 7419.
[140] Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* ***1992****, 65*, 1731.
[141] Barnette, W.E. *J. Am. Chem. Soc.* ***1984****, 106,* 452; Ma, J.-A. For an example with asymmetric induction, see Cahard, D. *Tetrahedron Asymm* ***2004****, 15*, 1007.
[142] Differding, E.; Lang, R.W. *Tetrahedron* ***1988****, 29*, 6087.
[143] Chambers, R.D.; Greenhall, M.P.; Hutchinson, J. *J. Chem. Soc. Chem. Commun.* ***1995***, 21.
[144] Gupta, O.D.; Shreeve, J.M. *Tetrahedron Lett.* ***2003****, 44*, 2799.
[145] Rozen, S.; Brand, M. *Synthesis* ***1985***, 665. For another reagent, see Davis, F.A.; Han, W. *Tetrahedron Lett.* ***1991****, 32,* 1631.
[146] Beeson, T.D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2005****, 127*, 8826.
[147] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* ***2005****, 127,* 10164.
[148] Steiner, D.D.; Mase, N.; Barbas III, C.F. *Angew. Chem. Int. Ed.* ***2005****, 44,* 3706.
[149] For chlorination this is reversed if the solvent is methanol: Gallucci, R.R.; Going, R. *J. Org. Chem.* ***1981****, 46*, 2532.
[150] Rappe, C. *Ark. Kemi* ***1965****, 24*, 321. But see also, Teo, K.E.; Warnhoff, E.W. *J. Am. Chem. Soc.* ***1973****, 95,* 2728.
[151] Garbisch Jr., E.W. *J. Org. Chem.* ***1965****, 30*, 2109.
[152] Nobrega, J.A.; Goncalves, S.M.C.; Reppe, C. *Synth. Commun.* ***2002****, 32*, 3711.
[153] Terent'ev, A.O.; Khodykin, S.V.; Troitskii, N.A.; Ogibin, Y.N.; Nikishin, G.I. *Synthesis* ***2004***, 2845.
[154] Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn.* ***1987****, 60,* 2667.

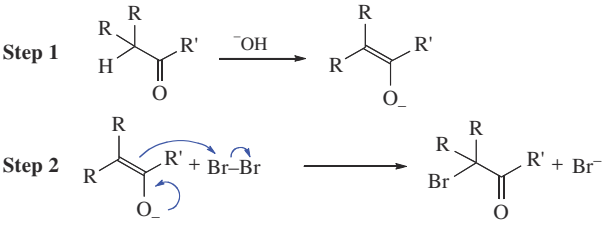
with NCS and $Mg(ClO_4)_2$.[155] Similar chlorination in the presence of a chiral copper catalyst led to α-chlorination with modest enantioselectivity.[156]

It is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate (Reaction **12-3**). The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is



The first step, as seen in Reaction **12-3**, actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (Sec. 15.A.i). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) bromine does not appear in the rate expression at all,[157] a fact consistent with a rate-determining first step;[158] (3) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;[159] (4) the reaction shows an isotope effect; and (5) the rate of the step 2–step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.[160]

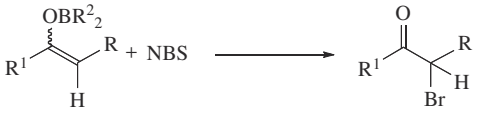
With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:



It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three α halogens on the same side of

[155] Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* ***2002****, 67,* 7429.
[156] Marigo, M.; Kumaragurubaran, N.; Jørgensen, K.A. *Chem. Eur. J.* ***2004****, 10,* 2133.
[157] See Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982****, 104,* 5758. Also see Pinkus, A.G.; Gopalan, R. *J. Am. Chem. Soc.* ***1984****, 106,* 2630; Pinkus, A.G.; Gopalan, R. *Tetrahedron* ***1986****, 42,* 3411.
[158] See, however, Deno, N.C.; Fishbein, R. *J. Am. Chem. Soc.* ***1973****, 95,* 7445.
[159] Bell, R.P.; Yates, K. *J. Chem. Soc.* ***1962***, 1927.
[160] Hochstrasser, R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1988****, 110*, 7875.

the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogen atoms; that is, a CHX group is more acidic than a CH_2 group, so that the initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate. Other halogenating agents can be used in this reaction.



An enol borinate

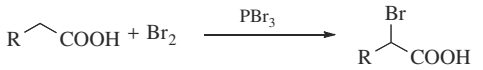
Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with NBS or NCS.[161] The desired halo ketone is formed in high yield. The appropriate lithium enolate can be brominated at a low temperature[162] (see Reaction **10-68**, category 4 for the regioselective formation of enolate ions). α-Halo aldehydes have been prepared in good yield by treatment of silyl enol ethers ($R_2C{=}CHOSiMe_3$) with Br_2 or Cl_2,[163] with sulfuryl chloride (SO_2Cl_2),[164] or with I_2 and silver acetate.[165] Silyl enol ethers generate α-chloroketones with good enantioselectivity using $ZrCl_4$ in conjunction with an α,α-dichloromalonate ester.[166] Silyl enol ethers can also be fluorinated, with XeF_2[167] or with 5% F_2 in N_2 at −78 °C in $FCCl_3$.[168] Enol acetates have been regioselectively iodinated with I_2 and either Th(I) acetate[169] or Cu(II) acetate.[170]

α,β-Unsaturated ketones can be converted to α-halo-α,β-unsaturated ketones by treatment with phenylselenium bromide or chloride,[171] and to α-halo-β,γ-unsaturated ketones by two-phase treatment with HOCl.[172] Conjugated ketones were converted to the α-bromo conjugated ketone (a vinyl bromide) using the *Dess–Martin periodinane* (see Reaction **19-3**, category 5) and tetraethylammonium bromide.[173]

OS **I**, 127; **II**, 87, 88, 244, 480; **III**, 188, 343, 538; **IV**, 110, 162, 590; **V**, 514; **VI**, 175, 193, 368, 401, 512, 520, 711, 991; **VII**, 271; **VIII**, 286. See also, OS **VI**, 1033; **VIII**, 192.

12-5 Halogenation of Carboxylic Acids and Acyl Halides

Halogenation or **Halo-de-hydrogenation**



[161] Hooz, J.; Bridson, J.N. *Can. J. Chem.* ***1972****, 50*, 2387.
[162] Stotter, P.L.; Hill, K.A. *J. Org. Chem.* ***1973****, 38,* 2576.
[163] Blanco, L.; Amice, P.; Conia, J.M. *Synthesis* ***1976***, 194.
[164] Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; Prakash, G.K.S. *J. Org. Chem.* ***1984****, 49*, 2032.
[165] Rubottom, G.M.; Mott, R.C. *J. Org. Chem.* ***1979****, 44,* 1731.
[166] Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004****, 126*, 15038.
[167] Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* ***1982****, 23*, 1165.
[168] Purrington, S.T.; Bumgardner, C.L.; Lazaridis, N.V.; Singh, P. *J. Org. Chem.* ***1987****, 52*, 4307.
[169] Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 126.
[170] Horiuchi, C.A.; Satoh, J.Y. *Synthesis* ***1981***, 312.
[171] Ley, S.V.; Whittle, A.J. *Tetrahedron Lett.* ***1981****, 22*, 3301.
[172] Hegde, S.G.; Wolinsky, J. *Tetrahedron Lett.* ***1981****, 22,* 5019.
[173] Fache, F.; Piva, O. *Synlett* ***2002***, 2035.

The α hydrogen atoms of carboxylic acids are replaced by bromine or chlorine using a phosphorus halide as catalyst.[174] The reaction, known as the *Hell–Volhard–Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α hydrogen atoms, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed initially from the carboxylic acid and the halogenating reagent. This means that each molecule of acid is α halogenated while it is in the acyl halide stage. The acids alone are inactive, except for those with relatively high enol content (e.g., malonic acid). Less than one full molar equivalent of catalyst (per molar equivalent of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see Reaction **16-79**). The halogen from the catalyst is *not* transferred to the α position. For example, the use of Cl_2 and PBr_3 results in α-chlorination, not bromination. As expected from the foregoing, acyl halides undergo a halogenation without a catalyst. An enantioselective α-halogenation was reported to give chiral α-haloesters via an alkaloid-catalyzed reaction of acyl halides with perhaloquinone-derived reagents.[175] So do anhydrides and many compounds that enolize easily (e.g., malonic ester and aliphatic nitro compounds). The mechanism is usually regarded as proceeding through the enol as in Reaction **12-4**.[176] If chlorosulfuric acid ($ClSO_2OH$) is used as a catalyst, carboxylic acids can be α-iodinated,[177] as well as chlorinated or brominated.[178] *N*-Bromosuccinimide in a mixture of sulfuric acid–trifluoroacetic acid can monobrominate simple carboxylic acids.[179]

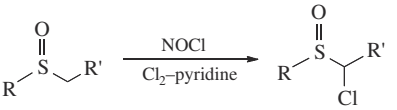
A number of other methods exist for the α halogenation of carboxylic acids or their derivatives.[180] Under electrolytic conditions with NaCl, malonates are converted to 2-chloro malonates.[181] Acyl halides can be a brominated or chlorinated by use of NBS or NCS and HBr or HCl.[182] The latter is an ionic, not a free radical halogenation (see Reaction **14-3**). Direct iodination of carboxylic acids has been achieved with I_2-Cu(II) acetate in HOAc.[183] Acyl chlorides can be α iodinated with I_2 and a trace of HI.[184] Carboxylic acids, esters, and amides have been α-fluorinated at −78 °C with F_2 diluted in N_2.[185] Amides have been α-iodinated using iodine and s-collidine.[186]

OS **I**, 115, 245; **II**, 74, 93; **III**, 347, 381, 495, 523, 623, 705, 848; **IV**, 254, 348, 398, 608, 616; **V**, 255; **VI**, 90, 190, 403; **IX**, 526. Also see, OS **IV**, 877; **VI**, 427.

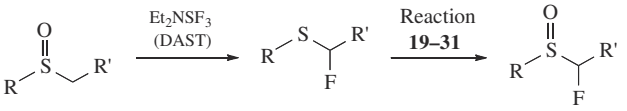
[174] See Harwood, H.J. *Chem. Rev.* ***1962****, 62,* 99, pp. 102-103.
[175] Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2001****, 123*, 1531. See also, France, S.; Wack, H.; Taggi, A.E.; Hafez, A.M.; Wagerle, Ty.R.; Shah, M.H.; Dusich, C.L.; Lectka, T. *J. Am. Chem. Soc.* ***2004****, 126*, 4245.
[176] See, however, Kwart, H.; Scalzi, F.V. *J. Am. Chem. Soc.* ***1964****, 86,* 5496.
[177] Ogata, Y.; Watanabe, S. *J. Org. Chem.* ***1979****, 44*, 2768; ***1980****, 45,* 2831.
[178] Ogata, Y.; Adachi, K. *J. Org. Chem.* ***1982****, 47*, 1182.
[179] Zhang, L.H.; Duan, J.; Xu, Y.; Dolbier, Jr., W.R. *Tetrahedron Lett.* ***1998****, 39*, 9621.
[180] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 730–738.
[181] Okimoto, M.; Takahashi, Y. *Synthesis* ***2002***, 2215.
[182] Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.* ***1975****, 40,* 3420.
[183] Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1984***, 1509.
[184] Rathke, M.W.; Lindert, A. *Tetrahedron Lett.* ***1971***, 3995.
[185] Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1990****, 55,* 3423.
[186] Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* ***1992****, 33*, 1299.

12-6 Halogenation of Sulfoxides and Sulfones

Halogenation or Halo-de-hydrogenation



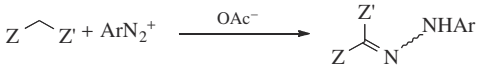
Sulfoxides can be chlorinated in the α position[187] by treatment with Cl_2[188] or NCS,[189] in the presence of pyridine. These methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2,[190] or with $TsNCl_2$.[191] The bromination of sulfoxides with bromine[192] and with NBS–bromine[193] have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases (RSO_2C^-HR') with various reagents, among them SO_2Cl_2, CCl_4,[194] or NCS.[195] The α-fluorination of sulfoxides was reported via treatment with diethylaminosulfur trifluoride (Et_2NSF_3, DAST) to give an α-fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperoxybenzoic acid gave the sulfoxide.[196]



C. Nitrogen Electrophiles

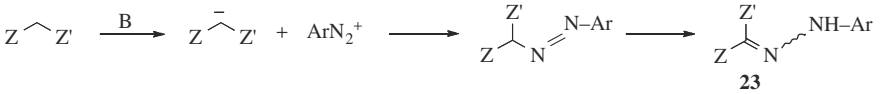
12-7 Aliphatic Diazonium Coupling

Arylhydrazono-de-dihydro-bisubstitution



If a C—H unit is acidic enough, that carbon couples with diazonium salts in the presence of a base (via the enolate anion), most often aq sodium acetate.[197] The reaction is commonly carried out on compounds of the form Z—CH_2—Z′, where Z and Z′ are as defined in Section **16-38** (e.g., β-keto esters, β-keto amides, malonic ester).

The mechanism is probably of the simple S_E1 type:

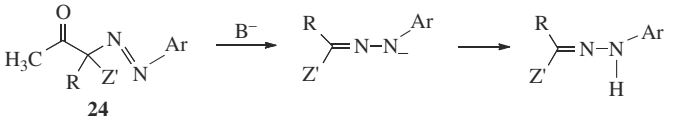


23

[187] For a review, see Venier, C.G.; Barager, III, H.J. *Org. Prep. Proced. Int.* ***1974****, 6*, 77, pp. 81–84.
[188] Tsuchihashi, G.; Iriuchijima, S. *Bull. Chem. Soc. Jpn.* ***1970****, 43*, 2271.
[189] Ogura, K.; Imaizumi, J.; Iida, H.; Tsuchihashi, G. *Chem. Lett.* ***1980***, 1587.
[190] Tin, K.; Durst, T. *Tetrahedron Lett.* ***1970***, 4643.
[191] Kim, Y.H.; Lim, S.C.; Kim, H.R.; Yoon, D.C. *Chem. Lett.* ***1990***, 79.
[192] Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1883. See also, Cinquini, M.; Colonna, S. *Synthesis* **1972**, 259.
[193] Iriuchijima, S.; Tsuchihashi, G. *Synthesis* ***1970***, 588.
[194] Regis, R.R.; Doweyko, A.M. *Tetrahedron Lett.* ***1982****, 23,* 2539.
[195] Paquette, L.A.; Houser, R.W. *J. Org. Chem.* ***1971****, 36,* 1015.
[196] McCarthy, J.R.; Pee, N.P.; LeTourneau, M.E.; Inbasekaran, M. *J. Am. Chem. Soc.* ***1985****, 107*, 735. See also, Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* ***1986****, 59,* 3625.
[197] See Parmerter, S.M. *Org. React.* ***1959****, 10*, 1.

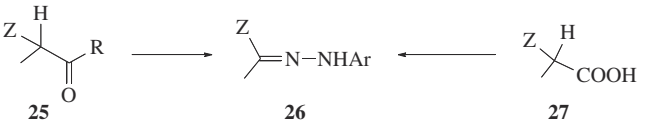
Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (**23**), which are the products of the reaction.

When the reaction is carried out on a compound of the form Z—CHR—Z′, the azo compound does not have a hydrogen that can lead to tautomerism, and at least one Z is acyl or carboxyl, this group usually cleaves:



24

so the product in this case is also the hydrazone, and not the azo compound. In fact, compounds of the type **24** are seldom isolable from the reaction, although this has been accomplished.[198] The cleavage step shown is an example of Reaction **12-43** and, when a carboxyl group cleaves, of Reaction **12-40**. The overall process in this case is called the *Japp–Klingemann reaction*[199] and involves conversion of a ketone (**25**) or a carboxylic acid (**26**)



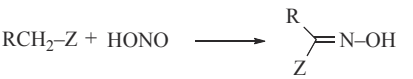
25 **26** **27**

to a hydrazone (**27**). When an acyl and a carboxyl group are both present, the leaving group order has been reported to be MeCO > COOH > PhCO.[200] When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

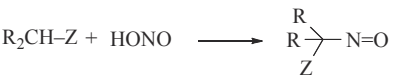
OS **III**, 660; **IV**, 633.

12-8 Nitrosation at a Carbon Bearing an Active Hydrogen

Hydroxyimino-de-dihydro-bisubstitution



Nitrosation or Nitroso-de-hydrogenation

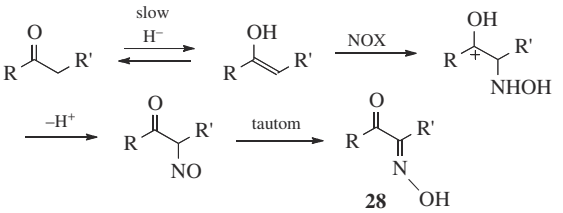


Carbons adjacent to a Z group (as defined in Reaction **10-67**) can be nitrosated with nitrous acid or alkyl nitrites.[201] The initial product is the *C*-nitroso compound, but these are stable only when there is no hydrogen that can undergo tautomerism. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds

[198] See Yao, H.C.; Resnick, P. *J. Am. Chem. Soc.* ***1962****, 84,* 3514.
[199] For a review, see Phillips, R.R. *Org. React.* ***1959****, 10*, 143.
[200] Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *J. Org. Chem. USSR* ***1989****, 25,* 2011. This paper also includes a sequence of leaving group ability for other Z groups.
[201] For a review, see Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, ***1988***, pp. 1–45.

and hydrazones (Reaction **12-7**). The mechanism is similar to that in Reaction **12-7**:[202] $R–H \rightarrow R^- + {}^+N{=}O \rightarrow R–N{=}O$. The reactive species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation Reaction **12-4**):

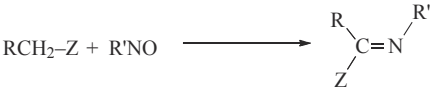
Evidence is that the reaction, in the presence of X^- (Br^-, Cl^-, or SCN^-) was first order in ketone and in H^+, but zero order in HNO_2 and X^-.[203] Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by $HONO + X^- + H^+ \rightarrow HOX + H_2O$. In the cases of $F_3CCOCH_2COCF_3$ and malononitrile, the nitrosation went entirely through the enolate ion rather than the enol.[204]



28

As in the *Japp–Klingemann reaction*, when Z is an acyl or carboxyl group (in the case of $R_2CH—Z$), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of Reaction **12-4**, the silyl enol ether of a ketone can be used instead of the ketone itself.[205] Good yields of α-oximinoketones (**28**) can be obtained by treating ketones with *tert*-butyl thionitrate.[206]

Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:

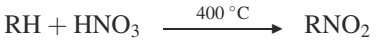


Alkanes can be nitrosated photochemically, by treatment with NOCl and UV light.[207] For nitration at an activated carbon, see Reaction **12-9**. Trialkyltin enol ethers ($C{=}C—O—SnR_3$) react with PhNO to give α-(*N*-hydroxylamino)ketones.[208]

OS **II**, 202, 204, 223, 363; **III**, 191, 513; **V**, 32, 373; **VI**, 199, 840. Also see, OS **V**, 650.

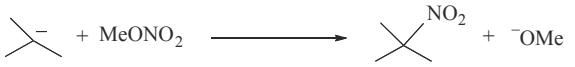
12-9 Nitration of Alkanes

Nitration or **Nitro-de-hydrogenation**



[202] For a review, see Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983****, 19*, 381. See also, Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, ***1988***.
[203] Leis, J.R.; Peña, M.E.; Williams, D.L.H.; Mawson, S.D. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 157.
[204] Iglesias, E.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 343; Crookes, M.J.; Roy, P.; Williams, D.L. H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1015. See also, Graham, A.; Williams, D.L.H. *J. Chem. Soc. Chem. Commun.* ***1991***, 407.
[205] Rasmussen, J.K.; Hassner, A. *J. Org. Chem.* ***1974****, 39*, 2558.
[206] Kim, Y.H.; Park, Y.J.; Kim, K. *Tetrahedron Lett.* ***1989****, 30*, 2833.
[207] See Pape, M. *Fortschr. Chem. Forsch.* ***1967****, 7,* 559.
[208] Momiyama, N.; Yamamoto, H. *Org. Lett.* ***2002****, 4*, 3579.

Nitration of alkanes[209] can be carried out in the gas phase at ~400 °C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.[210] A free radical mechanism is involved.[211]



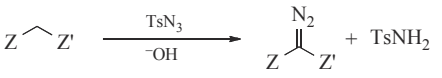
Activated positions (e.g., ZCH_2Z' compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,[212] or by alkyl nitrates under alkaline conditions.[213] In the latter case, it is the carbanionic form of the substrate that is actually nitrated. The conjugate base of the nitro compound is isolated under these alkaline conditions, but yields are not high. Of course, the mechanism in this case is not of the free radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of Reactions **12-7** and **12-8**). Positions activated by only one electron-withdrawing group (e.g., α positions of simple ketones, nitriles, sulfones, or *N,N*-dialkyl amides) can be nitrated with alkyl nitrates if a very strong base (e.g., *t*-BuOK or $NaNH_2$,) is present to convert the substrate to the carbanionic form.[214]

Electrophilic nitration of alkanes has been performed with nitronium salts (e.g., NO_2^+ PF_6^- and with HNO_3—H_2SO_4 mixtures), but mixtures of nitration and cleavage products are obtained and yields are generally low.[215] The reaction of alkanes with nitric acid and *N*-hydroxysuccinimide (NHS), however, gave moderate-to-good yields of the corresponding nitroalkane.[216] Similar nitration was accomplished with NO_2, NHS and air.[217] Aliphatic nitro compounds can be a nitrated [$R_2C\text{-}NO_2 \rightarrow R_2C(NO_2)_2$] by treatment of their conjugate bases $RCNO_2$ with NO_2^- and $K_3Fe(CN)_6$.[218]

OS **I**, 390; **II**, 440, 512.

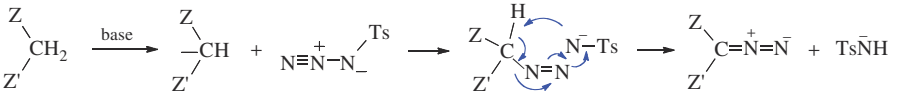
12-10 Direct Formation of Diazo Compounds

Diazo-de-dihydro-bisubstitution

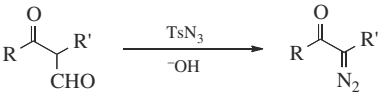


[209] See Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration*, VCH, NY, ***1989***, pp. 219–295; Ogata, Y. in Trahanovsky, W.S. *Oxidation in Organic Chemisry*, part C, Academic Press, NY, ***1978***, pp. 295–342; Ballod, A.P.; Shtern, V.Ya. *Russ. Chem. Rev.* ***1976****, 45,* 721.
[210] See Matasa, C.; Hass, H.B. *Can. J. Chem.* ***1971****, 49,* 1284.
[211] Titov, A.I. *Tetrahedron* ***1963****, 19*, 557.
[212] Sifniades, S. *J. Org. Chem.* ***1975****, 40,* 3562.
[213] See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 310–316.
[214] See Feuer, H.; Van Buren, II, W.D.; Grutzner, J.B. *J. Org. Chem.* ***1978****, 43,* 4676.
[215] Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1973****, 93,* 1259. See also, Bach, R.D.; Holubka, J.W.; Badger, R.C.; Rajan, S. *J. Am. Chem. Soc.* ***1979****, 101,* 4416.
[216] Isozaki, S.; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2001***, 1352.
[217] Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002****, 67*, 5663.
[218] Garver, L.C.; Grakauskas, V.; Baum, K. *J. Org. Chem.* ***1985****, 50*, 1699.

Compounds containing a CH_2 bonded to two Z groups (active methylene compounds, with Z as defined in Reaction **10-67**) can be converted to diazo compounds on treatment with tosyl azide in the presence of a base.[219] The use of phase-transfer catalysis increases the convenience of the method.[220] Sulfonyl azides also give the reaction.[221] The *diazo-transfer reaction* can also be applied to other reactive positions (e.g., the 5 position of cyclopentadiene).[222] The mechanism is probably as follows:



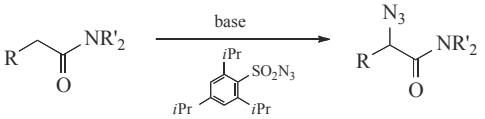
A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (Reaction **16-85**) and then treating it with tosyl azide. As in the similar cases of Reactions **12-7** and **12-8**, the formyl group is cleaved during the reaction.[223]



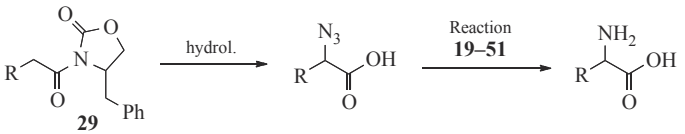
OS **V**, 179; **VI**, 389, 414.

12-11 Conversion of Amides to α-Azido Amides

Azidation or **Azido-de-hydrogenation**



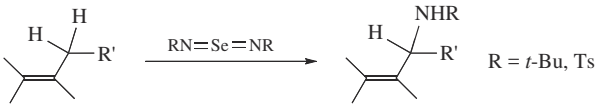
In Reaction **12-10**, treatment of $Z—CH_2—Z'$ with tosyl azide gave the α-diazo compound via diazo transfer. When this reaction is performed on a compound with a single Z group (e.g., an amide), formation of the azide becomes a competing process via the enolate anion.[224] Factors favoring azide formation rather than diazo transfer include K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzene-sulfonyl azide rather than TsN_3. When the reaction was applied to amides with a chiral R′ (e.g., the oxazolidinone derivative **29**), it was highly stereoselective, and the product could be converted to an optically active amino acid.[224]



[219] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 326–435; Regitz, M. *Synthesis* ***1972***, 351. See also, Koskinen, A.M.P.; Muñoz, L. *J. Chem. Soc. Chem. Commun.* ***1990***, 652.
[220] Ledon, H. *Synthesis* ***1974***, 347, *Org. Synth.* ***VI***, 414; Also see Ghosh, S.; Datta, I. *Synth. Commun.* ***1991****, 21*, 191.
[221] Taber, D.F.; Ruckle, Jr., R.E.; Hennessy, M.J. *J. Org. Chem.* ***1986****, 51*, 4077; Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* ***1987****, 17*, 1709.
[222] Doering, W. von E.; DePuy, C.H. *J. Am. Chem. Soc.* ***1953****, 75,* 5955.
[223] See also Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* ***1990****, 55*, 1959.
[224] Evans, D.A.; Britton, T.C. *J. Am. Chem. Soc.* ***1987****, 109,* 6881, and references cited therein.

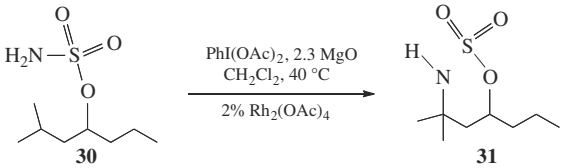
12-12 Direct Amination at an Activated Position

Alkyamino-de-hydrogenation, and so on



Alkenes can be aminated[225] in the allylic position by treatment with solutions of imido selenium compounds (R—N=Se=N—R).[226] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see Reaction **19-14**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used,[227] as well as PhNHOH—$FeCl_2$/$FeCl_3$.[228] Benzylic positions can be aminated with *t*-BuOOCONHTs in the presence of a catalytic amount of $Cu(OTf)_2$.[229] Enantioselective allylic amination has been reported using organocatalyts.[230] A Rh catalyzed amination of benzylic positions has also been reported.[231]

Tertiary alkyl hydrogen can be replaced in some cases via C—H nitrogen insertion. The reaction of sulfamate ester (**30**) with $PhI(OAc)_2$, MgO, and a dinuclear Rh carboxylate catalyst, for example, generated oxathiazinane (**31**).[232] This transformation is a formal oxidation, and primary carbamates have been similarly converted to oxazolidin-2-ones.[233]



Amination of 1,3-dicarbonyl compounds can be done using functionalized dimides and an appropriate catalyst, generating the corresponding hydrazone. Enantioselective amination using this method has been reported, using a chiral guanidine catalyst.[234]

See also, Reaction **10-39**.

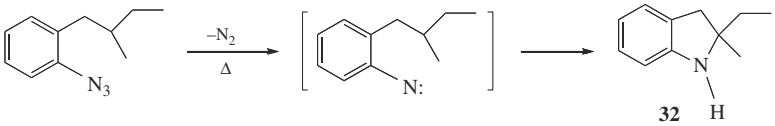
12-13 *Insertion by Nitrenes*

***CH*-[Acylimino]-insertion**, and so on



[225] See Sheradsky, T. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 395–416.
[226] Sharpless, K.B.; Hori, T.; Truesdale, L.K.; Dietrich, C.O. *J. Am. Chem. Soc.* ***1976****, 98*, 269; Kresze, G.; Münsterer, H. *J. Org. Chem.* ***1983****, 48,* 3561. For a review, see Cheikh, R.B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* ***1983***, 685, pp. 691–696.
[227] Sharpless, K.B.; Hori, T. *J. Org. Chem.* ***1979****, 41*, 176. For other reagents, see Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M.O.; Jones, N.D.; Swartzendruber, J.K. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 1167.
[228] Srivastava, R.S.; Nicholas, K.M. *Tetrahedron Lett.* ***1994****, 35*, 8739.
[229] Kohmura, Y.; Kawasaki, K.; Katsuki, T. *Synlett,* ***1997***, 1456.
[230] Poulsen, T.B.; Alemparte, C.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005****, 127*, 11614.
[231] Fiori, J.W.; Du Bois, J. *J. Am. Chem. Soc.* ***2007****, 129*, 562.
[232] Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem.Soc.* ***2001****, 123,* 6935.
[233] Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* ***2001****, 40,* 598.
[234] Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* ***2006****, 128,* 16044.

Carbonylnitrenes (:NCOW, W = R′, Ar, or OR′) are very reactive species (Sec. 5.E) and insert into the C—H bonds of alkanes to give amides (W = R′ or Ar) or carbamates (W = OR′).[235] The nitrenes are generated as discussed in Section 5.E. The order of reactivity among alkane C—H bonds is tertiary > secondary > primary.[236] Nitrenes are much more selective (and less reactive) in this reaction than carbenes (Reaction **12-17**).[237] It is likely that only singlet and not triplet nitrenes insert.[238] Retention of configuration is found at a stereogenic carbon.[239] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (Reaction **12-21**). Other nitrenes [e.g., cyanonitrene (NCN)[240] and arylnitrenes (NAr)[241]] can also insert into C—H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. The Au(III) catalyzed insertion of nitrenes into aromatic and benzylic C—H groups has been reported.[242] *N*-Carbamoyl nitrenes undergo insertion reactions that often lead to mixtures of products, but exceptions are known,[243] chiefly in cyclizations.[244] For example, heating of 2-(2-methylbutyl)phenyl azide gave ~60% 2-ethyl-2-methylindoline (**32**).[239] Enantioselective nitrene insertion reactions are known.[245]

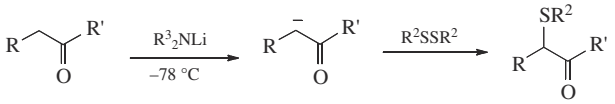


32

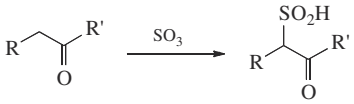
D. Sulfur Electrophiles

12-14 Sulfenylation, Sulfonation, and Selenylation of Ketones and Carboxylic Esters

Alkylthio-de-hydrogenation, and so on



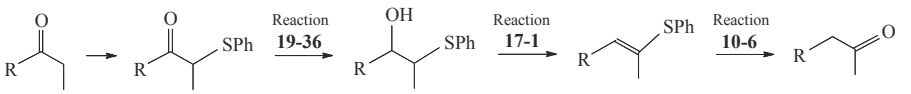
Sulfonation or **Sulfo-de-hydrogenation**



[235] See Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 199–207.
[236] See Maslak, P. *J. Am. Chem. Soc.* ***1989****, 111,* 8201.
[237] See Alewood, P.F.; Kazmaier, P.M.; Rauk, A. *J. Am. Chem. Soc.* ***1973****, 95*, 5466.
[238] See Inagaki, M.; Shingaki, T.; Nagai , T. *Chem. Lett.* ***1981***, 1419.
[239] Smolinsky, G.; Feuer, B.I. *J. Am. Chem. Soc.* ***1964****, 86,* 3085.
[240] See Anastassiou, A.G.; Shepelavy, J.N.; Simmons, H.E.; Marsh, F.D. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 305–344.
[241] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 95–204.
[242] Li, Z.; Capretto, D.A.; Rahaman, R.O.; He, C. *J. Am. Chem. Soc.* ***2007****, 129,* 12058.
[243] See also, Meinwald, J.; Aue, D.H. *Tetrahedron Lett.* ***1967***, 2317.
[244] For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1148–1149.
[245] See Müller, P.; Fruit, C. *Chem. Rev.* ***2003****, 103*, 2905.

Ketones, carboxylic esters (including lactones),[246] and amides (including lactams)[247] can be sulfenylated[248] in the α position by conversion to the enolate anion (see Sec. 8.F, part 7), and subsequent treatment with a disulfide.[249] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. α-Phenylseleno ketones [RCH(SePh)COR′] and α-phenylseleno esters [RCH(SePh)COOR′] can be similarly prepared[250] by treatment of the corresponding enolate anions with PhSeBr,[251] PhSeSePh,[252] or benzeneseleninic anhydride [PhSe(O)OSe(O)Ph].[253] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[254] This procedure is also successful for aldehydes but not for carboxylic esters. *N*-Phenylselenophthalimide has been used to convert ketones[255] and aldehydes[256] to the α- PhSe derivative. Silyl enol ethers are converted to α-alklylthio and α-arylthio ketones via a sulfenylation method, driven by aromatization of an added quinone mono-*O,S*-acetal in the presence of Me_3SiOTf.[257]

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (Reaction **17-12**). The sulfenylation reaction has also been used[258] as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.[259]



Aldehydes, ketones, and carboxylic acids containing α hydrogen atoms can be sulfonated with sulfur trioxide.[260] The mechanism is presumably similar to that of Reaction **12-4**. Sulfonation has also been accomplished at vinylic hydrogen.

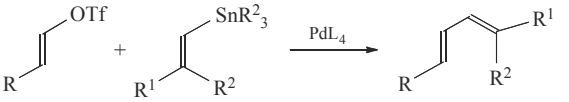
OS **VI**, 23, 109; **VIII**, 550. OS **IV**, 846, 862.

[246] See Trost, B.M. *Pure Appl. Chem.* ***1975****, 43*, 563, pp. 572–578; Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 278–282.
[247] Gassman, P.G.; Balchunis, R.J. *J. Org. Chem.* ***1977****, 42*, 3236.
[248] See Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* ***2004****, 69*, 6916.
[249] For another reagent, see Scholz, D. *Synthesis* ***1983***, 944.
[250] See Back, T.G. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 1–125; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 95–98.
[251] Brocksom, T.J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* ***1974****, 39,* 2114. See also, Liotta, D. *Acc. Chem. Res.* ***1984****, 17,* 28.
[252] Grieco, P.A.; Miyashita, M. *J. Org. Chem.* ***1974****, 39*, 120. See Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* ***1982****, 23*, 4813.
[253] Barton, D.H.R.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Chem. Commun.* ***1981***, 1044.
[254] Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc.* ***1973****, 95*, 6137.
[255] Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993****, 34*, 7755.
[256] Wang, W.; Wang, K.; Li, H. *Org. Lett.* ***2004****, 6,* 2817.
[257] Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.,* ***2001****, 66,* 2434.
[258] Trost, B.M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* ***1975****, 97*, 438.
[259] See OS **VI**, 23, 109; 68, 8. See also Morris, D.G. *Chem. Soc. Rev.* ***1982****, 11,* 397; Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron* ***1983****, 39,* 345.
[260] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 33–61.

E. Carbon Reagents

12-15 Alkylation and Alkenylation of Alkenes

Alkylation or **Alkyl-de-oxysulfonation (de-halogenation)**, **Arylation** or **Aryl-de-oxysulfonation (de-halogenation)**, and so on



Vinyl triflates (C=C—OSO_2CF_3) react with vinyl tin derivatives in the presence of Pd catalysts to form dienes, in what is known as *Stille coupling*.[261] Phosphine or bis (phosphine) ligands are most commonly used with the Pd catalyst,[262] but other ligands have been used,[263] including triphenylarsine.[264] Vinyl triflates can be prepared from the enolate anion by reaction with *N*-phenyl triflimide.[265] Vinyltin compounds are generally prepared by the reaction of an alkyne with an trialkyltin halide (see Reactions **15-17** and **15-21**).[266] *Stille cross-coupling* reactions are an important variation of the basic reaction,[267] including cross-coupling reactions of unactivated secondary halides and monoorganotin reagents.[268] Stille reactions are compatible with many functional groups. Vinyl halides can be used,[269] and allenic tin compounds have been used.[270] Intramolecular reactions are possible.[271] *Stille coupling* has been done using microwave irradiation,[272] in fluorous solvents,[273] and in supercritical carbon dioxide (see Sec. 9.D.ii).[274] *Stille coupling* using alkynes as a substrate are known.[275]

This reaction is highly stereoselective, and proceeds with a retention of geometry of the C=C units, and are usually regiospecific with respect to the newly formed C—C σ-bond. Cine substitution is known with this reaction, and its mechanism has been studied.[276] Using $ArSnCl_3$ derivatives, Stille coupling can be done in aq KOH.[277]

[261] Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.* ***1984****, 106*, 4630. See Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett.* ***1995****, 36*, 2191 for an optimized version of this reaction. Also see Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2005****, 44,* 3962; Reiser, O. *Angew. Chem. Int. Ed.* ***2006****, 45,* 2838.

[262] See Zhou, W.-J.; Wang, K.-H.; Wang, J.-X. *J. Org. Chem.* ***2009****, 74,* 5599.

[263] Gajare, A.S.; Jensen, R.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Synlett* ***2005***, 144. For a ligand free reaction, see Yabe, Y.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* ***2010****, 66,* 8654.

[264] Lau, K.C.Y.; Chiu, P. *Tetrahedron Lett.* ***2007****, 48,* 1813.

[265] McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* ***1983****, 24*, 979.

[266] See Maleczka Jr., R.E.; Lavis, J.M.; Clark, D.H.; Gallagher, W.P. *Org. Lett.* ***2000****, 2*, 3655.

[267] Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* ***1997****, 50,* 1; Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* ***2005****, 70,* 2832.

[268] Powell, D.A.; Maki, T.; Fu, G.C. *J. Am. Chem. Soc.* ***2005****, 127,* 510.

[269] Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W. *Tetrahedron Lett.* ***1992****, 33*, 919.

[270] Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* ***1994****, 35*, 5477.

[271] Segorbe, M.M.; Adrio, J.; Carretero, J.C. *Tetrahedron Lett.* ***2000****, 41,* 1983.

[272] Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D.P. *J. Org. Chem.* ***1997****, 62,* 5583.

[273] Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999****, 64*, 4539.

[274] Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* ***1999****, 99,* 475.

[275] Shi, Y.; Peterson, S.M.; Haberaecker III, W.W.; Blum, S.A. *J. Am. Chem. Soc.* ***2008****, 130,* 2168.

[276] Farina, V.; Hossain, M.A. *Tetrahedron Lett.* ***1996****, 37*, 6997.

[277] Rai, R.; Aubrecht, K.B.; Collum, D.B. *Tetrahedron Lett.* ***1995****, 36*, 3111.

Aryl halides,[278] heteroaryl halides,[279] and heteroaryl triflates[280] can be coupled to vinyltin reagents[281] using a Pd catalyst. A Mo catalyzed variation is known.[282] A Cu catalyzed cross coupling variation[283] has been reported in ionic liquids.[284] Vinyl halides can be coupled to alkenes to form dienes.[285] The reaction of dihydrofurans with vinyl triflates and a Pd catalyst leads to a nonconjugated diene,[286] illustrating that the product is formed by an elimination step, as with the *Heck reaction* (**13-10**), and double-bond migration can occur resulting in allylic rearrangement.

The accepted mechanism for the *Stille reaction* involves a catalytic cycle[287] in which an oxidative addition[288] and a reductive elimination step[289] are fast, relative to Sn/Pd transmetalation (the rate-determining step).[290] It appears that the greater the coordinating ability of the unsaturated species is important, and a coordinated solvent molecule is likely involved in the electrophilic substitution at tin. Another mechanism has been proposed, in which oxidative addition of the vinyl triflate to the ligated Pd gives a *cis*-Pd complex that isomerizes rapidly to a *trans*-Pd complex, which then reacts with the organotin compound following an S_E2 (cyclic) mechanism, with release of a ligand.[291] This pathway gives a bridged intermediate, and subsequent elimination of $XSnBu_3$ yields a three-coordinate species *cis*-Pd complex, which readily gives the coupling product.[291] Most of the major intermediates have been intercepted, isolated, and characterized using electrospray ionization mass spectrometry.[292]

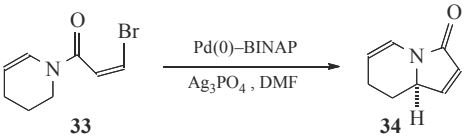
Cyclopropylboronic acids (Reaction **12-28**) couple with vinylic halides[293] or vinyl triflates[294] to give vinylcyclopropanes, using a Pd catalyst. Vinyl borates (Reaction **12-28**) were coupled to vinyl triflates using a Pd catalyst.[295] Vinyltrifluoroborates can be coupled to allylic chlorides using microwave irradiation[296] and vinyl halides react with vinyltrifluoroborates to give dienes with high stereoselectivity.[297] Stille coupling to enols has

[278] Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***1999****, 38*, 2411.
[279] Clapham, B.; Sutherland, A.J. *J. Org. Chem.* ***2001****, 66*, 9033.
[280] Schaus, J.V.; Panek, J.S. *Org. Lett.* ***2000****, 2*, 469.
[281] See Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* ***1999****, 1*, 701. Also see Minière, S.; Cintrat, J.-C. *J. Org. Chem.* ***2001****, 66*, 7385.
[282] Lindh, J.; Fardost, A.; Almeida, M.; Nilsson, P. *Tetrahedron Lett.* ***2010****, 51*, 2470; Sävmarker, J.; Lindh, J.; Nilsson, P. *Tetrahedron Lett.* ***2010****, 51*, 6886.
[283] Mee, S.P.H.; Lee, V.; Baldwin, J.E. *Chemistry: European J.* ***2005****, 11,* 3294.
[284] Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Xie, Y.-X.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* ***2006****, 71,* 7488.
[285] Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* ***1994***, 189.
[286] Gilbertson, S.R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* ***2001****, 42,* 365.
[287] Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* ***1986****, 108,* 3033; Stille, J.K. *Angew. Chem., Int. Ed.* ***1986****, 25,* 508; Farina, V. in Abel, E.W.; Stone, F.G.A.; Wilkinson, G. *Comprehensive Organometallic Chemistry II*, Vol. 12, Pergamon, Oxford, U.K., ***1995***, Chapter 3.4.; Brown, J.M.; Cooley, N.A. *Chem. Rev.* ***1988****, 88,* 1031.
[288] Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* ***1993****, 115,* 9531 and references cited therein.
[289] Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1986****, 5,* 2144; Tatsumi, K.; Hoffmann, R.; Moravski, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1981****, 103*, 4182; Loar, M.K.; Stille, J.K. *J. Am. Chem. Soc.* ***1981****, 103,* 4174.
[290] Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* ***1989****, 359,* 267.
[291] Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* ***2000****, 122,* 11771.
[292] Santos, L.S.; Rosso, G.B.; Pilli, R.A.; Eberlin, M.N. *J. Org. Chem.* ***2007****, 72*, 5809.
[293] Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* ***2000****, 41*, 3951.
[294] Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* ***2000****, 65,* 5034; Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* ***2000****, 41*, 9083.
[295] Occhiato, E.G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* ***2001****, 66*, 2459.
[296] Kabalka, G.W.; Dadush, E.; Al-Masum, M. *Tetrahedron Lett.* ***2006****, 47,* 7459.
[297] Molander, G.A.; Felix, L.A. *J. Org. Chem.* ***2005****, 70*, 3950.

been reported.[298] The coupling of vinyl silanes to give the symmetrically conjugated diene using CuCl and air has also been reported.[299]

Other methods are available to give Stille-like products. 1-Lithioalkynes were coupled to vinyl tellurium compounds (C=C—TeBu) using a Ni[300] or a Pd catalyst[301] to give a conjugated en-yne. 2-Alkynes (R—C≡C—Me) react with $HgCl_2$, *n*-butyllithium, and $ZnBr_2$, sequentially, and then with vinyl iodides and a Pd catalyst to give the nonconjugated en-yne.[302] Alkynyl groups can be coupled to vinyl groups to give ene-ynes, via reaction of silver alkynes (Ag—C≡C—R) with vinyl triflates and a Pd catalyst.[303] In the presence of CuI and a Pd catalyst, vinyl triflates[304] or vinyl halides[305] couple to terminal alkynes. Alkynyl zinc reagents (R—C≡C—ZnBr) can be coupled to vinyl halides with a Pd catalyst to give the conjugated en-yne.[306]

Alkyl groups can be coupled to a vinyl unit to give substituted alkenes. The reaction of vinyl iodides and EtZnBr, with a Pd catalyst, gave the ethylated alkene (C=C—Et).[307] Aliphatic alkyl bromides reacted with vinyltin compounds to give the alkylated alkene using a Pd catalyst.[308] Allylic tosylates were coupled to conjugated alkenes to give a non-conjugated diene using a Pd catalyst.[309] An internal coupling reaction was reported in which an alkenyl enamide (**33**) reacted with Ag_3PO_4 and a chiral palladium catalyst to give **34** enantioselectively.[310]

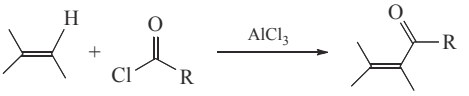


33 **34**

For the related coupling reaction of alkenes and aryl compounds (arylation of alkenes), see Reaction **13-10**.

12-16 Acylation at an Aliphatic Carbon

Acylation or **Acyl-de-hydrogenation**



[298] Fu, X.; Zhang, S.; Yin, J.; McAllister, T.L.; Jiang, S.A.; Tann, C.-H.; Thiruvengadam, T.K.; Zhang, F. *Tetrahedron Lett.* ***2002****, 43*, 573. See Vallin, K.S.A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* ***2000****, 65*, 4537.

[299] Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***2000****, 73,* 985.

[300] Raminelli, C.; Gargalak Jr., J.; Silveira, C.C.; Comasseto, J.V. *Tetrahedron Lett.* ***2004****, 45*, 4927; Silveira, C.C.; Braga, A.L.; Vieira, A.S.; Zeni, G. *J. Org. Chem.* ***2003****, 68,* 662.

[301] Zeni, G.; Comasseto, J.V. *Tetrahedron Lett.* ***1999****, 40*, 4619.

[302] Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* ***2000****, 65,* 2287.

[303] Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* ***2001****, 3*, 1661. See Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* ***2001****, 42*, 8641; Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem.* ***2001***, 4391.

[304] Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 369.

[305] Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* ***2002****, 4*, 1171. Also see Bates, C.G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* ***2004****, 6*, 1441.

[306] Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* ***2003****, 5*, 1597.

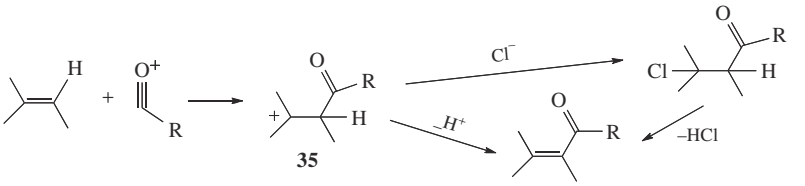
[307] Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem.* ***2000****, 65*, 7475.

[308] Menzel, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2003****, 125,* 3718.

[309] Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* ***2003***, 2404.

[310] Kiewel, K.; Tallant, M.; Sulikowski, G.A. *Tetrahedron Lett.* ***2001****, 42*, 6621.

Alkenes can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a *Friedel–Crafts Reaction* (**11-17**) at an aliphatic carbon.[311] The product can arise by two paths. The initial attack is by the π bond of the alkene unit on the acyl cation (RCO^+; or on the acyl halide free or complexed; see Reaction **11-17**) to give a carbocation, (**35**).



Ion **35** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone. The mechanism is similar to the *tetrahedral mechanism* in Section 16.A.i, but with the charges reversed. If it combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see Reaction **15-47**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical alkenes, the more stable alkene is formed (the more highly substituted and/or conjugated alkene, following *Markovnikov's rule*, see Sec. 15.B.ii). Anhydrides and carboxylic acids (the latter with a proton acid e.g., anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some substrates and catalysts, double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[312]

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π-allyl carbonyl derivatives[313] (π-allyl metal complexes were discussed in Sec. 3.C.i. The reaction is very general. With unsymmetrical dienes, the acyl group generally substitutes most readily at a cis double bond, next at a terminal alkenyl group, and least readily at a trans double bond. The most useful bases are strongly basic, hindered amines (e.g., dicyclohexylethylamine). Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a Pd catalyst: $ROCH{=}CH_2 \rightarrow ROCH{=}CHCOAr$.[314]

Formylation of alkenes can be accomplished with *N*-disubstituted formamides and $POCl_3$.[315] This is an aliphatic *Vilsmeier reaction* (see Reaction **11-18**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[316] A variation

[311] See Groves, E.E. *Chem. Soc. Rev.* ***1972****, 1,* 73; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 259–266, 270–273; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel–Crafts and Related Reactions,* Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

[312] Deno, N.C.; Chafetz, H. *J. Am. Chem. Soc.* ***1952****, 74*, 3940. For other examples, see Grignon-Dubois, M.; Cazaux, M. *Bull. Soc. Chim. Fr.* ***1986***, 332.

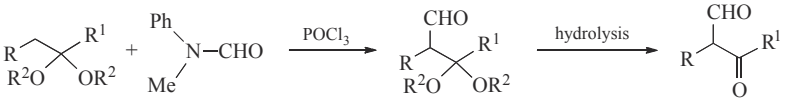
[313] See Heck, R.F. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 1, Wiley, NY, ***1968***, pp. 388–397.

[314] Andersson, C.; Hallberg, A. *J. Org. Chem.* ***1988****, 53,* 4257.

[315] See Burn, D. *Chem. Ind. (London)* ***1973***, 870; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 281–282.

[316] Youssefyeh, R.D. *Tetrahedron Lett.* ***1964***, 2161.

heated a 1,1-dibromoalkene with a secondary amine in aq DMF to give the corresponding amide.[317]

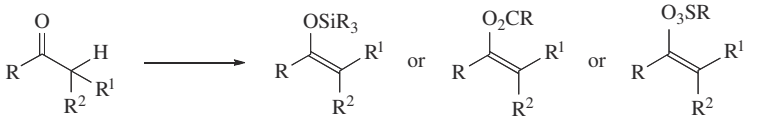


Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3–etherate.[318] The mechanism with acetals or ketals also involves attack at an alkenyl carbon, since enol ethers are intermediates.[318] Ketones can be formylated in the α position by treatment with CO and a strong base.[319]

OS **IV**, 555, 560; **VI**, 744. Also see, OS **VI**, 28.

12-17 Conversion of Enolates to Silyl Enol Ethers, Silyl Enol Esters, and Silyl Enol Sulfonate Esters

3/*O*-Trimethylsilyl-de-hydrogenation

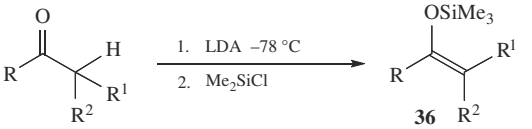


Sily enol ether | Enol ester | Enol sulfonate ester

Silyl enol ethers,[320] important reagents with a number of synthetic uses (see, e.g., Reactions **10-68**, **12-4**, **15-24**, **15-64**, and **16-36**), can be prepared by base treatment of a ketone (converting it to its enolate anion) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.[321] Both strong bases (e.g., LDA), and weaker bases (Et_3N) have been used for this purpose.[322] In some cases, the base and the silylating agent can be present at the same time.[323] Enolate anions prepared in other ways (e.g., as shown in Reaction **10-58**) also give the reaction.[324] The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.[325] A particularly mild method for conversion of ketones or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane [$(Me_3Si)_2NH$.][326] Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me_3SiBr, tetraphenylstibonium

[317] Shen, W.; Kunzer, A. *Org. Lett.* ***2002****, 4*, 1315.
[318] Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1963****, 85,* 3901.
[319] See van der Zeeuw, A.J.; Gersmann, H.R. *Recl. Trav. Chim. Pays-Bas* ***1965****, 84,* 1535.
[320] See Poirier, J. *Org. Prep. Proced. Int.* ***1988****, 20,* 319; Brownbridge, P. *Synthesis* ***1983***, 1, 85; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***; Colvin, E.W. in Hartley, C.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond,* Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev.* ***1982****, 11*, 493.
[321] See Mizhiritskii, M.D.; Yuzhelevskii, Yu.A. *Russ. Chem. Rev.* ***1987****, 56*, 355. For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1488–1491.
[322] Di-*tert*-butylmagnesium has also been used. See Kerr, W.J.; Watson, A.J.B.; Hayes, D. *Synlett* ***2008***, 1386.
[323] Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984****, 25*, 495. Also see Lipshutz, B.H.; Wood, M.R.; Lindsley, C.W. *Tetrahedron Lett.* ***1995****, 36*, 4385.
[324] See Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* ***1994****, 35*, 6295.
[325] Ladjama, D.; Riehl, J.J. *Synthesis* ***1979***, 504. See Orban, J.; Turner, J.V.; Twitchin, B. *Tetrahedron Lett.* ***1984****, 25*, 5099.
[326] Miller, R.D.; McKean, D.R. *Synth. Commun.* ***1982****, 12,* 319. See also, Ahmad, S.; Khan, M.A.; Iqbal, J. *Synth. Commun.* ***1988****, 18,* 1679.

bromide (Ph_4SbBr), and an aziridine.[327] bis(Trimethylsilyl)acetamide is an effective reagent for the conversion of ketones to the silyl enol ether, typically giving the thermodynamic product (see below).[328] Silyl enol ethers have also been prepared by the direct reaction of a ketone and a silane (R_3SiH) with a Pt catalyst.[329]



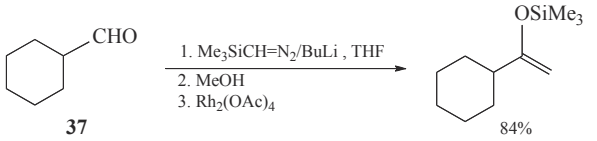
36

For substituted ketones, (*E*) and (*Z*) isomers are usually formed. For **36**, the enol is (*Z*) when R^1 is the priority group, but (E) when R^2 is the priority group. In some cases, it is possible to control the selectivity to favor more of one isomer than the other. Treatment of 2-methyl-3-pentanone with LDA (THF, -78 °C), for example, gave a 60:40 mixture of the (*Z*) and (*E*) enolates.[330] The base used to generate an enolate anion, the solvent and temperature, the conjugate acid of the base used, and the nature of the carbonyl substrate will all play a role in the selectivity. In general, equilibrating (thermodynamic) conditions [protic solvents (e.g., ethanol, water, or ammonia), a base generating a conjugate acid stronger than the starting ketone, more ionic counterions (e.g., K or Na), higher temperatures and longer reaction times] are expected to give more of the (*E*)-isomer. Conversely, kinetic conditions [aprotic solvents (e.g., ether or THF), a base generating a conjugate acid weaker than the starting ketone, more covalent counterions (e.g., Li, lower temperatures), and relatively short reaction times] usually give more of the (*Z*)-isomer. It is not always easy to predict the ratio, however. Either isomer is possible from aldehydes using the proper Rh catalyst.[331]

Magnesium diisopropylamide has been used to prepare kinetic silyl enol ethers in virtual quantitative yield.[332] Reaction with Me_3SiCl/KI in DMF gives primarily the thermodynamic silyl enol ether.[333]

An interesting synthesis of silyl enol ethers involves chain extension of an aldehyde. Aldehydes are converted to the silyl enol ether of a ketone upon reaction with lithium (trimethylsilyl)diazomethane and then a dirhodium catalyst.[334] For example, initial reaction of lithium(trimethylsilyl)diazomethane [LTMSD, prepared *in situ* by reaction of butyllithium with (trimethylsilyl)diazomethane] to the aldehyde (e.g., **37**) gave the alkoxide addition product. Protonation and then capture by a transition metal catalyst, and a 1,2-hydride migration gave the silyl enol ether, (**38**). Silyl enol ethers can be prepared from acyloin derivatives (see Reaction **19-78**).[335]

[327] Fujiwara, M.; Baba, A.; Matsuda, H. *Chem. Lett.* ***1989***, 1247.
[328] Smietana, M.; Mioskowski, C. *Org. Lett.* ***2001****, 3*, 1037. See also, Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* ***2002***, 1628.
[329] Ozawa, F.; Yamamoto, S.; Kayagishi, S.; Hiraoka, M.; Ideda, S.; Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett.* ***2001***, 972. See Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetahedron* ***2002****, 58*, 8247; Mori, A.; Kato, T. *Synlett* ***2002***, 1167.
[330] Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. *J. Org. Chem.* ***1980****, 45,* 1066.
[331] Vitale, M.; Lecourt, T.; Sheldon, C.G.; Aggarwal, V.K. *J. Am. Chem. Soc.* ***2006****, 128*, 2524.
[332] Lessène, G.; Tripoli, R.; Cazeau, P.; Biran, C.; Bordeau, M. *Tetrahedron Lett.* ***1999****, 40*, 4037. Also see Patonay, T.; Hajdu, C.; Jeko, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* ***1999****, 40,* 1373.
[333] Lin, J.-M.; Liu, B.-S. *Synth. Commun.* ***1997****, 27*, 739.
[334] Aggarwal, V.K.; Sheldon, C.G.; Macdonald, G.J.; Martin, W.P. *J. Am. Chem. Soc.* ***2002****, 124,* 10300.
[335] Robertson, B.D.; Hartel, A.M. *Tetrahedron Lett.* ***2008****, 49*, 2088.



37 **38**

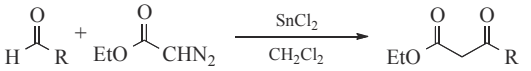
Enol acetates are generally prepared by the reaction of an enolate anion with a suitable acylating reagent.[336] Enolate anions react with acyl halides and with anhydrides to give the acylated product. Both C- and O-acylation are possible, but in general O-acylation predominates.[337] Note that the extent of O- versus C-acylation is very dependent on the local environment and electronic effects within the enolate anion.[338] *O*-Benzoate enols are formed in good yield from aldehydes or 1,3-diketones in the presence of CuBr and *tert*-butylhydroperoxide.[339] Silyl sulfonate esters can be prepared by similar methods, using sulfonic acid anhydrides rather than carboxylic anhydrides. A polymer-supported triflating agent was used to prepare silyl enol triflate from ketones, in the presence of diisopropylethylamine.[340]

When a silyl enol ether is the trimethylsilyl derivative ($Me_3Si—O-C=C$), treatment with methyllithium will regenerate the lithium enolate anion and the volatile trimethylsilane (Me_3SiH).[341]

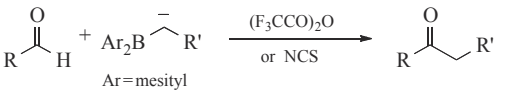
OS **VI**, 327, 445; **VII**, 282, 312, 424, 512; **VIII**, 1, 286, 460; **IX**, 573. See also, OS **VII**, 66, 266. For the conversion of ketones to vinylic triflates,[342] see OS **VIII**, 97, 126.

12-18 Conversion of Aldehydes to β-Keto Esters or Ketones

Alkoxycarbonylalkylation or **Alkoxycarbonylalkyl-de-hydrogenation**



β-Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid (e.g., $SnCl_2$, BF_3, or $GeCl_2$).[343] The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron, in the presence of $(F_3CCO)_2O$ or NCS, to give ketones.[344]

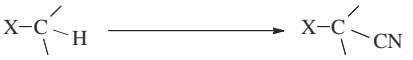


[336] For the synthesis of enol acetates, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, 1484–1485.
[337] See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth. Coll. Vol. V* ***1973***, 198.
[338] See Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* ***2000****, 41*, 5927.
[339] Yoo, W.-J.; Li, C.-J. *J. Org. Chem.* ***2006****, 71,* 6266.
[340] Wentworth, A.D.; Wentworth, Jr., P.; Mansoor, U.F.; Janda, K.D. *Org. Lett.* ***2000****, 2*, 477.
[341] House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1969****, 34*, 2324.
[342] Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* ***1992****, 33*, 6299.
[343] Holmquist, C.R.; Roskamp, E.J. *J. Org. Chem.* ***1989****, 54,* 3258.
[344] Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett.* ***1989****, 30,* 5643.

Ketones can be prepared from aryl aldehydes (ArCHO) by treatment with a Rh complex [$(Ph_3P)_2Rh(CO)Ar'$], whereby the Ar group is transferred to the aldehyde, producing the ketone (Ar—CO—Ar′).[345] In another Rh catalyzed reaction, aryl aldehydes (ArCHO) react with Me_3SnAr' to give the diaryl ketone (Ar—CO—Ar′).[346]

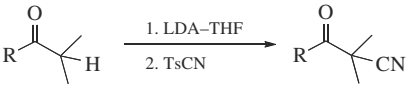
Acylation of aryl halides with aldehydes gives arylketones in the presence of a Pd catalyst.[347]

12-19 Cyanation or Cyano-de-hydrogenation



There are several reactions in which a C—H unit is replaced by C—CN. In virtually all cases, the hydrogen being replaced is on a carbon α to a heteroatom or functional group. There are several examples.

Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate anion with LDA in THF and addition of this solution to *p*-TsCN at −78 °C.[348] The products are formed in moderate to high yields but the reaction is not applicable to methyl ketones. Treatment of $TMSCH_2N(Me)C{=}Nt\text{-}Bu$ with *sec*-butyllithium and $R_2C{=}O$, followed by iodomethane and NaOMe leads to the nitrile ($R_2CH—CN$).[349]



Cyanation has been shown to occur α to a nitrogen, specifically in *N,N*-dimethylaniline derivatives. Treatment with a catalytic amount of $RuCl_3$ in the presence of oxygen and NaCN leads to the corresponding cyanomethylamine.[350] Conversion of tertiary amines to the α-cyanoamine has been reported in the presence of $FeCl_2$ and *t*-BuOOH.[351]

In a different kind of reaction, nitro compounds are α-cyanated by treatment with ^{-}CN and $K_3Fe(CN)_6$.[352] The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α-cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN.[353,354]

Another specialized reaction converts the methyl group of arenes (e.g., toluene) into a cyano group: toluene → benzonitrile, for example.[355]

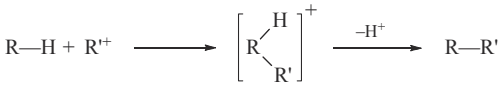
[345] Krug, C.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002****, 124,* 1674.
[346] Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* ***2004****, 126*, 15356.
[347] Ruan, J.; Saidi, O.; Iggo, J.A.; Xiao, J. *J. Am. Chem. Soc.* ***2008****, 130*, 10510.
[348] Kahne, D.; Collum, D.B. *Tetrahedron Lett.* ***1981****, 22,* 5011.
[349] Santiago, B.; Meyers, A.I. *Tetrahedron Lett.* ***1993****, 34*, 5839.
[350] North, M. *Angew. Chem. Int. Ed.* ***2004****, 43*, 4126.
[351] Han, W.; Ofial, A.R. *Chem. Commun.* ***2009***, 5024.
[352] Kornblum, N.; Singh, N.K.; Kelly, W.J. *J. Org. Chem.* ***1983****, 48*, 332.
[353] Barton, D.H.R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* ***1985****, 26*, 1229.
[354] Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* ***1988***, 1581. See also, Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* ***1987***, 1811.
[355] Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed* ***2009****, 48*, 7094.

12-20 Alkylation of Alkanes

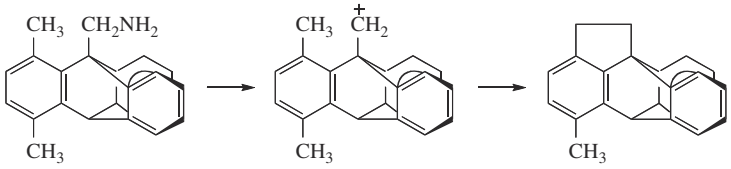
Alkylation or **Alkyl-de-hydrogenation**

$$RH + R'^{+} \longrightarrow R{-}R' + H^{+}$$

Alkanes can be alkylated by treatment with solutions of stable carbocations[356] (Sec. 5.A.ii), but the availability of such carbocations is limited and mixtures are usually obtained. In a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2HC^+ SbF_6^-) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by Reaction **12-47**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($RH + R'^{+} \rightarrow R^{+} + R'H$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *tert*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[357] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with superacids, Reaction **12-1**) as



It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *tert*-butyl cations in superacid solutions (Sec. 5.A.ii).[358]



39 **40** 46%

Intramolecular insertion has been reported. The positively charged carbon of the carbocation (**40**), generated from the diazonium salt of the triptycene compound (**39**), reacted with the CH_3 group in close proximity with it.[359]

[356] Olah, G.A.; Mo, Y.K.; Olah, J.A. *J. Am. Chem. Soc.* ***1973****, 95,* 4939. See Olah, G.A.; Farooq, O.; Prakash, G.K. S. in Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***, pp. 27–78; Ref. 48; Fabre, P.; Devynck, J.; Trémillon, B. *Chem. Rev.* ***1982****, 82*, 591. See also, Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.

[357] Olah, G.A.; DeMember, J.R.; Shen, J. *J. Am. Chem. Soc.* ***1973****, 95*, 4952. See also, Sommer, J.; Muller, M.; Laali, K. *Nouv. J. Chem.* ***1982****, 6*, 3.

[358] For example, see Hogeveen, H.; Roobeek, C.F. *Recl. Trav. Chim. Pays-Bas* ***1972****, 91*, 137.

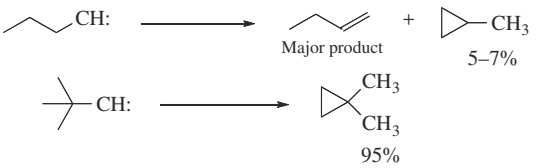
[359] Yamamoto, G.; Oki, M. *Chem. Lett.* ***1987***, 1163.

12-21 Insertion by Carbenes

CH-Methylene-insertion

$$RH + :CH_2 \longrightarrow RCH_3$$

The highly reactive species methylene ($:CH_2$) inserts into C—H bonds,[360] both aliphatic and aromatic,[361] although with aromatic compounds subsequent ring expansion is also possible (see Reaction **15-64**). This is effectively a homologation reaction.[362] The methylene insertion reaction has limited utility because of its nonselectivity (see Sec. 5.D.i). The insertion reaction of carbenes has been used for synthetic purposes.[363]



The carbenes can be generated in any of the ways mentioned in Chapter 5 (Sec. 5.D.ii). Alkylcarbenes usually rearrange rather than give insertion (Sec. 5.D.ii, category 4), but, when this is impossible, *intramolecular* insertion[364] is found rather than intermolecular.[365] Methylene ($:CH_2$) generated by photolysis of diazomethane (CH_2N_2) in the liquid phase is indiscriminate (totally nonselective) in its reactivity (Sec. 5.D.ii, category 2). Methylene ($:CH_2$) generated in other ways and monoalkyl and dialkyl carbenes are less reactive and insert in the order tertiary > secondary > primary.[366] Carbene insertion with certain allylic systems can proceed with rearrangement of the double bond.[367] Carbenes have been generated using ultrasound.[368] Halocarbenes ($:CCl_2$,$:CBr_2$, etc.) insert much less readily, although a number of instances have been reported.[369]

Insertion at an allylic carbon of alkenes has been reported.[370] Dirhodium catalyzed insertion into H—C^{sp2} bonds is known,[371] and also H—C^{sp} bonds.[372] Note that

[360] First reported by Meerwein, H.; Rathjen, H.; Werner, H. *Ber.* ***1942****, 75,* 1610. See Doyle, M.P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* ***2010****, 110*, 704; Bethell, D. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 92–101; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 209–266.

[361] Terao, T.; Shida, S. *Bull. Chem. Soc. Jpn.* ***1964****, 37*, 687. See also, Moss, R.A.; Fedé, J.-M.; Yan, S. *J. Am. Chem. Soc.* ***2000****, 122*, 9878.

[362] See Marek, I. *Tetrahedron* ***2002****, 58*, 9463.

[363] See Paquette, L.A.; Kobayashi, T.; Gallucci, J.C. *J. Am. Chem. Soc.* ***1988****, 110*, 1305; Doyle, M.P.; Bagheri, V.; Pearson, M.M.; Edwards, J.D. *Tetrahedron Lett.* ***1989****, 30,* 7001.

[364] Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961****, 83,* 492, 500. See Padwa, A.; Krumpe, K.E. *Tetrahedron* ***1992****, 48*, 5385.

[365] See Burke, S.D.; Grieco, P.A. *Org. React.* ***1979****, 26*, 361.

[366] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1961****, 83,* 1989.

[367] Carter, D.S.; Van Vranken, D.L. *Org. Lett.* ***2000****, 2,* 1303; Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, NY, ***1998***.

[368] Bertram, A.K.; Liu, M.T.H. *J. Chem. Soc. Chem. Commun.* ***1993***, 467.

[369] See Steinbeck, K. *Tetrahedron Lett.* ***1978***, 1103; Boev, V.I. *J. Org. Chem. USSR* ***1981****, 17*, 1190.

[370] Davies, H.M.L.; Ren, P.; Jin, Q. *Org. Lett.* ***2001****, 3*, 3587.

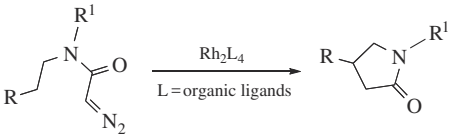
[371] Gibe, R.; Kerr, M.A. *J. Org. Chem.* ***2002****, 67,* 6247.

[372] Arduengo, III, A.J.; Calabrese, J.C.; Davidson, F.; Dias, H.V.R.; Goerlich, J.R.; Krafczyk, R.; Marshall, W.J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta.* ***1999****, 82*, 2348.

cyclopropanation may compete with C—H insertion with electron-rich highly substituted alkenes.[373] Palladacycles formed by C—H insertion reactions with biphenylene have been intercepted.[374] Such species have been impicated in the *Heck reaction* (Reaction **13-10**). Insertion of diazoalkane and diazocarbonyl compounds can be catalyzed by copper compounds[375] and silver compounds[376] as well. Insertion into the α-C—H bond of an aldehyde gives an α-substituted aldehyde.[377] Intramolecular insertion at the α carbon of a ketone by a diazoketone, using $TiCl_4$, gives a bicyclic 1,3-diketone.[378] The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate and is considered in Reaction **18-9**. Note that aryl ketenes react with Me_3SiCHN_2 and then silica to give 2-indanone derivatives.[379] A three component coupling reaction of vinyl iodides, secondary amines, and diazo(trimethylsilyl)methane gives allylic amines.[380] A gold-catalyzed reaction is known that uses alkynes as an α-diazo ketone equivalent.[381]

Insertion into the O—H bond of alcohols, to produce ethers, has been reported using a diazocarbonyl compound and an $In(OTf)_3$ catalyst.[382] The Cu catalyzed insertion of a diazo ester into an oxetane gives the ring-expanded THF derivative.[383] Insertion is also possible with other ethers, including silyl ethers.[384] Metal-catalyzed silylene insertion into allylic ethers leads to allylic silanes.[385] Similar insertion at the α carbon of an ether leads to cyclic ethers, with high enantioselectivity when a chiral ligand is used with a Rh catalyst.[386]

The insertion of the diazocarbonyl unit into the C—H bond of an α-diazo amide gives the lactam shown in the reaction.[387] Insertion into a 2-pyrrolidinone derivative using $Me_3SiCH_2N_2$ followed by $AgCO_2Ph$ with ultrasound gave the ring-expanded 2-piperidone derivative.[388] Intramolecular insertion reactions are well known,[389] and tolerate a variety of functional groups.[390]

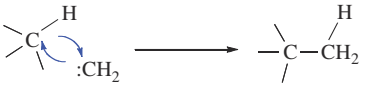


[373] Ventura, D.L.; Li, Z.; Coleman, M.G.; Davies, H.M.L. *Tetrahedron* ***2009****, 65*, 3052.
[374] Masselot, D.; Charmant, J.P.H.; Gallagher, T. *J. Am. Chem. Soc.* ***2006****, 128*, 694.
[375] See Caballero, A.; Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2003****, 125,* 1446.
[376] Dias, H.V.R.; Browning, R.G.; Polach, S.A.; Diyabalanage, H.V.K.; Lovely, C.J. *J. Am. Chem. Soc.* ***2003****, 125,* 9270.
[377] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* ***2008,*** *130,* 2434.
[378] Wee, A.G.H.; Duncan, S.C. *J. Org. Chem.* ***2005****, 70,* 8372.
[379] Dalton, A.M.; Zhang, Y.; Davie, C.P.; Danheiser, R.L. *Org. Lett.* ***2002****, 4,* 2465.
[380] Devine, S.K.J.; Van Vranken, D.L. *Org. Lett.* ***2007****, 9,* 2047.
[381] Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* ***2010****, 132,* 3258.
[382] Matusamy, S.; Arulananda, S.; Babu, A.; Gunanathan, C. *Tetrahedron Lett.* ***2002*** *43*, 3133.
[383] Lo, M.M.-C.; Fu, G.C. *Tetrahedron* ***2001****, 57*, 2621.
[384] Davies, H.M.L.; Hedley, S.J.; Brooks R.; Bohall, B.R. *J. Org. Chem.* ***2005****, 70,* 10737.
[385] Bourque, L.E.; Cleary, P.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2007****, 129*, 12602.
[386] Davies, H.M.L.; Grazini, M.V.A.; Aouad, E. *Org. Lett.* ***2001****, 3*, 1475.
[387] Doyle, M.P.; Protopopova, M.N.; Winchester, W.R.; Daniel, K.L. *Tetrahedron Lett.* ***1992****, 33*, 7819. See also, Clark, J.S.; Hodgson, P.B.; Goldsmith, M.D.; Street, L.J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3312.
[388] Coutts, I.G.C.; Saint, R.E.; Saint, S.L.; Chambers-Asman, D.M. *Synthesis* ***2001***, 247.
[389] See Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* ***2005****, 7*, 3103.
[390] See Doyle, M.P.; Kalinin, A.V. *Synlett,* ***1995***, 1075; Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* ***1995****, 36*, 1491; Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem.* ***1994****, 59*, 4725.

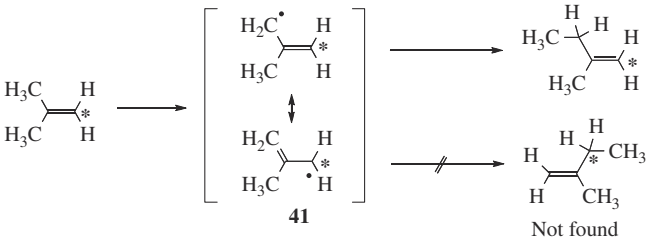
The metal carbene insertion reaction, in contrast to the methylene insertion reaction can be highly selective[391] and useful in synthesis.[392] There are numerous examples, usually requiring a transition metal catalyst.[393] The catalyst typically converts a diazoalkane or diazocarbonyl compound to the metal carbene *in situ*, allowing the subsequent insertion reaction. Intermolecular reactions are known, including diazoalkane insertion reaction with a dirhodium catalyst.[394] When chiral ligands are present good enantioselectivity is observed in the insertion product.[395]

The mechanism[396] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple one-step process involving a three-center cyclic transition state:



The most convincing evidence for this mechanism is that in the reaction between isobutene-1—^{14}C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.[397] This rules out a free radical or a carbocation or carbanion intermediate. If **41** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the 1 position:



Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.[398] An ylid intermediate was trapped in the reaction of $:CH_2$ with allyl alcohol.[399]

2. A free radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:

$$RH + CH_2 \longrightarrow R^{\bullet} + {}^{\bullet}CH_3$$
$$R^{\bullet} + {}^{\bullet}CH_3 \longrightarrow RCH_3$$

[391] See Sulikowski, G.A.; Cha, K.L.; Sulikowski, M.M. *Tetrahedron Asymmetry,* ***1998****, 9,* 3145.
[392] Ye, T.; McKervey, M.A. *Chem. Rev.* ***1994****, 94*, 1091.
[393] Doyle, M.P. *Pure Appl. Chem.* ***1998****, 70*, 1123. See Taber, D.F.; Malcolm, S.C. *J. Org. Chem.* ***1998****, 63*, 3717 for a discussion of transition state geometry in rhodium mediated C—H insertion.
[394] Davies, H.M.L.; Jin, Q. *Org. Lett.* ***2004****, 6*, 1769; Davies, H.M.L.; Loe, ∅. *Synthesis* ***2004***, 2595.
[395] See Davies, H.M.L.; Beckwith, R.E.J. *Chem. Rev.* ***2003****, 103*, 2861. See also Davies, H.M.L.; Nikolai, J. *Org. Biomol. Chem.* ***2005****, 3,* 4176; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* ***2009****, 131*, 14218.
[396] See Bethell, D. *Adv. Phys. Org. Chem.* ***1969****, 7,* 153, pp. 190–194.
[397] Doering, W. von E.; Prinzbach, H. *Tetrahedron* ***1959****, 6,* 24.
[398] See Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc.* ***1971****, 93*, 4072.
[399] Sobery, W.; DeLucca, J.P. *Tetrahedron Lett.* ***1995****, 36*, 3315.

One fact supporting this mechanism is that among the products obtained (beside butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[400] which could arise, respectively, by

$$2\,CH_3CH_2CH_2^{\bullet} \longrightarrow \underset{\text{(disproportionation)}}{CH_3CH{=}CH_2 + CH_3CH_2CH_3}$$

and

$$CH_3CH_2CH_3 + :CH_2 \longrightarrow CH_3CH_2CH_2^{\bullet} + {}^{\bullet}CH_3$$
$$2\,{}^{\bullet}CH_3 \longrightarrow CH_3CH_3$$

That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling[401] and by other means.[402] However, the formation of disproportionation and dimerization products does not always mean that the free radical abstraction process takes place. In some cases, these products arise in a different manner.[403] The product of the reaction between a carbene and a molecule may have excess energy (see Sec. 5.D.ii). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

The mechanism of cyclopropylcarbene reactions has also been discussed.[404]

It has been suggested[405] that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free radical process. In support of this suggestion, CIDNP signals[406] (Sec. 5.C.i) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[407] Carbenoids (e.g., compounds of the form R_2CMCl, see Reaction **12-39**) can insert into a C—H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.[408]

For the similar insertion reaction of nitrenes, see Reaction **12-13**.

OS **VII**, 200.

F. Metal Electrophiles

12-22 Metalation with Organometallic Compounds

Metalation or **Metalo-de-hydrogenation**

$$RH + R'M \longrightarrow RM + R'M$$

[400] Frey, H.M. *Proc. Chem. Soc.* ***1959***, 318.
[401] McNesby, J.R.; Kelly, R.V. *Int. J. Chem. Kinet.* ***1971****, 3,* 293.
[402] Ring, D.F.; Rabinovitch, B.S. *J. Am. Chem. Soc.* ***1966****, 88*, 4285; *Can J. Chem.* ***1968****, 46*, 2435.
[403] Bell, J.A. *Prog. Phys. Org. Chem.* ***1964****, 2,* 1, pp. 30–43.
[404] Cummins, J.M.; Porter, T.A.; Jones, Jr., M. *J. Am. Chem. Soc.* ***1998****, 120*, 6473.
[405] Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961****, 83*, 1934.
[406] See Roth, H.D. *Acc. Chem. Res.* ***1977****, 10,* 85.
[407] Roth, H.D. *J. Am. Chem. Soc.* ***1972****, 94,* 1761. See also, Bethell, D.; McDonald, K. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 671.
[408] See Oku, A.; Yamaura, Y.; Harada, T. *J. Org. Chem.* ***1986****, 51*, 3730; Ritter, R.H.; Cohen, T. *J. Am. Chem. Soc.* ***1986****, 108,* 3718.

Many organic compounds can be metalated by treatment with an organometallic compound.[409] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid.[410] For example, fluorene reacts with *n*-butyllithium to give butane and 9-fluorenyllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is probably butyllithium.[411] Reductive lithiation is an important method for the preparation of organolithium reagents.[412] Normally, only active aromatic rings react with butyllithium. Benzene itself reacts very slowly and in low yield, although benzene can be metalated by butyllithium either in the presence of *tert*-BuOK[413] or by *n*-butyllithium that is coordinated with various diamines.[414] Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,[415] etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Trimethylsilylmethyl potassium (Me_3SiCH_2K)[416] and also a combination of an organolithium compound with a bulky alkoxide (LICKOR superbase)[417] are very good reagents for allylic metalation. The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.[418] The reaction can be used to determine relative acidities of very weak acids by allowing two R—H compounds to compete for the same R′M and to determine which proton in a molecule is the most acidic.[419]

Note that organolithium compounds are aggregated species and can form hetero-aggregates containing different organic groups.[420] *N*-Lithio-*N*-(trialkylsilyl)allylamines are deprotonated in ether solvents at the cis-vinylic position to give 3,*N*-dilithio-*N*-(trialkylsilyl)allylamines.[421]

In general, the reaction can be performed only with organometallics of active metals (e.g., Li, Na, and K), but *Grignard reagents* abstract protons from a sufficiently acidic C—H bond, as in $R—C{\equiv}C—H \rightarrow R—C{\equiv}C—MgX$. This is the best method for the

[409] See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 44–107; Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 1–157, pp. 27–71; Narasimhan, M.S.; Mali, R.S. *Synthesis* ***1983***, 957; Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1; Mallan, J.M.; Bebb, R.L. *Chem. Rev.* ***1969***, *69,* 693.

[410] See Saá, J.M.; Martorell, G.; Frontera, A. *J. Org. Chem.* ***1996***, *61*, 5194.

[411] See Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291, pp. 265–279. For an article on the safe handling of RLi compounds, see Anderson, R. *Chem. Ind. (London)* ***1984***, 205.

[412] Ivanov, R.; Marek, I.; Cohen, T. *Tetrahedron Lett.* ***2010***, *51*, 174.

[413] Schlosser, M. *J. Organomet. Chem.* ***1967***, *8*, 9. See also, Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett,* ***1990***, 747.

[414] Rausch, M.D.; Ciappenelli, D.J. *J. Organomet. Chem.* ***1967***, *10,* 127.

[415] See Klein, J. *Tetrahedron* ***1983***, *39*, 2733; Klein, J. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 343–379.

[416] Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* ***1976***, *59,* 453.

[417] Schlosser, M. *Pure Appl. Chem.* ***1988***, *60*, 1627. For sodium analogues, see Schlosser, M.; Hartmann, J.; Stähle, M.; Kramar, J.; Walde, A.; Mordini, A. *Chimia,* ***1986***, *40*, 306.

[418] Brandsma, L.; Verkruijsse, H.D.; Schade, C.; Schleyer, P.v.R. *J. Chem. Soc. Chem. Commun.* ***1986***, 260.

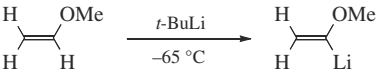
[419] See Shirley, D.A.; Hendrix, J.P. *J. Organomet. Chem.* ***1968***, *11*, 217.

[420] Gossage, R.A.; Jastrzebski, J.T.B.H.; van Koten, G. *Angew. Chem. Int. Ed.* ***2005***, *44*, 1448.

[421] Jacobson, M.A.; Keresztes, I.; Williard, P.G. *J. Am. Chem. Soc.* ***2005***, *127*, 4965. For a computational study of mixed aggregates of chloromethyllithium and lithium dialkylamides, see Pratt, L.M.; Lê, L.T.; Truong, T.N. *J. Org. Chem.* ***2005***, *70,* 8298. Also see Gupta, L.; Hoepker, A.C.; Singh, K.J.; Collum, D.B. *J. Org. Chem.* ***2009***, *74*, 2231 for a LiCl catalyzed reaction.

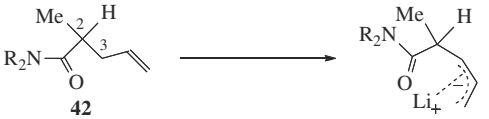
preparation of alkynyl *Grignard reagents*.[422] Lewis acids have been used to promote α-lithiation of amines.[423] Triethylgallium has been used to generate enolate anions from ketones.[424]

When a heteroatom (e.g., N, O, S,[425] or a halogen),[426] is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.[427] It has been shown that fluorine is more effective for stabilization of carbanions when compared to the heavier halogens.[428] In such compounds, the lithium usually bonds with the sp^2 carbon closest to the heteroatom, probably because the attacking species coordinates with the heteroatom.[429] This type of reaction with compounds such as anisole are often called directed metalations.[430] In the case of aromatic rings, this means attack at the ortho position,[431] but this is considered in Reaction **13-17**.



Ref. 432

In the case of γ,δ-unsaturated disubstituted amides (**42**), the lithium does not go to the closest position, but in this case too the regiochemistry is controlled by coordination to the oxygen.[433] Cyclopropyllithium reagents are rather stable.[434]



42

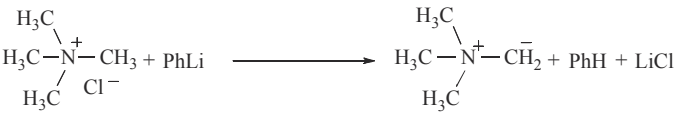
The mechanism involves an attack by R'^- (or a polar R′) on the *hydrogen*[435] (an acid–base reaction) Evidence is that resonance effects of substituents in R seem to make little difference. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta

[422] See Blagoev, B.; Ivanov, D. *Synthesis* ***1970***, 615.
[423] Kessar, S.V.; Singh, P.; Singh, K.N.; Venugopalan, P.; Kaur, A.; Bharatam, P.V.; Sharma, A.K. *J. Am. Chem. Soc.* ***2007****, 129,* 4506.
[424] Nishimura, Y.; Miyake, Y.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2006****, 8,* 5077.
[425] See Figuly, G.D.; Loop, C.K.; Martin, J.C. *J. Am. Chem. Soc.* ***1989****, 111*, 654; Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* ***1989****, 111*, 658; Smith, K.; Lindsay, C.M.; Pritchard, G.J. *J. Am. Chem. Soc.* ***1989****, 111,* 665.
[426] See Gilday, J.P.; Negri, J.T.; Widdowson, D.A. *Tetrahedron* ***1989****, 45,* 4605.
[427] See Katritzky, A.R.; Lam, J.N.; Sengupta, S. *Prog. Heterocycl. Chem.* ***1989****, 1,* 1.
[428] Bickelhaupt, F.M.; Hermann, H.L.; Boche, G. *Angew. Chem. Int. Ed.* ***2006****, 45, 823*.
[429] See Beak, P.; Meyers, A.I. *Acc. Chem. Res.* ***1986****, 19,* 356; Beak, P.; Snieckus, V. *Acc. Chem. Res.* ***1982****, 15*, 306; Narasimhan, N.S.; Mali, R.S. *Top. Curr. Chem.* ***1987****, 138,* 63; Reuman, M.; Meyers, A.I. *Tetrahedron* ***1985****, 41,* 837.
[430] Slocum, D.W.; Coffey, D.S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* ***1994****, 35*, 389.
[431] See Snieckus, V. *Chem. Rev.* ***1990****, 90,* 879; *Pure Appl. Chem.* ***1990****, 62*, 2047. For a discussion of the mechanism, see Bauer, W.; Schleyer, P. v.R. *J. Am. Chem. Soc.* ***1989****, 111*, 7191.
[432] Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* ***1974****, 96*, 7125.
[433] Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* ***1987****, 109*, 5403. See also, Stork, G.; Polt, R. L.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1988****, 110*, 8360; Barluenga, J.; Foubelo, F.; Fañanas, F.J.; Yus, M. *J. Chem. Res. (S)* ***1989***, 200.
[434] Peñafiel, I.; Pastor, I.M.; Yus, M. *Tetrahedron* ***2010****, 66*, 2928.
[435] Benkeser, R.A.; Trevillyan, E.A.; Hooz, J. *J. Am. Chem. Soc.* ***1962****, 84*, 4971.

and para (mostly meta).[436] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[437] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order R′ = allyl > Bu > Ph > vinyl > Me, although this order changed with changing concentration of R′Li, because of varying degrees of aggregation of the R′Li.[438] With respect to the reagent, this reaction is a special case of Reaction **12-24**.

Enantioselective reactions are known. The preparation of chlorodeuteriomethylithium proceeds with inversion from the corresponding enantiopure stannyl derivative.[439] Although highly reactive chemically, it is configurationally stable at temperatures up to −78 °C. Enantioselective catalytic deprotonation with chiral ligands has been used for the deprotonation of *N*-Boc amines to give chiral α-trimethylsilyl derivatives.[440] A barrier to enantiomerization has been observed for unstablized, chelated, and dipole-stabilized organolithium compounds. Studies of lithiopyrrolidines show free energies for enantiomerization in the range of 19–22 kcal mol^{-1} (79.5–92.1 kJ mol^{-1}) at 0 °C.[441]

A closely related reaction is formation of nitrogen ylids[442] from quaternary ammonium salts (see Reaction **17-8**):



Phosphonium salts undergo a similar reaction (see Reaction **16-44**).

OS **II**, 198; **III**, 413, 757; **IV**, 792; **V**, 751; **VI**, 436, 478, 737, 979; **VII**, 172, 334, 456, 524; **VIII**, 19, 391, 396, 606.

12-23 Metalation with Metals and Strong Bases

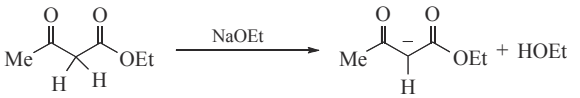
Metalation or **Metalo-de-hydrogenation**

$$2\,RH + M \longrightarrow 2\,RM + H_2$$

Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases.[443] The reaction has been used to study the acidities of very weak acids (see Sec. 5.B.i). The conversion of terminal alkynes to acetylide ions is one important

[436] Bryce-Smith, D. *J. Chem. Soc.* ***1963***, 5983; Benkeser, R.A.; Hooz, J.; Liston, T.V.; Trevillyan, E.A. *J. Am. Chem. Soc.* ***1963****, 85,* 3984.
[437] Pocker, Y.; Exner, J.H. *J. Am. Chem. Soc.* ***1968****, 90,* 6764.
[438] West, P.; Waack, R.; Purmort, J.I. *J. Am. Chem. Soc.* ***1970****, 92,* 840.
[439] Kapeller, D.C.; Hammerschmidt, F. *J. Am. Chem. Soc.* ***2008****, 130,* 2329.
[440] McGrath, M.J.; O'Brien, P. *J. Am. Chem. Soc*. **2005**, 127, 16378.
[441] Ashweek, J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R.E.; Hæffner, F.; Klein, R.; Sanchez-Jimenezy, G. *J. Am. Chem. Soc.* ***2005****, 127,* 449.
[442] Zugravescu, I.; Petrovanu, M. *Nitrogen–Ylid Chemistry*, McGraw Hill, NY, ***1976***, pp. 251–283; Wittig, G.; Rieber, M. *Ann.* ***1949****, 562*, 177; Wittig, G.; Polster, R. *Ann.* ***1956****, 599*, 1.
[443] See Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291; Wardell, J.L. Ref. 388; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 32–44.

application.[444] A gold-catalyst conversion of trimethylsilyl substituted esters and carbonates to the corresponding enolate anion has been reported[445]. Synthetically, an important use of the method is to convert aldehydes and ketones,[446] carboxylic esters, and similar compounds to their enolate forms,[447] for example,



for use in nucleophilic substitutions (Reactions **10-67**, **10-68**, and **13-14**) and in additions to multiple bonds (Reactions **15-24** and **16-53**). Note that the reaction of carbonyl compounds with lithium dialkylamides leads to the corresponding enolate anion. This reaction was discussed in Reaction **10-68**, in connection with the alkylation reaction of enolate anions.

OS **I**, 70, 161, 490; **IV**, 473; **VI**, 468, 542, 611, 683, 709; **VII**, 229, 339. Conversions of ketones or esters to enolates are not listed.

12.C.ii. Metals as Leaving Groups

A. Hydrogen as the Electrophile

12-24 Replacement of Metals by Hydrogen

Hydro-de-metalation or **Demetalation**

$$RM + HA \longrightarrow RH + MA$$

Organometallic compounds, including enolate anions, react with acids in reactions that replace the metal with hydrogen.[448] The R group may be aryl (see Reaction **11-41**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For *Grignard reagents*, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process $RX \rightarrow RMgX \rightarrow RH$.

The organometallic compounds that are hydrolyzed by water are the ones high in the electromotive series: Na, K, Li, Zn, and so on. Enantioselective protonation of lithium enolates[449] and cyclopropyllithium compounds[450] have been reported. When the metal is less active, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, although the latter can be cleaved with

[444] See Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 170–185. For an improved method, see Fisch, A.; Coisne, J.M.; Figeys, H.P. *Synthesis* ***1982***, 211.
[445] Wang, S.; Zhang, L. *Org. Lett.* ***2006***, *8,* 4585.
[446] Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998***, *120*, 2290.
[447] See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 95–145, 284–291.
[448] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond,* Vol. 2, Wiley, NY, pp. 25–149, pp. 105–136; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***, pp. 107–134; Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3,* 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5,* 238.
[449] Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* ***2006***, *8,* 1721.
[450] Walborsky, H.M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett.* ***1992***, *33*, 761.

concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 reacts violently with water. However, BR_3 can be converted to RH with carboxylic acids.[451] For less active metals, it is often possible to cleave just one R group from a multivalent metal. For example,

$$R_2Hg + HCl \longrightarrow RH + RHgCl$$

Organometallic compounds of less active metals and metalloids (e.g., Si,[452] Sb, and Bi), are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2, $NaBH_4$, or other reducing agents.[453] The reduction with $NaBH_4$ takes place by a free radical mechanism.[454] Alkyl-Si bonds are cleaved by H_2SO_4 [e.g., $HOOCCH_2CH_2SiMe_3 \rightarrow 2CH_2 + (HOOCCH_2CH_2SiMe_3)_2O$].[455]

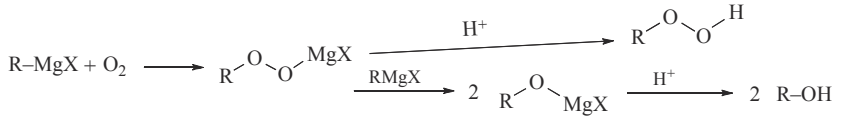
When the hydrogen of the HA is attached to carbon, this reaction is the same as **12-22**.

This section does not list the many hydrolyses of Na or K enolates, and so on found in *Organic Syntheses*. The hydrolysis of a *Grignard reagent* to give an alkane is found at OS **II**, 478; the reduction of a vinylic tin compound at OS **VIII**, 381; and the reduction of an alkynylsilane at OS **VIII**, 281.

B. Oxygen Electrophiles

12-25 The Reaction between Organometallic Reagents and Oxygen[456]

Hydroperoxy-de-metalation; **Hydroxy-de-metalation**



Oxygen reacts with *Grignard reagents* to give either hydroperoxides[457] or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl *Grignard reagents*, yields are lower and only phenols are obtained, not hydroperoxides. Because of this reaction, oxygen should be excluded when *Grignard reagents* are prepared and used in various reactions.

Most other organometallic compounds also react with oxygen. Trialkylboranes and alkyldichloroboranes ($RBCl_2$) can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[458] Dilithiated carboxylic acids (see Reaction **10-70**) react with oxygen to give (after hydrolysis) α-hydroxy carboxylic

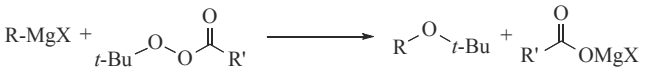
[451] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, see pp. 242–244.
[452] See Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989****, 37,* 57, pp. 89–97, 194–243.
[453] See Makarova, L.G. *Organomet. React.* ***1970****, 1,* 119, see pp. 251–270, 275–300.
[454] See Barluenga, J.; Yus, M. *Chem. Rev.* ***1988****, 88*, 487.
[455] Sommer, L.H.; Marans, N.S.; Goldberg, G.M.; Rockett, J.; Pioch, R.P. *J. Am. Chem. Soc.* ***1951****, 73,* 882. See also, Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond,* Vol. 2, Wiley, NY, p. 117.
[456] See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***; Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, see pp. 219–338, pp. 311–316.
[457] See Harada, T.; Kutsuwa, E. *J. Org. Chem.* ***2003****, 68*, 6716.
[458] Brown, H.C.; Midland, M.M. *Tetrahedron* ***1987****, 43,* 4059.

acids.[459] There is evidence that the reaction between *Grignard reagents* and oxygen involves a free radical mechanism.[460]

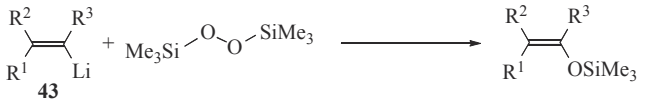
OS **V**, 918. See also, OS **VIII**, 315.

12-26 Reaction between Organometallic Reagents and Peroxides

tert-Butoxy-de-metalation



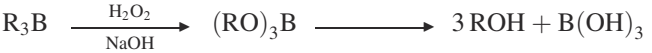
A convenient method of preparation of *tert*-butyl ethers consists of treating *Grignard reagents* with *tert*-butyl acyl peroxides.[461] Both alkyl and aryl *Grignard reagents* can be used. The application of this reaction to *Grignard reagents* prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *tert*-butyl ethers of cyclopropanols,[462] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by Reaction **10-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.



Vinyllithium reagents (**43**) react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.[463] Since the preparation of **43** from vinylic halides (Reaction **12-39**) also proceeds with retention, the overall procedure is a method for the stereospecific conversion of a vinylic halide to a silyl enol ether. Dialky ethers have been prepared from organotrifluoroborates and acetals[464].

OS **V**, 642, 924.

12-27 Oxidation of Trialkylboranes to Borates



The reaction of alkenes with borane, monoalkyl, and dialkylboranes leads to a new organoborane (see Reaction **15-16**). Treatment of organoboranes with alkaline H_2O_2 oxidizes trialkylboranes to esters of boric acid.[465] This reaction does not affect double

[459] Adam, W.; Cueto, O. *J. Org. Chem.* ***1977****, 42*, 38.

[460] Garst, J.F.; Smith, C.D.; Farrar, A.C. *J. Am. Chem. Soc.* ***1972****, 94,* 7707. See Davies, A.G. *J. Organomet. Chem.* ***1980****, 200,* 87.

[461] Lawesson, S.; Frisell, C.; Denney, D.B.; Denney, D.Z. *Tetrahedron* ***1963****, 19,* 1229. See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***; Razuvaev, G.A.; Shushunov, V.A.; Dodonov, V.A.; Brilkina, T.G. in Swern, D. *Organic Peroxides*, Vol. 3, Wiley, NY, ***1972***, pp. 141–270.

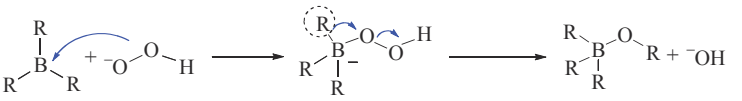
[462] Longone, D.T.; Miller, A.H. *Tetrahedron Lett.* ***1967***, 4941.

[463] Davis, F.A.; Lal, G.S.; Wei, J. *Tetrahedron Lett.* ***1988****, 29,* 4269.

[464] Mitchell, T.A.; Bode, J.W. *J. Am. Chem. Soc.* ***2009****, 131*, 18057.

[465] See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents,* Aademic Press, NY, ***1988***, pp. 244–249; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 321–325. See also, Brown, H.C.; Snyder, C.; Subba Rao, B.C.; Zweifel, G. *Tetrahedron* ***1986****, 42*, 5505.

or triple bonds, aldehydes, ketones, halides, or nitriles that may be present elsewhere in the molecule. There is no rearrangement of the R group itself, and this reaction is a step in the hydroboration method of converting alkenes to alcohols (Reaction **15-16**). The mechanism has been formulated as involving initial formation of an ate complex when the hydroperoxide anion attacks the electrophilic boron atom. Subsequent rearrangement from boron to oxygen,[465] as shown, leads to the B—O—R unit.



Similar migration of the other two R groups and hydrolysis of the B—O bonds leads to the alcohol and boric acid. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,[466] with sodium perborate ($NaBO_3$)[467] and with trimethylamine oxide, either anhydrous[468] or in the form of the dihydrate.[469] The reaction with oxygen is free radical in nature.[470]

OS **V**, 918; **VI**, 719, 852, 919.

12-28 Preparation of Borates and Boronic Acids

$$\text{R-M} \longrightarrow \text{R-B(OH)}_2$$

$$\text{Ar-M} \longrightarrow \text{Ar-B(OH)}_2$$

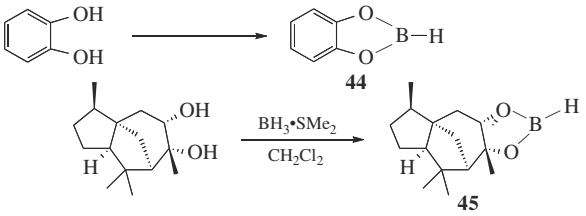
$$\text{R-OH} + \text{BX}_3 \quad \text{or} \quad \text{B(OH)}_3 \longrightarrow \text{B(OR)}_3$$

Alkylboronic and arylboronic acids [$RB(OH)_2$, and $ArB(OH)_2$], respectively, are increasingly important in organic chemistry. The Pd catalyzed coupling reaction of aryl halides and aryl triflates with arylboronic acids (the *Suzuki–Miyaura reaction*, **13-12**) is probably the most notable example. A simple synthesis involves the reaction of a *Grignard reagent* (e.g., phenylmagnesium bromide) with an alkyl borate to give phenylboronic acid.[471] Alkylboronic acids are similarly prepared.[472] Note that boronic acids are subject to cyclic trimerization with loss of water to form boroxines. Tetrahydroxydiboron has been used to prepare allylboronic acids, as well as potassium trifluoro(allyl)borates.[473]

Trimethylborate [$B(OMe)_3$] can be used in place of tri-*n*-butyl borate.[474] Newer methods involve the Pd mediated borylation of alcohols with bis(pinacolato)diboron[475] or pinacolborane,[476] but deprotection of the boronate esters can be a problem. Diolboranes (e.g., catecholborane **44**)[477] are prepared by the reaction of a diol with borane.

[466] Brown, H.C.; Midland, M.M.; Kabalka, G.W. *Tetrahedron* ***1986****, 42*, 5523.
[467] Kabalka, G.W.; Shoup, T.M.; Goudgaon, N.M. *J. Org. Chem.* ***1989****, 54*, 5930.
[468] Köster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed.* ***1969****, 8,* 205.
[469] Kabalka, G.W.; Slayden, S.W. *J. Organomet. Chem.* ***1977****, 125*, 273.
[470] Midland, M.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1971****, 93*, 1506.
[471] Bean, F.R.; Johnson, J.R. *J. Am. Chem Soc.* ***1932***, *54*, 4415; Lappert, M.F. *Chem. Rev.* ***1956****, 56,* 959.
[472] Khotinsky, E.; Melamed, M. *Chem. Ber.* ***1909****, 42,* 3090.
[473] Sebelius, S.; Olsson, V.J.; Szabó, K.J. *J. Am. Chem. Soc.* ***2005****, 127*, 10478.
[474] Soloway, A.H. *J. Am. Chem. Soc.* ***1959****, 81*, 3017.
[475] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* ***1995****, 60*, 7508.
[476] Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* ***2000****, 65*, 164; Song, Y.L. *Synlett* ***2000***, 1210.
[477] Kanth, J.V.B.; Periasamy, M.; Brown, H.C. *Org. Process Res. Dev.* ***2000****, 4,* 550.

Cedranediolborane (**45**, prepared from the cedrane-8,9-diol[478] by treatment with borane•dimethyl sulfide) can be coupled to aryl iodides with a palladium catalyst, and generates the free boronic acid by treatment with diethanolamine and then aq acid.[479] Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.[480]



Alkeneboronic esters and acids are also readily available, as in the addition of vinylmagnesium chloride[481] to trimethyl borate below −50 °C, followed by hydrolysis.[482] A nonaqueous workup procedure has been reported for the preparation of arylboronic esters [ArB(OR′$_2$)].[483] Uncontrollable polymerization or oxidation of much of the boronic acid occurred during the final stages of the isolation procedure, but could be avoided by *in situ* conversion to the dibutyl ester by adding the crude product to 1-butanol. The Sm(III) catalyzed hydroboration of olefins with catecholborane is a good synthesis of boronate esters.[484]

Trialkyl borates (sometimes called orthoborates) can be prepared by heating the appropriate alcohol with boron trichloride in a sealed tube, but the procedure works well only for relatively simple alkyl groups.[485] Heating alcohols with boron trioxide (B_2O_3) in an autoclave at 110–170 °C give the trialkyl borate.[486] Boric acid can be used for the preparation of orthoborates[487] by heating with alcohols in the presence of either hydrogen chloride or concentrated sulfuric acid. Removal of water as an azeotrope with excess alcohol improves the yield,[488] and good yields can be obtained. for trialkyl borates[489] and even for triphenyl borate.[490] This method is unsuccessful for those borates whose parent alcohols do not form azeotropes with water and for the tertiary alkyl borates,[489] impure samples are usually obtained.[491]

[478] Song, Y.; Ding, Z.; Wang, Q.; Tao, F. *Synth. Commun.* ***1998****, 28,* 3757.
[479] Song, Y.-L.; Morin, C. *Synlett* ***2001***, 266.
[480] Lightfoot, A.P.; Maw, G.; Thirsk, C.; Twiddle, S.J.R.; Whiting, A. *Tetrahedron Lett.* ***2003****, 44,* 7645.
[481] Ramsden, H.E.; Leebrick, J.R.; Rosenberg, S.D.; Miller, E.H.; Walburn, J.J.; Balint , A.E.; Cserr, R. *J. Org, Chem.,* ***1957****, 22,* 1602.
[482] Matteson, D.S. *Acc. Chem. Res.* ***1970****, 3,* 186; Matteson, D.S. *Progr. Boron Chem.* ***1970****, 3,* 117.
[483] Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* ***2002****, 67*, 1041.
[484] Evans, D.A.; Muci, A.R.; Stuermer, R. *J. Org. Chem.,* ***1993****, 58,* 5307.
[485] Councler, C. *Ber.* ***1876****, 9,* 485; ***1877****, 10,* 1655; ***1878****, 11,* 1106.
[486] Schiff, H. *Ann. Suppl.* ***1867****, 6*, 158; Councler, C. *J. Prakt. Chem.* ***1871****, 16,* 371.
[487] Cohn, G. *Pharm. Zentr.* ***1911****, 62,* 479.
[488] Bannister, W.J. U.S. Patent 1,668,797 (*Chem. Abstr.* ***1928****, 22:*2172).
[489] Haider, S.Z.; Khundhar, M.H.; Siddiqulah, Md. *J. Appl. Chem.* ***1954****, 4,* 93.
[490] Colclough, T.; Gerrard, W.; Lappert, M.F. *J. Chem. Soc.* ***1955***, 907.
[491] Ahmad, T.; Khundkar, M.H. *Chem. Ind.* ***1954***, 248.

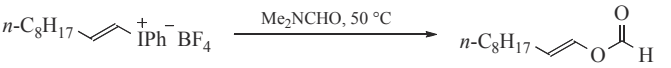
Potassium organotrifluoroborates (RBF_3K) are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.[492] They are monomeric, crystalline solids that are readily isolated and indefinitely stable in the air. These reagents can be used in several of the applications where boronic acids or esters are used (Reactions **13-10–13-13**).[493] Note that vinylboronic acid and even vinylboronate esters are unstable to polymerization,[494] whereas the analogous vinyltrifluoroborate is readily synthesized and completely stable.[495]

OS 13, 16; **81**, 134.

12-29 Oxygenation of Organometallic Reagents and Other Substrates to O-Esters and Related Compounds

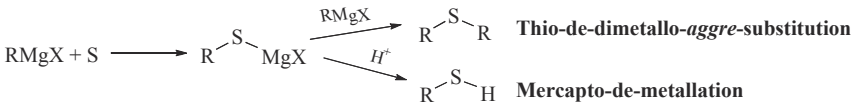
$$R-M \longrightarrow R-OOCR' \qquad R-Y \longrightarrow R-OOCR'$$

In some cases, it is possible to oxygenate a nonaromatic carbon atom using various reagents, where the product is an *O*- ester rather than an alcohol. In one example, a vinyl iodonium salt was heated with DMF to produce the corresponding formate ester.[496]

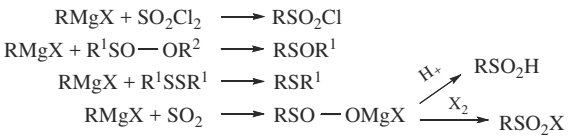


C. Sulfur Electrophiles

12-30 Conversion of Organometallic Reagents to Sulfur Compounds



Thiols and sulfides are occasionally prepared by treatment of *Grignard reagents* with sulfur.[497] Analogous reactions are known for selenium and tellurium compounds. *Grignard reagents* and other



[492] Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. *J. Am. Chem. Soc.* ***1999****, 121*, 2460.

[493] Molander, G.A.; Biolatto, B. *J. Org. Chem.* ***2003****, 68*, 4302; Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003****, 68,* 5534; Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* ***2003****, 125,* 11148.

[494] Matteson, D. S. *J. Am. Chem. Soc.* ***1960****, 82,* 4228.

[495] Molander, G. A.; Felix, L. A. *J. Org. Chem.* ***2005****, 70*, 3950.

[496] Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* ***1999***, 1363.

[497] See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 316–323; Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 211–215; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 135–142.

organometallic compounds[498] react with sulfuryl chloride to give sulfonyl chlorides,[499] with esters of sulfinic acids to give (stereospecifically) sulfoxides,[500] with disulfides to give sulfides,[501] and with SO_2 to give sulfinic acid salts,[502] which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[503]

OS **III**, 771; **IV**, 667; **VI**, 533, 979.

D. Halogen Electrophiles

12-31 Halo-de-metalation

$$RMgX + I_2 \longrightarrow RI + MgIX$$

Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[504]

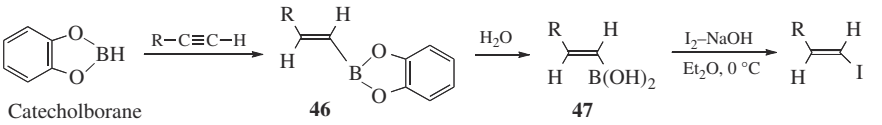
Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[505] The reaction can be used to convert acetylide ions to 1-haloalkynes.[506] Vinyliodonium tetrafluoroborates were converted to vinyl fluorides by heating.[507] Similarly, vinyl trifluoroborates were converted to the vinyl iodide with NaI and chloramine-T in aq THF.[508] The reaction of an alkene with $CuO{\cdot}BF_4$, iodine and triethylsilane gave the 2-iodoalkane.[509] Vinylzirconate reagents react with I_2 to give the corresponding vinyl iodide.[510]

Enolate anions can be converted to the corresponding vinyl phosphate, and subsequent reaction with triphenylphosphine dihalide leads to the vinyl halide.[511]

Trialkylboranes react rapidly with I_2[512] or Br_2[513] in the presence of NaOMe in methanol, or with $FeCl_3$ or other reagents[514] to give alkyl iodides, bromides, or chlorides,

[498] Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 210–216.
[499] Bhattacharya, S.N.; Eaborn, C.; Walton, D.R.M. *J. Chem. Soc. C* ***1968***, 1265. For similar reactions with organolithiums, see Hamada, T.; Yonemitsu, O. *Synthesis* ***1986***, 852.
[500] Harpp, D.N.; Vines, S.M.; Montillier, J.P.; Chan, T.H. *J. Org. Chem.* ***1976****, 41,* 3987.
[501] See Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 243–247.
[502] See Kitching, W.; Fong, C.W. *Organomet. Chem. Rev. Sect. A* ***1970****, 5*, 281.
[503] Asinger, F.; Laue, P.; Fell, B.; Gubelt, C. *Chem. Ber.* ***1967****, 100,* 1696.
[504] Zakharkin, L.I.; Gavrilenko, V.V.; Paley, B.A. *J. Organomet. Chem.* ***1970****, 21*, 269.
[505] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 72–105; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 158–178; Makarova, L.G. *Organomet. React.* ***1970****, 1*, 119, pp. 325–348.
[506] See Delavarenne, S.Y.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 665–688. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 655–656. For an improved procedure, see Brandsma, L.; Verkruijsse, H.D. *Synthesis* ***1990***, 984.
[507] Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* ***2000****, 41*. 5125.
[508] Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett.* ***2004****, 45*, 1417.
[509] Campos, P.J.; García, B.; Rodríguez, M.A. *Tetrahedron Lett.* ***2002****, 43*, 6111.
[510] Zhang, D.; Ready, J.M. *J. Am. Chem. Soc.* ***2007****, 129,* 12088.
[511] Kamei, K.; Maeda, N.; Tatsuoka, T. *Tetrahedron Lett.* ***2005****, 46*, 229.
[512] Brown, H.C.; Rathke, M.W.; Rogic, M.M.; De Lue, N.R. *Tetrahedron* ***1988****, 44*, 2751.
[513] Brown, H.C.; Lane, C.F. *Tetrahedron* ***1988****, 44,* 2763; Brown, H.C.; Lane, C.F.; De Lue, N.R. *Tetrahedron* ***1988****, 44,* 2273. Also see Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1989****, 54,* 340.
[514] Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1988****, 53*, 5664. For other reagents, see Jigajinni, V.B.; Brown, H.C.; De Lue, N.R. *Tetrahedron* ***1988****, 44*, 2785.

respectively. Combined with the hydroboration reaction (Reaction **15-16**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an *anti-Markovnikov* orientation (see Reaction **15-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free radical process.[515] *trans*-1-Alkenylboronic acids (**47**), prepared by hydroboration of terminal alkynes with catecholborane to give **46**[516] (Reaction **15-16**), followed by hydrolysis, react with I_2 in the presence of NaOH at 0 °C in ethereal solvents to give *trans*-vinylic iodides.[517]



Treatment with ICl also gives the vinyl iodide.[518] This is an indirect way of accomplishing the *anti-Markovnikov* addition of HI to a terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br_2 (2 molar equivalents of Br_2 must be used) followed by base to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the *cis*-vinylic bromide.[519] Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.[520] Treatment of **47** (prepared from terminal alkynes) with Cl_2 gave vinylic chlorides with inversion.[521] Vinylic boranes can be converted to the corresponding vinylic halide by treatment with NCS or NBS.[522] Vinylic halides can also be prepared from vinylic silanes[523] and from vinylic copper reagents. The latter react with I_2 to give iodides,[524] and with NCS or NBS at −45 °C to give chlorides or bromides.[525] The reaction of an aryl alkyne with $HInCl_2/BEt_3$ and then iodine leads to a (*Z*)-vinyl iodide with respect to the aryl group and the iodine atom.[526] Boronic acids can be fluorinated in a reaction mediated by Ag(I) triflate.[527]

For the reaction of lithium enolate anions of esters with I_2 or CX_4, see Reaction **12-5**.

The conversion of terminal alkynes to 1-iodo-1-alkynes was reported using NaI under electrochemical conditions.[528] 1-Bromo-1-alkynes were converted to the 1-iodo-1-alkyne

[515] Suzuki, A.; Nozawa, S.; Harada, M.; Itoh, M.; Brown, H.C.; Midland, M.M. *J. Am. Chem. Soc.* ***1971****, 93*, 1508; Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972****, 11,* 692, pp. 699–700; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 442–446.

[516] See Kabalka, G.W. *Org. Prep. Proced. Int.* ***1977****, 9,* 131.

[517] Brown, H.C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N.G. *J. Org. Chem.* ***1989****, 54*, 6075. See also, Kabalka, G.W.; Gooch, E.E.; Hsu, H.C. *Synth. Commun.* ***1981****, 11*, 247.

[518] Stewart, S.K.; Whiting, A. *Tetrahedron Lett.* ***1995****, 36,* 3929.

[519] Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* ***1973****, 95*, 6456. See also, Brown, H.C.; Bhat, N.G. *Tetrahedron Lett.* ***1988****, 29,* 21.

[520] See Kabalka, G.W.; Sastry, K.A.R.; Knapp, F.F.; Srivastava, P.C. *Synth. Commun.* ***1983****, 13*, 1027.

[521] Kunda, S.A.; Smith, T.L.; Hylarides, M.D.; Kabalka, G.W. *Tetrahedron Lett.* ***1985****, 26*, 279.

[522] Hoshi, M.; Shirakawa, K. *Tetrahedron Lett.* ***2000****, 41,* 2595.

[523] See Chou, S.P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* ***1989****, 54,* 868.

[524] Normant, J.F.; Chaiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1974****, 77,* 269; *Synthesis* ***1974***, 803.

[525] Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1977****, 96*, 168; Levy, A.B.; Talley, P.; Dunford, J.A. *Tetrahedron Lett.* ***1977***, 3545.

[526] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2002****, 4*, 2993.

[527] Furuya, T.; Ritter, T. *Org. Lett.* ***2009****, 11,* 2860.

[528] Nishiguchi, I.; Kanbe, O.; Itoh, K.; Maekawa, H. *Synlett* ***2000***, 89.

with CuI.[529] 1-Trialkyldisilylalkynes were converted to the corresponding 1-bromoalkyne via reaction with NBS and AgF.[530] Terminal alkynes react with (diacetoxyiodo)benzene, KI, and CuI to give 1-iodo-alkynes.[531] Trichloroisocyanuric acid has been used to convert terminal alkynes to 1-chloroalkynes.[532]

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[533] In a number of cases, the reaction has been shown to involve inversion of configuration (see Sec. 12.A.i), indicating an S_E2 (back) mechanism, while in other cases retention of configuration has been shown,[534] implicating an S_E2 (front) or S_Ei mechanism. In still other cases, complete loss of configuration as well as other evidence demonstrated the presence of a free radical mechanism.[534,535]

OS **I**, 125, 325, 326; **III**, 774, 813; **V**, 921; **VI**, 709; **VII**, 290; **VIII**, 586; **IX**, 573. Also see, OS **II**, 150.

E. Nitrogen Electrophiles

12-32 The Conversion of Organometallic Compounds to Amines

Amino-de-metalation

$$RLi \xrightarrow[MeLi]{MeONH_2} RNH_2$$

There are several methods for conversion of alkyl- or aryllithium compounds to primary amines.[536] The two most important are treatment with hydroxylamine derivatives and with certain azides.[537] In the first of these methods, treatment of RLi with methoxyamine and MeLi in ether at $-78\,^{\circ}C$ gives RNH_2.[538] *Grignard reagents* from aliphatic halides give lower yields. The reaction can be extended to give secondary amines by the use of *N*-substituted methoxyamines (CH_3ONHR').[539] There is evidence[540] that the mechanism involves the direct displacement of OCH_3 by R on an intermediate $CH_2ONR'^-$ ($CH_2ONR'^-Li^+ + RLi \rightarrow CH_3OLi + RNR'^-Li^+$). Tosyl azide ($TsN_3$) is a highly useful azide.[541] The initial product is usually RN_3, but this is easily reduced to the amine (Reaction **19-51**). With some azides (e.g., azidomethyl phenyl sulfide, $PhSCH_2N_3$), the group attached to the N_3 is a poor leaving group, so the initial

[529] Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1999****, 72*, 787.
[530] Lee, T.; Kang, H.R.; Kim, S.; Kim, S. *Tetrahedron* ***2006****, 62,* 4081.
[531] Yan, J.; Li, J.; Cheng, D. *Synlett* ***2007***, 2442.
[532] Vilhelmsen, M.H.; Andersson, A.S.; Nielsen, M.B. *Synthesis* ***2009***, 1469.
[533] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond,* Vol. 2, Wiley, NY, p. 72; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 135–177; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 75–97.
[534] See Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1960****, 82*, 148.
[535] See de Ryck, P.H.; Verdonck, L.; Van der Kelen, G.P. *Bull. Soc. Chim. Belg.,* ***1985****, 94,* 621.
[536] See Erdik, E.; Ay, M. *Chem. Rev.* ***1989****, 89,* 1947.
[537] See Genet, J.P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* ***1991****, 32,* 2359.
[538] Beak, P.; Kokko, B.J. *J. Org. Chem.* ***1982****, 47,* 2822; Colvin, E.W.; Kirby, G.W.; Wilson, A.C. *Tetrahedron Lett.* ***1982****, 23*, 3835; Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* ***1982****, 23*, 5399; Boche, G.; Schrott, W. *Tetrahedron Lett.* ***1982****, 23,* 5403.
[539] Kokko, B.J.; Beak, P. *Tetrahedron Lett.* ***1983****, 24,* 561.
[540] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* ***1986****, 108,* 6016.
[541] Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* ***1982****, 47,* 3177; Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* ***1983****, 24*, 3795; Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1984****, 25*, 429.

product is a triazene (in this case ArNHN=NCH_2SPh from ArMgX), which can be hydrolyzed to the amine.[542]

$$R_3B \xrightarrow{NH_3-NaOCl} 2\,RNH_2 + RB(OH)_2$$

Organoboranes react with a mixture of aq NH_3 and NaOCl to produce primary amines.[543] It is likely that the actual reagent is chloramine (NH_2Cl). Chloramine itself,[544] hydroxylamine-*O*-sulfonic acid in diglyme,[545] and trimethylsilyl azide[546] also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (Reaction **15-16**), this is an indirect method for the addition of NH_3 to a double bond with *anti-Markovnikov* orientation. Secondary amines can be prepared[547] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides.

$$RBCl_2 + R'N_3 \longrightarrow RR'NBCl_2 \xrightarrow[^-HO]{H_2O} RNHR'$$

$$R_2BCl + R'N_3 \xrightarrow[2.\ H_2O]{1.\ Et_2O} RNHR'$$

The use of an optically active R*BCl_2 gave secondary amines of essentially 100% optical purity.[548] Aryllead triacetates [$ArPb(OAc)_3$] give secondary amines (ArNHAr′) when treated with primary aromatic amines $Ar'NH_2$ and $Cu(OAc)_2$.[549]

Secondary amines have been converted to tertiary amines by treatment with lithium dialkylcuprate reagents: $R_2CuLi + NHR \rightarrow RNR'_2$.[550] The reaction was also used to convert primary amines to secondary, but yields were lower.[551]

Terminal alkynes reacted with chlorodiphenylphosphine (Ph_3PCl) and a Ni catalyst to give the 1-diphenylphosphino alkyne (R-C≡C-PPh_2).[552] Alkynyl halides can be used for a similar reaction. Treatment of methyl carbamates with KHMDS and CuI, followed by 2 equiv of 1-bromophenylacetylene gave the *N*-substituted alkyne, Ph-C≡C-N(CO_2Me)R.[553]

Metal-catalyzed amination reactions are increasingly important in organic methodology. In a typical reaction, an amine is coupled to an alkyl, vinyl, or aryl halide (or with a different leaving group) in the presence of a transition metal, usually Pd. Presumably, the amination occurs via reaction with a transient organometallic species. Amination of aromatic compounds via this approach is discussed in section Reaction **13-5**. Aliphatic

[542] Trost, B.M.; Pearson, W.H. *J. Am. Chem. Soc.* ***1981****, 103,* 2483; ***1983****, 105*, 1054.
[543] Kabalka, G.W.; Wang, Z.; Goudgaon, N.M. *Synth. Commun.* ***1989****, 19,* 2409. See Kabalka, G.W.; Wang, Z. *Organometallics* ***1989****, 8,* 1093; *Synth. Commun.* ***1990****, 20*, 231.
[544] Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* ***1964****, 86,* 3565.
[545] Brown, H.C.; Kim, K.; Srebnik, M.; Singaram, B. *Tetrahedron* ***1987****, 43,* 4071. See Brown, H.C.; Kim, K.; Cole, T.E.; Singaram, B. *J. Am. Chem. Soc.* ***1986****, 106,* 6761.
[546] Kabalka, G.W.; Goudgaon, N.M.; Liang, Y. *Synth. Commun.* ***1988****, 18,* 1363.
[547] Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* ***1989***, 844.
[548] Brown, H.C.; Salunkhe, A.M.; Singaram, B. *J. Org. Chem.* ***1991****, 56*, 1170.
[549] Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.; Guiry, P.J. *Tetrahedron Lett.* ***1989****, 30,* 1377.
[550] Yamamoto, H.; Maruoka, K. *J. Org. Chem.* ***1980****, 45,* 2739.
[551] Merkushev, E.B. *Synthesis* ***1988***, 923
[552] Beletskaya, I.P.; Affanasiev, V.V.; Kazankova, M.A.; Efimova, I.V. *Org. Lett.* ***2003****, 5*, 4309.
[553] Dunetz, J.R.; Danheiser, R.L. *Org. Lett.* ***2003****, 5*, 4011.

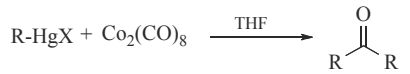
and vinyl substrates are treated here. In one example, a vinyl triflate is converted to an enamine via reaction with pyrrole in the presence of a Pd catalyst.[554]

OS **VI**, 943.

F. Carbon Electrophiles

12-33 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides

Acyl-de-metalation, and so on



Symmetrical ketones[555] can be prepared in good yields by the reaction of organomercuric halides[556] with dicobalt octacarbonyl in THF,[557] or with nickel carbonyl in DMF or certain other solvents.[558] The R group may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $CO_2(CO)_8$ reaction, although the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[559] Divinylic ketones (useful in the *Nazarov cyclization*, **15-20**) have been prepared in high yields by treatment of vinylic mercuric halides with CO and a Rh catalyst.[559] In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds (R_4Sn) are treated with a halide R′X (R′ = aryl, vinylic, benzylic), CO, and a Pd complex catalyst.[560] Similar reactions use *Grignard reagents*, $Fe(CO)_5$, and an alkyl halide.[561]

Grignard reagents react with formic acid to give good yields of aldehydes. Two molar equivalents of RMgX are used; the first converts HCO_2H to $HCOO^-$, which reacts with the second equivalent to give RCHO.[562] Alkyllithium reagents and Grignard reagents react with CO to give symmetrical ketones.[563] An interesting variation reacts CO_2 with an organolithium, which is then treated with a different organolithium reagent to give the unsymmetrical ketone.[564] α,β-Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and $TiCl_4$ at $-90\,^\circ C$.[565]

α,β-Unsaturated esters can be prepared by treating boronic esters (**27**) with CO, $PdCl_2$, and NaOAc in MeOH.[566] The synthesis of α,β-unsaturated esters has also been

[554] Movassaghi, M.; Ondrus, A.E. *J. Org. Chem.* ***2005****, 70,* 8638.

[555] See Narayana, C.; Periasamy, M. *Synthesis* ***1985***, 253; Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988****, 57*, 299.

[556] See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***; Larock, R.C. *Tetrahedron* ***1982****, 38,* 1713; *Angew. Chem. Int. Ed.* ***1978****, 17,* 27.

[557] Seyferth, D.; Spohn, R.J. *J. Am. Chem. Soc.* ***1969****, 91,* 3037.

[558] Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984****, 14,* 1175 and references cited therein. For another method, see Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.

[559] Larock, R.C.; Hershberger, S.S. *J. Org. Chem.* ***1980****, 45,* 3840.

[560] Tanaka, M. *Tetrahedron Lett.* ***1979***, 2601.

[561] Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 761. See also, Vitale, A.A.; Doctorovich, F.; Nudelman, N.S. *J. Organomet. Chem.* ***1987****, 332*, 9.

[562] Sato, F.; Oguro, K.; Watanabe, H.; Sato, M. *Tetrahedron Lett.* ***1980****, 21*, 2869. See Amaratunga, W.; Fréchet, J. M.J. *Tetrahedron Lett.* ***1983****, 24,* 1143.

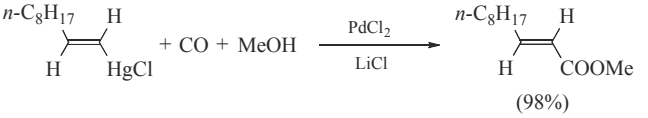
[563] Trzupek, L.S.; Newirth, T.L.; Kelly, E.G.; Sbarbati, N.E.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1973****, 95,* 8118.

[564] Zadel, G.; Breitmaier, E. *Angew. Chem. Int. Ed.* ***1992****, 31*, 1035.

[565] Yamamoto, K.; Yohitake, J.; Qui, N.T.; Tsuji, J. *Chem. Lett.* ***1978***, 859.

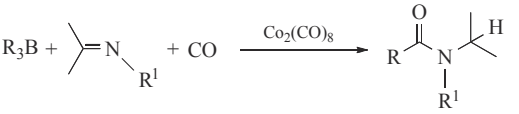
[566] Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1981***, 879. See also, Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989****, 30,* 6555.

accomplished by treatment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, for example,[567]



Alkyl and aryl *Grignard reagents* can be converted to carboxylic esters with $Fe(CO)_5$ instead of CO.[568]

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl[569]:



In another method for the conversion RM → RCONR, *Grignard reagents* and organolithium compounds are treated with a formamide ($HCONR'_2$) to give the intermediate $RCH(OM)NR'_2$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product $RCONR'_2$.[570]

Direct conversion of a hydrocarbon to an aldehyde (R—H → R—CHO) was reported by treatment of the hydrocarbon with $GaCl_3$ and CO.[571]

For carbonylation reactions of aryl halides, see Reaction **13-15**.

See also, Reactions **10-76**, **15-32**, and **18-23**–**18-24**.

OS **VIII**, 97.

12-34 Cyano-de-metalation

$$\text{R-M} + \text{CuCN} \longrightarrow \text{R-CN}$$

Vinylic copper reagents react with ClCN to give vinyl cyanides, although BrCN and ICN give the vinylic halide instead.[572] Vinylic cyanides have also been prepared by the reaction between vinylic lithium compounds and phenyl cyanate (PhOCN).[573] Alkyl nitriles (RCN) have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.[574] Vinyl bromides reacted with KCN, in the presence of a Ni complex and Zn metal to give the vinyl nitrile.[575] Vinyl triflates react with LiCN, in the presence of a Pd catalyst, to give the vinyl nitrile.[576]

[567] Larock, R.C. *J. Org. Chem.* ***1975****, 40*, 3237.
[568] Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 1477.
[569] Alper, H.; Amaratunga, S. *J. Org. Chem.* ***1982****, 47,* 3593.
[570] Screttas, C.G.; Steele, B.R. *J. Org. Chem.* ***1988****, 53,* 5151.
[571] Oshita, M.; Chatani, N. *Org. Lett.* ***2004****, 6*, 4323.
[572] Westmijze, H.; Vermeer, P. *Synthesis* ***1977***, 784.
[573] Murray, R.E.; Zweifel, G. *Synthesis* ***1980***, 150.
[574] Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *J. Chem. Soc. Chem. Commun.* ***1984***, 398.
[575] Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* ***1995****, 68*, 3137.
[576] Piers, E.; Fleming, F.F. *Can. J. Chem.* ***1993****, 71*, 1867.

For other electrophilic substitutions of the type RM → RC, which are discussed under nucleophilic substitutions in Chapter 10, see also, Reactions **16-81**–**16-85** and **16-99**.

OS IX, 548

G. Metal Electrophiles

12-35 Transmetalation with a Metal

Metalo-de-metalation

$$RM + M' \rightleftharpoons RM' + M$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal. The RM′ compound can be successfully prepared only when M′ is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M′ is a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls[556] are easy to prepare and mercury is far down in the electromotive series.[577] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, and so on, have been prepared this way. An important advantage of this method over Reaction **12-38** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.[578] If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS **V**, 1116.

12-36 *Transmetalation with a Metal Halide*

Metalo-de-metalation

$$RM + M'X \rightleftharpoons RM' + MX$$

In contrast to Reaction **12-35**, the reaction between an organometallic compound and a metal *halide* is successful only when M′ is *below* M in the electromotive series.[579] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction, the most common substrates are *Grignard reagents* and organolithium compounds.[580]

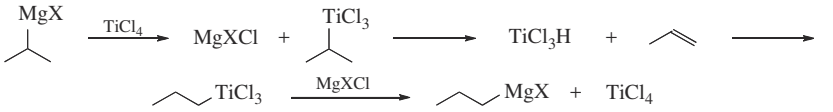
[577] See Makarova, L.G. *Organomet. React.* ***1970****, 1*, 119, pp. 190–226; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods,* Vol. 11, VCH, NY, ***1988***, pp. 31–44.

[578] See Pi, R.; Bauer, W.; Brix, B.; Schade, C.; Schleyer, P.v.R. *J. Organomet. Chem.* ***1986****, 306,* C1.

[579] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond,* Vol. 2, Wiley, NY, pp. 25–149; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 39–106; Jensen, F.R.; Rickborn, B. *Electrophilic Substituton of Organomercurials,* McGraw-Hill, NY, ***1968***, pp. 100–192. Also see, Schlosser, M. *Angew. Chem. Int. Ed.* ***1964****, 3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968****, 5,* 238.

[580] See Wakefield, B.J. *Organolithium Methods,* Academic Press, NY, ***1988***; Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.

The MgX of *Grignard reagents*[581] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[582] The proposed mechanism consists of metal exchange (Reaction **12-36**), elimination–addition, and metal exchange:



The addition step is similar to Reactions **15-16** or **15-17** and follows *Markovnikov's* rule, so the positive titanium goes to the terminal carbon.

Among others, alkyls of Be, Zn,[583] Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of *Grignard reagents* with the appropriate halide.[584] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B,[585] Ge, P, As, Sb, and Bi, can also be prepared in this manner.[586] Except for alkali-metal alkyls and *Grignard reagents*, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.[587] In the presence of Ir,[588] or Pd catalysts,[589] aromatic compunds react with boranes to give the corresponding arylborane.

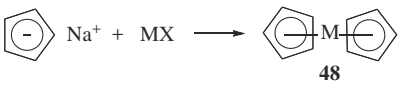
Lithium dialkylcopper reagents are prepared from 2 molar equivalents of RLi with 1 molar equivalent of a cuprous halide in ether at low temperatures:[590] The formation of organocuprates of this type are discussed in more detail in Reaction **10-58**, in connection with the coupling reaction of organocuprates with alkyl halides.

$$2\,RLi + CuX \longrightarrow R_2CuLi + LiX$$

Another way is to dissolve an alkylcopper compound in an alkyllithium solution. Higher order cuprates can also be prepared, as well as "non-ate" copper reagents.[591]

Metallocenes (**48**, see Sec. 2.I.ii) are usually made by this method. Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[592]

[581] See Hill, E.A. *Adv. Organomet. Chem.* ***1977****, 16*, 131; *J. Organomet. Chem.* ***1975****, 91*, 123.
[582] Fell, B.; Asinger, F.; Sulzbach, R.A. *Chem. Ber.* ***1970****, 103,* 3830. See also, Ashby, E.C.; Ainslie, R.D. *J. Organomet. Chem.* ***1983****, 250,* 1.
[583] See Erdik, E. *Tetrahedron* ***1987****, 43,* 2203.
[584] See Noltes, J.G. *Bull. Soc. Chim. Fr.* ***1972***, 2151.
[585] See Brown, H.C.; Racherla, U.S. *Tetrahedron Lett.* ***1985****, 26*, 4311.
[586] See Wakefield, B.J. *Organolithium Methods,* Academic Press, NY, ***1988***, pp. 149–158; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1306–1345.
[587] See Mole, T. *Organomet. React.* ***1970****, 1,* 1, pp. 31–43; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 9–26; Makarova, L.G. *Organomet. React.* ***1970****, 1*, 119, pp. 129–178, 227–240; van Koten, G. in Zuckerman, J.J. *Inorganic Reactions and Method*s, Vol. 11, VCH, NY, ***1988***, pp. 219–232; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods,* Vol. 11, VCH, NY, ***1988***, pp. 248–270.
[588] Chotana, G.A.; Rak, M.A.; Smith III, M.R. *J. Am. Chem. Soc.* ***2005****, 127*, 10539; Harrisson, P.; Morris, J.; Marder, T.B.; Steel, P.G. *Org. Lett.* ***2009****, 11*, 3586.
[589] Billingsley, K.L.; Buchwald, S.L. *J. Org. Chem.* ***2008****, 73*, 5589.
[590] House, H.O.; Chu, C.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* ***1975****, 40*, 1460. But see also, Lipshutz, B.H.; Whitney, S.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* ***1986****, 27,* 4273; Bertz, S.H.; Dabbagh, G. *Tetrahedron* ***1989****, 45,* 425.
[591] Stack, D.E.; Klein, W.R.; Rieke, R.D. *Tetrahedron Lett.* ***1993****, 34*, 3063.
[592] See Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* ***1969****, 17*, 1; Birmingham, J.M. *Adv. Organomet. Chem.* ***1965****, 2,* 365, pp. 375.



48

In a related reaction, sulfurated boranes ($R_2B—SSiR'_2$) react with *Grignard reagents* (e.g., methylmagneisum bromide) to give the β-alkyl borane (e.g., $R_2B—Me$) upon heating *in vacuo*.[593]

OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **VIII**, 23, 57, 268, 474, 586, 606, 609. Also see, OS **IV**, 476

12-37 Transmetalation with an Organometallic Compound

Metalo-de-metalation

$$RM + R'M' \rightleftharpoons RM' + R'M$$

This type of metallic exchange is used much less often than Reactions **12-35** and **12-36**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways,[594] for example, a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dialkylamino organolithium compounds from the corresponding organotin compounds[595]

$$RR'NCH_2SnBu_3 + BuLi \xrightarrow{0\,^\circ C} RR'NCH_2Li + Bu_4Sn$$

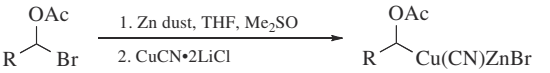
The reaction has also been used to prepare 1,3-dilithiopropanes[596] and 1,1-dilithiomethylenecyclohexane[597] from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (Sec. 5.B.i). The reaction proceeds with retention of configuration;[598] an S_Ei mechanism is likely.[599]

"Higher order" cuprates[600] (see Reaction **10-58**) have been produced by this reaction starting with a vinylic tin compound:[601]

$$RSnR_3' + Me_2Cu(CN)Li_2 \longrightarrow RCuMe(CN)Li_2 + MeSnR_{3-}{}' \qquad R = \text{A vinylic group}$$

[593] Soderquist, J.A.; DePomar, J.C.J. *Tetrahedron Lett.* ***2000****, 41*, 3537.
[594] See Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond,* Vol. 4, Wiley, NY, pp. 1–157, see pp. 81–89; Kauffmann, T. *Top. Curr. Chem.* ***1980****, 92,* 109, pp. 130.
[595] Pearson, W.H.; Lindbeck, A.C. *J. Org. Chem.* ***1989****, 54,* 5651.
[596] Seetz, J.W.F.L.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1982****, 104,* 6848.
[597] Maercker, A.; Dujardin, R. *Angew. Chem. Int. Ed.* ***1984****, 23,* 224.
[598] Sawyer, J.S.; Kucerovy, A.; Macdonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* ***1988****, 110,* 842.
[599] Dessy, R.E.; Kaplan, F.; Coe, G.R.; Salinger, R.M. *J. Am. Chem. Soc.* ***1963****, 85*, 1191.
[600] See Lipshutz, B.H. *Synlett*, ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.
[601] Behling, J.R.; Babiak, K.A.; Ng, J.S.; Campbell, A.L.; Moretti, R.; Koerner, M.; Lipshutz, B.H. *J. Am. Chem. Soc.* ***1988****, 110,* 2641.

These compounds are not isolated, but used directly *in situ* for conjugate addition reactions (Reaction **15-25**). Another method for the preparation of such reagents (but with Zn instead of Li) allows them to be made from α-acetoxy halides:[602]



OS **V**, 452; **VI**, 815; **VIII**, 97.

12.C.iii. Halogen as Leaving Group

The reduction of alkyl halides can proceed by an electrophilic substitution mechanism, but it is considered in Chapter 19 (Reaction **19-53**).

12-38 Metalo-de-halogenation

$$RX + M \longrightarrow RM$$

Alkyl halides react directly with certain metals to give organometallic compounds.[603] The most common metal is Mg, and of course this is by far the most common method for the preparation of *Grignard reagents*.[604] The *Grignard reaction* with aldehydes or ketones is discussed in Reaction **16-24**. The order of halide activity is I > Br > Cl. This reaction can be applied to many alkyl halides primary, secondary, and tertiary and to aryl halides, although aryl *chlorides* require the use of THF or another higher-boiling solvent instead of the usual ether, or special entrainment methods.[605] Aryl iodides and bromides can be treated in the usual manner. Allylic *Grignard reagents* can also be prepared in the usual manner (or in THF),[606] although in the presence of excess halide these may give *Wurtz-type coupling* products (see Reaction **10-56**).[607] Like aryl chlorides, vinylic halides require higher-boiling solvents (see OS **IV**, 258). A good procedure for benzylic and allylic halides is to use magnesium anthracene (prepared from Mg and anthracene in THF)[608] instead of ordinary magnesium,[609] although activated magnesium turnings have also been used.[610] Alkynyl *Grignard reagents* are generally prepared by the method in Reaction **12-22**.

Dihalides[611] can be converted to *Grignard reagents* if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain

[602] Chou, T.; Knochel, P. *J. Org. Chem.* ***1990****, 55,* 4791.
[603] See Massey, A.G.; Humphries, R.E. *Aldrichimica Acta* ***1989****, 22*, 31; Negishi, E. *Organometallics in Organic Synthesis,* Wiley, NY, ***1980***, pp. 30–37
[604] See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 159–306, 162–175; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Monmetallic substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 5–91.
[605] Pearson, D.E.; Cowan, D.; Beckler, J.D. *J. Org. Chem.* ***1959****, 24,* 504.
[606] See Benkeser, R.A. *Synthesis* ***1971***, 347.
[607] See Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* ***1984****, 25*, 3305.
[608] Bogdanovic, B.; Janke, N.; Kinzelmann, H. *Chem. Ber.* ***1990****, 123*, 1507, and other papers in this series.
[609] Gallagher, M.J.; Harvey, S.; Raston, C.L.; Sue, R.E. *J. Chem. Soc. Chem. Commun.* ***1988***, 289.
[610] Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991****, 56,* 698. See Lai, Y. *Synthesis* ***1981***, 585.
[611] See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond,* Vol. 4, Wiley, NY, pp. 187–193; Heaney, H. *Organomet. Chem. Rev.* ***1966****, 1*, 27. For a review of di-Grignard reagents, see Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1987****, 26,* 990.

dimagnesium compounds [e.g., $BrMg(CH_2)_4MgBr$].[612] 1,2-Dihalides give elimination[613] rather than *Grignard reagent* formation (Reaction **17-22**), and the reaction is seldom successful with 1,1-dihalides, although the preparation of *gem*-disubstituted compounds [e.g., $CH_2(MgBr)_2$], has been accomplished with these substrates.[614] α-Halo Grignard reagents and α-halolithium reagents can be prepared by the method given in Reaction **12-39**.[615] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.[616] Nitrogen-containing *Grignard reagents* have been prepared.[617]

The presence of other functional groups in the halide usually affects the preparation of the *Grignard reagent*. Groups that contain active hydrogen (defined as any hydrogen that will react with a *Grignard reagent*, e.g., OH, NH_2, and CO_2H), can be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups that react with *Grignard reagents* (e.g., C=O, C≡N, NO_2, CO_2R) inhibit *Grignard* formation entirely. In general, the only functional groups that may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β-halo ethers generally give β elimination when treated with Mg (see Reaction **17-24**), and *Grignard reagents* from α-halo ethers[618] can only be formed in THF or dimethoxymethane at a low temperature, for example,[619]

$$EtOCH_2Cl + Mg \xrightarrow[-30\ ^\circ C]{THF\ or\ CH_2(OMe)_2} EtOCH_2MgCl$$

because such reagents immediately undergo α elimination (see Reaction **12-39**) at room temperature in ether solution.

Because *Grignard reagents* react with water (Reaction **12-24**) and with oxygen (Reaction **12-25**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. *Grignard reagents* are generally neither isolated nor stored; solutions of *Grignard reagents* are used directly for the required synthesis. *Grignard reagents* can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[620] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[621] It is also possible to obtain *Grignard reagents* in powdered form, by complexing them with the chelating agent tris(3,6-dioxaheptyl)amine [$N(CH_2CH_2OCH_2CH_2OCH_3)_3$].[622]

[612] See Seetz, J.W.F.L.; Hartog, F.A.; Böhm, H.P.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Tetrahedron Lett.* ***1982,*** *23,* 1497.
[613] See van Eikkema Hommes, N.J.R.; Bickelhaupt, F.; Klumpp, G.W. *Angew. Chem. Int. Ed.* ***1988,*** *27*, 1083.
[614] See Bruin, J.W.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Organomet. Chem.* ***1985,*** *288,* 13.
[615] See Chivers, T. *Organomet. Chem. Rev. Sect. A* ***1970,*** *6*, 1.
[616] Yu, S.H.; Ashby, E.C. *J. Org. Chem.* ***1971,*** *36*, 2123.
[617] Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem.* ***2003,*** *68*, 2054.
[618] See Peterson, D.J. *Organomet. Chem. Rev. Sect. A* ***1972,*** *7,* 295.
[619] See Castro, B. *Bull. Soc. Chim. Fr.* ***1967***, 1533, 1540, 1547.
[620] Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* ***1970,*** *23,* 291.
[621] Smith, Jr., W.N. *J. Organomet. Chem.* ***1974,*** *64,* 25.
[622] Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R.J.P.; Reye, C. *Tetrahedron* ***1989,*** *45*, 171.

Next to the formation of *Grignard reagents*, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds,[623] but it has also been carried out with many other metals (e.g., Na, Be, Zn, Hg, As, Sb, and Sn). With Na, the *Wurtz Reaction* (**10-56**) is an important side reaction. In some cases, where the reaction between a halide and a metal is too slow, an alloy of the metal with K or Na can be used instead. The most important example is the preparation of tetraethyl-lead from ethyl bromide and a Pb—Na alloy.

The efficiency of the reaction can often be improved by use of the metal in its powdered[624] or vapor[625] form. These techniques have permitted the preparation of some organometallic compounds that cannot be prepared by the standard procedures. Among the metals produced in an activated form are Mg,[626] Ca,[627] Zn,[628] Al, Sn, Cd,[629] Ni, Fe, Ti, Cu,[630] Pd, and Pt.[631]

The mechanism of *Grignard reagent* formation involves free radicals,[632] and there is much evidence for this, from CIDNP[633] (Sec. 5.C.i) and from stereochemical, rate, and product studies.[634] Further evidence is that free radicals have been trapped,[635] and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that *Grignard reagent* formation does not take place by a single-step insertion mechanism.[636] The following SET mechanism has been proposed:[633]

$$\mathrm{R{-}X + Mg \longrightarrow R{-}X^{\bullet -} + Mg_s^{\bullet +}}$$

$$\mathrm{R{-}X^{\bullet -} \longrightarrow R^{\bullet} + X^{-}}$$

$$\mathrm{X^{-} + Mg_s^{\bullet +} \longrightarrow XMg_s^{\bullet}}$$

$$\mathrm{R^{\bullet} + X\mathit{M}^{\bullet}g_s \longrightarrow RMgX}$$

[623] See Wakefield, B.J. *Organolithium Methods,* Academic Press, NY, ***1988***, pp. 21–32; Wardell, J.L. in Hartley, F.R.; Patai, S. Vol. 4, pp. 1–157, 5–27; Newcomb, M.E. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 3–14. For a study of halogen–lithium exhange in hydrocarbon solvents, see Slocum, D.W.; Kusmic, D.; Raber, J.C.; Reinscheld, T.K.; Whitley, P.E. *Tetrahedron Lett.* ***2010****, 51*, 4793.

[624] See Rieke, R.D. *Science* ***1989****, 246,* 1260.

[625] See Klabunde, K.J. *React. Intermed. (Plenum)* ***1980****, 1,* 37; *Acc. Chem. Res.* ***1975****, 8*, 393; Skell, P.S. Havel, J.J.; McGlinchey, M.J. *Acc. Chem. Res.* ***1973****, 6,* 97.

[626] Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* ***1988****, 53,* 4482. See also, Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991****, 56,* 698.

[627] Wu, T.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* ***1990****, 55,* 5045.

[628] Rieke, R.D.; Li, P.T.; Burns, T.P.; Uhm, S.T. *J. Org. Chem.* ***1981****, 46*, 4323. See also, Zhu, L.; Wehmeyer, R.M.; Rieke, R.D. *J. Org. Chem.* ***1991****, 56,* 1445.

[629] Burkhardt, E.R.; Rieke, R.D. *J. Org. Chem.* ***1985****, 50,* 416.

[630] Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1991****, 113,* 4672, and references cited therein.

[631] See Lai, Y. *Synthesis* ***1981***, 585; Rieke, R.D. *Acc. Chem. Res.* ***1977****, 10*, 301.

[632] See Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143.

[633] Bodewitz, H.W.H.J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron* ***1975****, 31*, 1053. See also, Schaart, B.J.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Can. J. Chem.* ***1980****, 58*, 932.

[634] See Rogers, H.R.; Hill, C.L.; Fujiwara, Y.; Rogers, R.J.; Mitchell, H.L.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980****, 102*, 217; Barber, J.J.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980****, 102*, 239.

[635] Root, K.S.; Hill, C.L.; Lawrence, L.M.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1989****, 111,* 5405.

[636] Nuzzo, R.G.; Dubois, L.H. *J. Am. Chem. Soc.* ***1986****, 108,* 2881.

Other evidence has been offered to support a SET initiated radical process for the second step of this mechanism.[637] The species $R—X^{\bullet -}$ and $Mg^{\bullet +}$ are radical ions.[638] The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium. It is known that this is a surface reaction.[639] It has been suggested that some of the $R^{\bullet}$ radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the $XMg^{\bullet}$. There is evidence both for[640] and against[641] this suggestion. Another proposal is that the fourth step is not the one shown here, but that the $R^{\bullet}$ is reduced by Mg^{+} to the carbanion R^{-}, which combines with MgX^{+} to give RMgX.[642]

There are too many preparations of *Grignard reagents* in *Organic Syntheses* for us to list here. Chiral *Grignard reagents* are rare, since they are configurationally unstable in most cases. However, a few chiral *Grignard reagents* are known.[643] Use of the reaction to prepare other organometallic compounds can be found in OS **I**, 228; **II**, 184, 517, 607; **III**, 413, 757; **VI**, 240; **VII**, 346; **VIII**, 505. The preparation of unsolvated butylmagnesium bromide is described at OS **V**, 1141. The preparation of highly reactive (powdered) magnesium is given at OS **VI**, 845.

12-39 Replacement of a Halogen by a Metal from an Organometallic Compound

Metalo-de-halogenation

$$RX + R'M \longrightarrow RM + R'X$$

The exchange reaction between halides and organometallic compounds occurs most readily when M is Li and X is Br or I,[644] although it has been shown to occur with Mg.[645] The R′ group is usually, although not always, alkyl, and often butyl; R is usually aromatic.[646] Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give *Wurtz coupling*. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Despite the preponderance of reactions with bromides and iodides, it is noted that the reaction of 1-fluorooctane with 4–10 equiv of Li powder and 2–4 equiv of DTBB (4,4′-di-*tert*-butylbiphenyl) in THP (THP=tetrahydropyran) at 0 °C for 5 min, was shown to give a solution of the corresponding 1-octyllithium.[647] Vinylic halides

[637] Hoffmann, R.W.; Brönstrup, M.; Müller, M. *Org. Lett.* ***2003****, 5,* 313.
[638] See Sergeev, G.B.; Zagorsky, V.V.; Badaev, F.Z. *J. Organomet. Chem.* ***1983****, 243,* 123. See, however, de Souza-Barboza, J.C.; Luche, J.; Pétrier, C. *Tetrahedron Lett.* ***1987****, 28,* 2013.
[639] Walborsky, H.M.; Topolski, M. *J. Am. Chem. Soc.* ***1992****, 114,* 3455; Walborsky, H.M.; Zimmermann, C. *J. Am. Chem. Soc.* ***1992****, 114*, 4996; Walborsky, H.M. *Accts. Chem. Res.* ***1990****, 23*, 286.
[640] Garst, J.F. *Acc. Chem. Res.* ***1991****, 24*, 95; Garst, J.F.; Ungváry, F.; Batlaw, R.; Lawrence, K.E. *J. Am. Chem. Soc.* ***1991****, 113*, 5392.
[641] Walborsky, H.M. *Acc. Chem. Res.* ***1990****, 23,* 286.
[642] de Boer, H.J.R.; Akkerman, O.S.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1988****, 27,* 687.
[643] See Hölzer, B.; Hoffmann, R.W. *Chem. Commun.* ***2003***, 732; Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* ***1999****, 18*, 3342.
[644] See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods,* Vol. 11, VCH, NY, ***1988***, pp. 107–129; Parham, W.E.; Bradsher, C.K. *Acc. Chem. Res.* ***1982****, 15,* 300.
[645] See Tamborski, C.; Moore, G.J. *J. Organomet. Chem.* ***1971****, 26*, 153.
[646] See Bailey, W.F.; Punzalan, E.R. *J. Org. Chem.* ***1990****, 55,* 5404; Negishi, E.; Swanson, D.R.; Rousset, C.J. *J. Org. Chem.* ***1990****, 55,* 5406.
[647] Yus, M.; Herrera, R.P.; Guijarro, A. *Tetrahedron Lett.,* ***2003****, 44*, 5025.

react with retention of configuration.[648] The reaction can be used to prepare α-halo organolithium and α-halo organomagnesium compounds[649] Carbon tetrachloride reacts with butyllithium to give lithiotrichloromethane ($Cl_3C—Li$), for example.[650] Such compounds can also be prepared by hydrogen–metal exchange, for example,[651]

$$Br_3CH + i\text{PrMgCl} \xrightarrow[-95\,^\circ C]{\text{THF–HMPA}} Br_3C—MgCl + C_3H_8$$

This is an example of Reaction **12-22**. However, these α-halo organometallic compounds are stable (and configurationally stable as well[652]) only at low temperatures (ca. -100 °C) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures, they lose MX (α elimination) to give carbenes, which then react further, or carbenoid reactions. The α-chloro-α-magnesio sulfones [$ArSO_2CH(Cl)MgBr$] are exceptions, being stable in solution at room temperature and even under reflux.[653] Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.[654]

There is evidence that the mechanism[655] of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.[656]

$$RX + R'M \rightleftharpoons \underset{\text{Solvent cage}}{[R^\bullet, X, M, R'^\bullet]} \rightleftharpoons RM + R'X$$

Among the evidence is the fact that coupling and disproportionation products are obtained from $R^\bullet$ and $R'^\bullet$ and the observation of CIDNP.[656,657] However, in the degenerate exchange between PhI and PhLi the ate complex $Ph_2I^-\ Li^+$ has been shown to be an intermediate,[658] and there is other evidence that radicals are not involved in all instances of this reaction.[659]

In a completely different kind of process, alkyl halides can be converted to certain organometallic compounds by treatment with organometalate ions, for example,

$$RX + R_3'SnLi \longrightarrow RSnR_3' + LiX$$

[648] For examples of exchange, R = vinylic, see Miller, R.B.; McGarvey, G. *Synth. Commun.* ***1979****, 9*, 831; Sugita, T.; Sakabe, Y.; Sasahara, T.; Tsukuda, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1984****, 57*, 2319.

[649] See Siegel, H. Top. Curr. Chem. **1982**, 106, 55; Negishi, E. Organometallics in Organic Synthesis, Wiley, NY, **1980**, pp. 136–151; Köbrich, G. Angew. Chem. Int. Ed. **1972**, 11, 473. Also see Krief, A. Tetrahedron **1980**, 36, 2531; Normant, H. J. Organomet. Chem. **1975**, 100, 189.

[650] Hoeg, D.F.; Lusk, D.I.; Crumbliss, A.L. *J. Am. Chem. Soc.* ***1965****, 87*, 4147. See also, Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* ***1985***, 825.

[651] Villieras, J. *Bull. Soc. Chim. Fr.* ***1967***, 1520.

[652] Schmidt, A.; Köbrich, G.; Hoffmann, R.W. *Chem. Ber.* ***1991****, 124*, 1253; Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* ***1991****, 124,* 1259.

[653] Stetter, H.; Steinbeck, K. *Liebigs Ann. Chem.* ***1972****, 766*, 89.

[654] Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem. Int. Ed.* ***1988****, 27*, 943.

[655] For reviews of the mechanism, see Bailey, W.F.; Patricia, J.J. *J. Organomet. Chem.* ***1988****, 352,* 1; Beletskaya, I. P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976****, 45,* 330.

[656] Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1987****, 52*, 1291. See also, Bailey, W.F.; Patricia, J.J.; Nurmi, T.T.; Wang, W. *Tetrahedron Lett.* ***1986****, 27,* 1861.

[657] Ward, H.R.; Lawler, R.G.; Loken, H.Y. *J. Am. Chem. Soc.* ***1968****, 90,* 7359.

[658] See Reich, H.J.; Green, D.P.; Phillips, N.H. *J. Am. Chem. Soc.* ***1989****, 111*, 3444.

[659] Beak, P.; Allen, D.J.; Lee, W.K. *J. Am. Chem. Soc.* ***1990****, 112,* 1629.

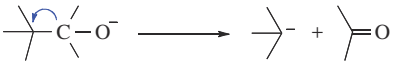
Most of the evidence is in accord with a free radical mechanism involving electron transfer, although an S_N2 mechanism can compete under some conditions.[660] Electrochemically genrated zinc has been used to prepare organozinc bomide from the corresponding alkyl halide.[661]

OS **VI**, 82; **VII**, 271, 326, 495; **VIII**, 430. See also, OS **VII**, 512; **VIII**, 479.

12.C.iv. Carbon Leaving Groups

In these reactions (**12-40**–**12-48**), a carbon–carbon bond cleaves. The substrate is the side that retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (Reaction **12-42**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,[662] although they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages These reactions follow the pattern:



The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol reactions (**16-34**) and cleavage of cyanohydrins (**16-52**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Reaction **17-32**.

12-40 Decarboxylation of Aliphatic Acids

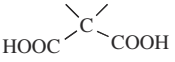
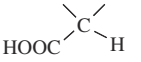
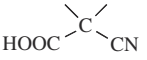
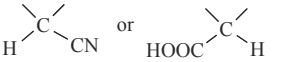
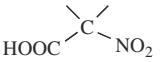
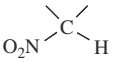
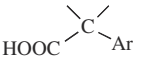
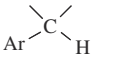
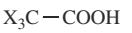
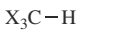
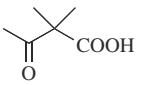
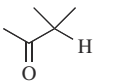
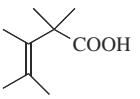
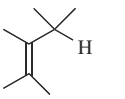
Hydro-de-carboxylation

$$RCOOH \longrightarrow RH + CO_2$$

Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple aliphatic acids.[663] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Malonic acid derivatives are the most common substrates for decarboxylation, giving the corresponding monocarboxylic acid. Decarboxylation of 2-substituted malonic acids has been reported using microwave irradiation.[664] Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 12.2.

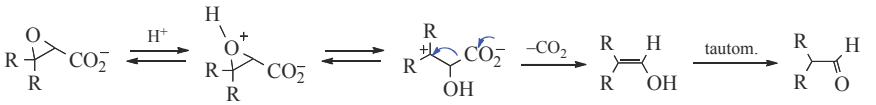
[660] See Ashby, E.C.; Su, W.; Pham, T.N. *Organometallics* ***1985****, 4,* 1493; Alnajjar, M.S.; Kuivila, H.G. *J. Am. Chem. Soc.* ***1985****, 107*, 416.
[661] Kurono, N.; Inoue, T.; Tokuda, M. *Tetrahedron* ***2005****, 61,* 11125.
[662] See Artamkina, G.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987****, 56,* 983.
[663] March, J. *J. Chem. Educ.* ***1963****, 40*, 212.
[664] Zara, C.L.; Jin, T.; Giguere, R.J. *Synth. Commun.* ***2000****, 30*, 2099.

TABLE 12.2 Some Acids That Undergo Decarboxylation Fairly Readily[a]

Acid Type	Decarboxylation Product
	
	
	
	
	
	
	

[a]Others are described in the text.

For decarboxylation of aromatic acids, see Reaction **11-35**. Decarboxylation of an α-cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.2, decarboxylation can be carried out on α,β-unsaturated[665] and α,β-acetylenic acids. Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:[666]

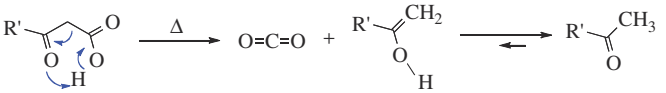


The direct product is an enol that tautomerizes to the aldehyde.[667] This is the usual last step in the *Darzens Reaction* (**16-40**).

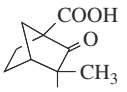
Decarboxylations can be regarded as reversal of the addition of carbanions to carbon dioxide (Reaction **16-82**), but free carbanions are not always involved.[668] When the carboxylate *ion* is decarboxylated, the mechanism can be either S_E1 or S_E2. In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing

[665] See Roy, S.C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* ***2001****, 42*, 9253.
[666] Singh, S.P.; Kagan, J. *J. Org. Chem.* ***1970****, 35*, 2203.
[667] Shiner, Jr., V.J.; Martin, B. *J. Am. Chem. Soc.* ***1962****, 84,* 4824.
[668] See Richardson, W.H.; O'Neal, H.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, pp. 447–482; Clark, L.W. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 589–622. See Dunn, G.E. *Isot. Org. Chem.* ***1977****, 3*, 1.

groups, which stabilize the carbanion.[669] Decarboxylation of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[670] The reaction without the metallic ion has also been performed in the gas phase.[671] Some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[672] but it is likely that malonic, α-cyano, α-nitro, and β,γ-unsaturated acids[673] behave similarly, since similar six-membered transition states can be written for them. Some α,β-unsaturated acids

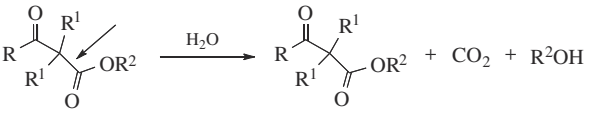


49

are also decarboxylated by this mechanism by isomerizing to the β,γ-isomers before they actually decarboxylate.[674] Evidence is that **49** and similar bicyclic β-keto acids resist decarboxylation.[675] In such compounds, the six-membered cyclic transition state cannot form for steric reasons,[676] and if it could, formation of the intermediate enol would violate *Bredt's rule* (Sec. 4.Q.iii).

Some carboxylic acids that cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an S_E1 or S_E2 mechanism.[677] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[678]), and is not subject to acid catalysis.[679] The rate of decarboxylation of a β,γ-unsaturated acid was increased $\sim 10^5$–10^6 times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.[680] Rate constants for decarboxylation reactions have been calculated using no barrier theory.[681]

[669] See Buncel, E.; Venkatachalam, T.K.; Menon, B.C. *J. Org. Chem.* ***1984****, 49*, 413.
[670] Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* ***1980****, 58,* 2271, and references cited therein.
[671] Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988****, 110*, 607.
[672] See Jencks, W.P. *Catalysis in Chemistry and Enzmology*, McGraw-Hill, NY, ***1969***, pp. 116–120.
[673] Bigley, D.B.; Clarke, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1, and references cited therein. For a review, see Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971****, 8,* 75, pp. 150–153.
[674] Bigley, D.B. *J. Chem. Soc.* ***1964***, 3897.
[675] Wasserman, H.H. in Newman *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, p. 352. See also, Buchanan, G.L.; Kean, N.B.; Taylor, R. *Tetrahedron* ***1975****, 31,* 1583.
[676] Sterically hindered β-keto acids decarboxylate more slowly: Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* ***1989****, 30*, 5253.
[677] See Ferris, J.P.; Miller, N.C. *J. Am. Chem. Soc.* ***1966****, 88,* 3522.
[678] Swain, C.G.; Bader, R.F.W.; Esteve Jr., R.M.; Griffin, R.N. *J. Am. Chem. Soc.* ***1961****, 83,* 1951.
[679] Noyce, D.S.; Metesich, M.A. *J. Org. Chem.* ***1967****, 32*, 3243.
[680] Bigley, D.B.; Al-Borno, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 15.
[681] Guthrie, J.P.; Peiris, S.; Simkin, M.; Wang, Y. *Can. J. Chem.* ***2010****, 88*, 79.



β-Keto acids[682] are easily decarboxylated, but such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.[683] This decarboxylation of β-keto esters involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (Reaction **12-43**). β-Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride (B_2O_3) at 150 °C.[684] The alkyl portion of the ester (R′) is converted to an alkene or, if it lacks a β hydrogen, to an ether (R′OR′). Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet DMSO containing NaCl, Na_3PO_4, or some other simple salt.[685] In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. α-Amino acids have been decarboxylated by treatment with a catalytic amount of 2-cyclohexenone.[686] Amino acids are decarboxylated by sequential treatment with NBS at pH 5 followed by $NaBH_4$ and $NiCl_2$.[687] Certain decarboxylations can also be accomplished photochemically.[688] See also, the decarbonylation of acyl halides, mentioned in Reaction **14-32**. In some cases, decarboxylations can give organometallic compounds: $RCOOM \rightarrow RM + CO_2$.[689] The Cu catalyzed decarboxylation of 2-alkynoic acids to terminal alkynes has been reported.[690]

Decarboxylative alkylation and arylation reactions are known. In the presence of a Ru catalyst and a B-phenyl borinate, decarboxylation of proline esters leads to 2-phenylpyrrolidine derivatives.[691] In the presence of a Pd catalyst, esters undergo decarboxylation with coupling between the alkyl groups on the carbonyl and the ester oxygen to give the corresponding hydrocarbon fragment.[692]

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I**, 290, 451, 523; **II**, 200, 391; **III**, 281, 286, 313, 326, 510, 513, 591; **IV**, 55, 93, 176, 441, 664, 708, 790, 804; **V**, 76, 288, 572, 687, 989; **VI**, 615, 781, 873, 932; **VII**, 50, 210, 319; **VIII**, 263.

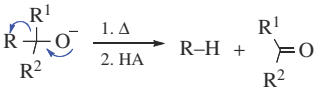
Simple decarboxylations: OS **I**, 351, 401, 440, 473, 475; **II**, 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III**, 213, 425, 495, 705, 733, 783; **IV**, 234, 254, 278, 337, 555, 560,

[682] See Oshry, L.; Rosenfeld, S.M. *Org. Prep. Proced. Int.* ***1982****, 14*, 249.
[683] For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1542–1543. See Yu, Y.; Zhang, Y. *Synth. Commun.* ***1999****, 29*, 243.
[684] Lalancette, J.M.; Lachance, A. *Tetrahedron Lett.* ***1970***, 3903.
[685] See Krapcho, A.P. *Synthesis* ***1982***, 805, 893. For other methods, see Dehmlow, E.V.; Kunesch, E. *Synthesis* ***1985***, 320; Taber, D.F.; Amedio, Jr., J.C.; Gulino, F. *J. Org. Chem.* ***1989****, 54*, 3474.
[686] Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* ***1986***, 893.
[687] Laval, G.; Golding, B.T. *Synlett* ***2003***, 542.
[688] See Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* ***1989****, 30,* 6733.
[689] See Deacon, G.B. *Organomet. Chem. Rev. A* ***1970***, 355; Deacon, G.B.; Faulks, S.J.; Pain, G.N. *Adv. Organomet. Chem.* ***1986****, 25*, 237.
[690] Kolarovi, A.; Fberov, Z. *J. Org. Chem.* ***2009****, 74,* 7199.
[691] Gribkov, D.V.; Pastine, S.J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* ***2007****, 129,* 11750.
[692] Waetzig, S.R.; Tunge, J.A. *J. Am. Chem. Soc.* ***2007****, 129,* 14860.

597, 630, 731, 857; **V**, 251, 585; **VI**, 271, 965; **VII**, 249, 359; **VIII**, 235, 444, 536; **75**, 195. Also see, OS **IV**, 633.

12-41 Cleavage of Alkoxides

Hydro-de-(α-oxidoalkyl)-substitution



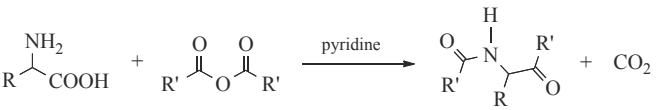
Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (Reaction **16-24**).[693] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups (e.g., the alkoxide of triethylcarbinol). Cleavage is accomplished with branched alkoxides (e.g., the alkoxides of diisopropylneopentylcarbinol or tri-*tert*-butylcarbinol).[694] Allylic,[695] benzylic,[696] and aryl groups also cleave (e.g., the alkoxide of triphenylcarbinol gives benzene and benzophenone). Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.[697] However, with some substrates in solution, substantial amounts of dimer R—R have been found, indicating a radical pathway.[698] Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.[699] The so-called retro-aldol (see Reaction **16-34**) is another example.

The reaction has been used for extensive mechanistic studies (see Sec. 12.A.ii).

OS **VI**, 268.

12-42 Replacement of a Carboxyl Group by an Acyl Group

Acyl-de-carboxylation



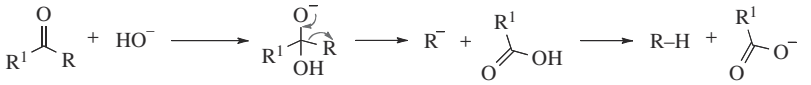
When an α-amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This is called the *Dakin–West reaction*.[700] The mechanism involves formation of an oxazolone.[701] The reaction sometimes takes place on carboxylic acids even when an a amino group is not present. A number of *N*-substituted amino acids [RCH(NHR′)COOH] give the corresponding N-alkylated products.

OS **IV**, 5; **V**, 27.

[693] Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* ***1978****, 100*, 2134.
[694] Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Org. Chem.* ***1978****, 43,* 815. See also, Lomas, J.S.; Dubois, J.E. *J. Org. Chem.* ***1984****, 49*, 2067.
[695] See Snowden, R.L.; Linder, S.M.; Muller, B.L.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1987****, 70*, 1858, 1879.
[696] Partington, S.M.; Watt, C.I.F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 983.
[697] Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988****, 110*, 2714; Ibrahim, S.; Watt, C.I.F.; Wilson, J.M.; Moore, C. *J. Chem. Soc. Chem. Commun.* ***1989***, 161.
[698] Paquette, L.A.; Gilday, J.P.; Maynard, G.D. *J. Org. Chem.* ***1989****, 54*, 5044; Paquette, L.A.; Maynard, G.D. *J. Org. Chem.* ***1989****, 54,* 5054.
[699] See Lomas, J.S.; Fain, D.; Briand, S. *J. Org. Chem.* ***1990****, 55,* 1052, and references cited therein.
[700] See Buchanan, G.L. *Chem. Soc. Rev.* ***1988****, 17,* 91.
[701] Allinger, N.L.; Wang, G.L.; Dewhurst, B.B. *J. Org. Chem.* ***1974****, 39,* 1730.

B. Acyl Cleavages

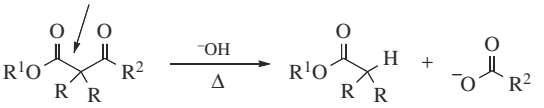
In these reactions (**12-43**–**2-46**), a carbonyl group is attacked by a hydroxide ion (or an amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Section 16.A.i.



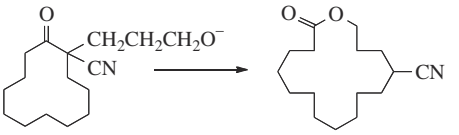
With respect to R this is of course electrophilic substitution. The mechanism is usually S_E1.

12-43 Basic Cleavage of β-Keto Esters and β-Diketones

Hydro-de-acylation



When β-keto esters are treated with concentrated base, cleavage occurs, but on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned in Reaction **12-40**. The products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β-keto esters and β-diketones, $^-$OEt can be used instead of $^-$OH, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of *Claisen condensation* (Reaction **16-85**). The related cleavage of cyclic α-cyano ketones, in an intramolecular fashion, has been used in a synthesis of macrocyclic lactones (e.g., **50**).[702]

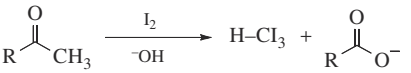


50

Activated F^- (from KF and a crown ether) has been used as the base to cleave an α-cyano ketone.[703] Treatment with ceric ammonium nitrate led to cleavage of β-diketones to give a carboxylic acid.[704]

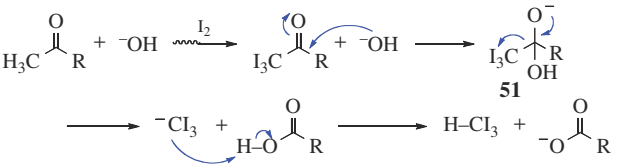
OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

12-44 Haloform Reaction



[702] Milenkov, B.; Hesse, M. *Helv. Chim. Acta* ***1987****, 70*, 308. For a similar preparation of lactams, see Wälchli, R.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* ***1985****, 68,* 484.
[703] Beletskaya, I.P.; Gulyukina, N.S.; Borodkin, V.S.; Solov'yanov, A.A.; Reutov, O.A. *Doklad. Chem.* ***1984****, 276*, 202. See also, Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* ***1987****, 28,* 5505.
[704] Zhang, Y.; Jiao, J.; Flowers II, R.A. *J. Org. Chem.* ***2006****, 71,* 4516.

In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.[705] The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of Reaction **12-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion to give tetrahedral intermediate (**51**).[706] The X_3C^- group is a sufficiently good leaving group (not HX_2C^- or H_2XC^-) that a carboxylic acid is formed, which quickly reacts with the carbanion to give the final products. Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed.

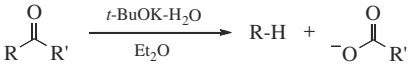


As with Reaction **12-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[707] A side reaction is α halogenation of the non-methyl R group. Sometimes these groups are also cleaved.[708] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[709] Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1 : 5.3 \times 10^{10} : 2.2 \times 10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.[710] In the past, the haloform reaction was used as a test for methylcarbinols and methyl ketones. Iodine was most often used as the test reagent, since iodoform (HCI_3) is an easily identifiable yellow solid. The reaction can be used for synthetic purposes. Methyl ketones ($RCOCH_3$) can be converted directly to methyl esters (RCO_2CH_3) by an electrochemical reaction.[711] Trifluoromethyl ketones have been converted to ethyl esters via treatment with NaH in aq DMF followed by reaction with bromoethane.[712]

OS **I**, 526; **II**, 428; **III**, 302; **IV**, 345; **V**, 8. Also see, OS **VI**, 618.

12-45 Cleavage of Nonenolizable Ketones

Hydro-de-acylation



Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of *t*-BuOK—H_2O in an aprotic solvent [e.g., ether, DMSO, 1,2-dimethoxyethane

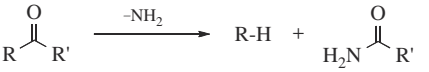
[705] See Chakrabartty, S.K. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 343–370.
[706] See Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64,* 1250; Zucco, C.; Lima, C.F.; Rezende, M.C.; Vianna, J.F.; Nome, F. *J. Org. Chem.* ***1987***, *52*, 5356.
[707] Pocker, Y. *Chem. Ind. (London)* ***1959***, 1383.
[708] Levine, R.; Stephens, J.R. *J. Am. Chem. Soc.* ***1950***, *72,* 1642.
[709] See Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 276–278.
[710] Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1990***, *68*, 1640.
[711] Nikishin, G.I.; Elinson, M.N.; Makhova, I.V. *Tetrahedron* ***1991***, *47*, 895.
[712] Delgado, A.; Clardy, J. *Tetrahedron Lett.* ***1992***, *33*, 2789.

(glyme),[713] or with solid *t*-BuOK in the absence of a solvent].[714] When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves that comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of strain).[714,715] In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.[716]

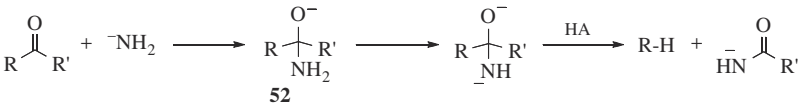
OS **VI**, 625. See also, OS **VII**, 297.

12-46 The Haller–Bauer Reaction

Hydro-de-acylation



Cleavage of ketones with sodium amide is called the *Haller–Bauer reaction*.[717] As with Reaction **12-45**, which is exactly analogous, the reaction is usually applied only to non-enolizable ketones, most often to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 (after hydrolysis) are not easily attainable by other methods. However, many other ketones have been used, although benzophenone is virtually unaffected. It has been shown that the configuration of optically active alkyl groups (R) is retained.[718] The NH_2 loses its proton from the tetrahedral intermediate (**52**) before the R group is cleaved.[719]



52

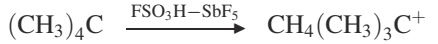
An extension of this cleavage process involves the reaction of α-nitro ketones ($O{=}C{-}CHRNO_2$) with a primary amine, neat, to give the corresponding amide, $O{=}C{-}NHR'$.[720]

OS **V**, 384, 1074.

C. Other Cleavages

12-47 The Cleavage of Alkanes

Hydro-de- *tert-* butylation, and so on



The C—C bonds of alkanes can be cleaved by treatment with superacids (Sec. 5.A.ii). For example, neopentane in $FSO_3H{-}SbF_5$ can cleave to give methane and the *tert*-butyl cation. The C—H cleavage (see Reaction **12-1**) is a competing reaction and, for example,

[713] Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.* ***1967****, 89*, 946.
[714] March, J.; Plankl, W. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 460.
[715] Davies, D.G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* ***1971***, 455.
[716] See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969****, 91*, 1009.
[717] See Gilday, J.P.; Paquette, L.A. *Org. Prep. Proced. Int.* ***1990****, 22*, 167.
[718] Paquette, L.A.; Gilday, J.P. *J. Org. Chem.* ***1988****, 53,* 4972; Paquette, L.A.; Ra, C.S. *J. Org. Chem.* ***1988****, 53*, 4978.
[719] Bunnett, J.F.; Hrutfiord, B.F. *J. Org. Chem.* ***1962****, 27,* 4152.
[720] Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* ***2003****, 59*, 1143.

neopentane can give H_2 and the *tert*-pentyl carbocation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C—H > C—C > secondary C—H ≫ primary C—H, although steric factors cause a shift in favor of C—C cleavage in such a hindered compound as tri-*tert*-butylmethane. The mechanism is similar to that shown in Reactions **12-1** and **12-20** and involves attack by H^+ on the C—C bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated C—C bonds (i.e., $R—R' + H_2 \rightarrow RH + R'H$), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a Ni-Al_2O_3 catalyst at ~250 °C.[721] Certain C—C bonds have been cleaved by alkali metals.[722]

The C—C bond of 2-allyl-2-arylmalonate derivatives was cleaved, with loss of the allylic group to give the 2-arylmalonate, by treatment with a Ni catalyst.[723]

12-48 Decyanation or Hydro-de-cyanation

$$RCN \xrightarrow{Na—NH_3 \text{ or } Na—Fe(acac)_3} RH$$

The cyano group of alkyl nitriles can be removed[724] by treatment with metallic Na, either in liquid ammonia,[725] or together with tris(acetylacetonato)iron(III) [$Fe(acac)_3$][726] or, with lower yields, titanocene. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the Na—NH_3 method gives high yields with R groups (e.g., trityl, benzyl, phenyl, and tertiary alkyl), but lower yields (~35–50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the Na—$Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical $R^\bullet$ that would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,[727] which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.[728]

α-Amino and α-amido nitriles $RCH(CN)NR'_2$ and $RCH(CN)NHCOR'$ can be decyanated in high yield by treatment with $NaBH_4$.[729]

[721] Grubmüller, P.; Schleyer, P.v.R.; McKervey, M.A. *Tetrahedron Lett.* ***1979***, 181.
[722] See Grovenstein Jr., E.; Bhatti, A.M.; Quest, D.E.; Sengupta, D.; VanDerveer, D. *J. Am. Chem. Soc.* ***1983****, 105*, 6290.
[723] Necas, D.; Tursky, M.; Kotora, M. *J. Am. Chem. Soc.* ***2004****, 126*, 10222.
[724] For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 75.
[725] Birch, A.J.; Hutchinson, E.G. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1546; Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* ***1976***, 61.
[726] Van Tamelen, E.E.; Rudler, H.; Bjorklund, C. *J. Am. Chem. Soc.* ***1971****, 93*, 7113.
[727] See Berkoff, C.E.; Rivard, D.E.; Kirkpatrick, D.; Ives, J.L. *Synth. Commun.* ***1980****, 10*, 939; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* ***1980****, 45,* 3227; Ozawa, F.; Iri, K.; Yamamoto, A. *Chem. Lett.* ***1982***, 1707.
[728] Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* ***1985****, 26*, 6103.
[729] Fabre, C.; Hadj Ali Salem, M.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1975***, 178. See also, Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* ***1991****, 56*, 2920.

12.C.v. Electrophilic Substitution at Nitrogen

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:

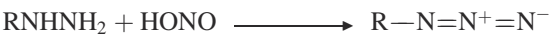


53

Further reaction of **53** depends on the nature of Y and of the other groups attached to the nitrogen.

12-49 The Conversion of Hydrazines to Azides

Hydrazine-azide transformation

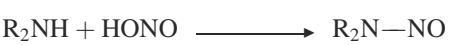


Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in Reaction **13-19**. Among other reagents used for this conversion have been N_2O_4[730] and nitrosyl tetrafluoroborate ($NOBF_4$).[731]

OS **III**, 710; **IV**, 819; **V**, 157.

12-50 N-Nitrosation

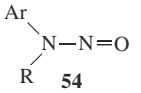
***N*-Nitroso-de-hydrogenation**



When secondary amines are treated with nitrous acid (typically formed from sodium nitrite and a mineral acid),[732] *N*-nitroso compounds (also called nitrosamines) are formed.[733] The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-*N*-substituted amides: $RCONHR' + HONO \rightarrow RCON(NO)R'$.[734] Tertiary amines have also been *N*-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[735] The group that cleaves appears as an aldehyde or ketone product. Other reagents have also been used (e.g., NOCl), which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the *N*-nitroso compounds are highly reactive. *N*-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3, N_2O_4,[736] or alkyl

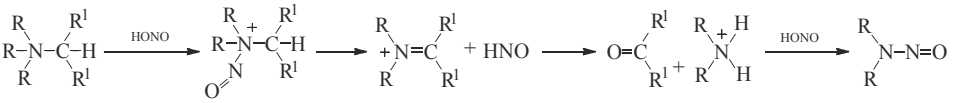
[730] Kim, Y.H.; Kim, K.; Shim, S.B. *Tetrahedron Lett.* ***1986****, 27*, 4749.
[731] Pozsgay, V.; Jennings, H.J. *Tetrahedron Lett.* ***1987****, 28,* 5091.
[732] See Zolfigol, M.A. *Synth. Commun.* ***1999****, 29,* 905; Zolfigol, M.A.; Ghaemi, E.; Madrikian, E.; Kiany-Burazjani, M. *Synth. Commun.* ***2000****, 30*, 2057.
[733] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Kostyukovskii, Ya.L.; Melamed, D.B. *Russ. Chem. Rev.* ***1988****, 57,* 350; Saavedra, J.E. *Org. Prep. Proced. Int.* ***1987****, 19,* 83; Challis, B.C.; Challis, J.A. in Patai, S.; Rappoport, Z. *The Chemistry of the Functional Groups Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1151–1223. Also see Zyranov, G.V.; Rudkevich, D.M. *Org. Lett.* ***2003****, 5*, 1253.
[734] Castro, A.; Iglesias, E.; Leis, J.R.; Peña, M.E.; Tato, J.V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1725.
[735] Hein, G.E. *J. Chem. Educ.* ***1963****, 40*, 181. See also, Verardo, G.; Giumanini, A.G.; Strazzolini, P. *Tetrahedron* ***1990****, 46,* 4303.
[736] Challis, B.C.; Kyrtopoulos, S.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 299.

nitrites,[737] and, in aqueous or organic solvents, by treatment with $BrCH_2NO_2$.[738] Secondary amines are converted to the *N*-nitroso compound with H_5IO_6 on wet silica.[739]



54

The mechanism of nitrosation is essentially the same as in Reaction **13-19** up to the point where **54** is formed. Since this species cannot lose a proton, it is stable and the reaction ends there. The attacking entity can be any of those mentioned in Reaction **13-19**. The following has been suggested as the mechanism for the reaction with tertiary amines:[740]

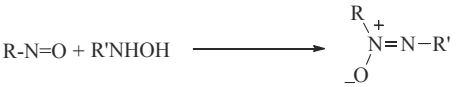


The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2HNO \rightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead and cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O[741] and with N_2O_4.[742]

Amines and amides can be *N*-nitrated[743] with nitric acid,[744] or NO_2^+,[745] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[746] *C*-Nitrosation is discussed at Reactions **11-3** and **12-8**.

OS **I**, 177, 399, 417; **II**, 163, 211, 290, 460, 461, 462, 464 (Also see, **V**, 842); **III**, 106, 244; **IV**, 718, 780, 943; **V**, 336, 650, 797, 839, 962; **VI**, 542, 981. Also see, OS **III**, 711.

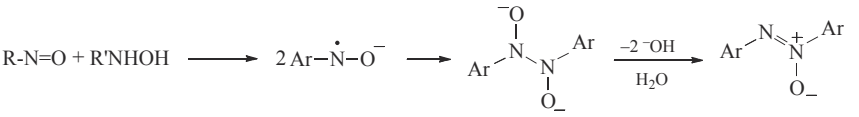
12-51 Conversion of Nitroso Compounds to Azoxy Compounds



In a reaction similar to **13-24**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[747] The position of the oxygen in the final product is

[737] Casado, J.; Castro, A.; Lorenzo, F.M.; Meijide, F. *Monatsh. Chem.* ***1986****, 117,* 335.
[738] Challis, B.C.; Yousaf, T.I. *J. Chem. Soc. Chem. Commun.* ***1990***, 1598.
[739] Zolfigol, M.A.; Choghamarani, A.G.; Shivini, F.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001****, 31,* 359. See Zolfigol, M.A.; Bagherzadeh, M.; Choghamarani, A.G.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001****, 31,* 1161.
[740] Gowenlock, B.G.; Hutchison, R.J.; Little, J.; Pfab, J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1110. See also, Loeppky, R.N.; Outram, J.R.; Tomasik, W.; Faulconer, J.M. *Tetrahedron Lett.* ***1983****, 24,* 4271.
[741] Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* ***1985***, 677.
[742] Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1751.
[743] See Bottaro, J.C.; Schmitt, R.J.; Bedford, C.D. *J. Org. Chem.* ***1987****, 52*, 2292; Suri, S.C.; Chapman, R.D. *Synthesis* ***1988***, 743; Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res. (S)* ***1989***, 260.
[744] Cherednichenko, L.V.; Dmitrieva, L.G.; Kuznetsov, L.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1976****, 12*, 2101, 2105.
[745] Andreev, S.A.; Lededev, B.A.; Tselinskii, I.V. *J. Org. Chem. USSR* ***1980****, 16*, 1166, 1170, 1175, 1179.
[746] See Vaughan, K.; Stevens, M.F.G. *Chem. Soc. Rev.* ***1978****, 7*, 377.
[747] Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.

determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R′ can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds (ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained[748] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction ($ArNO + Ar'NHOH \rightarrow Ar'NO + ArNHOH$).[749] The mechanism[750] has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



These radical anions have been detected by ESR.[751] This mechanism is consistent with the following result: When nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogen atoms and the two oxygen atoms become equivalent.[752] Unsymmetrical azoxy compounds can be prepared[753] by combination of a nitroso compound with an *N,N*-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents [$ArN(MgBr)_2$].[754]

12-52 N-Halogenation

N-Halo-de-hydrogenation

$$RNH_2 + NaOCl \longrightarrow RNHCl$$

Treatment with sodium hypochlorite or hypobromite converts primary amines into *N*-halo- or *N,N*-dihaloamines. Secondary amines can be converted to *N*-halo secondary amines. Similar reactions can be carried out on unsubstituted and *N*-substituted amides and on sulfonamides. With unsubstituted amides the *N*-halogen product is seldom isolated but usually rearranges (see Reaction **18-13**); however, *N*-halo-*N*-alkyl amides and *N*-halo imides are quite stable. The important reagents NBS and NCS are made in this manner. *N*-Halogenation has also been accomplished with other reagents (e.g., sodium bromite, $NaBrO_2$),[755] benzyltrimethylammonium tribromide ($PhCH_2NMe_3{}^+Br_3{}^-$),[756] NaCl with Oxone,[757] and NCS.[758] Sodium hypohalite in the presence of *tert*-butanol and acetic acid is

[748] See Ogata, Y.; Tsuchida, M.; Takagi, Y. *J. Am. Chem. Soc.* ***1957****, 79*, 3397.
[749] Knight, G.T.; Saville, B. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1550.
[750] For discussions of the mechanism in the absence of base, see Becker, A.R.; Sternson, L.A. *J. Org. Chem.* ***1980****, 45*, 1708. See also, Pizzolatti, M.G.; Yunes, R.A. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 759.
[751] Russell, G.A.; Geels, E.J.; Smentowski, F.J.; Chang, K.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* ***1967****, 89*, 3821.
[752] Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963****, 36,* 728.
[753] Zawalski, R.C.; Kovacic, P. *J. Org. Chem.* ***1979****, 44,* 2130. Also see Moriarty, R.M.; Hopkins, T.E.; Prakash, I.; Vaid, B.K.; Vaid, R.K. *Synth. Commun.* ***1990****, 20,* 2353.
[754] Okubo, M.; Matsuo, K.; Yamauchi, A. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 915, and other papers in this series.
[755] Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* ***1984***, 2045.
[756] Kajigaeshi, S.; Murakawa, K.; Asano, K.; Fujisaki, S.; Kakinami, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1702.
[757] Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O.; Tsadjout, A. *Synlett* ***2000***, 813.
[758] See Guillemin, J.; Denis, J.N. *Synthesis* ***1985***, 1131.

an efficient method for the preparation of *N*-haloamines.[759] Amides are *N*-chlorinated with trichloroisocyanuric acid.[760] The mechanisms of these reactions[761] involve attack by a positive halogen and are probably similar to those of Reactions **13-19** and **12-50**.[762] *N*-Fluorination can be accomplished by direct treatment of amines[763] or amides[764] with F_2. Fluorination of *N*-alkyl-*N*-fluoroamides [RRN(F)COR′] results in cleavage to *N,N*-difluoroamines (RNF_2).[764,765] Trichloroisocyanuric acid converts primary amines to the *N,N*-dichloroamine.[766]

OS **III**, 159; **IV**, 104, 157; **V**, 208, 663, 909; **VI**, 968; **VII**, 223; **VIII**, 167, 427.

12-53 The Reaction of Amines With Carbon Monoxide or Carbon Dioxide

***N*-Formylation** or ***N*-Formyl-de-hydrogenation**, and so on



Three types of product can be obtained from the reaction of amines with CO, depending on the catalyst. (1) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, Me_3N-H_2Se, and Rh or Ru complexes] to give *N*-substituted and *N,N*-disubstituted formamides, respectively.[767] Primary aromatic amines react with ammonium formate to give the formamide.[768] Tertiary amines react with CO and a Pd catalyst to give an amide.[769] (2) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO[770] in the presence of Se[771] or S.[772] The R source can be alkyl or aryl. The same thing can be done with secondary amines, using $Pd(OAc)_2$—I_2—K_2CO_3.[773] Primary aromatic amines react with β-keto esters and a Mo—ZrO_2 catalyst to give the symmetrical urea.[774] Treatment of a secondary amine with nitrobenzene, selenium and carbon monoxide leads to the unsymmetrical urea.[775] (3) When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[776] Isocyanates can also be obtained by treatment of CO with azides: $RN_3 + CO \rightarrow RNCO$,[777] or with an aromatic

[759] Zhong, Y.-L.; Zhou, H.; Gauthier, D.R.; Lee, J.; Askin, D.; Dolling, U.H.; Volante, R.P. *Tetrahedron Lett.* ***2005****, 46,* 1099.
[760] De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* ***2005***, 223.
[761] See Matte, D.; Solastiouk, B.; Merlin, A.; Deglise, X. *Can. J. Chem.* ***1989****, 67*, 786.
[762] See Thomm, E.W.C.W.; Wayman, M. *Can. J. Chem.* ***1969****, 47*, 3289; Higuchi, T.; Hussain, A.; Pitman, I.H. *J. Chem. Soc. B,* ***1969***, 626.
[763] Sharts, C.M. *J. Org. Chem.* ***1968****, 33*, 1008.
[764] Grakauskas, V.; Baum, K. *J. Org. Chem.* ***1969****, 34,* 2840; ***1970****, 35,* 1545.
[765] See Barton, D.H.R.; Hesse, R.H.; Klose, T.R.; Pechet, M.M. *J. Chem. Soc. Chem. Commun.* ***1975***, 97.
[766] DeLuca, L.; Giacomelli, G. *Synlett* ***2004***, 2180.
[767] See Bitsi, G.; Jenner, G. *J. Organomet. Chem.* ***1987****, 330*, 429.
[768] Reddy, P.G.; Kumar, .D.K.; Baskaran, S. *Tetrahedron Lett.* ***2000****, 41,* 9149.
[769] Troisi, L.; Granito, C.; Rosato, F.; Videtta, V. *Tetrahedron Lett.* ***2010****, 51*, 371; Wu, X.-F.; Neumann, H.; Beller, M. *Chemistry: Eur. J.* ***2010****, 16*, 9750.
[770] See Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* ***2004****, 69*, 4741.
[771] Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* ***1971****, 93*, 6344.
[772] Franz, R.A.; Applegath, F.; Morriss, F.V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* ***1961****, 26,* 3309.
[773] Pri-Bar, I.; Alper, H. *Can. J. Chem.* ***1990****, 68*, 1544.
[774] Reddy, B.M.; Reddy, V.R. *Synth. Commun.* ***1999****, 29*, 2789.
[775] Yang, Y.; Lu, S. *Tetrahedron Lett.* ***1999****, 40*, 4845.
[776] Stern, E.W.; Spector, M.L. *J. Org. Chem.* ***1966****, 31*, 596.
[777] Bennett, R.P.; Hardy, W.B. *J. Am. Chem. Soc.* ***1968****, 90,* 3295.

nitroso or nitro compound and a Rh complex catalyst.[778] Primary amines react with di-*tert*-butyltricarbonate to give the isocyanate.[779]

Lactams are converted to the corresponding *N*-chloro lactam with $Ca(OCl)_2$ with moist alumina in dichloromethane.[780] Ring-expanded lactams are obtained from cyclic amines via a similar reaction[781] (see also, Reaction **16-22**). Intramolecular carbonylation of amines also leads to lactams.[782]

A fourth type of product, a carbamate ($RNHCOOR'$), can be obtained from primary or secondary amines, if these are treated with CO, O_2, and an alcohol ($R'OH$) in the presence of a catalyst.[783] Primary amines react with dimethyl carbonate in supercritical CO_2 (see Sec. 9.D.ii) to give a carbamate.[784] Carbamates can also be obtained from nitroso compounds, by treatment with CO, $R'OH$, $Pd(OAc)_2$, and $Cu(OAc)_2$,[785] and from nitro compounds.[786] When allylic amines ($R_2C{=}CHRCHRNR'_2$) are treated with CO and a Pd–phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides ($R_2C{=}CHRCHRCONR'_2$) in good yields.[787] Silyloxy carbamates ($RNHCO_2SiR'_3$) can be prepared by the reaction of a primary amine with carbon dioxide and triethylamine, followed by reaction with triisopropylsilyl triflate and tetrabutylammonium fluoride.[788]

Carbon dioxide reacts with amines ($ArNH_2$) and alkyl halides, under electrolysis conditions, to give the corresponding carbamate ($ArNHCO_2Et$).[789] Secondary amines react with all halides and an onium salt in supercritical CO_2 (see Sec. 9.D.ii) to give the carbamate.[790] *N*-Phenylthioamines react with CO and a palladium catalyst to give a thiocarbamate ($ArSCO_2NR'_2$).[791] Urea derivatives were obtained from amines, CO_2, and an antimony catalyst.[792]

Aziridines can be converted to cyclic carbamates (oxazolidinones) by heating with carbon dioxide and a chromium–salen catalyst.[793] The reaction of aziridines with LiI, and then CO_2 also generates oxazolidinones.[794]

[778] Unverferth, K.; Tietz, H.; Schwetlick, K. *J. Prakt. Chem.* ***1985****, 327,* 932. See also, Kunin, A.J.; Noirot, M.D.; Gladfelter, W.L. *J. Am. Chem. Soc.* ***1989****, 111,* 2739.
[779] Peerlings, H.W.I.; Meijer, E.W. *Tetrahedron Lett.* ***1999****, 40*, 1021.
[780] Larionov, O.V.; Kozhushkov, S.I.; de Meijere, A. *Synthesis* ***2003***, 1916.
[781] Wang, M.D.; Alper, H. *J. Am. Chem. Soc.* ***1992****, 114*, 7018.
[782] Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* ***2005****, 127*, 14776.
[783] Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* ***2000****, 41*, 963.
[784] Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* ***2002****, 43*, 1217. Also see Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* ***2005****, 70,* 2771.
[785] Alper, H.; Vasapollo, G. *Tetrahedron Lett.* ***1987****, 28,* 6411.
[786] Cenini, S.; Crotti, C.; Pizzotti, M.; Porta, F. *J. Org. Chem.* ***1988****, 53,* 1243; Reddy, N.P.; Masdeu, A.M.; El Ali, B.; Alper, H. *J. Chem. Soc. Chem. Commun.* ***1994***, 863.
[787] Murahashi, S.; Imada, Y.; Nishimura, K. *J. Chem. Soc. Chem. Commun.* **1988**, 1578.
[788] Lipshutz, B.H.; Papa, P.; Keith, J.M. *J. Org. Chem.* ***1999****, 64, 3*792.
[789] Feroci, M.; Casadei, M.A.; Orsini, M.; Palombi, L.; Inesi, A. *J. Org. Chem.* ***2003****, 68*, 1548.
[790] Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* ***2000***, 151.
[791] Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* ***1999****, 64*, 7305.
[792] Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* ***1992****, 57*, 7339.
[793] Miller, A.W.; Nguyen, S.T. *Org. Lett.* ***2004****, 6*, 2301.
[794] Hancock, M.T.; Pinhas, A.R. *Tetrahedron Lett.* ***2003****, 44*, 5457.

CHAPTER 13

Aromatic Substitution: Nucleophilic and Organometallic

In Section 10.G, category 2, it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and these exceptions form the subject of this chapter.[1] Reactions that *are* successful at an aromatic substrate are largely of five kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (3) reactions initiated by electron donors; (4) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile; and (5) coupling reactions catalyzed by transition metals, primarily Pd,[2] Cu, Ni, and so on. Note that solvent effects can be important.[3] The transition metal catalyzed coupling reactions are included because they involve replacement of a leaving group on an aromatic ring.

13.A. MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.[4] Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

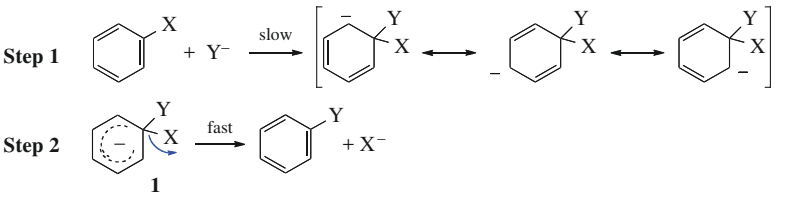
13.A.i. The S_NAr Mechanism[5]

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps, attack of the nucleophilic species at the ipso carbon of the aromatic ring

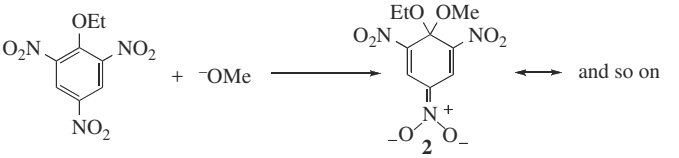
[1] See Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59,* 33.
[2] See Fairlamb, I.J.S. *Tetrahedron* ***2005***, *61*, 9661.
[3] Acevedo, O.; Jorgensen, W.L. *Org. Lett.* ***2004***, *6*, 2881.
[4] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***. For reviews, see Bernasconi, C.F. *Chimia* ***1980***, *34*, 1; *Acc. Chem. Res.* ***1978***, *11,* 147; Bunnett, J.F. *J. Chem. Educ.* ***1974***, *51*, 312; Ross, S.D. in Bamford, C. H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 407–431; Buck, P. *Angew. Chem, Int. Ed.* ***1969***, *8,* 120; Buncel, E.; Norris, A.R.; Russell, K.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 123; Bunnett, J. F. *Tetrahedron* ***1993***, *49*, 4477; Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59,* 33.
[5] See Barrett, I.C.; Kerr, M.A. *Tetrahedron Lett.* ***1999***, *40*, 2439.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

(the carbon bearing the leaving group in this case), followed by elimination of the leaving group and regeneration of the aromatic ring.



The first step is usually, but not always, rate determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 16 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution discussed in Chapter 11. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate (e.g., **1**) and then the leaving group departs: This mechanism is the S_NAr mechanism.[6] The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; cf. the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see Sec. 13.B.i).



There is a great deal of evidence for the mechanism.[4] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between 2,4,6-trinitrophenetole and methoxide ion.[7] Intermediates of this type are stable salts, called *Meisenheimer* or *Meisenheimer–Jackson salts*,[8] and many more have been isolated.[9] The structures of several of these intermediates have been proved by NMR[10] and by X-ray crystallography.[11] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the Ar—X bond would be broken in the rate-determining step. In the S_NAr mechanism, this bond is not broken until after the rate-determining step (i.e., if step 1 is rate

[6] Also see Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* ***2004***, *126*, 10632; Terrier, F.; Mokhtari, M.; Goumont, T.; Hallé, J.-C.; Buncel, E. *Org. Biomol. Chem.* ***2003***, *1,* 1757.

[7] Meisenheimer, J. *Liebigs Ann. Chem.* ***1902***, *323,* 205; Jackson, C.L.; see Jackson, C.L.; Gazzolo, F.H. *Am. Chem. J.* ***1900***, *23*, 376; Jackson, C.L.; Earle, R.B. *Am. Chem. J.,* ***1903***, *29*, 89.

[8] For heteroatom nucleophiles see Gallardo, I.; Guirado, G.; Marquet, J. *J. Org. Chem.* ***2002***, *67,* 2548.

[9] See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***; Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* ***1983***, *34,* 305; Terrier, F. *Chem. Rev.* ***1982***, *82*, 77; Strauss, M.J. *Acc. Chem. Res.* ***1974***, *7*, 181; Hall, T.N.; Poranski, Jr., C.F. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 329–384; Foster, R.; Fyfe, C.A. *Rev. Pure Appl. Chem.* ***1966***, *16,* 61.

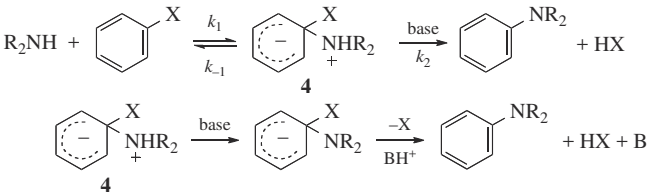
[10] Crampton, M.R.; Gold, V. *J. Chem. Soc. B* ***1966***, 893. See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***, pp. 15–133.

[11] Destro, R.; Gramaccioli, C.M.; Simonetta, M. *Acta Crystallogr.* ***1968***, *24,* 1369; Ueda, H.; Sakabe, M.; Tanaka, J.; Furusaki, A. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2866; Messmer, G.G.; Palenik, G.J. *Chem. Commun.* ***1969***, 470.

determining). There is some evidence that electron transfer may be operative during this process.[12] If the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compound **3** with piperidine, when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of ~5.[13] This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. The rates are not expected to be *identical*, because the nature of X affects the rate at which Y attacks.[14] An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (Sec. 10.F).



The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. Bases only catalyze these reactions when a relatively poor leaving group (e.g., OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[15] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily, but X does not, so that k_1 is large and step 2 is rate determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low-base concentrations: A plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see Sec. 11.A.i), is also evidence for the S_NAr mechanism. At low-base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high-base concentration, the process is virtually complete: There is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents, two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **4** followed by

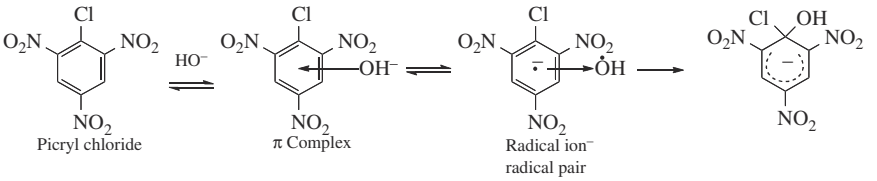


[12] Grossi, L. *Tetrahedron Lett.* ***1992***, *33*, 5645.
[13] Bunnett, J.F.; Garbisch, Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385. See Gandler, J.R.; Setiarahardjo, I.U.; Tufon, C.; Chen, C. *J. Org. Chem.* ***1992***, *57*, 4169.
[14] See Fernndez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* ***2010***, *75*, 2971.
[15] Chiacchiera, S.M.; Singh, J.O.; Anunziata, J.D.; Silber, J.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 987.

rapid loss of X, and that bases catalyze the reaction by increasing the rate of the deprotonation step.[16] According to the other proposal, loss of X assisted by BH^+ is rate determining.[17] Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents (e.g., benzene). In both proposals, the ordinary S_NAr mechanism operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),[18] while in the other there is a cyclic transition state.[19] Further evidence for the S_NAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[20]

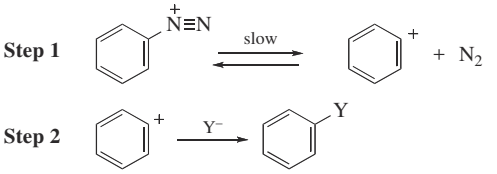
Step 1 of the S_NAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and ^-OH ions (Reaction **13-1**), and spectral evidence has been reported[21] for two intermediates, one a π complex (Sec. 11.A.i), and the other a radical ion–radical pair.

As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (Sec. 16.A.i) has been demonstrated with an aryl substrate, in certain cases.[22] There is also evidence of an interaction of anions with the π-cloud of aromatic compounds.[23]



13.A.ii. The S_N1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular S_N1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (*tert*-butyl or SiR_3).[24] It is in reactions with diazonium salts[25] that this mechanism is important[26]:



[16] Bernasconi, C.F.; de Rossi, R.H.; Schmid, P. *J. Am. Chem. Soc.* ***1977***, *99*, 4090.
[17] Bunnett, J.F.; Sekiguchi, S.; Smith, L.A. *J. Am. Chem. Soc.* ***1981***, *103*, 4865.
[18] See Nudelman, N.S. *J. Phys. Org. Chem.* ***1989***, *2*, 1. See also, Nudelman, N.S.; Montserrat, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1073.
[19] Jain, A.K.; Gupta, V.K.; Kumar, A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 11.
[20] Ayrey, G.; Wylie, W.A. *J. Chem. Soc. B* ***1970***, 738.
[21] Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* ***1991***, *113*, 238; Crampton, M.R.; Davis, A.B.; Greenhalgh, C.; Stevens, J.A. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 675.
[22] See Muscio, Jr., O.J.; Rutherford, D.R. *J. Org. Chem.* ***1987***, *52,* 5194.
[23] Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà. P.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3389.
[24] Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* ***1985***, *107,* 5286.
[25] See Glaser, R.; Horan, C.J.; Nelson, E.D.; Hall, M.K. *J. Org. Chem.* ***1992***, *57*, 215.
[26] Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free radical mechanism).

Among the evidence for the S_N1 mechanism[27] with aryl cations as intermediates,[28,29] is the following:[30]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide, but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[31]
4. When reactions were run with substrate deuterated in the ortho position, isotope effects of ~1.22 were obtained.[32] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation (see Sec. 2.M),[33] which is diminished when hydrogen is replaced by deuterium.



5. That the first step is reversible cleavage[34] was demonstrated by the observation that when $Ar^{15}N^+ \equiv N$ was the reaction species, recovered starting material contained not only $Ar^{15}N^+ \equiv N$, but also $Ar^{15}N^+ \equiv N$.[35,36] This could arise only if the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $PhN^+ \equiv N^{15}N$ with unlabeled N_2 at various pressures. At 300 atm, the recovered product had lost ~3% of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2.[36]

There is kinetic and other evidence[37] that step 1 is more complicated and involves two steps, both reversible:

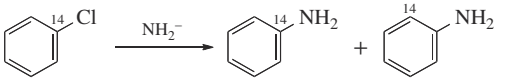
$$ArN_2^+ \rightleftharpoons \underset{\mathbf{5}}{[Ar^+N_2]} \rightleftharpoons Ar^+ + N_2$$

[27] Also see Lorand, J.P. *Tetrahedron Lett.* ***1989***, *30,* 7337.
[28] See Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353.
[29] Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. See Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819; Rappoport, Z. *Reactiv. Intermed. (Plenum)* ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271; Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64,* 902.
[30] See Zollinger, H. *Angew. Chem, Int. Ed.* ***1978***, *17,* 141; Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97,* 783, 796; Burri, P.; Wahl, Jr., G.H.; Zollinger, H. *Helv. Chim. Acta* ***1974***, *57*, 2099; Richey, Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 922–931; Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 29–40.
[31] Lewis, E.S.; Miller, E.B. *J. Am. Chem. Soc.* ***1953***, *75,* 429.
[32] Swain, C.G.; Sheats, J.E.; Gorenstein, D.G.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 791.
[33] See Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1985***, *107,* 5285.
[34] See Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* Vol. 5, Elsevier, Amsterdam, The Netherlands, ***1980***, pp. 147, 212; Zollinger, H. *Pure Appl. Chem.* ***1983***, *55,* 401.
[35] Lewis, E.S.; Kotcher, P.G. *Tetrahedron* ***1969***, *25*, 4873; Lewis, E.S.; Holliday, R.E. *J. Am. Chem. Soc.* ***1969***, *91,* 426; Tröndlin, F.; Medina, R.; Rüchardt, C. *Chem. Ber.* ***1979***, *112,* 1835.
[36] Bergstrom, R.G.; Landell, R.G.M.; Wahl, Jr., G.H.; Zollinger, H. *J. Am. Chem. Soc.* ***1976***, *98*, 3301.
[37] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64,* 2728.

Intermediate **5**, which is probably some kind of a tight ion–molecule pair, has been trapped with carbon monoxide.[38]

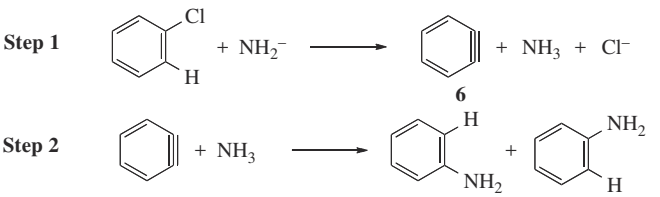
13.A.iii. The Benzyne Mechanism[39]

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur with aryl halides that have no activating groups; stronger bases are required than those normally used; and the incoming group does not always take the position vacated by the leaving group. The validity of the latter statement was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 and 2 positions.[40]

A mechanism that can explain all these facts involves elimination followed by addition. In step 1, a suitable base removes the ortho hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to



generate symmetrical intermediate **6**[41] called benzyne[42] (see below).[43] In step 2, benzyne is attacked by the NH_3 at either of two positions, which explains why about one-half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism follows:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[38]

[38] Ravenscroft, M.D.; Skrabal, P.; Weiss, B.; Zollinger, H. *Helv. Chim. Acta* ***1988***, *71,* 515.

[39] See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***; Gilchrist, T.L. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 383–419; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183; Levin, R.H. *React. Intermed. (Wiley)* ***1985***, *3*, 1; Fields, E.K. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 449–508.

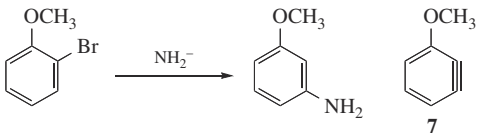
[40] Roberts, J.D.; Semenow, D.A.; Simmons, H.E.; Carlsmith, L.A. *J. Am. Chem. Soc.* ***1965***, *78,* 601.

[41] See Hess, Jr., B.A. *Eur. J. Org. Chem.* ***2001***, 2185.

[42] Wentrup, C. *Austr. J. Chem.* ***2010***, *63,* 979.

[43] See Kitamura, T.; Meng, Z.; Fujiwara, Y. *Tetrahedron Lett.* ***2000***, *41,* 6611; Kawabata, H.; Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43,* 4911. Microwave spectroscopy can be used to detect benzynes: see Godfrey, P.D. *Austr. J. Chem.* ***2010***, *63,* 1061.

2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*[44] and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[45] In this particular case, only the meta isomer is formed. The reason a 1:1 mixture is not formed is that the intermediate **7** is not symmetrical and the methoxy group directs the incoming group meta, but not ortho (see Sec. 13.B.i). However, not all cine substitutions proceed by this kind of mechanism (see Reaction **13-30**). A study of the influence of structure on the formation of substituted benzynes, along with rate studies, has been reported.[46]



7

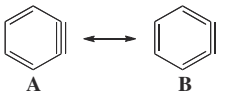
3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH_2 in liquid NH_3) shows that the S_NAr mechanism is not operating here.[40]

In the conversion of the substrate to **7**, either proton removal or subsequent loss of halide ion can be rate determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C—X bond is rate determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with $^-NH_2$.[47] In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.[47,48]

Species, such as **6** and **7**, are called *benzynes* (sometimes *dehydrobenzenes*), or more generally, *arynes*.[49] The mechanism in which such species are intermediates is known as the *benzyne mechanism*. Benzynes are very reactive, and neither benzyne nor any other aryne has yet been isolated under ordinary conditions,[50] but benzyne has been isolated in an Ar matrix at 8 K,[51] and its IR spectrum is observed. In addition, benzynes can be trapped (e.g., they undergo the *Diels–Alder reaction*, See Reaction **15-60**). Note that the extra pair of electrons does not affect the aromaticity. However, evaluation by a series of aromaticity indicators, including magnetic susceptibility anisotropies and exaltations,

[44] See Suwinski, J.; Swierczek, K. *Tetrahedron* ***2001***, *57*, 1639.
[45] See Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* ***1945***, *67,* 349. For a table of many such examples, see Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 385.
[46] Riggs, J.C.; Ramirez, A.; Cremeens, M.E.; Bashore, C.G.; Candler, J.; Wirtz, M.C.; Coe, J.C.; Collum, D.B. *J. Am. Chem. Soc.* ***2008,*** *130,* 3406.
[47] Bunnett, J.F.; Kearley, Jr., F.J. *J. Org. Chem.* ***1971***, *36*, 184.
[48] See Kalendra, D.M.; Sickles, B.R. *J. Org. Chem.* ***2003***, *68*, 1594.
[49] See Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.
[50] See Gaviña, F.; Luis, S.V.; Costero, A.M.; Gil, P. *Tetrahedron* ***1986***, *42*, 155.
[51] Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* ***1973***, *95*, 6134. For the IR spectrum of pyridyne trapped in a matrix, see Nam, H.; Leroi, G.E. *J. Am. Chem. Soc.* ***1988***, *110,* 4096. See Brown, R.D.; Godfrey, P.D.; Rodler, M. *J. Am. Chem. Soc.* ***1986***, *108*, 1296.

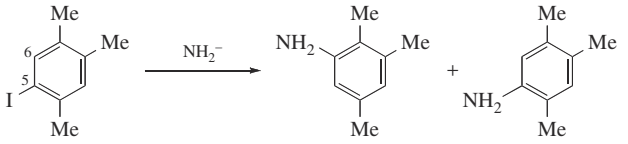
nucleus-independent chemical shifts (NICS), aromatic stabilization energies, and valence bond Pauling resonance energies point to the *o*-benzyne > *m*-benzyne > *p*-benzyne aromaticity order.[52] The relative order with respect to benzene depends on the aromaticity criterion.[48] Note that tunable reactivity for *m*-benzynes has been demonstrated.[53] The aromatic sextet from the aromatic precursor functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The Ir spectrum, mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings, but also other aromatic rings[54] and even non-aromatic rings (Sec. 10.F) can react through this kind of intermediate. Of course, the non-aromatic rings do have a formal triple bond. When a benzyne unit is fused to a small ring, strain induced regioselectivity was observed in its reactions.[55]



A **B**

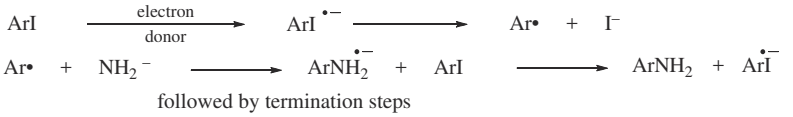
13.A.iv. The $S_{RN}1$ Mechanism

When 5-iodo-1,2,4-trimethylbenzene (**8**) was treated with KNH_2 in NH_3, **9** and **10** were formed in the ratio 0.63:1. The presence of an unactivated substrate, a strong base, and the occurrence of cine substitution along with normal substitution are strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **8** should have given **9** and **10** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **9** to **10** was 5.9:1 (the chloro and bromo analogues did give the same ratio (1.46:1), showing that the benzyne mechanism may be taking place there).



8 **9** **10**

To explain the iodo result, it has been proposed[56] that in addition to the benzyne mechanism, a free radical mechanism is also operating here:



[52] DeProft, F.; Schleyer, P.v.R.; van Lenthe, J.H.; Stahl, F.; Geerlings, P. *Chem. Eur. J.* ***2002***, *8*, 3402.
[53] Nash, J.J.; Nizzi, K.E.; Adeuya, A.; Yurkovich, M.J.; Cramer, C.J.; Kenttämaa, H.I. *J. Am. Chem. Soc.* ***2005***, *127,* 5760.
[54] For reviews of *hetarynes*, see van der Plas, H.C.; Roeterdink, F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 421–511; Reinecke, M.G. *Tetrahedron* ***1982***, *38*, 427; den Hertog, H.J.; van der Plas, H.C. *Adv. Heterocycl. Chem.* ***1971***, *40*, 121; Kauffmann, T.; Wirthwein, R. *Angew. Chem, Int. Ed.* ***1971***, *10*, 20.
[55] Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* ***2003***, *5*, 3551.
[56] Kim, J.K.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1970***, *92*, 7463, 7464.

This is called the $S_{RN}1$ mechanism,[57] and many other examples are known (see Reactions **13-3**, **13-4**, **13-6**, and **13-14**). The IUPAC designation is $T + D_N + A_N$.[58] Note that the last step of the mechanism produces $ArI^{\bullet -}$ radical ions, so the process is a chain mechanism[59] (see Sec. 14.A.i). An electron donor is required to initiate the reaction. In the case above, it was solvated electrons from KNH_2 in NH_3. Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution. Further evidence for the $S_{RN}1$ mechanism was that addition of radical scavengers, which would suppress a free radical mechanism, led to **9:10** ratios much closer to 1.46:1. Numerous other observations of $S_{RN}1$ mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.[60] Further evidence for the $S_{RN}1$ mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by $Ar^{\bullet}$ of H from the solvent NH_3. Besides initiation by solvated electrons,[61] $S_{RN}1$ reactions have been initiated photochemically,[62] electrochemically,[63] and even thermally.[64]

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product.[65] There is no requirement for activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases.[66] The reaction has also been done in liquid ammonia, promoted by ultrasound (Sec. 7.B),[67] and ferrous ion has been used as a catalyst.[68] Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N, O^-, and NO_2 groups do interfere. Cine substitution is not found.

13.A.v. Other Mechanisms

There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. A "clean" example of a $S_{RN}2$ reaction has been reported, the

[57] See Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society, Washington, ***1983***; Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Norris, R.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D,* pt. 1, Wiley, NY, ***1983***, pp. 681–701; Chanon, M.; Tobe, M.L. *Angew. Chem, Int. Ed.* ***1982***, *21,* 1; Rossi, R.A. *Acc. Chem. Res.* ***1982***, *15,* 164. Also see Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 193; Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* ***1999***, *121*, 4451.

[58] The symbol T is used for electron transfer.

[59] See Amatore, C.; Pinson, J.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1981***, *103*, 6930.

[60] Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413.

[61] Savéant, J.-M. *Tetrahedron* ***1994***, *50*, 10117.

[62] See Cornelisse, J.; de Gunst, G.P.; Havinga, E. *Adv. Phys. Org. Chem.* ***1975***, *11*, 225; Cornelisse, J. *Pure Appl. Chem.* ***1975***, *41*, 433; Pietra, F. *Q. Rev. Chem. Soc.* ***1969***, *23*, 504, p. 519.

[63] See Savéant, J. *Acc. Chem. Res.* ***1980***, *13*, 323. See also, Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J.N. *J. Org. Chem.* ***1990***, *55*, 6347.

[64] Swartz, J.E.; Bunnett, J.F. *J. Org. Chem.* ***1979***, *44,* 340, and references cited therein.

[65] Galli, C.; Gentili, P.; Guarnieri, A. *Gazz. Chim. Ital.,* ***1995***, *125*, 409.

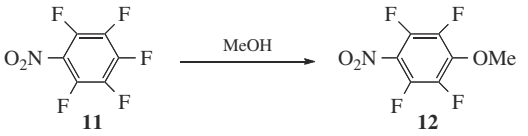
[66] Borosky, G.L.; Pierini, A.B.; Rossi, R.A. *J. Org. Chem.* ***1992***, *57*, 247.

[67] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.

[68] Galli, C.; Gentili, P. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1135.

conversion of **11** to **12** in methanol.[69] Both $S_{RN}1$ and $S_{RN}2$ reactions have been reviewed.[70]

Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see Reaction **13-17**). A new mechanism has been reported in aromatic chemistry, a reductively activated "polar" nucleophilic aromatic substitution.[71] The reaction of phenoxide with *p*-dinitrobenzene in DMF shows radical features that cannot be attributed to a radical anion, and it is not $S_{RN}2$. The new designation was proposed to account for these results.



11 **12**

13.B. REACTIVITY

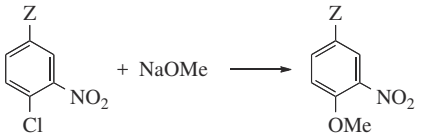
13.B.i. The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11), equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogen atoms that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

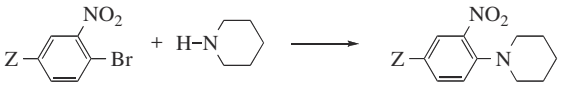
S_NAr Mechanism. These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group[72] and hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Section 11.A.i. When attached to a benzene ring, the rate of reaction depends on the substituent.[73] Activating groups include 2-nitro,[74,75] N_2^+, NO, or C=N units with stong nucleophiles and when a nitro group is attached to SO_2Me, NMe_3 CF_3 CN, CHO, COR CO_2H, SO_3, halogen, H, Me, or OMe activate.[73] Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.[73–76] Nitrogen

[69] Marquet, J.; Jiang, Z.; Gallardo, I.; Batlle, A.; Cayón, E. *Tetrahedron Lett.* ***1993***, *34*, 2801. Also see, Keegstra, M.A. *Tetrahedron* ***1992***, *48*, 2681.
[70] Rossi, R.A.; Palacios, S.M. *Tetrahedron* ***1993***, *49*, 4485.
[71] Marquet, J.; Casado, F.; Cervera, M.; Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* ***1995***, *67*, 703.
[72] With meta substituents, electron-withdrawing groups also increase the rate: See Nurgatin, V.V.; Sharnin, G.P.; Ginzburg, B.M. *J. Org. Chem*, *USSR* ***1983***, *19,* 343.
[73] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 61–136.
[74] For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, G. *Adv. Heterocycl. Chem.* ***1964***, *3*, 285; Shepherd, R.G.; Fedrick, J.L. *Adv. Heterocycl. Chem.* ***1965***, *4,* 145.
[75] See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 142–180; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 258–319, 550–553.
[76] Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951*** , *49*, 273, pp. 308.

TABLE 13.1 Groups Listed in Approximate Descending Order of Activating Ability in the SNAr Mechanism[73]



at 0 °C[74] *(a)*[a]



at 25 °C[75] *(b)*[b]

Comments[b]	Group Z	Relative Rate of Reaction *(a)* H = 1[73]	*(b)* $NH_2 = 1$[78]
Activates halide exchange at room temperature	N_2^+		
Activates reaction with strong nucleophiles at room temperature	 (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100 °C	NO	5.22×10^6	
	NO_2	6.73×10^5	Very fast
	 (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO_2Me		
	NMe_3^+		
	CF_3		
	CN	3.81×10^4	
	CHO	2.02×10^4	
With nitro also present, activate reactions with strong nucleophiles at 40–60 °C	COR		
	COOH		
	SO_3^-		
	Br		6.31×10^4
	Cl		4.50×10^4
	I		4.36×10^4
	COO^-		2.02×10^4
	H		8.06×10^3
	F		2.10×10^3
	CMe_3		1.37×10^3
	Me		1.17×10^3
	OMe		145
	NMe_2		9.77
	OH		4.70
	NH_2		1

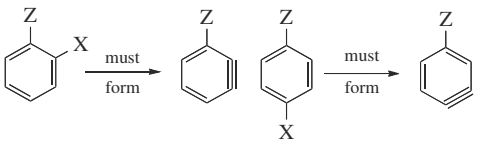
[a]For reaction (a) the rates are relative to **H**; for (b) they are relative to NH_2.

[b]The comments on the left are from Bunnett and Zahler.[76]

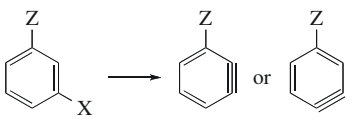
atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.[77] Both 2- and 4-chloropyridine, for example, are often used as substrates. Heteroaromatic amine *N*-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[78] The most highly activating group (N_2^+) is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound (e.g., *p*-nitroaniline or *p*-chloroaniline), the group para to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+ X^{-\bullet}$ untouched. By far, the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[79] Polyfluorobenzenes[80] (see **11**) also undergo aromatic nucleophilic substitution quite well.[81] Benzene rings that lack activating substituents are generally not useful substrates for the S_NAr mechanism, because the two extra electrons in **1** are in an antibonding orbital (Sec. 2.A). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the transition states leading to them. Reactions taking place by the S_NAr mechanism are also accelerated when the aromatic ring is coordinated with a transition metal.[82]

Just as electrophilic aromatic substitutions were found more or less to follow the *Hammett relationship* (with σ^+ instead of σ; see Sec. 9.C) so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.[83]

Benzyne Mechanism. Two factors affect the position of the incoming group, the first being the direction in which the aryne forms.[84] When there are groups ortho or para to the leaving group, there is no choice:

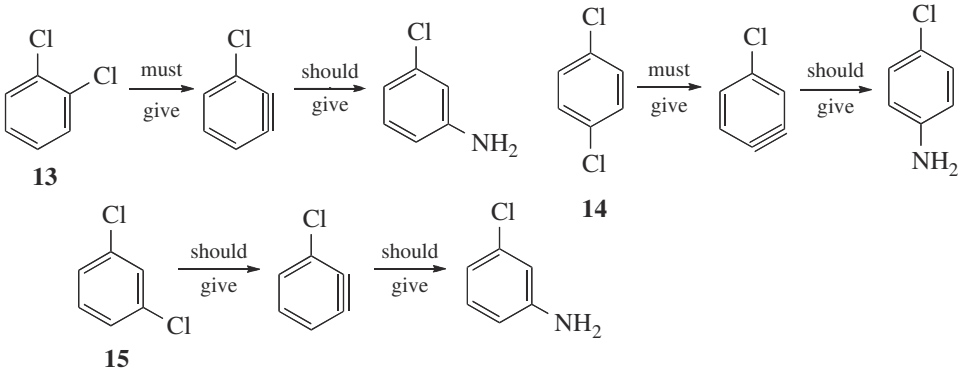


but when a meta group is present, the aryne can form in two different ways:



[77] Miller, J.; Parker, A.J. *Aust. J. Chem.* ***1958***, *11,* 302.
[78] Berliner, E.; Monack, L.C. *J. Am. Chem. Soc.* ***1952***, *74,* 1574.
[79] See de Boer, T.J.; Dirkx, I.P. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1970***, pp. 487–612.
[80] Fluorine significantly activates ortho and meta positions, and slightly deactivates para positions (see Table 13.1): See Chambers, R.D.; Seabury, N.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 255.
[81] See Yakobson, G.G.; Vlasov, V.M. *Synthesis* ***1976***, 652; Kobrina, L.S. *Fluorine Chem. Rev.* ***1974***, *7,* 1.
[82] See Balas, L.; Jhurry, D.; Latxague, L.; Grelier, S.; Morel, Y.; Hamdani, M.; Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* ***1990***, 401.
[83] See Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* ***1977***, *10,* 125; a list of σ^- values in Table 9.4.
[84] From Roberts, J.D.; Vaughan, C.W.; Carlsmith, L.A.; Semenow, D.A. *J. Am. Chem. Soc.* ***1956***, *78,* 611. See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 134–150.

In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate. This in turn also depends on the field effect of Z. For -*I* groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes (**13-15**) with alkali metal amides to give the predicted products shown. In each case, the predicted product was the one chiefly formed.[85] The observation that *m*-aminoanisole is obtained, mentioned in Section 13.A.iii, is also in accord with these predictions.



13.B.ii. The Effect of the Leaving Group[86]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R[87], and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[88] An approximate order of leaving-group ability is[89] $F > NO_2 > OTs > SOPh > Cl,\ Br,\ I > N_3 > NR_3^+ > OAr,\ OR,\ SR,\ NH_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, one methoxy group is replaced in preference to five chlorines.[90] As usual, OH can be a leaving group if it is converted to an

[85] Wotiz, J.H.; Huba, F. *J. Org. Chem.* ***1959***, *24,* 595. See also, Biehl, E.R.; Razzuk, A.; Jovanovic, M.V.; Khanapure, S.P. *J. Org. Chem.* ***1986***, *51,* 5157.
[86] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 137–179.
[87] See Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1839.
[88] See Beck, J.R. *Tetrahedron* ***1978***, *34,* 2057. See also, Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* ***1991***, *24,* 163.
[89] Loudon, J.D.; Shulman, N. *J. Chem. Soc.* ***1941***, 772; Suhr, H. *Chem. Ber.* ***1963***, *97,* 3268.
[90] Kobrina, L.S.; Yakobson, G.G. *J. Gen. Chem. USSR* ***1963***, *33,* 3238.

inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually Cl > Br > I, but not always.[91] The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the benzyne mechanism is operating. The four halogens, as well as SPh, NMe_3^+, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.[60] The only important leaving group in the S_N1 mechanism is N_2^+.

13.B.iii. The Effect of the Attacking Nucleophile[92]

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > {}^-OH > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[93] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions (e.g., ^-OH), a stronger base than ArO^-, is a poorer nucleophile.[94] In a series of similar nucleophiles (e.g., substituted anilines), nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the *von Richter* (**13-30**) and *Rosenmund–von Braun* (**13-8**) reactions, which are special cases. Studies on the nature of the nucleophile continue. Indeed, the second-order rate constants for vicarious nucleophilic substitution reactions of some carbanions were measured to define electrophilicity parameters for electron-deficient heteroarenes.[95]

13.C. REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

[91] Reinheimer, J.D.; Taylor, R.C.; Rohrbaugh, P.E. *J. Am. Chem. Soc.* ***1961***, *83*, 835; Ross, S.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2113; Litvinenko, L.M.; Shpan'ko, L.V.; Korostylev, A.P. *Doklad. Chem.* ***1982***, *266,* 309.

[92] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 180–233.

[93] From Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 340; Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72,* 294, p. 311; Bunnett, J.F. *Annu. Rev. Phys. Chem.* ***1963***, *14*, 271.

[94] See Amatore, C.; Combellas, C.; Robveille, S.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4754, and references cited therein.

[95] Seeliger, F.; Błażej, S.; Bernhardt, S.; Mąkosza, M.; Mayr, H. *Chemistry: European J.* ***2008***, *14,* 6108.

13.C.i. All Leaving Groups Except Hydrogen and N_2^+

A. Oxygen Nucleophiles

13-1 Hydroxylation of Aromatic Compounds

Hydroxy-de-halogenation

$$ArBr + {}^{-}OH \rightarrow ArOH$$

Direct hydroxylation of aryl halides to give phenols generally requires the presence of activating groups or exceedingly strenuous reaction conditions.[96] When the reaction is carried out at high temperatures, cine substitution is observed, indicating a benzyne mechanism.[97] However, phenols are prepared from aryl halides using KOH and a Pd catalyst at 100 °C.[98] Formation of phenols is possible using $AgNO_3$ with microwave irradiation,[99] or CuI.[100] There is a hydrogen peroxide promoted hydroxylation of aryl halides with metal hydroxide salts.[101] Other microwave-promoted phenol-forming reactions are known.[102]

A slightly related reaction involves the amino group of naphthylamines where can be replaced by a hydroxyl group after treatment with aq bisulfite.[103] The scope is greatly limited; the amino group, with very few exceptions may be NH_2 or NHR and must be on a naphthalene ring. The reaction is reversible (see **13-6**), and both the forward and reverse reactions are called the *Bucherer reaction*.

$$ArMgX \xrightarrow{B(OMe)_3} ArB(OMe)_2 \xrightarrow[H_2O_2]{H^+} ArOH$$

An indirect method for conversion of an aryl halide to a phenol involves initial conversion to an organometallic, followed by oxidation to the phenol. For the conversion of aryl *Grignard reagents* to phenols, a good procedure is the use of trimethyl borate followed by oxidation with H_2O_2 in acetic acid[104] (see Reaction **12-31**). Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal (e.g., lithium), followed by oxidation with alkaline H_2O_2.[105] Arylboronic acids [$ArB(OH)_2$] are oxidized by aq H_2O_2 to give the corresponding phenol.[106] The reaction of an aromatic compound

[96] See Fyfe, C.A. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 83–124.
[97] This benzyne mechanism is also supported by ^{14}C labeling experiments: Bottini, A.T.; Roberts, J.D. *J. Am. Chem. Soc.* ***1957***, *79*, 1458; Dalman, G.W.; Neumann, F.W. *J. Am. Chem. Soc.* ***1968***, *90,* 1601.
[98] Anderson, K.W.; Ikawa, T.; Tundel, R.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2006***, *128,* 10694. Also see Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 918; Sergeev, A.G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 7595.
[99] Hashemi, M.M.; Akhbari, M. *Synth. Commun.* ***2004***, *34*, 2783.
[100] Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* ***2010***, 976. See also Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* ***2010***, 4767.
[101] Cantrell, Jr., W.R.; Bauta, W.E.; Engles, T. *Tetrahedron Lett.* ***2006***, *47,* 4249.
[102] Kormos, C.M.; Leadbeater, N.E. *Tetrahedron* ***2006***, *62*, 4728.
[103] See Seeboth, H. *Angew. Chem, Int. Ed.* ***1967***, *6,* 307; Gilbert, E.E. *Sulfonation and Related Reactions*; Wiley, NY, ***1965***, pp. 166–169.
[104] Hawthorne, M.F. *J. Org. Chem.* ***1957***, *22*, 1001. For other procedures, see Lewis, N.J.; Gabhe, S.Y. *Aust. J. Chem.* ***1978***, *31*, 2091; Hoffmann, R.W.; Ditrich, K. *Synthesis* ***1983***, 107.
[105] Pickles, G.M.; Thorpe, F.G. *J. Organomet. Chem.* ***1974***, *76*, C23.
[106] Simon, J.; Salzbrunn, S.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 633. Also see Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* ***2010***, *12,* 1964.

with a borane in the presence of an Ir catalyst, followed by oxidation with aq Oxone, gave the corresponding phenol.[107] Aryllithium reagents have been converted to phenols by treatment with oxygen.[108] In a related indirect method, arylthallium bis(trifluoroacetates) (prepared by Reaction **12-23**) can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine, and then dilute NaOH.[109] Diarylthallium trifluoroacetates undergo the same reaction.[110]

OS **I**, 455; **II**, 451; **V**, 632. Also see, OS **V**, 918.

13-2 Alkali Fusion of Sulfonate Salts

Oxido-de-sulfonato-substitution

$$ArSO_3^- \xrightarrow[300-320\ ^\circ C]{\text{NaOH fusion}} ArO^-$$

Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is not clear, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[111]

OS **I**, 175; **III**, 288.

13-3 Replacement by OR or OAr

Alkoxy-de-halogenation

$$ArBr + RO^- \longrightarrow ArOR$$

This reaction is similar to **13-1** and, like that one, generally requires activated substrates.[96,112] With unactivated substrates, side reactions predominate, although aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.[113] This reaction gives better yields than **13-1** and is used more often. A good solvent is liquid ammonia. Aryl chlorides react with phenol and KOH with microwave irradiation to give the diaryl ether.[114] Potassium phenoxide reacts with iodobenzene in an ionic solvent at 100 °C with CuCl.[115] Sodium methoxide reacted with *o*- and *p*-fluoronitrobenzenes $\sim 10^9$ times faster in NH_3 at −70 °C than in MeOH.[116] Phase-transfer catalysis

[107] Maleczka, Jr., R.E.; Shi, F.; Holmes, D.; Smith III, M.R. *J. Am. Chem. Soc.* ***2003***, *125*, 7792.
[108] Parker, K.A.; Koziski, K.A. *J. Org. Chem.* ***1987***, *52*, 674. See Taddei, M.; Ricci, A. *Synthesis* ***1986***, 633; Einhorn, J.; Luche, J.; Demerseman, P. *J. Chem. Soc. Chem. Commun.* ***1988***, 1350.
[109] Taylor, E.C.; Altland, H.W.; Danforth, R.H.; McGillivray, G.; McKillop, A. *J. Am. Chem. Soc.* ***1970***, *92*, 3520.
[110] Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.
[111] Buzbee, L.R. *J. Org. Chem.* ***1966***, *31,* 3289; Oae, S.; Furukawa, N.; Kise, M.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1212.
[112] See Gujadhur, R.; Venkataraman, D. *Synth. Commun.* ***2001***, *31*, 2865.
[113] Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* ***1983***, *39,* 193.
[114] Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2003***, *33*, 1405.
[115] Chauhan, S.M.S.; Jain, N.; Kumar, A.; Srinivas, K.A. *Synth. Commun.* ***2003***, *33*, 3607.
[116] Kizner, T.A.; Shteingarts, V.D. *J. Org. Chem*, *USSR* ***1984***, *20,* 991.

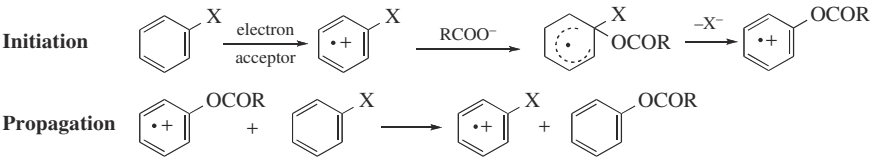
has also been used.[117] Phenols reacted with aryl fluorides[118] or aryl chlorides[119] to give the diaryl ether. Intramolecular versions are known that produce benzofurans.[120] Heating aryl iodides and phenols in an ionic liquid forms ethers.[121] In addition to halides, leaving groups can be other OR, or even OH.[122]

For aroxide nucleophiles, the reaction is promoted by Cu salts,[123] and activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*[124] and should not be confused with the *Ullmann biaryl synthesis* (**13-11**). The reactivity order is typical of nucleophilic substitutions, despite the presence of the Cu salts.[125] Copper-catalyzed coupling is known using ligand and additive-free conditions.[126] Because aryloxycopper(I) reagents (ArOCu) react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.[127] Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[128] Aryl halides are converted to aryl ethers with aliphatic alcohols in the presence of suitable Cu salts.[129]

An increasingly important variation of this reaction couples an alkoxide and an aryl halide to give aryl ethers in the presence of a Pd catalyst and a suitable ligand.[130] Ligand effects are important in such reactions.[131] A Pd catalyzed, intramolecular displacement of an aryl halide with a pendant alkoxide unit leads to dihydrobenzofurans.[132] Nickel catalysts have also been used.[133] Aryl iodides react with phenols in the presence of K_2CO_3, CuI, and Raney nickel alloy.[134] An Fe catalyzed etherification reaction is known.[135]

[117] Artamanova, N.N.; Seregina, V.F.; Shner, V.F.; Salov, B.V.; Kokhlova, V.M.; Zhdamarova, V.N. *J. Org. Chem, USSR* ***1989***, *25,* 554.
[118] See Agejas, J.; Bueno, A.B. *Tetrahedron Lett.* ***2006***, *47,* 5661.
[119] Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* ***2002***, 1278.
[120] Chen, C.-y.; Dormer, P.G. *J. Org. Chem.* ***2005***, *70,* 6964.
[121] Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett* ***2003***, 1734.
[122] Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* ***1964***, *37,* 770; ***1966***, *39*, 611.
[123] See Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* ***2005***, 1101.
[124] Naidu, A.B.; Raghunath, O.R.; Prasad, D.J.C.; Sekar, G. *Tetrahedron Lett.* ***2008***, *49,* 1057; Naidu, A.B.; Sekar, G. *Tetrahedron Lett.* ***2008***, *49,* 3147. See Moroz, A.A.; Shvartsberg, M.S. *Russ. Chem. Rev.* ***1974***, *43*, 679; Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* ***2003***, 2428.
[125] Weingarten, H. *J. Org. Chem.* ***1964***, *29*, 977, 3624. See Cai, Q.; Zou, B.; Ma, D. *Angew. Chem. Int. Ed.* ***2006***, *45,* 1276.
[126] Chang, J.W.W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P.W.H. *Tetrahedron Lett.* ***2008***, *49,* 2018.
[127] Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1972***, *45,* 1499.
[128] Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2829.
[129] Lipshutz, B.H.; Unger, J.B.; Taft, B.R. *Org. Lett.* ***2007***, *9,* 1089; Maiti, D.; Buchwald, S.L. *J. Org. Chem.* ***2010***, ***75***, 1791; Maiti, D.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2009***, *131*, 17423; Tlili, A.; Monnier, F.; Taillefer, M. *Chemistry: Eur. J.* ***2010***, *16*, 12299; Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* ***2009***, *48*, 8729.
[130] Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2498; Torraca, K.E.; Huang, X.; Parrish, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 10770.
[131] Burgos, C.H.; Barder, T.E.; Huang, X.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4321.
[132] Kuwabe, S.-i.; Torraca, K.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 12202.
[133] Manolikakes, G.; Dastbaravardeh, N.; Knochel, P. *Synlett* ***2007***, 2077.
[134] Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2071.
[135] Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* ***2008***, *47,* 586.

In a related reaction, acid salts ($RCOO^-$) are sometimes used as nucleophiles.[136] Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.[137] The following chain mechanism, called the $S_{ON}2$ mechanism,[138] has been suggested[138]:



OS **I**, 219; **II**, 445; **III**, 293, 566; **V**, 926; **VI**, 150; **X**, 418.

B. Sulfur Nucleophiles

13-4 Replacement by SH or SR

Mercapto-de-halogenation	$ArBr + SH^-$	$\longrightarrow ArSH$
Alkylthio-de-halogenation	$ArBr + SR^-$	$\longrightarrow ArSR$

Aryl thiols and thioethers can be prepared by reactions that are similar to **13-1** and **13-3**.[139] Activated aryl halides generally give good results, but side reactions are occasionally important. Some reagents give the thiol directly. 4-Bromonitrobenzene reacts with Na_3SPO_3, in refluxing methanol, to give 4-nitrothiophenol, for example.[140]

Diaryl sulfides can be prepared by the use of ^-SAr.[141] Even unactivated aryl halides react with ^-SAr if polar aprotic solvents (e.g., DMF,[142] DMSO[143] 1-methyl-2-pyrrolidinone,[144] or HMPA)[145] are used, though the mechanisms are still mostly or entirely nucleophilic substitution. 2-Iodothiophene reacts directly with thiophenol to give 2-(phenylthio)thiophene.[146]

Metal-catalyzed reactions of aryl halides and thiols lead to thioethers. Perhaps the most common metal used nowadays is Pd.[147] Copper catalysts have been used,[148] including

[136] See Desai, L.V.; Stowers, K.J.; Sanford, M.S. *J. Am. Chem. Soc.* ***2008***, *130,* 13285.
[137] Jönsson, L.; Wistrand, L. *J. Org. Chem.* ***1984***, *49*, 3340.
[138] First proposed by Alder, R.W. *J. Chem. Soc. Chem. Commun.* ***1980***, 1184.
[139] See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Group,* pt. 2, Wiley, NY, ***1974***, pp. 735–744.
[140] Bieniarz, C.; Cornwell, M.J. *Tetrahedron Lett.* ***1993***, *34*, 939.
[141] See Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* ***2000***, *41,* 1283.
[142] Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* ***1983***, 751. See Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* ***1983***, *48*, 4289.
[143] Bradshaw, J.S.; South, J.A.; Hales, R.H. *J. Org. Chem.* ***1972***, *37*, 2381.
[144] Caruso, A.J.; Colley, A.M.; Bryant, G.L. *J. Org. Chem.* ***1991***, *56*, 862; Shaw, J.E. *J. Org. Chem.* ***1991***, *56*, 3728.
[145] Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* ***1979***, *44,* 2642. See also, Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* ***1980***, *21*, 3099; Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* ***1980***, 1363.
[146] Lee, S.B.; Hong, J.-I. *Tetrahedron Lett.* ***1995***, *36*, 8439.
[147] Fernández-Rodríguez, M.A.; Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 2180.
[148] Sperotto, E.; van Klink, G.P.M.; de Vries, J.G.; van Koten, G. *J. Org. Chem.* ***2008***, *73,* 5625; Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* ***2006***, *47,* 5781; Feng, Y.-S.; Li, Y.-Y.; Tang, L.; Wu, W.; Xu, H.-J. *Tetrahedron Lett.* ***2010***, *51*, 2489; Feng, Y.; Wang, H.; Sun, F.; Li,Y.; Fu, X.; Jin, K. *Tetrahedron* ***2009***, *65*, 9737.

catalysis in aqueous media,[149] and also Ni[150] or In[151] catalysts. Copper-catalyzed coupling is known using ligand- and additive-free conditions.[152] Aryl iodides react with dialkyl disulfides and a nickel catalyst to give aryl alkyl sulfides.[153] Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^- in liquid ammonia under irradiation.[154] The mechanism in this case is probably $S_{RN}1$. The reaction (with unactivated halides) has also been carried out electrolytically, with a Ni catalyst.[155] In the presence of a Pd catalyst, thiophenols react with diaryliodonium salts ($Ar_2I^{+-}BF_4$) to give the unsymmetrical diaryl sulfide.[156]

Other sulfur nucleophiles also react with activated aryl halides:

$$2\,ArX + S_2^{2-} \rightarrow Ar{-}S{-}S{-}Ar \qquad ArX + SCN^- \rightarrow ArSCN$$
$$ArX + SO_3^{2-} \rightarrow Ar{-}SO_3^- \qquad ArX + RSO_2^- \rightarrow Ar{-}SO_2{-}R$$

Arylboronic acids [$ArB(OH)_2$] react with thiols and copper(II) acetate to give the corresponding alkyl aryl sulfide.[157] Arylboronic acids also react with *N*-methylthiosuccinimide, with a Cu catalyst, to give the aryl methyl sulfide.[158]

Aryl sulfones have been prepared from sulfinic acid salts, aryl iodides, and CuI.[159] A Pd catalyzed arylation of sulfenate anions leads to aryl sulfoxides.[160]The copper-catalyzed reaction of NaO_2SMe and aryl iodides give the aryl methyl sulfone,[161] and aryl sulfones have been prepared from arylboronic acids using a Cu catalyst.[162] A similar synthesis of diaryl sulfones has been reported using a Pd catalyst.[163]

Aryl selenides (ArSeAr and ArSeAr') can be prepared by similar methodology. Symmetrical diaryl selenides were prepared by the reaction of iodobenzene with diphenyl diselenide (PhSeSePh), in the presence of Mg and a Cu catalyst.[164] Aryl halides react with tin selenides ($ArSeSnR_3$), with a Cu catalyst, to give the diaryl selenide,[165] and a CuS—Fe catalyst was also used.[166]

Thiocyanates have been generated from unactivated aryl halides using charcoal supported copper(I) thiocyanate.[167]

[149] Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* ***2008***, 640.
[150] Gómez-Benítez, V.; Baldovino-Pantaleón, O.; Herrera-Álvarez, C.; Toscano, R.A.; Morales-Morales, D. *Tetrahedron Lett.* ***2006***, *47,* 5059; Yoon, H.-J.; Choi, J.-W.; Kang, H.; Kang, T.; Lee, S.-M.; Jun, B.-H.; Lee, Y.-S. *Synlett* ***2010***, 2518.
[151] Reddy, V.P.; Swapna, K.; Kumar, A.V.; Rama Rao, K. *J. Org. Chem.* ***2009***, *74,* 3189.
[152] Buranaprasertsuk, P.; Chang, J.W.W.; Chavasiri, W.; Chan, P.W.H. *Tetrahedron Lett.* ***2008***, *49,* 2023.
[153] Tankguchi, N. *J. Org. Chem.* ***204***, *69*, 6904.
[154] Bunnett, J.F.; Creary, X. *J. Org. Chem.* ***1974***, *39*, 3173, 3611.
[155] Meyer, G.; Troupel, M. *J. Organomet. Chem.* ***1988***, *354,* 249.
[156] Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31,* 1227.
[157] Herradua, P.S.; Pendola, K.A.; Guy, R.K. *Org. Lett.* ***2000***, *2*, 2019.
[158] Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2002***, *4*, 4309.
[159] Suzuki, H.; Abe, H. *Tetrahedron Lett.* ***1995***, *36*, 6239.
[160] Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* ***2006***, *8*, 5951.
[161] Baskin, J.M.; Wang, Z. *Org. Lett.* ***2002***, *4*, 4423.
[162] Kar, A.; Sayyed, I.A.; Lo, W.F.; Kaiser, H.M.; Beller, M.; Tse, M.K. *Org. Lett.* ***2007***, *9*, 3405.
[163] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M.; Bernini, R. *J. Org. Chem.* ***2004***, *69,* 5608.
[164] Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, 69, 915; Taniguchi, N.; Onami, T. *Synlett* ***2003***, 829.
[165] Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovlskii, P.V. *Tetrahedron Lett.* ***2003***, *44,* 7039.
[166] Li, Y.; Wang, H.; Li, X.; Chen, T.; Zhao, D. *Tetrahedron* ***2010***, *66,* 8583.
[167] Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 81. See also, Yadav, J.S.; Reddy, B.V.S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* ***2004***, *45*, 2951.

OS **I**, 220; **III**, 86, 239, 667; **V**, 107, 474; **VI**, 558, 824. Also see, OS **V**, 977.

C. Nitrogen Nucleophiles

13-5 Replacement of Halogen by NH_2, NHR, or NR_2

Amino-de-halogenation

Amido-de-halogenation

$$\underset{R=H}{R_3N} + Ar{-}X \xrightarrow[\text{alkyl}(1^\circ \text{ and } 2^\circ)]{} R_2N{-}Ar$$

Activated aryl halides react with ammonia and primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2-Chloronitrobenzene also reacts with aniline derivatives directly with microwave irradiation.[168] Other leaving groups in this reaction may be NO_2,[169] N_3, OSO_2R, OR, SR, N=NAr (where Ar contains electron-withdrawing groups)[170] and even NR_2.[171] Aryl triflates react directly with secondary amines in *N*-methylpyrrolidine solvent using microwave irradiation.[172] Aniline derivatives react with activated aromatic rings, in the presence of tetrabutylammonium fluoride and under photolysis conditions, to give a *N,N*-diarylamine.[173] Arylation of amines with aryl halides has also been done in ionic liquids[174] and in supercritical CO_2.[175] Flow reactor technology has been used for the direct, uncatalyzed amination of 2-chloropyridine.[176]

Aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR, or $NaNR_2$.[177] Lithium dialkylamides also react with aryl halides to give the *N*-arylamine.[178] With amide base reagents, the benzyne mechanism generally operates, so *cine* substitution (Sec. 13.A.iii, category 2) is often found. The amide base is usually generated by reaction of the amine with an organolithium reagent, but other bases may be used. The reaction of an amine, an aryl halide, and potassium *tert*-butoxide generates the *N*-aryl amine.[179] Triarylamines have been prepared in a similar manner from ArI and Ar'_2NLi, even with unactivated ArI.[180]

Aryl fluorides react in the presence of KF–alumina and 18-crown-6 in DMSO.[181] Aryl fluorides react with amines in the presence of potassium carbonate/DMSO and ultrasound,[182] and aryl chlorides react on basic alumina with microwave irradiation.[183]

[168] Xu, Z.-B.; Lu, Y.; Guo, Z.-R. *Synlett* ***2003***, 564. See Li, W.; Yun, L.; Wang, H. *Synth. Commun.* ***2002***, *32*, 2657.
[169] See Yang, T.; Cho, B.P. *Tetrahedron Lett.* ***2003***, *44*, 7549.
[170] Kazankov, M.V.; Ginodman, L.G. *J. Org. Chem*, *USSR* ***1975***, *11,* 451.
[171] Sekiguchi, S.; Horie, T.; Suzuki, T. *J. Chem. Soc. Chem. Commun.* ***1988***, 698.
[172] Xu, G.; Wang, Y.-G. *Org. Lett.* ***2004***, *6,* 985.
[173] Hertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* ***2000***, *41*, 279.
[174] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron Lett.* ***2003***, *44*, 2217.
[175] Smith, C.J.; Tsang, M.W.S.; Holmes, A.B.; Danheiser, R.L.; Tester, J.W. *Org. Biomol. Chem.* ***2005***, *3,* 3767.
[176] Hamper, B.C.; Tesfu, E. *Synlett* ***2007***, 2257.
[177] See Heaney, H. *Chem Rev.* ***1962***, *62,* 81, see p. 83.
[178] Tripathy, S.; Le Blanc, R.; Durst, T. *Org. Lett.* ***1999***, *1*, 1973. See Kanth, J.V.B.; Periasamy, M. *J. Org. Chem.* ***1993***, *58*, 3156.
[179] Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* ***2003***, *5*, 3515.
[180] Neunhoeffer, O.; Heitmann, P. *Chem. Ber.* ***1961***, *94,* 2511.
[181] Smith III, W.J.; Sawyer, J.S. *Tetrahedron Lett.* ***1996***, *37*, 299.
[182] Magdolen, P.; Meciarová, M.; Toma, S. *Tetrahedron* ***2001***, *57*, 4781.
[183] Kidwai, M.; Sapra, P.; Dave, B. *Synth. Commun.* ***2000***, *30*, 4479.

2-Fluoropyridine reacts with R_2NBH_3Li to give the 2-aminoalkylpyridine.[184] 2,4-Dinitrofluorobenzene, known as *Sanger's reagent,* is used to tag the amino end of a peptide or protein chain.[185]

The reaction of amines with aryl halides can be done under milder conditions using a catalyst to initiate or mediate the reaction. Both amines (aliphatic and aniline derivatives)[186] and amide bases[187] have been coupled to aryl halides using Pd catalysts and an appropriate ligand.[188] A considerable amount of work[189] has been done to vary the nature of the ligand and the Pd catalyst, as well as the base.[190] Work to discern the mechanism of this reaction has also received considerable attention.[191] This amination has come to be called the *Buchwald–Hartwig Cross-Coupling Reaction*.

Polymer-supported Pd catalysts,[192] polymer-bound phosphine ligands used in conjunction with a Pd catalyst,[193] and polymer-bound amines[194] have been used for *N*-arylation. These reactions have been done in ionic liquids using a Pd catalyst.[195] Palladium-catalyzed amination of aryl halides has been reported using microwave irradiation.[196] Catalysts are available for the amination of aryl halides in aqueous media.[197] The Pd-catalyzed amination of aryl substrates is not limited to halides, and the reaction with mesylates lead to arylamines.[198] Arylamines with chiral substituents on nitrogen can be prepared using a Pd-catalyst with optically active ligands.[199]

Aniline derivatives have been prepared by the reaction of aryl chlorides with silylamines (Ph_3SiNH_2) using lithium hexamethyldisilazide and a Pd catalyst.[200] Amines react with

[184] Thomas, S.; Roberts, S.; Pasumansky, .L; Gamsey, S.; Singaram, B. *Org. Lett.* ***2003***, *5*, 3867.
[185] Sanger, F *The Biochem. J.* ***1945***, *39,* 507.
[186] Ali, M.H.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2560; Kuwano, R.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* ***2002***, *67*, 6479; Reddy, Ch.V.; Kingston, J.V.; Verkade, J.G. *J. Org. Chem.* ***2008***, *73*, 3047; Shen, Q.; Hartwig, J.F. *Org. Lett.* ***2008***, *10,* 4109.
[187] Harris, M.C.; Huang, X.; Buchwald, S.L. *Org. Lett.* ***2003***, *4*, 2885. See Coldham, I.; Leonori, D. *Org. Lett.* ***2008***, *10,* 3923; Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 10028. For a discussion about the influence of water on this reaction, see Dallas, A.S.; Gothelf, K.V. *J. Org. Chem.* ***2005***, *70,* 3321.
[188] See Anderson, K.W.; Tundel, R.E.; Ikawa, T.; Altman, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45,* 6523.
[189] Gajare, A.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *J. Org. Chem.* ***2004***, *69*, 6504; Huang, X.; Anderson, K.W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *125*, 6653; Singer, R.A.; Tom, N.J.; Frost, H.N.; Simon, W.M. *Tetrahedron Lett.* ***2004***, *45*, 4715; Smith, C.J.; Early, T.R.; Holmes, A.B.; Shute, R.E. *Chem. Commun.* ***2004***, 1976.
[190] See Singh, U.K.; Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14104. For a study of rate enhancement by the added base, see Meyers, C.; Maes, B.U.W.; Loones, K.T.J.; Bal, G.; Lemière, G.L.F.; Dommisse, R.A. *J. Org. Chem.* ***2004***, *69*, 6010.
[191] See Strieter, E.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45,* 925; Fors, B.P.; Davis, N.R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2009***, *131*, 5766.
[192] Guinó, M.; Hii, K.K. *Tetrahedron Lett.* ***2005***, *46,* 7363. See Inasaki, T.; Ueno, M.; Miyamoto, S.; Kobayashi, S. *Synlett* ***2007***, 3209.
[193] Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66,* 3820.
[194] Weigand, K.; Pelka, S. *Org. Lett.* ***2002***, *4*, 4689.
[195] See Grasa, G.A.; Viciu, M.S.; Huang, J.; Nolan, S.P. *J. Org. Chem.* ***2001***, *66,* 7729.
[196] Jensen, T.A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* ***2004***, *69,* 4936.; Loones, K.T.J.; Maes, B.U.W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* ***2005***, *61,* 10338.
[197] Xu, C.; Gong, J.-F.; Wu, Y.-J. *Tetrahedron Lett.* ***2007***, *48*, 1619.
[198] So, C.M.; Zhou, Z.; Lau, C.P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2008***, *47,* 6402.
[199] Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron Asymmetry* ***2005***, *16,* 230.
[200] Huang, X.; Buchwald, S.L. *Org. Lett.* ***2001***, *3*, 3417.

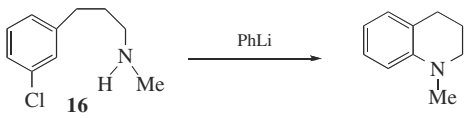
$Ph_2I^+BF_4^-$, in the presence of Pd catalysts,[201] or a CuI catalyst[202] to give the *N*-phenyl amine. Aminoalkylation of heteroaromatic rings is possible, as in the reaction of 3-bromothiophene with a primary amine and a Pd catalyst.[203] 2-Halopyridines react to give the 2-aminoalkyl pyridine.[204]

Copper catalysts have been used for the reaction of amines or aniline derivatives with aryl halides.[205] The selectivity of *O*- versus *N*-arylation for reactions of amino alcohols has been discussed.[206] Copper-catalyzed amination reactions can be done in aqueous media using 2-dimethylaminoethanol as a ligand.[207] Ammonium salts serve as a nitrogen source in some cases.[208] In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an *N*-acetyldiarylamine, which can be hydrolyzed to a diarylamine: $ArBr + Ar'NHAc \rightarrow ArAr'NAc$.[209]

Nickel catalysts have been used in the reaction of aryl halides with *N*-alkyl aniline derivatives[210] and also with aliphatic amines.[211] *N*-Arylation was also accomplished with butyllithium and a secondary amine using Ni/C-diphenylphosphinoferrocene (dppf).[212] An intramolecular reaction of a pendant aminoalkyl unit with an aryl chloride moiety, catalyzed by Ni(0) gave a dihydroindole.[213] An arylbismuth reagent reacts with aliphatic amines, in the presence of copper(II) acetate, to give an *N*-arylamine.[214] Diarylzinc reagents give the *N*-aryl amine in the presence of a Cu[215] or a Ni catalyst[216]. Aryl halides also react with $Zn(NTMS_2)_2$ in the presence of a Pd catalyst to give arylamines.[217] Iron-catalyzed arylation reactions are known.[218] A $Mo(CO)_6$ mediated, Pd catalyzed reaction is known for allylamines and aryl halides.[219]

[201] Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* ***1996***, *26*, 4219. See Carroll, M.A.; Wood, R.A. *Tetrahedron* ***2007***, *63*, 11349.
[202] Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* ***2000***, 1022.
[203] Ogawa, K.; Radke, K.R.; Rothstein, S.D.; Rasmussen, S.C. *J. Org. Chem.* ***2001***, *66*, 9067.
[204] Junckers, T.H.M.; Maes, B.U.W.; Lemière, G.L.F.; Dommisse, R. *Tetrahedron* ***2001***, *57*, 7027; Basu, B.; Jha, S.; Mridha, N.K.; Bhuiyan, Md.M.H. *Tetrahedron Lett.* ***2002***, *43,* 7967.
[205] Choudary, B.M.; Sridhar, C.; Kantam, M.L.; Venkanna, G.T.; Sreedhar, B. *J. Am. Chem. Soc.* ***2005***, *127*, 9948; Shafir, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2006***, *128,* 8742; Wolf, C.; Liu, S.; Mei, X.; August, A.T.; Casimir, M.D. *J. Org. Chem.* ***2006***, *71*, 3270; Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* ***2007***, *72,* 672; Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem.* ***2008***, *73,* 8639; Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* ***2005***, 496. For a ligand-free reaction, see Yong, F.F.; Teo, Y.-C. *Synlett* ***2010***, 3068.
[206] Shafir, A.; Lichtor, P.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2007***, *129*, 3490. For an amination using aq ammonia, see Meng, F.; Zhu, X.; Li, Y.; Xie, J.; Wang, B.; Yao, J.; Wan, Y. *Eur. J. Org. Chem.* ***2010***, 6149.
[207] Lu, Z.; Twieg, R.J. *Tetrahedron Lett.* ***2005***, *46*, 2997.
[208] Kim, J.; Chang, S. *Chem. Commun.* ***2008***, 3052.
[209] See Renger, B. *Synthesis* ***1985***, 856.
[210] Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 6054; Lipshutz, B.H.; Ueda, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4492.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* ***2002***, *58*, 6913; Chen, C.; Yang, L.-M. *J. Org. Chem.* ***2007***, *72*, 6324.
[211] Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* ***2008***, *73,* 1429; Gao, C.-Y.; Cao, X.; Yang, L.-M. *Org. Biomol. Chem.* ***2009***, ***7***, 3922.
[212] Tasler, S.; Lipshutz, B.H. *J. Org. Chem.* ***2003***, *68*, 1190.
[213] Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* ***2003***, *5*, 2311.
[214] Fedorov, A.Yu.; Finet, J.-P. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3775.
[215] Berman, A.M.; Johnson, J.S. *J. Am. Chem. Soc.* ***2004***, *126*, 5680.
[216] Berman, A.M.; Johnson, J.S. *Synlett* ***2005***, 1799.
[217] Lee, D.-Y.; Hartwig, J.F. *Org. Lett.* ***2005***, *7*, 1169.
[218] Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett.* ***2008***, *10*, 4513; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* ***2007***, *46,* 8862; Correa, A.; Carril, M.; Bolm, C. *Chemistry: European J.* ***2008***, *14,* 10919.
[219] Appukkuttan, P.; Axelsson, L.; Van der Eycken, E.; Larhed, M. *Tetrahedron Lett.* ***2008***, *49,* 5625.

Intramolecular versions of this reaction generate bicyclic or polycyclic amines.[220] An example is the conversion of **16** to the tetrahydroquinoline.[221] Larger ring amines can be prepared using this approach: 8- and even 12-membered.



Arylboronic acids react with aliphatic amines[222] or aq ammonia[223] in the presence of a Cu catalyst. *N*-Aryl imides have been prepared by similar methodology, from arylboronic acids.[224] Trifluoroarylboronates react with copper(II) acetate and then an aliphatic amine to give the *N*-phenylamine.[225] Primary aromatic amines ($ArNH_2$) were converted to diaryl amines (ArNHPh) by treatment with $Ph_3Bi(OAc)_2$[226] and a Cu powder catalyst.[227]

The metal-catalyzed reaction with ammonia or amines likely proceeds by the S_NAr mechanism.[228] This reaction, with phase-transfer catalysis, has been used to synthesize triarylamines.[229] In certain cases, the $S_{RN}1$ mechanism has been found (Reaction **10-26**). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the S_N(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.[230]

There are a number of indirect approaches for the preparation of aryl amines. Activated aromatic compounds can be directly converted to the *N*-aryl amine in high yield with hydroxylamine in the presence of strong bases.[231] Aryl halides can be converted to the corresponding *Grignard reagent* (Reaction **12-38**). Subsequent reaction with allyl azide followed by hydrolysis leads to the corresponding aniline derivative.[232] Aryl *Grignard reagents* react with nitroaryl compounds to give, after reduction with $FeCl_3/NaBH_4$, a diaryl amine.[233] Aryl halides can be converted to the aryllithium via halogen–lithium exchange or hydrogen–lithium exchange (Reactions **12-38** and **12-39**).

The use of transition metal catalysts allows aryl halides to react with the nitrogen of amides or carbamates to give the corresponding *N*-aryl amide or *N*-aryl carbamate.

[220] See Jordan-Hore, J.A.; Johansson, C.C.C.; Gulias, M.; Beck, E.M.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2008***, *130,* 16184; Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* ***2005***, *70,* 413.

[221] See Bunnett, J.F.; Hrutfiord, B.F. *J. Am. Chem. Soc.* ***1961***, *83,* 1691. Also see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 150–164.

[222] Chiang, G.C.H.; Olsson, T. *Org. Lett.* ***2004***, *6*, 3079; Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* ***2004***, 1095.

[223] Jiang, Z.; Wu, Z.; Wang, L.; Wu, D.; Zhou, X. *Can. J. Chem.* ***2010***, *88,* 964.

[224] Chernick, E.T.; Ahrens, M.J.; Scheidt, K.A.; Wasielewski, M.R. *J. Org. Chem.* ***2005***, *70,* 1486.

[225] Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5*, 4397.

[226] See Finet, J. *Chem. Rev.* ***1989***, *89,* 1487.

[227] See Barton, D.H.R.; Yadav-Bhatnagar, N.; Finet, J.; Khamsi, J. *Tetrahedron Lett.* ***1987***, *28*, 3111.

[228] See Bethell, D.; Jenkins, I.L.; Quan, P.M. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1789; Paine, A.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1496.

[229] Gauthier, S.; Fréchet, J.M.J. *Synthesis* ***1987***, 383.

[230] See van der Plas, H.C. *Tetrahedron* ***1985***, *41,* 237; *Acc. Chem. Res.* ***1978***, *11,* 462.

[231] See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454, p. 456.

[232] Kabalka, G.W.; Li, G. *Tetrahedron Lett.* ***1997***, *38*, 5777.

[233] Sapountzis, I.; Knochel, P. *J. Am.Chem. Soc.* ***2002***, *124*, 9390.

Amides react with aryl halides in the presence of a Pd[234] or a Cu catalyst.[235] *N*-Aryl lactams are prepared by the reaction of a lactam with an aryl halide in the presence of a Pd catalyst.[236] β-Lactams also react.[237] The reaction of 2-oxazolidinones with aryl halides in the presence of a Pd catalyst gave the *N*-aryl-2-oxazolidinone.[238] *N*-Aryl amides are prepared from amides using $PhSi(OMe)_3/Cu(OAc)_2/Bu_4NF$.[239] *N*-Boc hydrazine derivatives ($BocNHNH_2$) gave the *N*-phenyl derivative [$BocN(Ph)NH_2$] when reacted with iodobenzene and a catalytic amount of CuI and 10% of 1,10-phenanthroline.[240] 3-Bromothiophene was converted to the 3-amido derivative with an amide and CuI-dimethylethylenediamine.[241] *N*-(2-Thiophene)-2-pyrrolidinone was similarly prepared from 2-iodothiophene, the lactam, and a copper catalyst.[242] *N*-Arylation of urea is possible using a Cu catalyst.[243]

The transition metal catalyzed couplings of primary or secondary phosphines with aryl halides or sulfonate esters to give arylphosphines is known.[244] The Pd catalyzed conversion of aryl halides to aryl phosphines using (trimethylsilyl)diphenylphosphine tolerates many functional groups (not those that are easily reducible, e.g., aldehydes, because Zn metal[245] is often used as a coreagent), but it is mainly limited to aryl iodides.[246] Diphenylphosphine reacts with aryl iodides and a copper catalyst to give the triarylphosphine.[247] Aryl iodides also react with a secondary phosphine and 5% Pd/C to give the *P*-arylphosphine.[248] Tertiary phosphines can be used via aryl–aryl exchange, as in the reaction of an aryl triflate and triphenylphosphine and a Pd catalyst, for example, gave the arylphosphonium salt ($ArPPh_3$).[249] Aryl iodides can also be used.[250]

OS **I**, 544; **II**, 15, 221, 228; **III**, 53, 307, 573; **IV**, 336, 364; **V**, 816, 1067; **VII**, 15. OS **III**, 664. **OS X**, 423.

[234] Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* ***2005***, *127,* 3676; Fors, B.P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S.L. *Tetrahedron* ***2009***, *65*, 6576. For an intramolecular reaction, see Yang, B.H.; Buchwald, S.L. *Org. Lett.* ***1999***, *1*, 35.

[235] Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* ***2004***, 1517.

[236] Browning, R.G.; Badaringarayana, V.; Mahmud, H.; Lovely, C.J. *Tetrahedron* ***2004***, *60,* 359; Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* ***2004***, *45*, 2311. Also see Klapars, A.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 7421; Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* ***2004***, *6*, 4759.

[237] Also see Klapars, A.; Parris, S.; Anderson, K.W.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *126*, 3529.

[238] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* ***2001***, *3*, 2539.

[239] Lam, P.Y.S.; Deudon, S.; Hauptman, E.; Clark, C.G. *Tetrahedron Lett.* ***2001***, *42,* 2427.

[240] Wolter, M.; Klapars, A.; Buchwald, S.L. *Org. Lett.* ***2001***, *3*, 3803.

[241] Padwa, A.; Crawford, K.R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* ***2003***, *68*, 2609.

[242] Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* ***2002***, 427.

[243] Nandakumar, M.V. *Tetrahedron Lett.* ***2004***, *45*, 1989.

[244] Gelpke, A.E.S.; Kooijman, H.; Spek, A.L.; Hiemstra, H. *Chem. Eur. J.* ***1999***, *5,* 2472; Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* ***1999***, *5,* 1734; Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* ***1998***, *63,* 7738; Martorell, G.; Garcias, X.; Janura, M.; Saá, J. M. *J. Org. Chem.* ***1998***, *63,* 3463; Lipshutz, B.H.; Buzard, D.H.; Yun, C.S. *Tetrahedron Lett.* ***1999***, *40*, 201.

[245] Ager, D.J.; Laneman, S. *Chem. Commun.* ***1997***, 2359.

[246] Tunney, B.H.; Stille, J.K. *J. Org. Chem.* ***1987***, *52,* 748.

[247] Van Allen, D.; Venkataraman, D. *J. Org. Chem.* ***2003***, *68*, 4590.

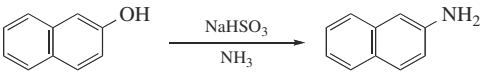
[248] Stadler, A.; Kappe, C.O. *Org. Lett.* ***2002***, *4*, 3541.

[249] Kwong, F.Y.; Lai, C.W.; Chan, K.S. *Tetrahedron Lett.* ***2002***, *43*, 3537.

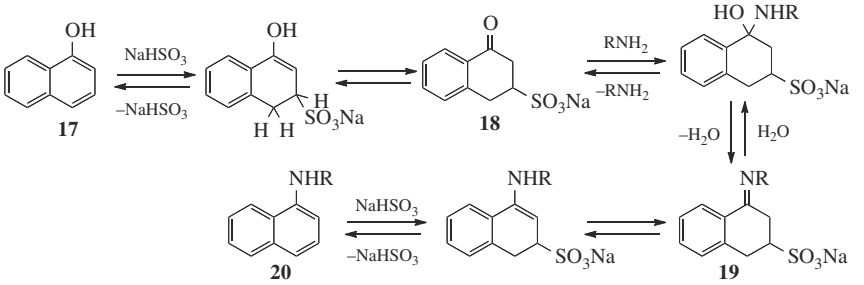
[250] Marcoux, D.; Charette, A.B. *J. Org. Chem.* ***2008***, *73*, 590.

13-6 Replacement of a Hydroxy Group by an Amino Group

Amino-de-hydroxylation



The reaction of naphthols with ammonia and sodium bisulfite is called the *Bucherer reaction.* Primary amines can be used instead of ammonia, in which case *N*-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary ($ArNH_2 + RNH_2 + NaSO_3 \rightarrow ArNHR$), by a transamination reaction. The mechanism of the *Bucherer reaction* amounts to a kind of overall addition–elimination, via **18** and **19**.[251]



The first step in either direction consists of addition of $NaHSO_3$ to one of the double bonds of the ring, which gives an enol from **17** (or enamine from **20**) that tautomerizes to the keto form **18** (or imine form, **19**). The conversion of **18** to **19** (or vice versa) is an example of Reaction **16-13** (or **16-2**). Evidence for this mechanism was the isolation of **18**[252] and the demonstration that for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[253] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[254]

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid ammonia gives the corresponding primary aromatic amines.[255] The mechanism of the second step is $S_{RN}1$.[256]

OS **III**, 78.

D. Halogen Nucleophiles

13-7 The Introduction of Halogens

Halo-de-halogenation, and so on

$$Ar{-}X + X'^{-} \rightleftharpoons ArX' + X^{-}$$

[251] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638,* 66.
[252] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638,* 43, 57.
[253] Kozlov, V.V.; Veselovskaia, I.K. *J. Gen. Chem. USSR* ***1958***, *28*, 3359.
[254] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638,* 76.
[255] Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1972***, *37,* 3570.
[256] See Scherrer, R.A.; Beatty, H.R. *J. Org. Chem.* ***1972***, *37*, 1681.

It is possible to replace a halogen on an aromatic ring by another halogen[257] if the ring is activated. In such cases, there is equilibrium, which is usually shifted in the desired direction by the use of an excess of added halide ion.[258] A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if the ring is activated. Unactivated phenols give phosphates when treated with $POCl_3$: $3\ ArOH + POCl_3 \rightarrow (ArO)_3PO$. Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2[259] (see Reaction **10-47**) and to aryl chlorides by treatment with $PhPCl_4$.[260]

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF, DMSO, or dimethyl sulfone.[261] Reaction of aryl halides with Bu_4PF/HF is also effective for exchanging a halogen with fluorine.[262]

Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $I > Br > Cl \gg F$, which means that iodides cannot normally be made by this method, the S_NAr mechanism is probably not operating.[263] However, aryl iodides have been prepared from bromides, by the use of Cu supported on charcoal or Al_2O_3,[264] with an excess of NaI and a Cu catalyst,[265] and by treatment with excess KI and a Ni catalyst.[266] Interestingly, aryl chlorides have been prepared from aryl iodides using 2 molar equivalents of $NiCl_2$ in DMF, with microwave irradiation.[267] Aryl and vinyl triflates can be converted to the corresponding bromide or chloride using a Pd catalyst.[268]

Aryl iodides[269] and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see Reaction **12-23**), indirectly achieving the $ArH \rightarrow ArI$ and $ArH \rightarrow ArF$ conversions. The bis(trifluoroacetates) react with KI to give ArI in high yields.[270] Aryllead triacetates [$ArPb(OAc)_3$] can be converted to aryl fluorides by treatment with BF_3–etherate.[271] Treatment of $PhB(OH)_2$ with NIS gives iodobenzene.[272] Arylboronic acids (Reaction **12-28**) can be converted to the corresponding aryl bromides by reaction with

[257] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 671–672.
[258] Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294, p. 297.
[259] Schaefer, J.P.; Higgins, J. *J. Org. Chem.* ***1967***, *32,* 1607.
[260] Bay, E.; Bak, D.A.; Timony, P.E.; Leone-Bay, A. *J. Org. Chem.* ***1990***, *55*, 3415.
[261] Kimura, Y.; Suzuki, H. *Tetrahedron Lett.* ***1989***, *30,* 1271. See Dolby-Glover, L. *Chem. Ind. (London)* ***1986***, 518.
[262] Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H. *Synlett* ***1992***, 345.
[263] Bacon, R.G.R.; Hill, H.A.O. *J. Chem. Soc.* ***1964***, 1097, 1108. See also, Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Res. (S)* ***1989***, 238.
[264] Clark, J.H.; Jones, C.W. *J. Chem. Soc. Chem. Commun.* ***1987***, 1409.
[265] Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14844.
[266] Yang, S.H.; Li, C.S.; Cheng, C.H. *J. Org. Chem.* ***1987***, *52,* 691.
[267] Arvela, R.K.; Leadbeater, N.E. *Synlett* ***2003***, 1145.
[268] Shen, X.; Hyde, A.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2010***, *132,* 14076.
[269] See Merkushev, E.B. *Synthesis* ***1988***, 923; *Russ. Chem. Rev.* ***1984***, *53,* 343.
[270] Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285,* C9. See Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054; Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.
[271] De Meio, G.V.; Pinhey, J.T. *J. Chem. Soc. Chem. Commun.* ***1990***, 1065.
[272] Thiebes, C.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *Synlett* ***1998***, 141.

1,3-dibromo-5,5-dimethylhydantoin and 5 mol% NaOMe.[273] Other aryl halides can be prepared using 1,3-dihalo-5,5-dimethylhydantoins.

OS **III**, 194, 272, 475; **V**, 142, 478; **VIII**, 57; **81**, 98.

The reduction of phenols and phenolic esters and ethers is discussed in Reactions **19-38** and **19-35**. The reaction ArX → ArH is treated in **11-39**, although, depending on reagent and conditions, it can be nucleophilic or free radical substitution, as well as electrophilic.

E. Carbon Nucleophiles[274]

Some formations of new aryl–carbon bonds formed from aryl substrates have been considered in Reactions **10-57**, **10-68**, **10-76**, and **10-77**.

13-8 Cyanation of Aromatic Rings

Cyano-de-halogenation

Cyano-de-metalation

$$\text{Ar-X} \rightarrow \text{Ar-CN}$$

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund–von Braun reaction*.[275] Reactivity of the aryl halide is in the order I > Br > Cl > F, indicating that the S_NAr mechanism does not apply.[276] Cyanides (e.g., KCN and NaCN) do not react with aryl halides, even activated ones, but this reaction has been done in ionic liquids using CuCN.[277] The reaction has also been done in water using CuCN, a phase-transfer catalyst, and microwave irradiation.[278] L-Proline has been used to promote the reaction.[279]

Aryl halides react with metal cyanides, often with another transition metal catalyst, to give aryl nitriles (aryl cyanides). Alkali cyanides convert aryl halides to nitriles[280] in dipolar aprotic solvents in the presence of Pd(II) salts[281] or Cu[282] or Ni[283] complexes. In the presence of a Pd- catalyst,[284] several cyanide-containing compounds react with aryl halides. Several different sources of cyanide may be used with the Pd catalyzed reaction, including: $Zn(CN)_2$,[285] CuCN,[286] sodium cyanoborohydride/catechol,[287]

[273] Szumigala, Jr., R.H.; Devine, P.N.; Gauthier, Jr., D.R.; Volante, R.P. *J. Org. Chem.* ***2004***, *69,* 566.
[274] See Artamkina, G.A.; Kovalenko, S.V.; Beletskaya, I.P.; Reutov, O.A. *Russ. Chem. Rev.* ***1990***, *59,* 750.
[275] See Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* ***1987***, *87*, 779.
[276] See Connor, J.A.; Leeming, S.W.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1127.
[277] Wu, J.X.; Beck, B.; Ren, R.X. *Tetrahedron Lett.* ***2002***, *43*, 387.
[278] Arvela, R.K.; Leadbeater, N.W.; Torenius, H.M.; Tye, H. *Org. Biomol. Chem.* ***2003***, *1*, 1119.
[279] Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* ***2008***, 69.
[280] For a list of reagents that convert aryl halides to cyanides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1705–1709.
[281] Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 1118.
[282] Connor, J.A.; Gibson, D.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 619.
[283] Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61,* 1985.
[284] See Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* ***2005***, *46,* 1815; Zhu, Y.-Z.; Cai, C. *Eur. J. Org. Chem.* ***2007***, 2401.
[285] Marcantonio, K.M.; Frey, L.F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D.J.; Chen, C.-y. *Org. Lett.* ***2004***, *6*, 3723. See Erker, T.; Nemec, S. *Synthesis* ***2004***, 23.
[286] Sakamoto, T.; Ohsawa, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2323.
[287] Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* ***2001***, *57,* 1581.

potassium ferricyanide,[288] and KCN.[289] Microwave irradiation has been used to facilitate Pd catalyzed cyanation.[290] Aryl triflates may be used in aryl cyanation reactions, as well as aryl halides.[291] Benzylthiocyanate reacts with boronic acids to give aryl cyanides in a "cyanide-free" reaction, catalyzed by a Pd complex and mediated by Cu(I).[292] Cyanation reactions catalyzed by copper salts are common.[293] Aryl bromides react with $Ni(CN)_2$ with microwave irradiation to give ArCN.[294] A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.[295] Iridium-catalyzed borylation of arenes also leads to aryl nitriles.[296]

Alternative procedures are available. One uses excess aq KCN followed by photolysis of the resulting complex ion $[ArTl(CN)_3^-]$ in the presence of excess KCN.[297] Alternatively, arylthallium acetates react with $Cu(CN)_2$ or CuCN to give aryl nitriles.[298] Yields from this procedure are variable, ranging from almost nothing to 90 or 100%.

Metal-free methods have been reported. For example, conversion of an aromatic compound to the corresponding iminium salt used $POCl_3$ and DMF, and subsequent reaction with molecular iodine in aq ammonia gave the nitrile.[299] An indirect method involves the reaction of an aromatic ring with *tert*-butyllithium, particularly when there is a directing group (see Reaction **13-17**), followed by reaction with PhOCN (phenyl cyanate) to give the aryl nitrile.[300] Aromatic ethers (ArOR)[301] have been photochemically converted to ArCN.

OS **III**, 212, 631.

13-9 Coupling of Aryl and Alkyl Organometallic Compounds with Functionalized Aryl Compounds

Aryl-de-halogenation, and so on

$$\mathrm{Ar{-}X + Ar'{-}M \rightarrow Ar - Ar'}$$
$$\mathrm{Ar{-}X + R{-}M \rightarrow Ar - R}$$

A number of methods involving transition metals have been used to prepare unsymmetrical biaryls[302] (see also, Reaction **13-11**). The uncatalyzed coupling of aryl halides and metalated aryls (particularly aryllithium reagents) is also known, including

[288] Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* ***2007***, *129*, 15372; Weissman, S.A.; Zewge, D.; Chen, C. *J. Org. Chem.* ***2005***, *70,* 1508; Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* ***2007***, *48,* 1087; Velmathi, S.; Leadbeater, N.E. *Tetrahedron Lett.* ***2008***, *49,* 4693.
[289] Yang, C.; Williams, J.M. *Org. Lett.* ***2004***, *6*, 2837.
[290] Chobanian, H.R.; Fors, B.P.; Lin, L.S. *Tetrahedron Lett.* ***2006***, *47,* 3303.
[291] Zhu, Y.-Z.; Cai, C. *Synth. Commun.* ***2008***, *38,* 2753; Yeung, P.Y.; So, C.M.; Lau. C.-P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8918.
[292] Zhang, Z.; Liebeskind, L.S. *Org. Lett.* ***2006***, *8*, 4331.
[293] Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chemistry: European J.* ***2005***, *11,* 2483.
[294] Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* ***2003***, *68,* 9122.
[295] Chambers, M.R.I.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1365; Takagi, K.; Sakakibara, Y. *Chem. Lett.* ***1989***, 1957.
[296] Liskey, C.W.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2010***, *132*, 11389.
[297] Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.
[298] Uemura, S.; Ikeda, Y.; Ichikawa, K. *Tetrahedron* ***1972***, *28,* 3025.
[299] Ushijima, S.; Togo, H. *Synlett* ***2010***, 1067; Ushijima, S.; Togo, H. *Synlett* ***2010***, 1562.
[300] Sato, N. *Tetrahedron Lett.* ***2002***, *43,* 6403.
[301] Letsinger, R.L.; Colb, A.L. *J. Am. Chem. Soc.* ***1972***, *94,* 3665.
[302] Alberico, D.; Scott, M.E.; Lautens, M. *Chem. Rev.* ***2007***, *107,* 174.

cyclization of organolithium reagents to aromatic rings.[303] Noncatalyzed coupling reactions of aryllithium reagents and haloarenes can proceed via the well-known aryne route, but a novel addition–elimination pathway is possible when substituents facilitate a chelation-driven nucleophilic substitution pathway.[304] Such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield.[304] 2-Bromopyridine reacts with pyrrolidine, at 130 °C with microwave irradiation, to give 2-(2-pyrrolidino)pyridine.[305] Aryl iodides undergo homocoupling to give the biaryl by heating with triethylamine in an ionic liquid.[306] Note that alkyl bromides are coupled to pyrrolidine by heating in an ionic liquid.[307]

Palladium-catalyzed coupling reactions that generate biaryls are increasingly important in synthesis. Aryl halides undergo homocoupling to give the biaryl with a Pd[308] or a Ni catalyst.[309] Aryl iodides have been coupled to form symmetric biphenyls with a Pd catalyst,[310] and homocoupling occurs with aryl triflates under electrolysis conditions with a Pd catalyst.[311] A recyclable Pd catalyst for use in ionic liquids has been developed.[312] Other alternative solvents include PEG.[313]

Thiophene derivatives,[314] pyrrole,[315] azoles,[316] quinoline,[317] and indolizine[318] have been coupled to aryl halides using a Pd catalyst. Fused polycyclic aromatic compounds can also be prepared from halobiaryls.[319] Trimethylsilylpyridine derivatives are coupled to aryl halides in the presence of a Pd catalyst.[320] A related reaction is the Pd catalyzed decarboxylative coupling of arylcarboxylic acids with aryl iodides.[321]

Palladium catalysts are often used in conjunction with another metal compound or complex. Arylgermanium compounds are coupled with aryl iodides using tetrabutylammonium fluoride and a Pd catalyst.[322] Homocoupling of triphenylbismuth is known,[323] as well as the coupling of arylbismuth reagents to aryliodonium salts[324] and to aryltin compounds[325] with Pd compounds or complexes. Aryl triflates were coupled to triphenylbismuth using a Pd catalyst.[326] Specialized arylbismuth compounds

[303] See Clayden, J.; Kenworthy, M.N. *Synthesis* ***2004***, 1721.
[304] See Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* ***2003***, *9*, 3209.
[305] Narayan, S.; Seelhammer, T.; Gawley, R.E. *Tetrahedron Lett.* ***2004***, *45*, 757.
[306] Park, S.B.; Alper, H. *Tetrahedron Lett.* ***2004***, *45*, 5515.
[307] Jorapur, Y.R.; Lee, C.-H.; Chi, D.Y. *Org. Lett.* ***2005***, *7,* 1231.
[308] Silveira, P.B.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Tetrahedron Lett.* ***2002***, *43,* 2327; Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* ***2002***, 637. See also, Venkatraman, S.; Li, C.-J. *Org. Lett.* ***1999***, *1*, 1133.
[309] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron Lett.* ***1999***, *40,* 4243.
[310] Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* ***1998***, *39*, 2559.
[311] de Franca, K.W.R.; Navarro, M.; Léonel, É; Durandetti, M.; Nédélec, J.-Y. *J. Org. Chem.* ***2002***, *67*, 1838.
[312] Wang, R.; Twamley, B.; Shreeve, J.M. *J. Org. Chem.* ***2006***, *71*, 426.
[313] Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* ***2006***, *71,* 1284.
[314] Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F. *Org. Lett.* ***2003***, *5,* 301.
[315] See Rieth, R.D.; Mankand, N.P.; Calimano, E.; Sadighi, J.P. *Org. Lett.* ***2004***, *6*, 3981.
[316] Sezen, B.; Sames, D. *Org. Lett.* ***2003***, *5*, 3607.
[317] Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* ***2002***, *43,* 3547.
[318] Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* ***2004***, *6,* 1159.
[319] Liu, Z.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* ***2005***, *127*, 15716.
[320] Napier, S.; Marcuccio, S.M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* ***2008***, *49,* 6314. See also, Denmark, S.E.; Smith, R.C.; Chang, W.-T.T.; Muhuhi, J.M. *J. Am. Chem. Soc.* ***2009***, *131*, 3104.
[321] Wang, Z.; Ding, Q.; He, X.; Wu, J. *Tetrahedron* ***2009***, *65*, 4635.
[322] Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 3165.
[323] Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C.S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1851.
[324] Kang, S.-K.; Ryu, H.-C.; Kim, J.-W. *Synth. Commun.* ***2001***, *31*, 1021.
[325] Wang, J.; Scott, A.I. *Tetrahedron Lett.* ***1996***, *37*, 3247; Kim, Y.M.; Yu, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1696.
[326] Rao, M.L.N.; Yamazaki, O.; Shimada, S.; Tanaka, T.; Suzuki, Y.; Tanaka, M. *Org. Lett.* ***2001***, *3,* 4103.

have been used with a Pd catalyst to convert aryl chlorides to biaryls.[327] An aryltin–aryl halide coupling has been done in ionic liquids.[328] Aryl halides react with cyclopentadiene and Cp_2ZrCl_2 and a Pd catalyst to give pentaphenylcyclopentadiene.[329] The homocoupling of arylzinc iodides with a Pd catalyst has been reported.[330] In a related reaction, arylsulfonyl chlorides also react with $ArSnBu_3$ with Pd and Cu catalysts to give the biaryl.[331]

Aryl triflates (halides) couple with ArZn(halide) reagents in the presence of a Ni catalyst.[332] A homocoupling-type reaction was reported in which $PhSnBu_3$ was treated with 10% $CuCl_2$, 0.5 equiv of iodine, and heated in DMF to give biphenyl.[333] Similar coupling was accomplished with aryltellurium compounds.[334] A Co(II) catalyzed cross-coupling of arylcopper compounds with aryl halides gives the corresponding biaryl.[335] Another homocoupling reaction of pyridyl bromides was reported using $NiBr_2$ under electrolytic conditions. Both alkylmanganese compounds (RMnCl)[336] and Ph_3In[337] react with aryl halides or aryl triflates to give the arene. Aryl halides also react with phenols to form biaryls using a Rh catalyst.[338] Diaryliodonium salts react with $PhPb(OAc)_3$ and a Pd catalyst to give the biaryl.[339] Coupling of trialkylbismuth compounds with aryl halides leads to the arene in the presence of a Pd catalyst.[340] A cross-coupling reaction of benzylindium compounds and aryl halides in the presence of a Pd catalyst has been reported.[341]

Grignard reagents couple with aryl halides without a Pd catalyst, by the benzyne mechanism,[342] but metal-catalyzed reactions are known. Typical catalysts include Fe,[343] Ni[344] Co,[345] or Ti,[346] and Pd- catalyzed reactions are important.[347] Aryl *Grignard reagents* react with aryltrimethylammonium triflates in the presence of a Pd catalyst to give the corresponding biaryl.[348] Arylmagnesium halides couple with aryl tosylates in the presence

[327] Yamazaki, O.; Tanaka, T.; Shimada, S.; Suzuki, Y.; Tanaka, M. *Synlett* ***2004***, 1921.
[328] Grasa, G.A.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 119.
[329] Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.-I.; Pivsa-Ast, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* ***2000***, *6*, 3426.
[330] With NCS, Hossain, K.M.; Kameyama, T.; Shibata, T.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 2415. See also, Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2000***, *41,* 4831.
[331] Dubbaka, S.R.; Vogel, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15292.
[332] Chen, C. *Synlett* ***2000***, 1491. See Walla, P.; Kappe, C.O. *Chem. Commun.* ***2004***, 564.
[333] Kang, S.-K.; Baik, T.-G.; Jiao, X.H.; Lee, Y.-T. *Tetrahedron Lett.* ***1999***, ***40***, 2383.
[334] Kang, S.-K.; Lee, S.-W.; Kim, M.-S.; Kwon, H.S. *Synth. Commun.* ***2001***, *31*, 1721.
[335] Korn, T.J.; Knochel, P. *Angew. Chem. Int. Ed.* ***2005***, *44,* 2947.
[336] Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* ***2004***, *6*, 4395.
[337] Pérez, I.; Sestelo, J.P.; Sarandeses, L.A. *J. Am. Chem. Soc.* ***2001***, *123*, 4155.
[338] Bedford, R.B.; Limmert, M.E. *J. Org. Chem.* ***2003***, *68*, 8669.
[339] Kang, S.-K.; Choi, S.-C.; Baik, T.-G. *Synth. Commun.* ***1999***, *29,* 2493.
[340] Gagnon, A.; Duplessis, M.; Alsabeh, P.; Barabé, F. *J. Org. Chem.* ***2008***, *73*, 3604.
[341] Chupak, L.S.; Wolkowski, J.P.; Chantigny, Y.A. *J. Org. Chem.* ***2009***, *74,* 1388.
[342] Du, C.F.; Hart, H.; Ng, K.D. *J. Org. Chem.* ***1986***, *51*, 3162.
[343] Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* ***2005***, *7*, 1943.
[344] Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* ***2005***, *127*, 17978.
[345] Korn, T.J.; Cahiez, G.; Knochel, P. *Synlett* ***2003***, 1892.
[346] Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 9601.
[347] Manabe, K.; Ishikawa, S. *Synthesis* ***2008***, 2645.
[348] Reeves, J.T.; Fandrick, D.R.; Tan, Z.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* ***2010***, *12,* 4388.

of a Pd catalyst to give unsymmetrical biaryls,[349] and to halopyridines to give the arylated pyridine.[350] Aryl *Grignard reagents* are coupled to aryliodonium salts, with $ZnCl_2$ and a Pd catalyst, to give the biaryl.[351]

The coupling reaction of an excess of a *Grignard reagent* (RMgX) with methoxy aromatic compounds, when the aromatic ring contains multiple alkoxy groups, proceeds with replacement of the OMe group by R.[352] Aryl sulfones were coupled with aryl *Grignard reagents* in the presence of a Ni catalyst.[353]

Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an $S_{RN}1$ reaction.[354] Methyl chloroacetate coupled with aryl iodides under electrolysis conditions, using a Ni catalyst.[355] Unsymmetrical biaryls were prepared from two aryl iodides using a CuI catalyst and microwave irradiation.[356]

It is possible to couple metalated alkyl compounds to aryl compounds. Alkyl halides[357] are coupled to aryl halide using a Ni catalyzed reductive cross coupling.[358] Organozinc compounds, available by reaction of an alkyl halide and zinc metal, are coupled to aryl halides using a Pd- catalyst.[359] Specialized alkyl indium complexes have been used with a Pd catalyst to give arenes.[360] Iron complexes have been used for coupling reactions.[361] Triarylbismuth compounds are coupled with aryl bromides in the presence of a Pd catalyst.[362] Organolithium reagents are coupled to aryl bromides in the presence of a Ni catalyst,[363] as are arylzinc compounds.[364] The lithium enolate anion of an ester was coupled to an aryl halide using a Pd catalyst.[365] Other ketones can be coupled to aryl triflates, in the presence of a Pd catalyst, and with good enantioselectivity.[366]

OS **VI**, 916; **VIII**, 430, 586; **X**, 9, 448.

13-10 Arylation and Alkylation of Alkenes

Alkylation or **Alkyl-de-hydrogenation**, and so on

$$R_2C{=}CH_2 + \text{Ar-X} \xrightarrow{\text{Pd(0)}} R_2C{=}CH{-}Ar$$

[349] Roy, A.H.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125,* 8704.
[350] Bonnet, V.; Mongin, F.; Trècourt, F.; Quèguiner, G.; Knochel, P. *Tetrahedron Lett.* ***2001***, *42*, 5717.
[351] Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2000***, *30,* 3607.
[352] Kojima, T.; Ohishi, T.; Yamamoto, I.; Matsuoka, T.; Kotsuki, H. *Tetrahedron Lett.* ***2001***, *42,* 1709.
[353] Clayden, J.; Cooney, J.J.A.; Julia, M. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 7.
[354] Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *Tetrahedron Lett.* ***1988***, *29*, 1705. See Pierini, A.B.; Baumgartner, M.T.; Rossi, R.A. *Tetrahedron Lett.* ***1988***, *29*, 3429.
[355] Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* ***1996***, *61*, 1748.
[356] He, H.; Wu, Y.-J. *Tetrahedron Lett.* ***2003***, *44,* 3445.
[357] For a review of coupling reactions using various metals, see Terao, J.; Kambe, N. *Acc. Chem. Res.* ***2008***, *41*,1545.
[358] Everson, D.A.; Shrestha, R.; Weix, D.J. *J. Am. Chem. Soc.* ***2010***, *132*, 920.
[359] Hama, T.; Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 4976.
[360] Shenglof, M.; Gelman, D.; Heymer, B.; Schumann, H.; Molander, G.A.; Blum, J. *Synthesis* ***2003***, 302.
[361] Sherry, B.D.; Fürstner, A. *Acc. Chem. Res.* ***2008***, *41*,1500.
[362] Rao, M.L.N.; Banerjee, D.; Jadhav, D.N. *Tetrahedron Lett.* ***2007***, *48*, 2707.
[363] Jhaveri, S.B.; Carter, K.R. *Chemistry: European J.* ***2008***, *14,* 685.
[364] Wang, L.; Wang, Z.-X. *Org. Lett.* ***2007***, *9*, 4335.
[365] Moradi, W.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 7996.
[366] Liao, X.; Weng, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2008***, *130*, 195.

Arylation of alkenes[367] is an important reaction using an "arylpalladium" reagent, typically generated *in situ* from an aryl halide or other suitably functionalized aromatic compound and a Pd catalyst.[368] The Pd catalyzed aryl–alkene coupling reaction is known as *the Heck reaction*.[369] Mizoroki[370] had earlier described the coupling between iodobenzene and styrene to form stilbene in methanol at 120 °C in the presence of potassium acetate and a palladium chloride catalyst leading some to call this the *Mizoroki–Heck reaction*. The reaction works best with aryl iodides, but conditions are available for aryl bromides and aryl chlorides.[371] Aryldiazonium salts (see Reactions **13-25** and **13-26**) have also been used.[372] Activated aromatic compounds couple readily,[373] but unactivated aromatic compounds often require special reaction conditions. The *Heck reaction* can be done with heterocyclic compounds,[374] and heteroaryl halides can be used in the coupling reaction.[375] Intramolecular *Heck reactions* are increasingly important.[376] A silane-tethered, intramolecular *Heck reaction* is known.[377] Other nucleophiles can be coupled to aryl halides.[378]

Phosphine–free catalysts,[379] halogen-free reactions,[380] and base-free reactions[381] have been developed for the *Heck reaction*. Improvements to the Pd catalyst system are constantly being reported,[382] including polymer-supported[383] silca-supported,[384] and

[367] See Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 179–321; Ryabov, A.D. *Synthesis* ***1985***, 233; Heck, R.F. *Org. React.* ***1982***, *27,* 345; Moritani, I.; Fujiwara, Y. *Synthesis* ***1973***, 524. See Cabri, W.; Candiani, I. *Accts. Chem. Res.* ***1995***, *28*, 2.

[368] See Heck, R.F. *Acc. Chem. Res.* ***1979***, *12,* 146; Kozhevnikov, I.V. *Russ. Chem. Rev.* ***1983***, *52*, 138. See also, Spencer, A. *J. Organomet. Chem.* ***1983***, *258*, 101; Andersson, C.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* ***1985***, *50,* 3891; Larock, R.C.; Johnson, P.L. *J. Chem. Soc. Chem. Commun.* ***1989***, 1368.

[369] See Alonso, F.; Beletskaya, I.P.; Yus, M. *Tetrahedron* ***2005***, *61,* 11771.

[370] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn* ***1971***, *4*, 581.

[371] See Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4176.

[372] Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. C*hem. Rev.* ***2006***, *106,* 4622;

[373] Myers, A.G.; Tanaka, D.; Mannion, M.R. *J. Am. Chem. Soc.* ***2002***, *124*, 11250.

[374] Pyridines: Draper, T.L.; Bailey, T.R. *Synlett* ***1995***, 157.

[375] See Park, S.B.; Alper, H. *Org. Lett.* ***2003***, *5*, 3209. See also, Zeni, G.; Larock, R.C. *Chem. Rev.* ***2004***, *104*, 2285.

[376] See Firmansjah, L.; Fu, G.C. *J. Am. Chem. Soc.* ***2007***, *129,* 11340. Also see, Echavarren, A.M.; Gómez-Lor, B.; González, J.J.; de Frutos, Ó. *Synlett* ***2003***, 585.

[377] Mayasundari, A.; Young, D.G.J. *Tetrahedron Lett.* ***2001***, *42,* 203.

[378] For a review, see Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* ***2002***, *58*, 2041.

[379] Consorti, C.S.; Zanini, M.L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett.* ***2003***, *5,* 983; Senra, J.D.; Malta, L.F.B.; de Souza, A.L.F.; Medeiros, M.E.; Aguiar, L.C.S.; Antunes, O.A.C. *Tetrahedron Lett.* ***2007***, *48*, 8153.

[380] Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39*, 7893.

[381] Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* ***2008***, *130,* 2424; Martinez, R.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* ***2007***, *9,* 3213.

[382] Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* ***2002***, *4,* 3031; Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2002***, *43*, 2191. For the use of palladium nanoparticles, see Calò, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* ***2003***, *68*, 2929. See Lindh, J.; Enquist, P.-A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* ***2007***, *72,* 7957. See also Seki, M. *Synthesis* ***2006***, 2975.

[383] Kim, J.-H.; Kim, J.W.; Shokouhimehr, M.; Lee, Y.-S. *J. Org. Chem.* ***2005***, *70*, 6714.

[384] Polshettiwar, V.; Molnár, Á. *Tetrahedron* ***2007***, *63*, 6949.

recoverable catalysts.[385] Considerable work has been done to study and improve the ligand.[386] Efforts have been made to produce a homogeneous catalyst for the Heck reaction.[387] The *Heck reaction* can be done in aq media,[388] in perfluorinated solvents,[389] in polyethylene glycol,[390] in neat tricaprylmethylammonium chloride,[391] and in supercritical CO_2 (See Sec. 9.D.ii).[392] The reaction has been done on solid support,[393] including Montmorillonite clay,[394] glass beads,[395] on a reverse-phase silica support,[396] and using microwave irradiation.[397] A microwave irradiated *Heck coupling* was done in water using a Pd catalyst.[398] A noncatalytic reaction was reported using supercritical water.[399] The effects of high pressure have been studied.[400] The *Heck reaction* has also been done in ionic liquids,[401] and it is known that the nature of the halide is important in such reactions.[402] Ionic liquids have been shown to actually promote the *Heck reaction*.[403]

Ethylene is the most reactive alkene, and increasing substitution lowers the reactivity. Coupling generally takes place at the less highly substituted side of the double bond.[404] Unlike the diazonium coupling reaction in Reaction **13-26**, the *Heck reaction* is not limited

[385] Karimi, B.; Enders, D. *Org. Lett.* ***2006***, *8,* 1237; Ambulgekar, G.V.; Bhanage, B.M.; Samant, S.D. *Tetrahedron Lett.* ***2005***, *46,* 2483; Papp, A.; Galbács, G.; Molnár, Á. *Tetrahedron Lett.* ***2005***, *46,* 7725; Li, H.; Wang, L.; Li, P. *Synthesis* ***2007***, 1635.

[386] See Qadir, M.; Möchel, T.; Hii, K.K. *Tetrahedron* ***2000***, *56*, 7975. Also see Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69,* 1221; Yang, D.; Chen, Y.-C.; Zhu, N.-Y. *Org. Lett.* ***2004***, *6*, 1577; Eberhard, M.R. *Org. Lett.* ***2004***, *6*, 2125; Liu, J.; Li, S.; Xie, H.; Zhang, S.; Lin, Y.; Xu, J.; Cao, J. *Synlett* ***2005***, 1885; Schultz, T.; Pfaltz, A. *Synthesis* ***2005***, 1005; Iranpoor, N.; Firouzabadi, H.; Tarassoli, A.; Fereidoonnezhad, M. *Tetrahedron* ***2010***, *66*, 2415.

[387] Nair, D.; Scarpello, J.T.; White, L.S.; dos Santes, L.M.F.; Vankelecom, I.F.J.; Livingston, A.G. *Tetrahedron Lett.* ***2001***, *42*, 8219.

[388] See Botella, L.; Nájera, C. *J. Org. Chem.* ***2005***, *70,* 4360; Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M.-M. *J. Org. Chem.* ***2006***, *71,* 4339; Bhattacharya, S.; Srivastava, A.; Sengupta, S. *Tetrahedron Lett.* ***2005***, *46,* 3557.

[389] Moineau, J.; Pozzi, G.; Quici, S.; Sinou, D. *Tetrahedron Lett.* ***1999,*** *40*, 7683.

[390] Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S.S.; Reddy, N.R. *Org. Lett.* ***2002***, *4*, 4399.

[391] Perosa, A.; Tundo, P.; Selva, M.; Zinovyev, S.; Testa, A. *Org. Biomol. Chem.* ***2004***, *2*, 2249.

[392] Early, T.R.; Gordon, R.S.; Carroll, M.A.; Holmes, A.B.; Shute, R.E.; McConvey, I.F. *Chem. Commun.* ***2001***, 1966. See Kayaki, Y.; Noguchi, Y.; Ikariya, T. *Chem. Commun.* ***2000***, 2240.

[393] Franzén, R. *Can. J. Chem.* ***2000***, *78*, 457.

[394] Ramchandani, R.K.; Uphade, B.S.; Vinod, M.P.; Wakharkar, R.D.; Choudhary, V.R.; Sudalai, A. *Chem. Commun.* ***1997***, 2071.

[395] Tonks, L.; Anson, M.S.; Hellgardt, K.; Mirza, A.R.; Thompson, D.F.; Williams, J.M.J. *Tetrahedron Lett.* ***1997***, *38*, 4319.

[396] Anson, M.S.; Mirza, A.R.; Tonks, L.; Williams, J.M.J. *Tetrahedron Lett.* ***1999,*** *40*, 7147.

[397] Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* ***2005***, *70,* 1786; Leadbeater, N.E.; Williams, V.A.; Barnard, T. M.; Collins, Jr., M.J. *Synlett* ***2006***, 2953; Declerck, V.; Martinez, J.; Lamaty, F. *Synlett* ***2006***, 3029; Zhu, M.; Song, Y.; Cao, Y. *Synthesis* ***2007***, 853; Du, L.-H.; Wang, Y.-G. *Synth. Commun.* ***2007***, *37*, 217. See Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* ***2002***, 1611.

[398] Wang, J.-X.; Liu, Z.; Hu, Y.; Wei, B.; Bai, L. *Synth. Commun.* ***2002***, *32*, 1607.

[399] Zhang, R.; Sato, O.; Zhao, F.; Sato, M.; Ikushima, Y. *Chem. Eur. J.* ***2004***, *10,* 1501.

[400] Buback, M.; Perkovic, T.; Redlich, S.; de Meijere, A. *Eur. J. Org. Chem.* ***2003***, 2375.

[401] Hagiwara, H.; Sugawara, Y.; Isobe, K.; Hoshi, T.; Suzuki, T. *Org. Lett.* ***2004***, *6*, 2325; Handy, S.T. *Synlett* ***2006***, 3176; Jung, J.-Y.; Taher, A.; Kim, H.-J.; Ahn, W.-S.; Jin, M.-J. *Synlett* ***2009***, 39; Zhou, L.; Wang, L. *Synthesis* ***2006***, 2653; Iranpoor, N.; Firouzabadi, H.; Azadi, R. *Eur. J. Org. Chem.* ***2007***, 2197; Cárdenas, J.C.; Fadini, L.; Sierra, C.A. *Tetrahedron Lett.* ***2010***, *51*, 6867.

[402] Handy, S.T.; Okello, M. *Tetrahedron Lett.* ***2003***, *44*, 8395.

[403] Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* ***2005***, *127,* 751.

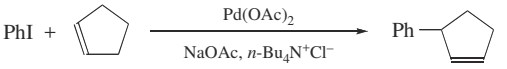
[404] Heck, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 6707; ***1971***, *93,* 6896.

to activated substrates. Both electron-deficient alkenes (e.g., acrylates),[405] and electron-rich alkenes[406] undergo the *Heck reaction*. The substrate can be an unactivated alkene,[407] and the alkene can contain a variety of functional groups (e.g., esters, ether,[408] enol ethers,[409] enamides,[410] carboxyl, phenolic, or cyano groups).[411] The aryl halide or aryl triflate can be coupled to dienes,[412] allenes,[413] allylic acetates,[414] allylic silanes,[415] allylic amines,[416] vinyl phosphonate esters,[417] and with terminal alkynes.[418] Aryliodonium salts can be coupled to conjugated alkenes in a *Heck-like* manner using a Pd catalyst.[419] Double-coupling reactions have been reported, generating diaryl aromatic compounds.[420] *Heck-type reactions* have been reported with imines.[421]

Control of regiochemistry is a serious problem in the coupling to unsymmetrical alkenes. Some regioselectivity can be obtained by the use of alkenes attached to an auxiliary coordinating group,[422] or by using special ligands and acrylate or styrene as substrates.[423] Neighboring-group effects play a role in the *Heck reaction*.[424] Steric effects are thought to control regioselectivity,[425] but electronic influences have also been proposed.[426] It has been shown that the presence of steric effects generally improves 1,2-selectivity, and that electronic effects can be used to favor 1,2- or 2,1-selectivity.[427] A 1,4-Pd migration between the *o*- and *o′*-positions of biaryls has been observed in organopalladium intermediates derived from *o*-halobiaryls.[428] Migration of the double bond is a problem in some cases, and reaction conditions play a significant role in such migrations.[429] It has been

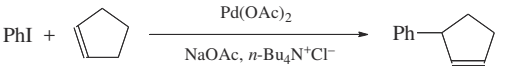
[405] Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2009***, *131,* 1372.
[406] Mo, J.; Xiao, J. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4152.
[407] Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 1476.
[408] Larhed, M.; Hallberg, A. *J. Org. Chem.* ***1996***, *61*, 9582.
[409] Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2006***, *47,* 459; Andappan, M.M.S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* ***2004***, *69*, 5212. For a review pertaining to enol ethers, see Daves, Jr., G.D. *Adv. Met. Org. Chem.* ***1991***, *2,* 59.
[410] Liu, Z.; Xu, D.; Tang, W.; Xu, L.; Mo, J.; Xiao, J. *Tetrahedron Lett.* ***2008***, *49,* 2756.
[411] See Daves, Jr., G.D.; Hallberg, A. *Chem. Rev.* ***1989***, *89,* 1433.
[412] Jeffery, T. *Tetrahedron Lett.* ***1992***, *33*, 1989.
[413] Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* ***2000***, *65*, 1767.
[414] Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* ***2005***, *7*, 4745.
[415] Jeffery, T. *Tetrahedron Lett.* ***2000***, *41*, 8445.
[416] Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2000***, *65*, 7235; Wu, J.; Marcoux, J.-F.; Davies, I.W.; Reider, P.J. *Tetrahedron Lett.* ***2001***, *42*, 159.
[417] Kabalka, G.W.; Guchhait, S.K.; Naravane, A. *Tetrahedron Lett.* ***2004***, *45,* 4685.
[418] Kundu, N.G.; Pal, M.; Mahanty, J.S.; Dasgupta, S.K. *J. Chem. Soc. Chem. Commun.* ***1992***, 41. See also, Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 299–306.
[419] Xia, M.; Chen, Z.C. *Synth. Commun.* ***2000***, *30,* 1281.
[420] Handy, S.T.; Wilson, T.; Muth, A. *J. Org. Chem.* ***2007***, *72,* 8496.
[421] Li, Z.; Fu, Y.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *Chemistry: Asian J.* ***2010***, *5,* 1475.
[422] Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* ***2001***, *123,* 8217 and earlier references therein.
[423] Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* ***1999***, *18,* 970.
[424] Oestreich, M. *Eur. J. Org. Chem.* ***2005***, 783.
[425] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry,* 2nd ed., University Science Books, Mill Valley, CA, ***1987***; Cornils, B.; Herrmann, A.W., Eds., *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley, NY, ***1996***; Vol. 2; Heck, R.F. *Acc. Chem. Res.* ***1979***, *12,* 146.
[426] Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28,* 2.
[427] von Schenck, H.; Akermark, B.; Svensson, M. *J. Am. Chem. Soc.* ***2003***, *125,* 3503.
[428] Campo, M.A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R.D.; Huang, Q.; Zhao, J.; Jenks, W.S.; Larock, R.C. *J. Am. Chem. Soc.* ***2007***, *129*, 6298.
[429] Fall, Y.; Berthiol, F.; Doucet, H.; Santelli, M. Synthesis **2007**, 1683.

reported that double-bond isomerization can be suppressed in intramolecular *Heck reactions* done in supercritical CO_2 (see Sec. 9.D.ii).[430]



21
(89%)

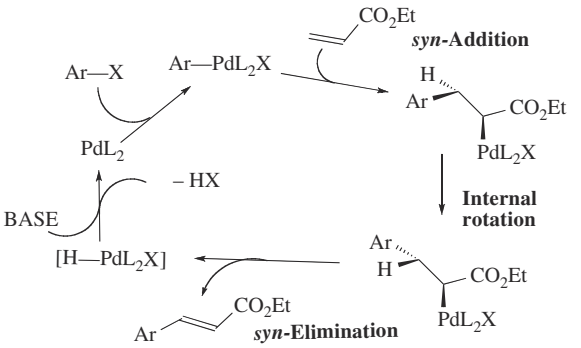
The Pd catalyzed reactions are usually stereospecific,[431] yielding products expected from syn addition followed by syn elimination.[432] Because the product is formed by an elimination step, with suitable substrates, double-bond migration can occur, resulting in allylic rearrangement (as in the reaction of cyclopentene and iodobenzene to give **21**).[433] Asymmetric *Heck reactions* are known,[434] including asymmetric intramolecular *Heck reactions*.[435] Dihydrofurans react with aryl triflates and a Pd catalyst that includes a chiral ligand, to give the 5-phenyl-3,4-dihydrofuran with good enantioselectivity.[436] A similar reaction was reported for an *N*-carbamoyl dihydropyrrole.[437]



21
(89%)

An addition–elimination mechanism (addition of ArPdX followed by elimination of HPdX) operates in most cases.[438] In the conventionally accepted reaction mechanism,[439] which is shown,[440] a four-coordinate arylPd(II) intermediate (a palladacycle)[441] is formed by oxidative addition of the aryl halide to a Pd(0) complex prior to olefin addition.[442] This description suggests that cleavage of the dimeric precursor complex, reduction

[430] Shezad, N.; Clifford, A.A.; Rayner, C.M. *Tetrahedron Lett.* ***2001***, *42*, 323.
[431] Su, Y.; Jiao, N. *Org. Lett.* ***2009***, *11,* 2980.
[432] Heck, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 6707; See Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Plexats, R.; Roglans, A. *Synthesis* ***2002***, 1903. See Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* ***2006***, *45,* 762.
[433] Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* ***1988***, *29*, 905. Also see, Larock, R.C.; Gong, W.H.; Baker, B.E. *Tetrahedron Lett.* ***1989***, *30*, 2603.
[434] Wu, W.-Q.; Peng, Q.; Dong, D.-X.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* ***2008***, *130,* 9717.
[435] Lapierre, A.J.B.; Geib, S.J.; Curran, D.P. *J. Am. Chem. Soc.* ***2007***, *129,* 494. See Dounay, A.B.; Overman, L.E. *Chem. Rev.* ***2002***, *102*, 2945.
[436] Gilbertson, S.R.; Xie, D.; Fu, Z. *J. Org. Chem.* ***2001***, *66*, 7240; Gilbertson, S.R.; Fu, Z. *Org. Lett.* ***2001***, *3*, 161; Hennessy, A.J.; Connolly, D.J.; Malone, Y.M.; Buiry, P.J. *Tetrahedron Lett.* ***2000***, *41*, 7757.
[437] Servino, E.A.; Correia, C.R.D. *Org. Lett.* ***2000***, *2*, 3039.
[438] Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* ***1972***, 3720; Henriksen, S.T.; Norrby, P.-O.; Kaukoranta, P.; Andersson, P.G. *J. Am. Chem. Soc.* ***2008***, *130,* 10414.
[439] Heck, R.F. *Comprehensive Organic Synthesis* Vol. 4, Trost, B.M.; Fleming, I., Eds., Pergamon, Oxford, NY, ***1991***, p. 833; de Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed.* ***1994***, *33*, 2379; Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28,* 2; Crisp, G.T. *Chem. Soc. Rev.* ***1998***, *27,* 427.
[440] See Diederich, F.; Stang, P.J., Eds. *Metal-Catalyzed Cross-Coupling Reactions,* Wiley–VCH, Weinheim, ***1998***; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***.
[441] Masselot, D.; Charmant, J.P.H.; Gallagher, T. *J. Am. Chem. Soc.* ***2006***, *128*, 694.
[442] See Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Chemistry: European J.* ***2007***, *13,* 2002.



of Pd^{2+}, and ligand dissociation combine to give a viable catalytic species.[443] σ-Alkyl Pd(II) intermediates are thought to be involved.[444] An analysis of reaction kinetics under dry conditions was reported.[435] In this study, the mechanism requires a first-order dependence on olefin concentration, and anomalous kinetics may be observed when the rate-limiting step is not directly on the catalytic cycle.[435] The mechanism requires a proton abstraction step, and there are substituent effects for this step.[445] A mechanistic study has been reported for the Pd catalyzed decarboxylative reaction of alkenes and arylcarboxylic acids.[446] The kinetics and mechanism of the *Heck reaction* promoted by a C—N palladacycle has been studied.[447] The mechanistic implications of asymmetric Heck reactions have been examined.[448]

There are a number of variations of this reaction, including the use of transition metal catalysts other than Pd. Rhodium-catalyzed *Heck reactions* are known,[449] and there are Co-,[450] Ru-,[451] and Ni catalyzed variations.[452] Iron-mediated arylation of alkenes has been reported,[453] and vinylgermanes are coupled to aryl halides with a Pd catalyst.[454] Aryl chlorides were coupled to conjugated esters using a $RuCl_3 \bullet 3\ H_2O$, in an atmosphere of O_2 and CO.[455] Aryl halides have been coupled to allenyltin compounds ($C{=}C{=}C\text{-}SnR_3$).[456] Divinylindium chloride [$(CH_2{=}CH)_2InCl$] reacted with an aryl iodide in aq THF with a Pd catalyst to give the styrene derivative.[457] Trialkenylindium reagents reacted similarly with

[443] Rosner, T.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* ***2001***, *123,* 4621.
[444] For related work, see Kalyani, D.; Sanford, M.S. *J. Am. Chem. Soc.* ***2008,*** *130*, 2150.
[445] García-Cuadrado, D.; de Mendoza, P,; Braga, A.C.; Maseras, F.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2007***, *129,* 6880.
[446] Tanaka, D.; Romeril, S.P.; Myers, A.G. *J. Am. Chem. Soc.* ***2005***, *127*, 10323.
[447] Consorti, C.S.; Flores, F.R.; Dupont, J. *J. Am. Chem. Soc.* ***2005***, *127,* 12054.
[448] Hii, K.K.; Claridge, T.D.W.; Brown, J.M.; Smith, A.; Deeth, R.J. *Helv. Chim. Acta* ***2001***, *84,* 3043.
[449] Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem. Int. Ed.* ***2006***, *45,* 6336.
[450] Zhou, P.; Li, Y.; Sun, P.; Zhou, J.; Bao, J. *Chem. Commun.* ***2007***, 1418; Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* ***2005***, 989.
[451] Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* ***2007***, *129,* 9858.
[452] Inamoto, K.; Kuroda, J.; Danjo, T.; Sakamoto, T. *Synlett* ***2005***, 1624; Denmark, S.E.; Butler, C.R. *Chem. Commun.* ***2009***, 20.
[453] Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem. Int. Ed.* ***2008***, *47,* 8897; Liu, W.; Cao, H.; Lei, A. *Angew. Chem. Int. Ed.* ***2010***, *49*, 2004.
[454] Torres, N.M.; Lavis, J.M.; Maleczka, Jr., R.E. *Tetrahedron Lett.* ***2009***, *50*, 4407.
[455] Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* ***2001***, *123,* 337.
[456] Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* ***2003***, *59*, 3635.
[457] Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* ***2001***, *3* , 1997.

aryl halides in the presence of a Pd catalyst.[458] Arylzinc chlorides (ArZnCl) were coupled to vinyl chlorides using a Pd catalyst,[459] and vinyl zinc compounds were coupled to aryl iodides.[460] In the presence of trimethylsilylmagnesium chloride, primary alkyl halides coupled to aryl alkenes to give the substituted alkene (R′—CH=CHAr), using a Co catalyst.[461]

Potassium vinyltrifluoroborates can be coupled to aryl halides in *Heck-like* coupling reactions.[462] Likewise, the reaction of aryltrifluoroborates with vinyl halides, in the presence of a Pd catalyst, leads to the aryl alkene.[463] In a related reaction, alkyltrifluoroborates react with aryl halides in the presence of a Pd and a Rh catalyst.[464]

Although related to chemistry found in Reaction **10-57**, metal-catalyzed alkylation reactions are easily viewed as *Heck-like* reactions. For that reason, they are discussed here. Alkyl halides are coupled to alkenes to form substituted alkenes using a Co catalyst, promoted by Me_3SiCH_2MgCl.[465] Alkylation requires that the alkyl group lacks a β-hydrogen, and the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.[466] However, vinylic groups, even those possessing β-hydrogen atoms, have been successfully introduced (to give 1,3-dienes) by the reaction of the alkene with a vinylic halide in the presence of a trialkylamine and a Pd(0) catalyst.[467]

OS **VI**, 815; **VII**, 361; **81**, 42, 54, 63, 263

13-11 Homo-Coupling of Aryl Halides: The Ullmann Reaction

de-halogen-coupling

$$2\ \mathrm{ArI} \xrightarrow[\Delta]{\mathrm{Cu}} \mathrm{Ar{-}Ar}$$

The coupling of aryl halides with copper is called the *Ullmann reaction*.[468] The reaction is clearly related to Reaction **13-9**, but involves aryl copper intermediates. The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.[469] When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used. New ligands have been developed to promote the reaction, including an air-stable

[458] Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* ***2003***, *5*, 2405.
[459] Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123,* 2719.
[460] Jalil, A.A.; Kurono, N.; Tokuda, M. *Synlett* ***2001***, 1944.
[461] Ikeda, Y.; Makamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2002***, *124*, 6514.
[462] Molander, G.A.; Brown, A.R. *J. Org. Chem.* ***2006***, *71,* 9681. Also see Alacid, E.; Njera, C. *J. Org. Chem.* ***2009***, *74*, 2321.
[463] Molander, G.A.; Fumagalli, T. *J. Org. Chem.* ***2006***, *71,* 5743.
[464] Molander, G.A.; Jean-Gérard, L. *J. Org. Chem.* ***2007***, *72*, 8422.
[465] Affo, W.; Ohmiya, H.; Fujioka T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* ***2006***, *128,* 8068.
[466] Heck, R.F. *J. Organomet. Chem.* ***1972***, *37*, 389; Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* ***1972***, 3720.
[467] Kim, J.I.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* ***1981***, *46*, 1067; Heck, R.F. *Pure Appl. Chem.* ***1981***, *53*, 2323. See also, Jeffery, T. *J. Chem. Soc. Chem. Commun.* ***1991***, 324; Larock, R.C.; Gong, W.H. *J. Org. Chem.* ***1989***, *54*, 2047. Also see Varma, R.S.; Naicker, K.P.; Liesen, P.J. *Tetrahedron Lett.* ***1999***, *40*, 2075.
[468] See Fanta, P.E. *Synthesis* ***1974***, 9; Goshaev, M.; Otroshchenko, O.S.; Sadykov, A.S. *Russ. Chem. Rev.* ***1972***, *41*, 1046.
[469] See Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem, Int. Ed.* ***1990***, *29*, 977. Also see, Meyers, A.I.; Price, A. *J. Org. Chem.* ***1998***, *63*, 412.

diazaphospholane ligand.[470] The Cu catalyst has been immobilized.[471] Intramolecular reactions are known.[472] The coupling reaction can be applied to heterocyclic compounds.[473]

The effects of other groups on the ring are not easily predicted. The nitro group is strongly activating, but only in the ortho (not meta or para) position.[474] Both R and OR groups activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do CO_2H (but not CO_2R), SO_2NH_2, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the *Wurtz reaction* (**10-56**), which can be represented schematically by

$$\textbf{Step 1} \quad \mathrm{ArI + Cu \rightarrow ArCu}$$

$$\textbf{Step 1} \quad \mathrm{ArCu + ArI \rightarrow Ar{-}Ar}$$

Organocopper compounds have been trapped by coordination with organic bases.[475] In addition, aryl copper compounds (ArCu) have been independently prepared and shown to give biaryls (Ar—Ar′) when treated with aryl iodides (Ar′I).[476] A similar reaction has been used for ring closure[477]: Copper-catalyzed coupling of aryl halides and heterocycles has been reported.[478]

An important alternative to the *Ullmann method* is the use of certain Ni complexes.[479] Aryl halides (ArX) can also be converted to Ar—Ar[480] by treatment with activated Ni metal,[481] with Zn and Ni complexes,[482] with aq alkaline sodium formate, Pd—C and a phase-transfer catalyst,[483] and in an electrochemical process catalyzed by a Ni complex.[484]

An asymmetric *Ullmann reaction* has been reported.[485]

OS **III**, 339; **V**, 1120.

[470] Yang, M.; Liu, F. *J. Org. Chem.* ***2007***, *72,* 8969.
[471] Wu, Q.; Wang, L. *Synthesis* ***2008***, 2007.
[472] See for example, Karimipour, M.; Semones, A.M.; Asleson, G.L.; Heldrich, F.J. *Synlett*, ***1990***, 525.
[473] D'Angelo, N.D.; Peterson, J.J.; Booker, S.K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P.J.; Kim, T.-S. Tetrahedron Lett. **2006**, 47, 5045.
[474] Forrest, J. *J. Chem. Soc.* ***1960***, 592.
[475] Lewin, A.H.; Cohen, T. *Tetrahedron Lett.* ***1965***, 4531.
[476] See Mack, A.G.; Suschitzky, H.; Wakefield, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1682.
[477] Salfeld, J.C.; Baume, E. *Tetrahedron Lett.* ***1966***, 3365; Lothrop, W.C. *J. Am. Chem. Soc.* ***1941***, *63*, 1187.
[478] Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* ***2007***, *129*, 12404.
[479] See Lourak, M.; Vanderesse, R.; Fort, Y.; Caubere, P. *J. Org. Chem.* ***1989***, *54,* 4840, 4844; Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* ***1990***, *63,* 80. For a review of the mechanism, see Amatore, C.; Jutand, A. *Acta Chem. Scand.* ***1990***, *44,* 755.
[480] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 82–84.
[481] Matsumoto, H.; Inaba, S.; Rieke, R.D. *J. Org. Chem.* ***1983***, *48*, 840; Chao, C.S.; Cheng, C.H.; Chang, C.T. *J. Org. Chem.* ***1983***, *48*, 4904.
[482] Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1887.
[483] Bamfield, P.; Quan, P.M. *Synthesis* ***1978***, 537.
[484] Meyer, G.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* ***1987***, *333*, 263.
[485] Nelson, T.D.; Meyers, A.I. *J. Org. Chem.* ***1994***, *59*, 2655; Nelson, T.D.; Meyers, A.I. *Tetrahedron Lett.* ***1994***, *35*, 3259.

13-12 Coupling of Aryl Compounds with Arylboronic Acid Derivatives

Aryl-de-halogenation, and so on

Aryl-de-boronylation, and so on

$$\mathrm{Ar{-}Br} + \mathrm{Ar'B(OH)_2} \xrightarrow{\mathrm{PdL_4}} \mathrm{Ar{-}Ar'}$$

Arylboronic acids are coupled to aryl halides using a Pd catalyst to give the arene in what is called *Suzuki coupling* (or *Suzuki–Miyaura coupling*).[486] Aryl triflates react with arylboronic acids [$ArB(OH)_2$, Reaction **12-28**],[487] or with organoboranes,[488] in the presence of a Pd catalyst.[489] Even hindered boronic acids give good yields of the coupled product.[490] Homocoupling of arylboronic acids has been reported.[491] Some aromatic compounds are so reactive that a catalyst may not be required. Using tetrabutylammonium bromide, phenylboronic acid was coupled to 2-bromofuran without a catalyst.[492]

Different conditions (including additives and solvent) for the reaction have been reported,[493] often focusing on the Pd catalyst[494] or the ligand.[495] Phosphine-[496] and

[486] Miyaura, N.; Suzuki, A. *Chem. Rev.* ***1995***, *95*, 2457; Alonso, F.; Beletskaya, I.P.; Yus, M. *Tetrahedron* ***2008***, *64,* 3047; Doucet, H. *Eur. J. Org. Chem.* ***2008***, 2013; Molander, G.A.; Yun, C.-S. *Tetrahedron* ***2002***, *58*, 1465. See Kotha, S.; Lahiri, K.; Kasshinath, D. *Tetrahedron* ***2002***, *58*, 9633.

[487] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* ***1981***, *11,* 513; Badone, D.; Baroni, M.; Cardomone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* ***1997***, *62*, 7170. See Torrell, E.; Brookes, P. *Synthesis* ***2003***, 469.

[488] Fürstner, A.; Seidel, G. *Synlett,* ***1998***, 161.

[489] For a review, see Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* ***2004***, 2419.

[490] Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* ***1992***, 207.

[491] Lei, A.; Zhang, X. *Tetrahedron Lett.* ***2002***, *43*, 2525; Parrish, J.P.; Jung, Y.C.; Floyd, R.J.; Jung, K.W. *Tetrahedron Lett.* ***2002***, *43,* 7899.

[492] Bussolari, J.C.; Rehborn, D.C. *Org. Lett.* ***1999***, *1*, 965.

[493] Fairlamb, I.J.S.; Kapdi, A.R.; Lee, A.F. *Org. Lett.* ***2004***, *6,* 4435; Arentsen, K.; Caddick, S.; Cloke, G.N.; Herring, A.P.; Hitchcock, P.B. *Tetrahedron Lett.* ***2004***, *45,* 3511; Artok, L.; Bulat, H. *Tetrahedron Lett.* ***2004***, *45,* 3881, Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* ***2003***, 4080.

[494] See Schweizer, S.; Becht, J.-M.; Le Drian, C. *Org. Lett.* ***2007***, *9,* 3777; Burns, M.J.; Fairlamb, I.J.S.; Kapdi, A. R.; Sehnal, P.; Taylor, R.J.K. *Org. Lett.* ***2007***, *9,* 5397; Guo, M; Jian, F.; He, R. *Tetrahedron Lett.* ***2006***, *47,* 2033; Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* ***2006***, *62,* 10888; Kantam, M.L.; Subhas, M.S.; Roy, S.; Roy, M. *Synlett* ***2006***, 633; Alonso, D.A.; Cívicos, J.F.; Nájera, C. *Synlett* ***2009***, 3011; You, E.; Li, P.; Wang, L. *Synthesis* ***2006***, 1465; Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* ***2006***, 2679; Lee, D.-H.; Jung, J.-Y.; Lee, I.-M.; Jin, M.-J. *Eur. J. Org. Chem.* ***2008***, 356; Subhas, M.S.; Racharlawar, S.S.; Sridhar, B.; Kennady, P.K.; Likhar, P.R.; Kantam, M.L.; Bhargava, S.K. *Org. Biomol. Chem.* ***2010***, ***8***, 3001; Bhayana, B.; Fors, B.P.; Buchwald, S.L. *Org. Lett.* ***2009***, *11*, 3954; Nishikata, T.; Abela, A.R.; Huang, S.; Lipshutz, B.H. *J. Am. Chem. Soc.* ***2010***, *132*, 4978; Guo, M.; Zhang, Q. *Tetrahedron Lett.* ***2009***, *50*, 1965. For a discussion of catalysts in this reaction, see Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2005***, *127,* 4685. For a precatalyst that is useful with unstable 2-heteroaryl boronic acids, see Kinzel, T.; Zhang, Y.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2010***, *132*, 14073.

[495] So, C.M.; Yeung, C.C.; Lau, C.P.; Kwong, F.Y.*J. Org. Chem.* ***2008***, *73,* 7803; Lipshutz, B.H.; Petersen, T.B.; Abela, A.R. *Org. Lett.* ***2008***, *10,* 1333; Dai, W.-M.; Zhang, Y. *Tetrahedron Lett.* ***2005***, *46,* 1377; Villemin, D.; Jullien, A.; Bar, N. *Tetrahedron Lett.* ***2007***, *48,* 4191; Lai, Y.-C.; Chen, H.-Y.; Hung, W.-C.; Lin, C.-C.; Hong, F.-E. *Tetrahedron* ***2005***, *61,* 9484; Kuriyama, M.; Shimazawa, R.; Shirai, R. *Tetrahedron* ***2007***, *63,* 9393; Mai, W.; Gao, L. *Synlett* ***2006***, 2553; Ghosh, R.; Adarsh, N.N.; Sarkar, A. *J. Org. Chem.* ***2010***, *75*, 5320.

[496] Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* ***2005***, *70*, 2191; Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* ***2005***, *70,* 6122; Yamamoto, Y.; Suzuki, R.; Hattori, K.; Nishiyama, H. *Synlett* ***2006***, 1027; Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* ***2008***, 2711; Zhang, G. *Synthesis* ***2005***, 537; Cui, X.; Qin, T.; Wang, J.R.; Liu, L.; Guo, Q.-X. *Synthesis* ***2007***, 393.

ligand-free conditions[497] have been developed. Recyclable catalysts have been developed.[498] Catalysts have been developed for deactivated aryl chlorides.[499] *Suzuki coupling* has also been done in ionic liquids,[500] in supercritical CO_2[501] (see Sec. 9.D.ii), and there are solvent-free procedures.[502] Several procedures for coupling in aqueous media have been reported.[503] The reaction has been done neat on alumina,[504] and on alumina with microwave irradiation.[505] Several procedures have been reported using microwave irradiation.[506] Modifications to the basic procedure include tethering the aryl triflate[507] or the boronic acid[508] to a polymer, allowing a polymer-supported *Suzuki reaction*. Polymer-bound Pd complexes have been used.[509] There is even a Pd free cross-coupling.[510]

Arylboronic acids have been coupled to vinyl halides[511] or vinyl tosylates[512] using a Pd catalyst. Halogenated heteroaromatic compounds react, as do aryl carbamates, carbonates and sulfamates,[513] and aryl phosphoramides.[514] Aryl sulfonates have been used.[515]

[497] Liu, L.; Zhang, Y.; Xin, B. *J. Org. Chem.* ***2006***, *71,* 3994; Korolev, D.N.; Bumagin, N.A. *Tetrahedron Lett.* ***2006***, *47,* 4225; Li, J.-H.; Li, J.-L.; Xie, Y.-X. *Synthesis* ***2007***, 984; Saha, D.; Chattopadhyay, K.; Ranu, B.C. *Tetrahedron Lett.* ***2009***, *50*, 1003; da Conceição Silva, A.; Senra, J.D.; Aguiar, L.C.S.; Simas, A.B.C.; de Souza, A.L.F.; Malta, L.F.B.; Antunes, O.A.C. *Tetrahedron Lett.* ***2010***, *51*, 3883; Zhou, W.-J.; Wang, K.-H.; Wang, J.-X.; Gao, Z.-R. *Tetrahedron* ***2010***, *66,* 7633.

[498] Li, J.-H.; Liu, W.-J.; Xie, Y.-X. *J. Org. Chem.* ***2005***, *70,* 5409; Felpin, F.-X. *J. Org. Chem.* ***2005***, *70,* 8575; Masllorens, J.; González, I.; Roglans, A. *Eur. J. Org. Chem.* ***2007***, 158.

[499] Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4153.

[500] See Calò, V.; Nacci, A.; Monopoli, A.; Montingelli, F. *J. Org. Chem.* ***2005***, *70,* 6040; Yang, C.-H.; Tai, C.C.; Huang, Y.-T.; Sun, I.-W. *Tetrahedron* ***2005***, *61,* 4857; Hagiwara, H.; Ko, K.H.; Hoshi, T.; Suzuki, T. *Chem. Commun.* ***2007***, 2838; Xin, B.; Zhang, Y.; Liu, L.; Wang, Y. *Synlett* ***2005***, 3083.

[501] Early, T.R.; Gordon, R.S.; Carroll, M.A.; Holmes, A.B.; Shute, R.E.; McConvey, I.F. *Chem. Commun.* ***2001***, 1966.

[502] Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synth. Commun.* ***2007***, *37,* 2433.

[503] For a review, see Franzén, R.; Xu, Y. *Can. J. Chem.* ***2005***, *83*, 266. See Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* ***2006***, *47,* 197; Arvela, R.K.; Leadbeater, N.E.; Mack, T.L.; Kormos, C.M. *Tetrahedron Lett.* ***2006***, *47,* 217; Hattori, H.; Fujita, K.; Muraki,T.; Sakaba, A. *Tetrahedron Lett.* ***2007***, *48,* 6817; Del Zotto, A.; Amoroso, F.; Baratta, W.; Rigo, P. *Eur. J. Org. Chem.* ***2009***, 110; Xu, K.; Hao, X.-Q.; Gong, J.-F.; Song, M.-P.; Wu, Y.-J. *Austr. J. Chem.* ***2010***, *63*, 315.

[504] Kabalka, G.W.; Pagni, R.M.; Hair, C.M. *Org. Lett.* ***1999***, *1*, 1423. See Basu, B.; Das, P.; Bhuiyan, Md.M.H.; Jha, S. *Tetrahedron Lett.* ***2003***, *44,* 3817.

[505] Villemin, D.; Caillot, F. *Tetrahdron Lett.* ***2001***, *42*, 639.

[506] Chanthavong, F.; Leadbeater, N.E. *Tetrahedron Lett.* ***2006***, *47,* 1909; Arvela, R.K.; Leadbeater, N.E.; Sangi, M.S.; Williams, V.A.; Granados, P.; Singer, R.D. *J. Org. Chem.* ***2005***, *70*, 161; Miao, G.; Ye, P.; Yu, L.; Baldino, C.M. *J. Org. Chem.* ***2005***, *70,* 2332; Arvela, R.K.; Leadbeater, N.E. *Org. Lett.* ***2005***, *7,* 2101; Baxendale, I.R.; Griffiths-Jones, C.M.; Ley, S.V.; Tranmer, G.K. *Chemistry: European J.* ***2006***, *12,* 4407; Yan, J.; Zhu, M.; Zhou, Z. *Eur. J. Org. Chem.* ***2006***, 2060.

[507] Blettner, C.G.; König, W.A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* ***1999***, *64*, 3885. For other reactions on solid support, see Franzén, R. *Can. J. Chem.* ***2000***, *78*, 957.

[508] Hebel, A.; Haag, R. *J. Org. Chem.* ***2002***, *67*, 9452.

[509] Kantam, M.L.; Roy, M.; Roy, S.; Sreedhar, B.; Madhavendra, S.S.; Choudary, B.M.; De, R.L. *Tetrahedron* ***2007***, *63*, 8002; Schweizer, S.; Becht, J.-M.; Le Drian, C. *Tetrahedron* ***2010***, *66*, 765; Islam, M.; Mondal, P.; Tuhina, K.; Hossain, D.; Roy, A.S. *Chem. Lett.* ***2010***, *39*, 1200.

[510] Guo, Y.; Young, D.J.; Hor, T.S.A. *Tetrahedron Lett.* ***2008***, *49*, 5620.

[511] Poondra, R.R.; Fischer, P.M.; Turner, N.J. *J. Org. Chem.* ***2004,*** *69*, 6920.

[512] Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* ***2003***, *68*, 670.

[513] Quasdorf, K.W.; Riener, M.; Petrova, K.V.; Garg, N.K. *J. Am. Chem. Soc.* ***2009***, *131*, 17748. See Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* ***2009***, *131*, 17750.

[514] Zhao, Y.-L.; Li, Y.; Li, Y.; Gao, L.-X.; Han, F.-S. *Chemistry: Eur. J.* ***2010***, *16,* 4991.

[515] Zhang, W.; Chen, C.H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* ***2004***, *6*, 1473; Riggleman, S.; DeShong, P. *J. Org. Chem.* ***2003***, *68*, 8106.

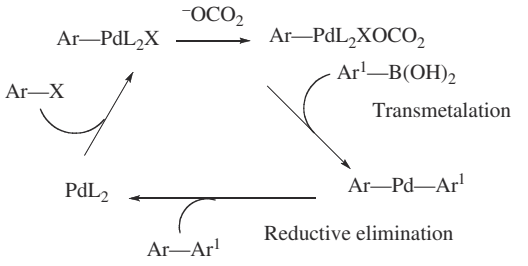
Arylboronic acids couple with aryl sulfonate esters.[516] Many different heterocycles have been arylated.[517] 4-Pyridylboronic acids have been used.[518] 3-Iodopyridine reacted with NaBPh and palladium acetate, with microwave irradiation, to give 3-phenylpyridine.[519]

A variety of functional groups are compatible with Suzuki coupling, including $Ar_2P{=}O$,[520] CHO,[521] C=O of a ketone,[522] CO_2R,[523] cyclopropyl,[524] NO_2,[525] CN, and halogen substituents.[526] Vinyl halides react with arylboronic acids to give alkenyl derivatives (vinyl arenes, C=C—Ar),[527] in what is clearly a *Heck-like* reaction. In a variation, vinylboronic acids coupled to aryl halides to give the vinyl-coupling product.[528] Vinylboronic acids have been coupled to aryldiazonium salts (see Reaction **13-25**) without added base, using a Pd catalyst with an imidazolium ligand.[529]

Alkylation can accompany arylation if alkyl halides are added, as in the conversion of iodobenzene to 2,6-dibutylbiphenyl.[530] Alkyl groups may be coupled to aryls, as in the Pd catalyzed reaction of arylboronic acids with benzylic carbonates.[531] Arylboronic acids also couple with alkyl halides using either a palladium(II) acetate[532] or a Ni catalyst.[533] Conversely, arylboronic acids can be coupled to aliphatic halides.[534] Arylboronic acids can be coupled to allylic alcohols as well.[535] Benzylic phosphonates have also been used.[536] Double *Suzuki coupling* reactions are known.[537] An alkyl–alkyl coupling reaction has been classified as a *Suzuki cross-coupling* reaction.[538] The reaction of an arylboronic acid and 1,2-dibromoethane, with KOH and a Pd catalyst, leads to the styrene derivative.[539]

[516] So, C.M.; Lau, C.P.; Chan, A.S.C.; Kwong, F.Y. *J. Org. Chem.* ***2008***, *73,* 7731; So, C.M.; Lau, C.P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2008***, *47,* 8059.
[517] Lane, B.S.; Sames, D. *Org. Lett.* ***2004***, *6*, 2897; Denmark, S.E.; Baird, J.D. *Org. Lett.* ***2004***, *6*, 3649; Prieto, M.; Zurita, E.; Rosa, E.; Muñoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* ***2004***, *69*, 6812; Dvorak, C.A.; Rudolph, D.A.; Ma, S.; Carruthers, N.I. *J. Org. Chem.* ***2005***, *70,* 4186; Kudo, N.; Perseghini, M.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1282; Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Y.-J. *Angew. Chem. Int. Ed.* ***2008***, *47,* 1473.
[518] Morris, G.A.; Nguyen, S.T. *Tetrahedron Lett.* ***2000***, *42*, 2093.
[519] Villemin, D.; Gómez-Escalonilla, M.J.; Saint-Clair, J.-F. *Tetrahedron Lett.* ***2001***, *42*, 635.
[520] Baillie, C.; Chen, W.; Xiao, J. *Tetrahedron Lett.* ***2001***, *42*, 9085.
[521] Phan, N.T.S.; Brown, D.H.; Stgring, P. *Tetrahedron Lett.* ***2004***, *45*, 7915.
[522] Baillie, C.; Zhang, L.; Xiao, J. *J. Org. Chem.* ***2004***, *69*, 7779.
[523] Mutele, I.; Suna, E. *Tetrahedron Lett.* ***2004***, *45*, 3909.
[524] Ma, H.-r.; Wang, X.-L.; Deng, M.-z. *Synth. Commun.* ***1999***, *29*, 2477.
[525] Tao, B.; Boykin, D.W. *J. Org. Chem.* ***2004***, *69*, 4330; Li, J.-H.; Liu, W.-J. *Org. Lett.* ***2004***, *6*, 2809.
[526] Colacot, T.J.; Shea, H.A. *Org. Lett.* ***2004***, *6,* 3731; DeVasher, R.B.; Moore, L.R.; Shaughnessy, K.H. *J. Org. Chem.* ***2004***, *69,* 7919.
[527] Shen, W. *Synlett* ***2000***, 737.
[528] Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* ***2004***, 1075.
[529] Andrus, M.B.; Song, C.; Zhang, J. *Org. Lett.* ***2002***, *4*, 2079.
[530] Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* ***2000***, 157. See Yin, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2000***, *122,* 112051.
[531] Kuwano, R.; Yokogi, M. *Org. Lett.* ***2005***, *7,* 945.
[532] Kirchhoff, J.H.; Netherton, M.R.; Hills, I.D.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 13662.
[533] Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126,* 1340.
[534] Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Tetrahedron Lett.* ***2004***, *45*, 6959.
[535] Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* ***2004***, 1200; Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* ***2004***, 4989.
[536] McLaughlin, M. *Org. Lett.* ***2005***, *7*, 4875.
[537] Habashneh, A.Y.; Dakhil, O.O.; Zein, A.; Georghiou, P.E. *Synth. Commun.* ***2009***, *39*, 4221.
[538] Lu, Z.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2010***, *49,* 6676.
[539] Lando, V.R.; Moneitro, A.L. *Org. Lett.* ***2003***, *5*, 2891.

Since many biaryls are chiral due to atropisomerism (see Sec. 4.C, category 5), the use of a chiral catalyst, and/or a chiral ligand can lead to enantioselectivity in the *Suzuki coupling*.[540]



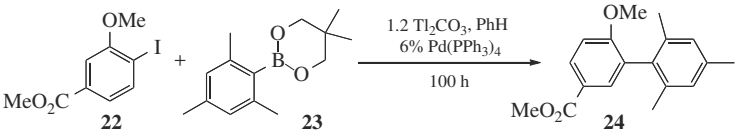
For a mechanistic viewpoint,[541] the *Suzuki coupling* proceeds via oxidative addition of areneboronic acids to give a Pd species, followed by 1,2-arene migration to an electron-deficient Pd atom, eventually leading to very fast reductive elimination to afford biaryls.[542] This mechanism is illustrated.[543] Several intermediates of the oxidative coupling process have been identified by electrospray ionization mass spectrometry.[544] Palladium peroxo complexes have been shown to be key intermediates.[545]

Other transition metals have been employed in these coupling reactions, sometimes as cocatalysts. Arylboronic acids have been coupled to conjugated alkenes to give the aryl–alkene coupling product using a Pd catalyst,[546] a Ru catalyst with copper(II) acetate,[547] a Ni catalyst,[548] or a Rh catalyst.[549] Aryl boronic acids are coupled with aryl ammonium salts to give the biaryl, with a Ni catalyst.[550] Allylic acetates have been coupled to arylboronic acids using nickel bis(acetylacetonate) and diisobutylaluminum hydride.[551] Arylboronic acids (Reaction **12-28**) were shown to react directly with benzene in the presence of $Mn(OAc)_3$.[552] Aryl halides couple with $ArB(IR'_2)$ species with a Pd catalyst.[553] Iron catalysts have been developed for coupling with alkyl halides.[554] Arylboronic

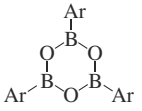
[540] Navarro, O.; Kelly, III, R.A.; Nolan, S.P. *J. Am. Chem. Soc.* ***2003***, *125*, 16194; Baudoin, O. *Eur. J. Org. Chem.* ***2005***, 4223.
[541] See Esponet, P.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4704.
[542] Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* ***1996***, *61,* 2346.
[543] See *Metal–Catalyzed Cross–Coupling Reactions*, Diederich, F.; Stang, P.J. Wiley–VCH, Weinheim, ***1998***, p. 212.
[544] Aramendia, M.A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* ***1999***, *64,* 3592.
[545] Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Hakim Lakmini, H. *J. Am. Chem. Soc.* ***2006***, *128,* 6829.
[546] Jung, Y.C.; Mishra, R.K.; Yoon, C.H.; Jung, K.W. *Org. Lett.* ***2003***, *5*, 2231.
[547] Farrington, E.J.; Brown, J.M.; Barnard, C.F.J.; Rowsell, E. *Angew. Chem. Int. Ed.* ***2002***, *41,* 169.
[548] Percec, V.; Golding, G.M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* ***2004***, *69,* 3447. See Quasdorf, K.W.; Tian, X.; Garg, N.K. *J. Am. Chem. Soc.* ***2008***, *130,* 14422; Chen, C.; Yang, L.-M. *Tetrahedron Lett.* ***2007***, *48,* 2427; González-Bobes, F.; Fu, G.C. *J. Am. Chem. Soc.* ***2006***, *128,* 5360.
[549] Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* ***2001***, *123,* 5358.
[550] Blakey, S.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2003***, *125*, 6046.
[551] Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 15.
[552] Demir, A.S.; Reis, Ö; Emrullahoglu, M. *J. Org. Chem.* ***2003***, *68*, 578.
[553] Bumagin, N.A.; Tsarev, D.A. *Tetrahedron Lett.* ***1998***, *39*, 8155.
[554] Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* ***2010***, *132,* 10674. However, see Bedford, R.B.; Nakamura, M.; Gower, N.J.; Haddow, M.F.; Hall, M.A.; Huwe, M.; Hashimoto, T.; Okopie, R.A. *Tetrahedron Lett.* ***2009***, *50*, 6110.

acids couple with the phenyl group of Ph_2TeCl_2 with a Pd catalyst.[555] Tributyltin aryl compounds were coupled to the aryl group of $Ar_2I^+BF_4^-$ with a Ni catalyst.[556]

Suzuki-type coupling reactions have been reported involving acyl halides. When arylboronic acids were reacted with benzoyl chloride and $PdCl_2$, the product was the diaryl ketone.[557] This coupling reaction was also accomplished using a Pd(0) catalyst.[558] Cyclopropylboronic acids couple with benzoyl chloride, in the presence of Ag_2O and a Pd catalyst, to give the cyclopropyl ketone.[559] A Ni catalyst has been used,[560] and Ph_3P/Ni/C—BuLi has also been used.[561] Arylboronic acids have also been coupled to anhydrides,[562] and the methoxy group of anisole derivatives has been replaced with phenyl using phenylboronic acid and a Ru catalyst.[563]



Arylborates (see Reaction **12-28**), $ArB(OR)_2$, can be used in place of the boronic acid.[564] The coupling reaction of aryl iodide (**22**) with boronate (**23**), for example, gave biaryl **24**.[565] Base-free conditions, using nitrogen ligands, have been reported.[566] Aryl and heteroarylboroxines (**25**) can be coupled to aryl halides using a Pd catalyst.[567] Vinylboranes have been coupled to aryl iodides to give the aryl alkene, in the presence of a Pd catalyst.[568] Organoboranes are coupled to aryl halides with a Pd catalyst.[569]



25

[555] Kang, S.-K.; Hong, Y.-T.; Kim, D.-H.; Lee, S.-H. *J. Chem. Res. (S)* ***2001***, 283.
[556] Kang, S.-K.; Ryu, H.-C.; Lee, S.-W. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2661.
[557] Bumagin, N.A.; Korolev, D.N. *Tetrahedron Lett.* ***1999***, *40,* 3057.
[558] Haddach, M.; McCarthy, J.R. *Tetrahedron Lett.* ***1999***, *40* , 3109.
[559] Chen, H.; Deng, M.-Z. *Org. Lett.* ***2000***, *2*, 1649.
[560] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron* ***1999***, *55*, 11889.
[561] Lipshutz, B.H.; Sclafani, J.A.; Blomgren, P.A. *Tetrahedron* ***2000***, *56*, 2139.
[562] Gooßen, L.J.; Ghosh, K. *Angew. Chem. Int. Ed.* ***2001***, *40,* 3458.
[563] Kakiuchi, F.; Usai, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2004***, *126*, 2706.
[564] Lu, G.; Franzén, R.; Zhang, Q.; Xu, Y. *Tetrahedron Lett.* ***2005***, *46,* 4255.
[565] Chameil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* ***2000***, *56*, 9655. Also see Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* ***2005***, *127,* 5936.
[566] Yoo, K.S.; Yoon, C.H.; Jung, K.W. *J. Am. Chem. Soc.* ***2006***, *128,* 16384.
[567] Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org.Chem.* ***2004***, *69*, 2210.
[568] Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* ***2007***, *129,* 12634.
[569] Iglesias, B.; Alvarez, R.; de Lera, A.R. *Tetrahedron* ***2001***, *57,* 3125.

In a useful variation, aryltrifluoroborates ($ArBF_3^+ X^-$) (Reaction **12-28**), are coupled to aryl halides with a Pd catalyst to give the biaryl.[570] Alkyltrifluoroborates[571] (RBF_3K, see Reaction **12-28**) react with aryl triflates[572] aryl halides,[573] or aryliodonium salts[574] with a Pd catalyst, to give the arene. In a related reaction, vinyltrifluoroborates ($C{=}C{-}BF_3^+ X^-$ see Reaction **12-28**), are coupled to aryl halides with a Pd catalyst to give the styrene derivative.[575] *Suzuki coupling* with trifluoroborates has also been done using microwave irradiation.[576] Aryltellurides have been used in this reaction.[577] A Pd catalyzed reaction with enamino ketones, mediated by Cu(II) salts, led to coupling to give the aryl derivative.[578] Ruthenium catalysts have also been used.[579]

OS **75**, 53, 61

The coupling reactions of alkylboronic acids are covered in Reaction **13-17**.

OS CV, 102, 467; OS **81**, 89.

13-13 Aryl–Alkyne Coupling Reactions

Alkynyl-de-halogenation, and so on

$$ArI + RC{\equiv}CCu \longrightarrow ArC{\equiv}CR$$

When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Stephens–Castro coupling*.[580] Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides have been used. Benzonitrile was shown to react with alkynyl zinc bromides, with a Ni catalyst and after electrolysis to give the diarylalkyne, where the cyano unit was replaced with an alkyne unit.[581]

$$Ar\text{-}X + RC{\equiv}CH \xrightarrow{Pd(0)} Ar\text{-}C{\equiv}CR$$

[570] Molander, G.A.; Canturk, B.; Kennedy, L.E. *J. Org. Chem.* ***2009***, *74*, 973; Molander, G.A.; Jean-Grard, L. *J. Org. Chem.* ***2009***, *74*, 1297; Barder, T.E.; Buchwald, S.L. *Og. Lett.* ***2004***, *6*, 2649. See Ito, T.; Iwai, T.; Mizuno, T.; Ishino, Y. *Synlett* ***2003***, 1435.

[571] Darses, S.; Genet, J.-P. *Chem. Rev.* ***2008***, *108*, 288.

[572] Molander, G.A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534.

[573] Dreher, S.D.; Dormer, P.G.; Sandrock, D.L.; Molander, G.A. *J. Am. Chem. Soc.* ***2008***, *130,* 9257; Dreher, S.D.; Lim, S.-E.; Sandrock, D.L.; Molander, G.A. *J. Org. Chem.* ***2009***, *74*, 3626.

[574] Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29*, 2457.

[575] Molander, G. A.; Bernardi, C.R. *J. Org. Chem.* ***2002***, *67,* 8424.

[576] Kabalka, G.W.; Al-Masum, M. *Tetrahedron Lett.* ***2005***, *46*, 632; Kabalka, G.W.; Zhou, L.-L.; Naravane, A. *Tetrahedron Lett.* ***2006***, *47,* 6887; Harker, R.L.; Crouch, R.D. *Synthesis* ***2007***, 25; Kabalka, G.W.; Naravane, A.; Zhao, L.L. *Tetrahedron Lett.* ***2007***, *48,* 7091; Kabalka, G.W.; Al-Masum, M.; Mereddy, A.R.; Dadush, E. *Tetrahedron Lett.* ***2006***, *47,* 1133.

[577] Cella, R.; Cunha, R.L.O.R.; Reis, A.E.S.; Pimenta, D.C.; Klitzke, C.F.; Stefani, H.A. *J. Org. Chem.* ***2006***, *71,* 244.

[578] Ge, H.; Niphakis, M.J.; Georg, G.I. *J. Am. Chem. Soc.* ***2008***, *130,* 3708.

[579] Wu, J.; Zhang, L.; Gao, K. *Eur. J. Org. Chem.* ***2006***, 5260.

[580] Castro, C.E.; Stephens, R.D. *J. Org. Chem.* ***1963***, *28,* 2163; Stephens, R.D.; Castro, C.E. *J. Org. Chem.* ***1963***, *28*, 3313. See Sladkov, A.M.; Gol'ding, I.R. *Russ. Chem. Rev.* ***1979***, *48*, 868; Bumagin, N.A.; Kalinovskii, I.O.; Ponomarov, A.B.; Beletskaya, I.P. *Doklad. Chem.* ***1982***, *265*, 262.

[581] Penney, J.M.; Miller, J.A. *Tetrahedron Lett.* ***2004***, *45*, 4989.

A Pd catalyzed variation is known in which an aryl halide reacts with a terminal alkyne to give 1-aryl alkynes is called *Sonogashira coupling*.[582] Terminal aryl alkynes react with aryl iodides and Pd(0)[583] to give the corresponding diaryl alkyne,[584] but monoalkynes are easily prepared.[585] Aryl iodides are more reactive than aryl fluorides.[586] Alkynes can be coupled to heteroaromatic compounds.[587] As with all of the metal-catalyzed reactions in this chapter, work has been done to vary reaction conditions, including the catalyst,[588] the ligand,[589] the solvent, and additives.[590] There are copper-[591] and ligand-free variations.[592] Transition metal free coupling has been reported using a 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical as an oxidant.[593] Variations include *Sonogashira coupling* in water, without Cu,[594] and other reactions are done in aqueous media.[595] The coupling has been done in aq polyethylene glycol,[596] and in ionic liquids.[597] Microwave irradiation is an important tool in this reaction.[598] *Sonogashira coupling* was reported on microbeads,[599] with

[582] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* ***1975***, 4467; Chinchilla, R.; Nájera, C. *Chem. Rev.* ***2007***, *107,* 874; Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proceed. Int.* ***1995***, *27,* 127; Sonogashira, K. in Diederich, F.; Stang, P.J. *Metal–Catalyzed Cross–Coupling Reactions,* Wiley–VCH, NY, ***1998***, Chapter 5.

[583] See Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* ***2003***, *68*, 3327.

[584] Böhm, V.P.W.; Herrmann, W.A. *Eur. J. Org. Chem.* ***2000***, 3679. See Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* ***2001***, 649.

[585] Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* ***2005***, *70*, 391.

[586] See Mio, M.J.; Kopel, L.C.; Braun, J.B.; Gadzikwa, T.L.; Hull, K.; Brisbois, R.G.; Markworth, C.J.; Grieco, P. A. *Org. Lett.* ***2002***, *4*, 3199.

[587] Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* ***2004***, *2*, 2161; Chen, Y.; Markina, N.A.; Larock, R.C. *Tetrahedron* ***2009***, *65*, 8908; R'kyek, O.; Halland, N.; Lindenschmidt, A.; Alonso, J.; Lindemann, P.; Urmann, M.; Nazaré, M. *Chemistry: Eur. J.* ***2010***, *16*, 9986.

[588] Yi, C.; Hua, R. *J. Org. Chem.* ***2006***, *71,* 2535; Tang, B.X.; Wang, F.; Li, J.-H.; Xie, Y.-X.; Zhang, M.-B. *J. Org. Chem.* ***2007***, *72,* 6294; Li, P.; Wang, L.; Li, H. *Tetrahedron* ***2005***, *61,* 8633; Plenio, H. *Angew. Chem. Int. Ed.* ***2008***, *47,* 6954.

[589] Mori, S.; Yanase, T.; Aoyagi, S.; Monguchi, Y.; Maegawa, T.; Sajiki, H. *Chemistry: European J.* ***2008***, *14,* 6994.

[590] See Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* ***2004***, *6*, 1527; Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* ***2004***, *45,* 1367; Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V.V. *Org. Lett.* ***2004***, *6,* 3473.

[591] Yi, C.; Hua, R. *J. Org. Chem.* ***2006***, *71*, 2535; Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* ***2006***, *47,* 3023; Komáromi, A.; Tolnai, G.L.; Novák, Z. *Tetrahedron Lett.* ***2008***, *49,* 7294; Teratani, T.; Ohtaka, A.; Kawashima, T.; Shimomura, O.; Nomura, R. *Synlett* ***2010***, 2271; Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Synthesis* ***2005***, 804; Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Eur. J. Org. Chem.* ***2005***, 4256; Ren, T.; Zhang, Y.; Zhu, W.; Zhou, J. *Synth. Commun.* ***2007***, *37*, 3279; Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* ***2009***, *50*, 1557. For a variation using Au-nanoparticles, see de Souza, R.O.M.A.; Bittar, M.S.; Mendes, L.V.P.; da Silva, C.M.F.; da Silva, V.T.; Antunes, O.A.C. *Synlett* ***2008***, 1777.

[592] Gholap, A.R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R.J.; Srinivasan, K.V. *J. Org. Chem.* ***2005***, *70,* 4869; Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett.* ***2009***, *50*, 5044.

[593] Maji, M.S.; Murarka, S.; Studer, A. *Org. Lett.* ***2010***, *12,* 3878.

[594] Lipshutz, B.L.; Chung, D.W.; Rich, B. *Org. Lett.* ***2008***, *10,* 3793; Guan, J.T.; Weng, T.Q.; Yu, G.-A.; Liu, S.H. *Tetrahedron Lett.* ***2007***, *48,* 7129.

[595] Özdemir, I.; Gürbüz, N.; Gök, Y.; Çetinkaya, E.; Çetinkaya, B. *Synlett* ***2005***, 2394; Chen, G.; Zhu, X.; Cai, J.; Wan, Y. *Synth. Commun.* ***2007***, *37*, 1355.

[596] Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003***, *5*, 3919.

[597] See Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* ***2002***, *4*, 1691; Park, S.B.; Alper, H. *Chem. Commun.* ***2004***, 1306; de Lima, P.G.; Antunes, O.A.C. *Tetrahedron Lett.* ***2008***, *49,* 2506.

[598] Appukkuttan, P.; Dehaen, W.; van der Eyken, E. *Eur. J. Org. Chem.* ***2003***, 4713. See also, Kabalka, G.W.; Wang, L.; Namboodiri, V.; Pagni, R.M. *Tetrahedron Lett.* ***2000***, *41*, 515.

[599] Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* ***2001***, *42*, 1815; Gonthier, E.; Breinbauer, R. *Synlett* ***2003***, 1049.

nanoparticulate nickel powder,[600] and the aryl iodide was tethered to a polymer for a solid-state reaction.[601] Polymer-supported catalysts are known.[602] A variation scavenged the triphenylphosphine byproduct by addition of *Merrifield* resin.[603]

Coupling of the alkynes to form a diyne (see Reaction **14-16**) can be a problem is some cases, although the aryl–alkyne coupling usually predominates.[604] There are many variations. Alkyl groups are coupled to alkynes under *Sonogashira conditions*, including unactivated secondary alkyl halides.[605] Coupling propargyl bromide and an aryl iodide, in the presence of an amine, gives the aryl aminomethylalkyne.[606] 4-Chloroacetophenone reacts with 1-phenylethyne, showing that the carbonyl group is compatible with this reaction.[607] Arenediazonium salts can be used for the coupling reaction.[608] Similar Pd catalyzed coupling of bromoalkynes with heterocycles also leads to the alkynyl derivative.[609] Ynamides are coupled using cooper-free conditions.[610]

There are variations of the *Sonogashira reaction* that use other metals as catalysts or cocatalysts. A Pd free reaction is known, using Cu complexes as the catalyst.[611] An In catalyzed reaction is known that does not use Cu, Pd, or phosphine ligands.[612] Gold(I) has been used to catalyze *Sonogashira reactions*,[613] and there are Ni[614] and Fe catalyzed[615] reactions. Silver iodide has been used to catalyze the reaction.[616] Conversion of 1-lithioalkynes to the corresponding alkynyl zinc reagent allows coupling with aryl iodides when a Pd catalyst is used.[617] A 1-lithioalkyne was directly coupled to aryl bromides in the presence of $B(OiPr)_3$ and a Pd catalyst,[618] where an alkynylboronic acid was generated *in situ*. Lithium alkynyltrimethylborates are coupled to aryl chlorides as well.[619] Terminal alkynes are coupled to acylpyridinium salts in the presence of a Cu catalyst, giving a product with high enantioselectivity when a chiral ligand is used.[620] Coupling with alkynyl tin compounds is known.[621] A triphenylstibine [$Ph_3Sb(OAc)_2$] was used to transfer a phenyl group to the alkyne carbon of $PhC{\equiv}CSiMe_3$, using Pd and CuI catalysts.[622]

[600] Wang, M.; Li, P.; Wang, L. *Synth. Commun.* ***2004***, *34*, 2803.
[601] Erdélyi, M.; Gogoll, A. *J. Org. Chem.* ***2003***, *68*, 6431.
[602] Bakherad, M.; Amin, A.H.; Keivanloo, A.; Bahramian, B.; Raeissi, M. *Tetrahedron Lett.* ***2010***, *51*, 5653.
[603] Lipshutz, B.H.; Blomgren, P.A. *Org. Lett.* ***2001***, *3*, 1869.
[604] See Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* ***2001***, *66*, 1910.
[605] Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* ***2006***, *47*, 2925.
[606] Olivi, N.; Spruyt, P.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* ***2004***, *45*, 2607.
[607] Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2004***, *45*, 8443.
[608] Fabrizi, G.; Goggiamani, AA.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.* ***2010***, *49*, 4067.
[609] Seregin, I.V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2007***, *129,* 7742.
[610] Wakamatsu, H.; Takeshita, M. *Synlett* ***2010***, 2322.
[611] Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* ***2008***, *10*, 3203. For a mcirowave induced variation of this reacation, see Colacino, E.; Daïch, L.; Martinez, J.; Lamaty, F. *Synlett* ***2007***, 1279.
[612] Borah, H.N.; Prajapati, D.; Boruah, R.C. *Synlett* ***2005***, 2823.
[613] Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* ***2008***, 5946. However, see Lauterbach, T.; Livendahl, M.; Roselln, A.; Espinet, P.; Echavarren, A.M. *Org. Lett.* ***2010***, *12*, 3006, and Panda, B.; Sarkar, T.K. *Tetrahedron Lett.* ***2010***, *51*, 301. See also, Beaumont, S.K.; Kyriakou, G.; Lambert, R.M. *J. Am. Chem. Soc.* ***2010***, *132*, 12246.
[614] Bakherad, M.; Keivanloo, A.; Mihanparast, S. *Synth. Commun.* ***2010***, *40,* 179.
[615] Sawant, D.N.; Tambade, P.J.; Wagh, Y.S.; Bhanage, B.M. *Tetrahedron Lett.* ***2010***, *51*, 2758.
[616] Li, P.; Wang, L. *Synlett* ***2006***, 2261.
[617] Anastasia, L.; Negishi, E. *Org. Lett.* ***2001***, *3*, 3111.
[618] Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* ***2000***, *2*, 3559.
[619] Torres, G.H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* ***2006***, 1450.
[620] Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* ***2007***, *129,* 9300.
[621] See Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* ***2004***, *6*, 2821.
[622] Kang, S.-K.; Ryu, H.-C.; Hong, Y-T. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 736.

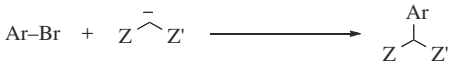
A variation of this aryl–alkyne coupling reaction reacted methylthioalkynes (R—C≡C—SMe) with arylboronic acids and a Pd catalyst to give the aryl alkyne (R—C≡C—Ar).[623] The boron trifluoride induced Pd catalyzed cross-coupling reaction of 1-aryltriazenes with areneboronic acids has been reported.[624] Aryl halides are coupled to alkynyltrifluoroboronates (R—C≡C—BF_3K, Reaction **12-28**) using a Pd catalyst.[625] Aryl iodides were also coupled to lithium alkynyl borate complexes, Li[R—C≡C—$B(OR')_3$], to give the aryl alkyne.[626]

Diaryliodonium salts react with terminal alkynes to give the phenyl alkyne.[627] A variation couples the phenyl group of $Ph_2I^+OTf^-$ with an en-yne using a Pd catalyst.[628] Aryl sulfonate esters can be coupled to terminal alkynes using a Pd catalyst in polymethylhydrosiloxane.[629]

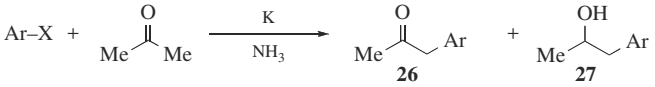
OS 11, **2009**, 234.

13-14 Arylation at a Carbon Containing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



The arylation of compounds of the form ZCH_2Z' is analogous to Reaction **10-67**, where Z is defined as an electron-withdrawing group (ester, cyano, sulfonyl, etc.). Activated aryl halides generally give good results.[630] Treatment with an aryl halide in liquid ammonia containing Na or K, for example, leads in the formation of **26** and **27**.[631] When the solution is irradiated with near-UV light, but Na or K is omitted, the same products are

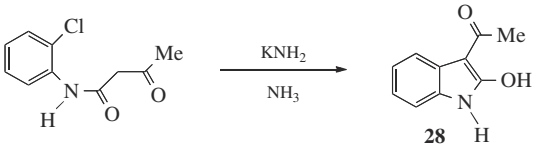


obtained (though in different proportions).[632] In either case, other leaving groups can be used instead of halogens (e.g., NR_3^+, SAr) and the mechanism is the $S_{RN}1$ mechanism. *N*-Heterocyclic carbene ligands in the presence of alkoxide bases lead to coupling of ketones and aryl halides, at the α-position of the ketone.[633] The reaction can also take place without an added initiator. The reaction of 2-fluoroanisole and KHMDS, and 4 equiv

[623] Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2001***, *3*, 91.
[624] Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* ***2004***, *6,* 617.
[625] Molander, G.A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* ***2002***, *67*, 8416.
[626] Oh, C.H.; Jung, S.H. *Tetrahedron Lett.* ***2000***, *41*, 8513.
[627] Kang, S.-K.; Yoon, S.-K.; Kim, Y.-M. *Org. Lett.* ***2001***, *3,* 2697.
[628] Radhakrishnan, U.; Stang, P.J. *Org. Lett.* ***2001***, *3*, 859.
[629] Gallagher, W.P.; Maleczka, Jr., R.E. *J. Org. Chem.* ***2003***, *68*, 6775.
[630] There is evidence for both the S_NAr mechanism (see Leffek, K.T.; Matinopoulos-Scordou, A.E. *Can. J. Chem.* ***1977***, *55,* 2656, 2664) and the $S_{RN}1$ mechanism (see Zhang, X.; Yang, D.; Liu, Y.; Chen, W.; Cheng, J. *Res. Chem. Intermed.* ***1989***, *11*, 281).
[631] Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1973***, *38*, 3020; Bunnett, J.F.; Gloor, B.F. *J. Org. Chem.* ***1973***, *38*, 4156; ***1974***, *39,* 382.
[632] Rajan, S.; Muralimohan, K. *Tetrahedron Lett.* ***1978***, 483; Rossi, R.A.; Alonso, R.A. *J. Org. Chem.* ***1980***, *45*, 1239; Beugelmans, R. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 547.
[633] Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* ***2007***, *72,* 5069.

of 2-cyanopropane, leads to substitution of the fluorine atom by CMe_2CN.[634] β-Keto esters were coupled to aryl fluorides using CsOH and a chiral quaternary ammonium salt, leading to the aryl substitution product with good enantioselectivity.[635]

Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base (e.g., $NaNH_2$[636] or LDA). Compounds of the form ZCH_2Z', and even simple ketones[637] or carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: It removes a proton from ZCH_2Z' and catalyzes the benzyne mechanism. The reaction has been used for ring closure, as in the formation of indole **28**.[638]



28

A similar reaction was reported using a Pd catalyst.[639] Nitroethane was converted to 2-phenylnitroethane using bromobenzene and a Pd catalyst.[640] Palladium catalysts have been developed for the α-arylation of ketones.[641] α-Arylation of esters has been accomplished using Pd catalysts.[642] Malonate esters are coupled unactivated aryl halides using a Pd catalyst.[643] Bis-(sulfones) $[CH_2(SO_2Ar)_2]$, react with aryl halides in the presence of a Pd catalyst.[644] Iron(II) salts have also been used to initiate this reaction.[645] The coupling of active methylene compounds and unactivated aryl halides can also be done with copper halide catalysts[103] (the *Hurtley reaction*).[646] Similar coupling was accomplished with $CH_2(CN)_2$ and a Ni catalyst.[647] A variation of α-arylation reacts α-halocarbonyl compounds with arylboronic acids, in the presence of a Ni catalyst.[648] Malonic and β-keto esters can be arylated at the α-carbon in high yields by treatment

[634] Caron, S.; Vasquez, E.; Wojcik, J.M. *J. Am. Chem. Soc.* ***2000***, *122*, 712.
[635] Bella, M.; Kobbelgaard, S.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 3670.
[636] Leake, W.W.; Levine, R. *J. Am. Chem. Soc.* ***1959***, *81,* 1169, 1627.
[637] See Caubere, P.; Guillaumet, G. *Bull. Soc. Chim. Fr.* ***1972***, 4643, 4649.
[638] Bunnett, J.F.; Kato, T.; Flynn, R.; Skorcz, J.A. *J. Org. Chem.* ***1963***, *28*, 1. See Biehl, E.R.; Khanapure, S.P. *Acc. Chem. Res.* ***1989***, *22*, 275; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 150–164. See also, Kessar, S.V. *Acc. Chem. Res.* ***1978***, *11*, 283.
[639] You, J.; Verkade, J.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5051.
[640] Vogl, E.M.; Buchwald, S.L. *J. Org. Chem.* ***2002***, *67,* 106.
[641] Grasa, G.A.; Colacot, T.J. *Org. Lett.* ***2007***, *9,* 5489.
[642] Hama, T.; Hartwig, J.F. *Org. Lett.* ***2008***, *10*, 1545, 1549; Biscoe, M.R.; Buchwald, S.L. *Org. Lett.* ***2009***, *11*, 1773.
[643] Aramendía, M.A.; Borau, V.; Jiménez, C.; Marinas, J.M.; Ruiz, J.R.; Urbano, F.J. *Tetrahedron Lett.* ***2002***, *43*, 2847.
[644] Kashin, A.N.; Mitin, A.V.; Beletskaya, I.P.; Wife, R. *Tetrahedron Lett.* ***2002***, *43*, 2539.
[645] Galli, C.; Bunnett, J.F. *J. Org. Chem.* ***1984***, *49*, 3041.
[646] See Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* ***1983***, 67; Hennessy, E.J.; Buchwald, S.L. *Org. Lett.* ***2002***, *4,* 269.
[647] Cristau, H.J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* ***2000***, *41,* 8457.
[648] Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* ***2007***, *9,* 5601.

with aryllead tricarboxylates [$ArPb(OAc)_3$],[649] with triphenylbismuth carbonate (Ph_2BiCO_3),[650] and other Bi reagents.[651] In a related process, manganese(III) acetate was used to convert a mixture of ArH and ZCH_2Z' to $ArCHZZ'$.[652] Arylzinc reagents have also been used.[653]

Enolate ions of ketones react with PhI in the dark.[654] In this case, it has been suggested[655] that initiation takes place by formation of a radical (e.g., **29**).



29

This is a SET mechanism (see Sec. 10.B). The photostimulated reaction has also been used for ring closure.[656] In certain instances of the intermolecular reaction, there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.[657]

The reaction of the enolate anions of ketones and aldehydes, generated *in situ* by addition of a suitable base, with aryl halides can be accomplished by treatment with a Pd catalyst.[658] Formation of an enolate anion of a conjugated ketone (cyclohexenone) via reaction with LDA (see Sec. 8.F, category 7), in the presence of Ph_3BiCl_2, leads to the α-phenyl conjugated ketone (6-phenylcyclohex-2-enone).[659] An ester reacted with $TiCl_4$ and *N,N*-dimethylanline to give the para-substitution product ($Me_2N—Ar—2Et$).[660] Nickel-catalyzed α-arylation of ketone enolate anions is also known.[661] The enolate anion of lactams will react with aryl halides in the presence of a Pd catalyst via the 3-aryl lactam.[662] When the enolate anion of a ketone is generated in the presence of a Pd catalyst and a chiral phosphine ligand, the α-aryl ketone is formed with good enantioselectivity.[663]

OS **V**, 12, 263; **VI**, 36, 873, 928; **VII**, 229.

[649] Elliott, G.I.; Konopelski, J.P.; Olmstead, M.M. *Org. Lett.* ***1999***, *1,* 1867 and refs. 3–7 therein.
[650] See Elliott, G.I.; Konopelski, J.P. *Tetrahedron* ***2001***, *57*, 5683.
[651] Barton, D.H.R.; Blazejewski, J.; Charpiot, B.; Finet, J.; Motherwell, W.B.; Papoula, M.T.B.; Stanforth, S.P. *J. Chem. Soc, Perkin Trans. 1* ***1985***, 2667; O'Donnell, M.J.; Bennett, W.D.; Jacobsen, W.N.; Ma, Y. *Tetrahedron Lett.* ***1989***, *30*, 3913.
[652] Citterio, A.; Santi, R.; Fiorani, T.; Strologo, S. *J. Org. Chem.* ***1989***, *54*, 2703; Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem.* ***1989***, *54*, 2713.
[653] Lundin, P.M.; Esquivias, J.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2009***, *48,* 154.
[654] Scamehorn, R.G.; Hardacre, J.M.; Lukanich, J.M.; Sharpe, L.R. *J. Org. Chem.* ***1984***, *49*, 4881.
[655] Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwjima, I. *J. Am. Chem. Soc.* ***1988***, *110*, 3296.
[656] See Semmelhack, M.F.; Bargar, T. *J. Am. Chem. Soc.* ***1980***, *102,* 7765; Bard, R.R.; Bunnett, J.F. *J. Org. Chem.* ***1980***, *45*, 1546.
[657] Bard, R.R.; Bunnett, J.F.; Creary, X.; Tremelling, M.J. *J. Am. Chem. Soc.* ***1980***, *102*, 2852; Tremelling, M.J.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1980***, *102*, 7375.
[658] See Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* ***2003***, *36*, 234.
[659] Arnauld, T.; Barton, D.H.R.; Normant, J.-F.; Doris, E. *J. Org. Chem.* ***1999***, *64,* 6915
[660] Periasamy, M.; KishoreBabu N.; Jayakumar, K.N. *Tetrahedron Lett.* ***2003***, *44,* 8939.
[661] Chen, G.; Kwong, F.Y.; Chan, H.O.; Yu, W.-Y.; Chan, A.S.C. *Chem. Commun.* ***2006***, 1413.
[662] Cossy, J.; de Filippis, A.; Pardo, D.G. *Org. Lett.* ***2003***, *5*, 3037.
[663] Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 1261.

13-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones[664]

Alkoxycarbonyl-de-halogenation, and so on

$$ArX + CO + ROH \xrightarrow[\text{Pd complex}]{\text{base}} ArCOOR$$

Carbonylation of aryl halides[665] and aryl triflates[666] with CO, an alcohol and a base (which gives an alkoxide), and a Pd catalyst, gives carboxylic esters. Similar carbonylation reactions are possible with alkyl halides. Aryl carboxylic acids were also prepared from aryl iodides by heating in DMF with lithium formate, LiCl, acetic anhydride, and a Pd catalyst.[667] Even very sterically hindered alkoxides can be used to produce the corresponding ester.[668] The use of H_2O, RNH_2, or an alkali metal or calcium carboxylate[669] instead of ROH, gives the carboxylic acid,[670] amide,[671] or mixed anhydride, respectively.[672] Ester formation via carbonylation was done is supercritical CO_2 (see Sec. 9.D.ii).[673] Microwave promoted carbonylation reactions have been reported.[674]

Variations including a silica-supported Pd reagent have been used to convert iodobenzene to butyl benzoate, in the presence of CO and butanol.[675] 2-Chloropyridine was converted to the butyl pyridine 2-carboxylate with this procedure.[676] Dicobalt octacarbonyl [$Co_2(CO)_8$] may be used as a surrogate reagent for CO.[677] Heating an aryl iodide, CO in ethanol and DBU, with a Pd catalyst, gave the ethyl ester of the aryl carboxylic acid.[678] A similar result was obtained when an aryl iodide was heated in ethanol with triethylamine, CO, and Pd/C.[679] Phenols and aryl halides react with a Pd catalyst, and carbonylation leads to the phenyl ester.[680] Arylthallium bis(trifluoroacetates) [$ArTl(O_2CCF_3)_2$, (see Reaction **12-23**], can be carbonylated with CO, an alcohol, and a $PdCl_2$ catalyst to give esters.[681] Note that seleno esters (ArCOSeAr) were prepared

[664] See Weil, T.A.; Cassar, L.; Foà, M. in Wender, I.; Pino, P. *Organic Synthesis Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 517–543.
[665] Liu, J.; Liang, B.; Shu, D.; Hu, Y.; Yang, Z.; Lei, A. *Tetrahedron* ***2008***, *64*, 9581; Berger, P.; Bessmernykh, A.; Caille, J.-C.; Mignonac, S. *Synthesis* ***2006***, 3106.
[666] Garrido, F.; Raeppel, S.; Mann, A.; Lautens, M. *Tetrahedron Lett.* ***2001***, *42,* 265.
[667] Cacchi, S.; Babrizi, G.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 4269.
[668] Antebi, S.; Arya, P.; Manzer, L.E.; Alper, H. *J. Org. Chem.* ***2002***, *67*, 6623. For an interesting variation that generated a lactone ring, see Cho, C.S.; Baek, D.Y.; Shim, S.C. *J. Heterocyclic Chem.* ***1999***, *36*, 289.
[669] Pri-Bar, I.; Alper, H. *J. Org. Chem.* ***1989***, *54*, 36.
[670] See Bumagin, N.A.; Nikitin, K.V.; Beletskaya, I.P. *Doklad. Chem.* ***1990***, *312*, 149.
[671] Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2002***, *67*, 6232.
[672] See Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–358.
[673] Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P.G.; Murry, J.A. *Org. Lett.* ***2004***, *6*, 2097.
[674] Kormos, C.M.; Leadbeater, N.E. *Synlett* ***2006***, 1663.
[675] Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Soc. Perkin Trans. I,* ***1997***, 2273.
[676] Beller, M. ; Mägerlein, W.; Indolese, A.F.; Fischer, C. *Synthesis* ***2001***, 1098.
[677] Brunet, J.; Sidot, C.; Caubere, P. *J. Org. Chem.* ***1983***, *48*, 1166. See also, Kudo, K.; Shibata, T.; Kashimura, T.; Mori, S.; Sugita, N. *Chem. Lett.* ***1987***, 577.
[678] Ramesh, C.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2002***, 2171.
[679] Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2003***, 501.
[680] Watson, D.A.; Fan, X.; Buchwald, S.L. *J. Org. Chem.* ***2008***, *73,* 7096.
[681] Larock, R.C.; Fellows, C.A. *J. Am. Chem. Soc.* ***1982***, *104,* 1900.

from aryl iodides, CO, $PhSeSnBu_3$, and a Pd catalyst.[682] Aminocarbonylation reactions are known.[683]

Modification of this approach allows the synthesis of ketones, and aryl iodides can be converted to aldehydes.[684] Aryl ketones can be prepared from aryltrimethylsilanes ($ArSiMe_3$) and acyl chlorides in the presence of $AlCl_3$.[685] Aryllithium and *Grignard reagents* react with iron pentacarbonyl to give aldehydes ArCHO.[686] The reaction of CO with aryllithium may occur by electron transfer.[687] Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: $ArI + Ar'HgX + Ni(CO)_4 \rightarrow ArCOAr'$.[688] Aryl iodides are carbonylated to give the aryl alkyl ketone with CO and R_3In.[689] Aryl iodides are coupled with aryl acid chlorides in the presence of an In complex to form a diaryl ketone.[690] Organomercury compounds undergo a similar reaction.[691] The aryllead reagent [$PhPb(OAc)_2$] was converted to benzophenone using NaOMe, CO, and a Pd catalyst.[692] Aryl iodides containing an ortho substituent with a β-cyano group that served as the source of a carbonyl group, was converted to a bicyclic ketone with a Pd catalyst at 130 °C in aq DMF.[693]

Diaryl ketones can also be prepared by coupling aryl iodides with phenylboronic acid (Reaction **12-28**), in the presence of CO and a Pd catalyst.[694] This reaction has been extended to heteroaromatic systems, with the preparation of phenyl 4-pyridyl ketone from phenylboronic acid and 4-iodopyridine.[695] 2-Bromopyridine as coupled with phenylboronic acid, CO, and a Pd catalyst to give phenyl 2-pyridyl ketone.[696] Carbonylation of an alkyne and an aryl halide, with CO and Pd and Cu catalysts, gave the alkynyl ketone $RC{\equiv}C(C{=}O)Ar$.[697]

13-16 Arylation of Silanes

Silyl and Silyloxy-de-halogenation, Aryl-de-silylation, and so on

$$Ar{-}X + Ar'SiR_2 \rightarrow Ar{-}SiR_3$$

[682] Nishiyama, Y.; Tokunaga, K.; Kawamatsu, H.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43*, 1507.
[683] Wu, X.; Larhed, M. *Org. Lett.* ***2005***, *7*, 3327; Ju, J.; Jeong, M.; Moon, J.; Jung, H.M.; Lee, S. *Org. Lett.* ***2007***, *9,* 4615; Csajági, C.; Borcsek, B.; Niesz, K.; Kovács, I.; Székelyhidi, Z.; Bajkó, Z.; Ürge, L.; Darvas, F. *Org. Lett.* ***2008***, *10,* 1589; Letavic, M.A.; Ly, K.S. *Tetrahedron Lett.* ***2007***, *48,* 2339; Tambade, P.J.; Patil, Y.P.; Bhanushali, M.J.; Bhanage, B.M. *Synthesis* ***2008***, 2347.
[684] Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* ***1990***, *31*, 6887.
[685] Dey, K.; Eaborn, C.; Walton, D.R.M. *Organomet. Chem. Synth.* ***1971***, *1,* 151.
[686] Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1663.
[687] Nudelman, N.S.; Doctorovich, F. *Tetrahedron* ***1994***, *50*, 4651.
[688] Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14,* 1175 and cited references. See Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.
[689] Lee, S.W.; Kee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, S.; Lee, P.H. *J. Org. Chem.* ***2004***, *69*, 4852.
[690] Papoian, V.; Minehan, T. *J. Org. Chem.* ***2008***, *73,* 7376.
[691] Baird, Jr., W.C.; Hartgerink, R.L.; Surridge, J.H. *J. Org. Chem.* ***1985***, *50,* 4601.
[692] Kang, S.-K.; Ryu, H.-C.; Choi, S.-C. *Synth. Commun.* ***2001***, *31*, 1035.
[693] Pletnev, A.A.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 9428.
[694] Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1993***, *34*, 7595.
[695] Couve-Bonnaire, S.; Caprentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* ***2001***, *42*, 3689.
[696] Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentiere, J.-F.; Castanet, Y. *Synlett* ***2003***, 1874.
[697] Ahmed, M.S.M.; Mori, A. *Org. Lett.* ***2003***, *5*, 3057. For a Pd-catalyzed reaction, see Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* ***2005***, *70,* 6097.

In the presence of transition metal catalysts (e.g., Pd), trialkoxysilanes [$HSi(OR)_3$] react with aryl halides to give the corresponding arylsilane.[698] This transformation is an alternative to the *Suzuki coupling* (Reaction **13-12**).[699] The influence of silicon substituents on the cross-coupling reaction has been studied.[700] A similar reaction was reported using a Rh catalyst.[701] Similar coupling of aryl halides with trialkylsilanes ($HSiR_3$) in the presence of a Pd,[702] or Rh catalyst,[703] or PtO_2[704] gives the arylsilane. Cyclic alkoxysilanes are prepared using Pd catalyzed cross-coupling reactions.[705] Vinylsilanes are coupled to aryl halides to give the aryl alkene.[706] Disilanes have also been employed, using a Pd catalyst.[707] Arylsilanes can be coupled to aryl iodides using a Pd catalyst[708] and in aqueous media.[709] Arylsilanes react with alkyl halides to give the corresponding arene, in the presence of a Pd catalyst.[710]

Other variations include the conversion of vinyl silanes to styrene derivatives upon treatment with Bu_4NF (TBAF), an aryl iodide and a Pd catalyst.[711] Arylsilanes were coupled to alkenes to give the styrene derivative using palladium acetate in an oxygen atmosphere,[712] or TBAF and an Ir catalyst.[713] Aryl iodides can be coupled to 1-methyl-1-vinyl- and 1-methyl-1-(prop-2-enyl)silacyclobutane with desilyation, using a Pd catalyst and TBAF, to give the corresponding styrene derivative.[714] Aryl silanes can be coupled to aryl iodides using Ag_2O and a Pd catalyst,[715] and arylsiloxanes [$ArSi(OR)_3$] are coupled to aryl halides with TBAF and a Pd catalyst.[716] 1-Trialkylsilylalkynes ($R_3Si—C\equiv C—R'$) were coupled to aryl iodides using a Pd catalyst.[717]

An alternative approach reacts aryllithium reagents with siloxanes [$Si(OR)_4$], to give the aryl derivative $ArSi(OR)_3$.[718] Biaryl derivatives are similarly prepared from

[698] Yamanoi, Y.; Nishihara, H. *J. Org. Chem.* ***2008***, *73,* 6671; Gordillo, Á.; de Jesús, E.; López-Mardomingo, C. *Org. Lett.* ***2006***, *8,* 3517; Murata, M.; Yamasaki, H.; Ueta, T.; Nagata, M.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Tetrahedron* ***2007***, *63,* 4087; Murata, M.; Yoshida, S.; Nirei, S.; Watanabe, S.; Masuda, Y. *Synlett* ***2006***, 118; Ye, Z.; Chen, F.; Luo, F.; Wang, W.; Lin, B.; Jia, X.; Cheng, J. *Synlett* ***2009***, 2198. See also, Denmark, S.E.; Kallemeyn, J.M. *J. Am. Chem. Soc.* ***2006***, *128,* 15958.

[699] Seganish, W.M.; DeShong, P. *Org. Lett.* ***2004***, *6*, 4379.

[700] Denmark, S.E.; Neuville, L.; Christy, M.E.L.; Tymonko, S.A. *J. Org. Chem.* ***2006***, *71*, 8500.

[701] Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* ***2002***, *4*, 1843.

[702] Yamanoi, Y. *J. Org. Chem.* ***2005***, *70,* 9607.

[703] Omachi, H.; Itami, K. *Chem. Lett.* ***2009***, *38,* 186.

[704] Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* ***2006***, *8,* 931.

[705] Nakao, Y.; Imanaka, H.; Sahoo, A.K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* ***2005***, *127,* 6952.

[706] Denmark, S.E.; Tymonko, S.A. *J. Am. Chem. Soc. 2005, 127,* 8004; Denmark, S.E.; Butler, C.R. *J. Am. Chem. Soc. 2008, 130,* 3690.

[707] McNeill, E.; Barder, T.E.; Buchwald, S.L. *Org. Lett.* ***2007***, *9,* 3785.

[708] Denmark, S.E.; Wu, Z. *Org. Lett.* ***1999***, *1*, 1495; Lee, H.M.; Nolan, S.P. *Org. Lett.* ***2000***, *2,* 2053.

[709] Denmark, S.E.; Ober, M.H. *Org. Lett.* ***2003***, *5*, 1357.

[710] Lee, J.-y.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5616.

[711] Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* ***2003***, *68*, 6354. See also, Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* ***2002***, *67*, 8450.

[712] Parrish, J.P.; Jung, Y.C.; Shin, S.I.; Jung, K.W. *J. Org. Chem.* ***2002***, *67*, 7127.

[713] Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem. Int. Ed.* ***2003***, *42,* 89.

[714] Denmark, S.E.; Wang, Z. *Synthesis* ***2000***, 999.

[715] Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* ***1999***, *1*, 299.

[716] Mowery, M.E.; DeShong, P. *Org. Lett.* ***1999***, *1,* 2137.

[717] Kabalka, G.W.; Wang, L.; Pagni, R.M. *Tetrahedron* ***2001***, *57*, 8017; Denmark, S.E.; Tymonko, S.A. *J. Org. Chem.* ***2003***, *68*, 9151.

[718] Manoso, A.S.; Ahn, C.; Soheili, A.; Handy, C.J.; Correia, R.; Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 8305.

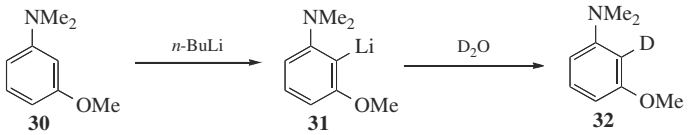
aryl halides.[719] Arylsiloxanes are similarly coupled at the ortho position of anilide derivatives.[720]

The reaction of $NaBPh_4$ (sodium tetraphenylborate) and a silyl dichloride (Ph_2SiCl_2) gives biphenyl.[721]

13.C.ii. Hydrogen as Leaving Group[722]

13-17 Alkylation and Arylation

Alkylation or Alkyl-de-hydrogenation, and so on



The alkylation of aromatic rings was introduced, in part, in Reaction **10-57**. The reaction of an aromatic ring with an organolithium reagent can give H–Li exchange to form an aryllithium. This reaction tends to be slow if there are activating substituents on the aryl halide, or in the absence of diamine additives.[723] When heteroatom substituents are present as in **30**, however, the reaction is facile and the Li goes into the 2 position (as in **31**).[724] This regioselectivity can be quite valuable synthetically, and is now known as *directed ortho metalation*[725] (see Reaction **10-57**). Subsequent reaction with a suitable electrophilic agent (e.g., D_2O) leads to **32** in this case. Aryllithium reagents give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.[726] Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. With respect to C-2, the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: It becomes the new unshared pair on the nitrogen.

With TMEDA/*n*-butyllithium mediated arene lithiation reactions, the viability of directive effects (complex-induced proximate effects) has been questioned,[727] although it is not clear if this extends to other systems (particularly when there is a strong coordinating group (e.g., carbamate).[728] The 2 position is much more acidic than the 3 position (see Table 8.1), but a negative charge at C-3 is in a more favorable position to be

[719] Mori, A.; Suguro, M. *Synlett* ***2001***, 845; Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* ***2001***, 2231.
[720] Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* ***2007***, *129,* 6066.
[721] Sakurai, H.; Morimoto, C.; Hirao, T. *Chem. Lett.* ***2001***, 1084. See also, Powell, D.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126,* 7788.
[722] See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454. See Chupakhin, O.N.; Charushin, V.N.; van der Plas, H.C. *Tetrahedron* ***1988***, *44,* 1.
[723] See Becht, J.-M.; Gissot, A.; Wagner, A.; Misokowski, C. *Tetrahedron Lett.* ***2004***, *45*, 9331.
[724] Slocum, D.W.; Jennings, C.A. *J. Org. Chem.* ***1976***, *41,* 3653. However, the regioselectivity can depend on reaction conditions: See Meyers, A.I.; Avila, W.B. *Tetrahedron Lett.* ***1980***, 3335.
[725] See Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1; Green, L.; Chauder, B.; Snieckus, V. *J. Heterocylic Chem.* ***1999***, *36*, 1453. Also see, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453; Slocum, D.W.; Dietzel, P. *Tetrahedron Lett.* ***1999***, *40*, 1823.
[726] Armstrong, D.R.; Mulvey, R.E.; Barr, D.; Snaith, R.; Reed, D. *J. Organomet. Chem.* ***1988***, *350*, 191.
[727] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122,* 8640.
[728] Hay, D. R.; Song, Z.; Smith, S.G.; Beak, P. *J. Am. Chem. Soc.* ***1988***, *110,* 8145.

stabilized by the Li^+. Lithiation reactions do not necessarily rely on a complex-induced proximity effect.[729] *N,N*-Dialkyl aryl-*O*-sulfamates are substrates for ortho metalation.[730] Phenylaziridines also undergo this reaction.[731] Formation of the ortho arylmagnesium compound has been accomplished with bases of the form $(R_2N)_2Mg$.[732] A directed meta metalation has been reported, using alkali metal mediated zincation.[733] Note that the substrate-dependent mechanism of the ortho lithiation of aryloxazolines using butyllithium has been studied.[734]

Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithium reagents, although the usual reaction with these reagents is Reaction **12-22**,[735] and *Grignard reagents* have been used to alkylate naphthalene.[736] The addition–elimination mechanism apparently applies in these cases too. A protected form of benzaldehyde (protected as the benzyl imine) has been similarly alkylated at the ortho- position with butyllithium.[737] The alkylation of heterocyclic nitrogen compounds[738] with alkyllithium reagents is called *Ziegler alkylation*. The reaction of 2-chloropyridine with 3 equiv of butyllithium–$Me_2NCH_2CH_2OLi$ and then iodomethane gave 2-chloro-6-methylpyridine.[739] Note that H–Li exchange can be faster than Cl–Li exchange. Treatment of 2-chloro-5-phenylpyridine with *tert*-butyllithium leads to lithiation on the phenyl ring rather than Li–Cl exchange, and subsequent treatment with dimethyl sulfate gave 2-chloro-5-(2-methylphenyl)pyridine.[740] The reaction of *N*-triisopropylsilyl indole with *tert*-butyllithium and then iodomethane gave the 3-methyl derivative.[741] Heteroaromatic compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.[742]

Mercuration of aromatic compounds[743] can be accomplished with mercuric salts, most often $Hg(OAc)_2$,[744] to give ArHgOAc. This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (Sec. 11.A.i).[745] Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) [$ArTl(OOCCF_3)_2$] by treatment

[729] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640; Collum, D. B. *Acc. Chem. Res.* ***1992***, *25*, 448. For a discusison of mechanistic possibilities, see Nguyen, T.-H.; Chau, N.T.T.; Castanet, A.-S.; Nguyen, K.P.P.; Mortier, J. *Org. Lett.* ***2005***, *7*, 2445.

[730] Macklin, T.K.; Snieckus, V. *Org. Lett.* ***2005***, *7,* 2519.

[731] Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* ***2005***, *7,* 3749.

[732] Eaton, P.E.; Lee, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 8016. Also see Kronenburg, C.M.P.; Rijnberg, E.; Jastrzebski, J.T.B.H.; Kooijman, H.; Lutz, M.; Spek, A.L.; Gossage, R.A.; van Koten, G. *Chemistry: European J.* ***2005***, *11*, 253.

[733] Armstrong, D.R.; Clegg, W.; Dale, S.H.; Hevia, E.; Hogg, L.M.; Honeyman, G.W.; Mulvey, R.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3775.

[734] Chadwick, S.T.; Ramirez, A.; Gupta, L.; Collum, D.B. *J. Am. Chem. Soc.* ***2007***, *129,* 2259.

[735] Eppley, R.L.; Dixon, J.A. *J. Am. Chem. Soc.* ***1968***, *90,* 1606.

[736] Bryce-Smith, D.; Wakefield, B.J. *Tetrahedron Lett.* ***1964***, 3295.

[737] Flippin, L.A.; Carter, D.S.; Dubree, N.J.P. *Tetrahedron Lett.* ***1993***, *34*, 3255.

[738] See Vorbrüggen, H.; Maas, M. *Heterocycles*, ***1988***, *27,* 2659. Also see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44,* 199.

[739] Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* ***2000***, *2*, 803.

[740] Fort, Y.; Rodriguez, A.L. *J. Org. Chem.* ***2003***, *68*, 4918.

[741] Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* ***2001***, *42,* 7621.

[742] Yadav, J.S.; Reddy, B.V.S.; Reddy, P.M.; Srinivas, Ch. *Tetrahedron Lett.* ***2002***, *43*, 5185.

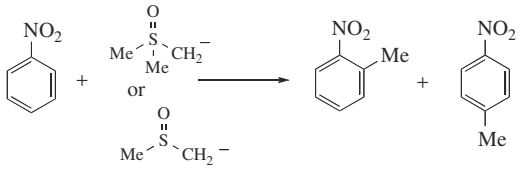
[743] See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 60–97; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods,* Vol. 11, VCH, NY, ***1988***, pp. 308–318.

[744] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[745] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 186–194. An alternative mechanism, involving radial cations, has been reported: Courtneidge, J.L.; Davies, A.G.; McGuchan, D.C.; Yazdi, S.N. *J. Organomet. Chem.* ***1988***, *341*, 63.

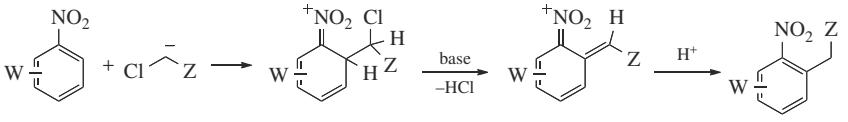
with thallium(III) trifluoroacetate[746] in trifluoroacetic acid.[747] These arylthallium compounds can be converted to phenols, aryl iodides or fluorides (Reaction **12-31**), aryl cyanides (Reaction **12-34**), aryl nitro compounds,[748] or aryl esters (Reaction **12-33**). The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place.[749] Transient metalated aryl complexes can be formed that react with another aromatic compound. Aryl iodides reacted with benzene to form a biaryl in the presence of an Ir catalyst.[750] Aniline derivatives reacted with $TiCl_4$ to give the para-homo coupling product ($R_2N—Ar—Ar—NR_2$).[751]

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylid[752] or the methylsulfinyl carbanion (obtained by treatment of DMSO with a strong base)[753]:



The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the *Friedel–Crafts* procedure (Reaction **11-10**).

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:[754]



This type of process is called *vicarious nucleophilic substitution of hydrogen*.[755] The Z group is electron withdrawing (e.g., SO_2R, SO_2OR, SO_2NR_2, COOR, or CN); it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group.[756] Hydride ion (H^-) is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a "vicarious" leaving group. Other leaving groups have been used (e.g., OMe and SPh), but Cl is generally the best. Many W groups in the ortho, meta, or para positions do not interfere. The reaction is

[746] See Uemura, S. in Pizey, J.S. *Synthetic Reagents,* Vol. 5, Wiley, NY, ***1983***, pp. 165–241.
[747] Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285,* C9. See Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054.
[748] Uemura, S.; Toshimitsu, A.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2582.
[749] Lau, W.; Kochi, J.K. *J. Am. Chem. Soc.* ***1984***, *106,* 7100; ***1986***, *108*, 6720.
[750] Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* ***2004***, 1926.
[751] Periasamy, M.; Jayakumar, K.N.; Bharathi, P. *J. Org. Chem.* ***2000***, *65,* 3548.
[752] Traynelis, V.J.; McSweeney, J.V. *J. Org. Chem.* ***1966***, *31,* 243.
[753] Russell, G.A.; Weiner, S.A. *J. Org. Chem.* ***1966***, *31*, 248.
[754] See Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* ***1988***, *53,* 690.
[755] See Makosza, M. *Synthesis* ***1991***, 103; *Russ. Chem. Rev.* ***1989***, *58*, 747; Makosza, M.; Winiarski, J. *Acc. Chem. Res.* ***1987***, *20,* 282.
[756] For a discussion of the mechanism of vicarious nucleophilic aromatic substitution, see Makosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* ***2002***, *67,* 394.

also successful for di- and trinitro compounds, for nitronaphthalenes,[757] and for many nitro heterocycles, $^{-}Z—CR—Cl$ may also be used.[758] When the nucleophile is Br_3C^- or Cl_3C^-, the product is $ArCHX_2$, which can easily be hydrolyzed to ArCHO.[759] This is therefore an indirect way of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Reaction **11-1**–**11-18**.

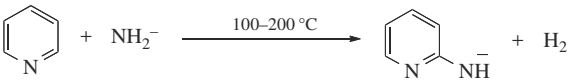
Replacement of an amino group is possible. When aniline derivatives were treated with allyl bromide and *tert*-butyl nitrite (*t*-BuONO), the aryl–allyl coupling product was formed ($Ar—NH_2 \rightarrow Ar—CH_2CH=CH_2$).[760]

For the introduction of CH_2SR groups into phenols, see Reaction **11-23**. See also, Reaction **14-19**.

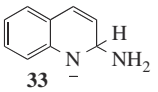
OS **II**, 517.

13-18 Amination of Nitrogen Heterocycles

Amination or **Amino-de-hydrogenation**



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali metal amides in a process called the *Chichibabin reaction*.[761] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali metal amides (e.g., RNH^- and R_2N^-), have also been used. The mechanism is probably similar to that of Reaction **13-17.** The existence of intermediate ions (e.g., **33**)



33

(from quinoline) has been demonstrated by NMR spectra.[762] A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine[763] and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,[764] but they have been aminated ($ArH \rightarrow ArNH_2$ or ArNHR) via the vicarious substitution principle (see Reaction **13-17**), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.[765] The vicarious leaving group in this case is the triazole ring. Note, however, that 3-nitropyridine was converted to 6-amino-3-nitropyridine by reaction with KOH, hydroxylamine, and $ZnCl_2$.[766]

[757] Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* ***1987***, 711.
[758] See Mudryk, B.; Makosza, M. *Tetrahedron* ***1988***, *44,* 209.
[759] Makosza, M.; Owczarczyk, Z. *J. Org. Chem.* ***1989***, *54,* 5094.
[760] Ek, F.; Axelsson, O.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2002***, *67*, 6376.
[761] See Vorbrüggen, H. *Adv. Heterocycl. Chem.* ***1990***, *49*, 117; McGill, C.K.; Rappa, A. *Adv. Heterocycl. Chem.* ***1988***, *44,* 1; Pozharskii, A.F.; Simonov, A.M.; Doron'kin, V.N. *Russ. Chem. Rev.* ***1978***, *47,* 1042.
[762] Wozniak, M.; Baránski, A.; Nowak, K.; van der Plas, H.C. *J. Org. Chem.* ***1987***, *52*, 5643.
[763] Ban, Y.; Wakamatsu, T. *Chem. Ind. (London)* ***1964***, 710.
[764] See Levitt, L.S.; Levitt, B.W. *Chem. Ind. (London)* ***1975***, 520.
[765] Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* ***1986***, *51,* 5039; ***1988***, *53*, 3978.
[766] Bakke, J.M.; Svensen, H.; Trevisan, R. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 376.

Analogous reactions have been carried out with hydrazide ions (R_2NNH^-).[767] A mixture of NO_2 and O_3, with excess $NaHSO_3$, converted pyridine to 3-aminopyridine.[768] For other methods of aminating aromatic rings, see Reaction **11-6**.

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

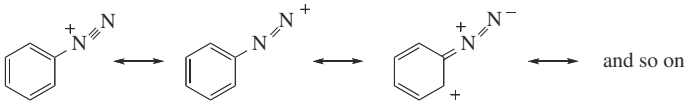
13.C.iii. Nitrogen as Leaving Group

The diazonium group can be replaced by a number of groups.[769] Some of these are nucleophilic substitutions, with S_N1 mechanisms (Sec. 10.A.ii), but others are free radical reactions and are treated in Chapter 14. The solvent in diazonium group reactions is usually water. With other solvents it has been shown that the S_N1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free radical mechanisms.[770] The N_2^+ group[771] can be replaced by Cl^-, Br^-, and CN^-, by a nucleophilic mechanism (see OS **IV**, 182), but the *Sandmeyer reaction* is much more useful (Reaction **14-20**). Transition metal catalyzed reactions are known involving aryldiazonium salts, and diazonium variants of the *Heck reaction* (**13-10**) and *Suzuki coupling* (**13-12**) were mentioned previously. As mentioned in Section 13.B.i, it must be kept in mind that the N_2^+ group can activate the removal of another group on the ring. In a few cases, nitrogen groups (e.g., nitro or ammonium) can be replaced.

13-19 Diazotization

$$\text{Ar—NH}_2 + \text{HONO} \longrightarrow \text{Ar—N+N}$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[772] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see Sec. 10.G.iii). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogen atoms and the ring:



34 **35**

[767] Kauffmann, T.; Hansen, J.; Kosel, C.; Schoeneck, W. *Liebigs Ann. Chem.* ***1962***, *656*, 103.
[768] Suzuki, H.; Iwaya, M.; Mori, T. *Tetrahedron Lett.* ***1997***, *38*, 5647.
[769] See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley, NY, ***1978***, pp. 286–297.
[770] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1978***, *61*, 1721.
[771] See Pérez, P. *J. Org. Chem.* ***2003***, *68,* 5886.
[772] See in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, Wiley, NY, ***1978***, the articles by Hegarty, A.F. pt. 2, pp. 511–591, and Schank, K. pt. 2, pp. 645–657; Godovikova, T.I.; Rakitin, O.A.; Khmel'nitskii, L.I. *Russ. Chem. Rev.* ***1983***, *52*, 440; Challis, B.C.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 305–320. See Butler, A.R. *Chem. Rev.* ***1975***, *75,* 241.

Incidentally, **34** contributes more than **35**, as shown by bond-distance measurements.[773] In benzenediazonium chloride, the C—N distance is ~1.42 Å, and the N—N distance ~1.08 Å,[774] and these values fit more closely to a single and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are unstable at temperatures other than about <5 °C. A few are more stable (e.g., the diazonium salt obtained from sulfanilic acid), which is stable up to 10 or 15 °C. Diazonium salts are usually prepared in aqueous solution and *used without isolation*.[775] While it is possible to prepare solid diazonium salts (see Reaction **13-23**), many dry diazonium salts are explosive if not handled with great care and extreme caution should be exercised. The stability of aryl diazonium salts can be increased by crown ether complexion.[776]

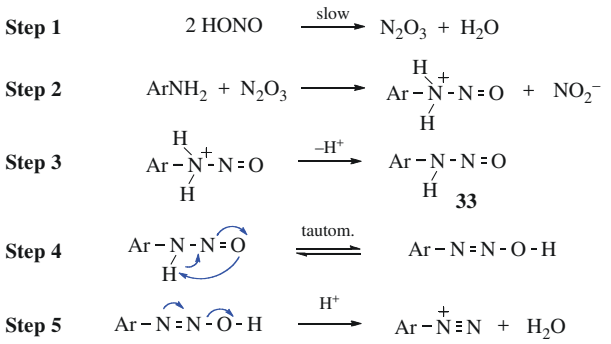
For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, and so on, groups do not interfere. Since aliphatic amines do not react with nitrous acid below a pH of ~3, it is even possible, by working at a pH ~1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.[777]

$$EtOOC—CH_2—NH_2 + HONO \rightarrow EtOOC—CH{=}N{=}N^+$$

If an aliphatic amino group is α to a COOR, CN, CHO, COR, and so on, and has a hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*.[778] Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite ($Me_2CHCH_2CH_2ONO$) and a small amount of acid.[779] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[780]

Despite the fact that diazotization takes place in acid solution, the actual reactive species is not the salt of the amine, but is the small amount of free amine present.[781] Because aliphatic amines are stronger bases than aromatic ones that at pH values <3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid, the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[782] Under these conditions the mechanism is

[773] See Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 95–105.
[774] Rømming, C. *Acta Chem. Scand.* ***1963***, *17*, 1444; Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, p. 98; Ball, R.G.; Elofson, R.M. *Can. J. Chem.* ***1985***, *63,* 332.
[775] See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 247–339.
[776] Korzeniowski, S.H.; Leopold, A.; Beadle, J.R.; Ahern, M.F.; Sheppard, W.A.; Khanna, R.K.; Gokel, G.W. *J. Org. Chem.* ***1981***, *46,* 2153, and references cited therein; Bartsch, R.A. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt.1, Wiley, NY, ***1983***, pp. 889–915.
[777] Kornblum, N.; Iffland, D.C. *J. Am. Chem. Soc.* ***1949***, *71*, 2137.
[778] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, the articles by Regitz, M. pt. 2, pp. 659–708, 751–820, and Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F. pt. 2, pp. 821–976.
[779] Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* ***1975***, *31,* 227.
[780] Butler, R.N. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, p. 305.
[781] Challis, B.C.; Larkworthy, L.F.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5203.
[782] Hughes, E.D.; Ingold, C.K.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 58, 65, 77, 88; Hughes, E.D.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 70, 82.



Other evidence exists for this mechanism.[783] Other attacking species can be NOCl, $H_2NO_2^+$, and at high acidities even NO^+. Nucleophiles (e.g., Cl^-, SCN^-, and thiourea) catalyze the reaction by converting the HONO to a better electrophile (e.g., $HNO_2 + Cl^- + H^+ \rightarrow NOCl + H_2O$).[784]

N-Aryl ureas are converted to the aryldiazonium nitrate upon treatment with $NaNO_2$ and H_2SO_4 in dioxane[785] or with DMF—NO_2 in DMF.[786]

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. They are listed under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also, OS **VI**, 840.

13-20 Hydroxylation of Aryldiazonium Salts

Hydroxy-de-diazoniation

$$ArN_2^+ + H_2O \rightarrow ArOH$$

This reaction is formally analogous to **13-1**, but with a N_2^+ leaving group rather than a halide. Water is usually present whenever diazonium salts are made, but at these temperatures (0–5 °C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, for example, boiling with aq H_2SO_4 or with trifluoroacetic acid containing potassium trifluoroacetate.[787] The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-.

A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $Cu(NO_3)_2$.[788] Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least

[783] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418, p. 422.
[784] Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 84–93.
[785] Zhang, Z.; Zhang, Q.; Zhang, S.; Liu, X.; Zhao, G. *Synth. Commun.* ***2001***, *31*, 329.
[786] Zhang, O.Z.; Zhang, S.; Zhang, J. *Synth. Commun.* ***2001***, *31*, 1243.
[787] Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.* ***1973***, *51*, 2347.
[788] Cohen, T.; Dietz, Jr., A.G.; Miser, J.R. *J. Org. Chem.* ***1977***, *42*, 2053.

partly involved when ordinary hydroxy-de-diazoniation is carried out in weakly alkaline aqueous solution.[789] Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.[790]

OS **I**, 404; **III**, 130, 453, 564; **V**, 1130.

13-21 Replacement by Sulfur-Containing Groups

Mercapto-de-diazoniation, and so on

$$ArN_2^+ + HS^- \rightarrow ArSH$$
$$ArN_2^+ + S^{2-} \rightarrow ArSAr$$
$$ArN_2^+ + RS^- \rightarrow ArSR$$
$$ArN_2^+ + SCN^- \rightarrow ArSCN + ArNCS$$

These reactions are convenient methods for incorporating a sulfur-containing group onto an aromatic ring. With $Ar'S^-$, diazosulfides (Ar—N=N—S—Ar′) are intermediates,[791] which can in some cases be isolated.[792] Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO—CSS^- or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. Aryldiazonium salts are prepared by the reaction of an aniline derivative with an alkyl nitrite (RONO), and when formed in the presence of dimethyl disulfide (MeS—SMe), the product is the thioether (Ar—S—Me).[793] Aryl triflates have been converted to the aryl thiol using NaST(P5) and a Pd catalyst, followed by treatment with tetrabutylammonium fluoride[794] (see also, Reaction **14-22**).

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see, OS **II**, 238.

13-22 Replacement by Iodine

Iodo-de-diazoniation

$$ArN_2^+ + I^- \rightarrow ArI$$

One of the best methods for the introduction of iodine into aromatic rings (see Reaction **13-7**) is the reaction of diazonium salts with iodide ions.[795] Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and Reactions **14-20** and **13-23** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products. Aniline has also been converted to fluorobenzene by treatment with *t*-BuONO and SiF_4 followed by heating.[796] A related reaction between PhN=N—NR_2 and iodine gave iodobenzene.[797]

[789] Dreher, E.; Niederer, P.; Rieker, A.; Schwarz, W.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 488.
[790] Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* ***1991***, 459.
[791] Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.* ***1986***, *108*, 8227, and references cited therein.
[792] See Price, C.C.; Tsunawaki, S. *J. Org. Chem.* ***1963***, *28,* 1867.
[793] Allaire, F.S.; Lyga, J.W. *Synth. Commun.* ***2001***, *31*, 1857.
[794] Arnould, J.C.; Didelot, M.; Cadilhac, C.; Pasquet, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4523.
[795] See Krasnokutskaya, E.A.; Semenischeva, N.I.; Filimonov, V.D.; Knochel, P. *Synthesis* ***2007***, 81; Filimonov, V.D.; Semenischeva, N.I.; Krasnokutskaya, E.A.; Tretyakov, A.N.; Hwang, H.Y.; Chi, K.W. *Synthesis* ***2008***, 185.
[796] Tamura, M.; Shibakami, M.; Sekiya, A. *Eur. J. Org. Chem.* ***1998***, 725.
[797] Wu, Z.; Moore, J.S. *Tetrahedron Lett.* ***1994***, *35*, 5539.

The actual attacking species is probably not only I^- if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^-; this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+ I_3^-$ salts, which, on standing, gave ArI.[798] From this, it can be inferred that the reason the other halide ions give poor results is *not* that they are poor nucleophiles but *rather* they are poor reducing agents (compared with iodide). There is also evidence for a free radical mechanism.[799]

The hydroxyl group of a phenol can be replaced with iodine. The reaction of phenol with a boronic ester and a Pd catalyst, followed by reaction with NaI and chloramine-T (see Reaction **15-52**) converts phenol to iodobenzene.[800] Arylboronic acids are converted to the aryl fluoride with Selectfluor, in the presence of a Pd catalyst.[801]

OS **II**, 351, 355, 604; **V**, 1120.

13-23 The Schiemann Reaction

Fluoro-de-diazoniation (overall transformation)

$$ArN_2^+BF_4^- \xrightarrow{\Delta} ArF + N_2^+BF_3$$

Heating diazonium fluoroborates (the *Schiemann* or *Balz–Schiemann reaction*) is by far the best way to introduce fluorine into an aromatic ring.[802] In the most common procedure, the tetrafluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successful (since diazonium salts are generally unstable, care should be exercised any time a diazonium salt is dried). In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *tert*-butyl nitrite and BF_3–etherate.[803] The reaction has also been carried out on $ArN_2^+ PF_6^-$ $ArN_2^+ SbF_6^-$, and $ArN_2^+ AsF_6^-$ salts, in many cases with better yields.[804] Aryl chlorides and bromides are commonly prepared by the *Sandmeyer reaction* (**14-20**). In an alternative procedure, aryl fluorides are prepared by treatment of aryltriazenes $Ar—N{=}N—NR_2$ with 70% HF in pyridine.[805]

The mechanism is of the S_N1 type. That aryl cations are intermediates was shown by the following experiments[806]: Aryl diazonium chlorides are known to arylate other aromatic rings by a free radical mechanism (see Reaction **13-27**). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species.

[798] Carey, J.G.; Millar, I.T. *Chem. Ind. (London)* ***1960***, 97.
[799] Packer, J.E.; Taylor, R.E.R. *Aust. J. Chem.* ***1985***, *38*, 991; Abeywickrema, A.N.; Beckwith, A.L.J. *J. Org. Chem.* ***1987***, *52,* 2568.
[800] Thompson, A.L.S.; Kabalka, G.W.; Akula, M.R.; Huffman, J.W. *Synthesis* ***2005***, 547.
[801] Furuya, T.; Kaiser, H.M.; Ritter, T. *Angew. Chem. Int. Ed.* ***2008***, *47,* 5993.
[802] See Suschitzky, H. *Adv. Fluorine Chem.* ***1965***, *4,* 1.
[803] Doyle, M.P.; Bryker, W.J. *J. Org. Chem.* ***1979***, *44*, 1572.
[804] Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* ***1968***, 2317.
[805] Rosenfeld, M.N.; Widdowson, D.A. *J. Chem. Soc. Chem. Commun.* ***1979***, 914. For another alternative procedure, see Yoneda, N.; Fukuhara, T.; Kikuchi, T.; Suzuki, A. *Synth. Commun.* ***1989***, *19,* 865.
[806] See also, Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Becker, H.G.O.; Israel, G. *J. Prakt. Chem.* ***1979***, *321,* 579.

If an aryl radical were an intermediate in the *Schiemann reaction* and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: Mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the *Schiemann reaction*, compounds containing meta-directing groups (i.e., meta-directing for *electrophilic* substitutions), should be meta arylated and those containing ortho–para directing groups should be ortho and para arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[807] that such orientation is observed, demonstrating that the *Schiemann reaction* has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[808]

OS **II**, 188, 295, 299; **V**, 133.

13-24 Conversion of Amines to Azo Compounds

N-Arylimino-de-dihydro-bisubstitution

$$ArNH_2 + Ar'NO \xrightarrow{HOAc} Ar{-}N{=}N{-}Ar'$$

Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[809] A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds ($ArNO_2$) and *N*-acyl aromatic amines (Ar′NHAc).[810] The use of phase-transfer catalysis increased the yields.

13-25 Methylation, Vinylation, and Arylation of Diazonium Salts

Methyl-de-diazoniation, and so on

$$ArN_2^+ + Me_4Sn \xrightarrow[MeCN]{Pd(OAc)_2} ArMe$$

A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a Pd catalyst.[811] The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can be introduced with $CH_2{=}CHSnBu_3$. When an aryl amine is treated with *tert*-butyl hyponitrite (*t*-BuONO) and allyl bromide, the nitrogen is displaced to give the allyl–aryl compound.[812]

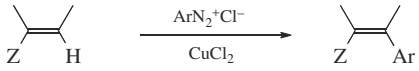
Aryl diazonium salts can be used coupled with alkenes in a *Heck-like reaction* (Reaction **13-10**).[813] Other reactive aryl species also couple with aryldiazonium salts in the presence of a Pd catalyst.[814] A *Suzuki-type* coupling (Reaction **13-12**) has also been reported using arylboronic acids, aryldiazonium salts, and a Pd catalyst.[815]

[807] Makarova, L.G.; Matveeva, M.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 548; Makarova, L.G.; Matveeva, M.K.; Gribchenko, E.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 1399.
[808] Swain, C.G.; Rogers, R.J. *J. Am. Chem. Soc.* ***1975***, *97,* 799.
[809] See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.
[810] Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* ***1989***, *30*, 7253.
[811] Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1983***, *48,* 1333.
[812] Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2003***, *68,* 1911.
[813] Sengupta, S.; Bhattacharya, S. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1943.
[814] Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 4393.
[815] Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1996***, *37,* 3857.

Aryltrifluoroborates (Reaction **12-28**) react with aryldiazonium salts in the presence of a Pd catalyst to give the corresponding biaryl.[816] See Reaction **13-12**. Arylborate esters also react using a Pd catalyst, and the aryl diazonium unit reacts faster than an aryl halide.[817]

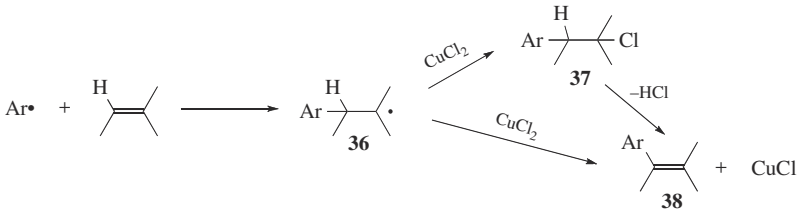
13-26 Arylation of Activated Alkenes by Diazonium Salts: Meerwein Arylation

Arylation or **Aryl-de-hydrogenation**



Alkenes activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride[818] catalyst. This is called the *Meerwein arylation reaction*.[819] Addition of ArCl to the double bond (to give Z(Cl)C—CHAr) is a side reaction (**15-46**). In an improved procedure, an arylamine is treated with an alkyl nitrite (generating ArN_2^+ *in situ*) and a copper(II) halide in the presence of the alkene.[820]

The mechanism is probably of the free radical type, with Ar• (**36**) forming as in Reaction **14-20**, and then halogen transfer to give **37** or elimination to give **38**.[821]

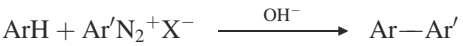


The radical **36** can react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl. Note that radical reactions are presented in Chapter 14, but the coupling of an alkene with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the *Heck reaction* in Reaction **13-10**.

OS **IV**, 15.

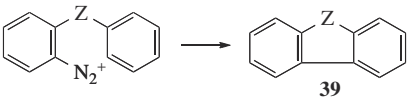
13-27 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or **Aryl-de-hydrogenation**



[816] Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875.
[817] Willis, D.M.; Strongin, R.M. *Tetahedron Lett.* ***2000***, *41,* 6271.
[818] See Ganushchak, N.I.; Obushak, N.D.; Luka, G.Ya. *J. Org. Chem. USSR* ***1981***, *17*, 765.
[819] Dombrovskii, A.V. *Russ. Chem. Rev.,* ***1984***, *53,* 943; Rondestvedt, Jr., C.S. *Org. React.,* ***1976***, *24,* 225.
[820] Doyle, M.P.; Siegfried, B.; Elliott, R.C.; Dellaria, Jr., J.F. *J. Org. Chem.* ***1977***, *42*, 2431.
[821] Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84,* 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152.

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg–Bachmann reaction*,[822] it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually <40%) because of the many side reactions undergone by diazonium salts, although higher yields have been obtained under phase-transfer conditions.[823] The conditions of the *Meerwein reaction* (**13-26**), treatment of the solution with a copper-ion catalyst, have also been used, as has the addition of sodium nitrite in DMSO (to benzenediazonium tetrafluoroborate).[824] When the *Gomberg–Bachmann reaction* is performed intramolecularly as in the formation of **39**, either by the alkaline solution or by the copper-ion procedure, it is called the *Pschorr reaction*[825] and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the *Pschorr reaction* electrochemically.[826] The *Pschorr reaction* has been carried out for Z = CH=CH, CH_2CH_2, NH, C=O, CH_2, and quite a few others. A rapid and convenient way to diazotize the amine substrate uses isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.[827] Palladium-catalyzed arylation of arenediazonium salts are known.[828]



39

Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are *N*-nitroso amides [ArN(NO)COR], triazenes,[829] and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.[830]

In each case, the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution, diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see Sec. 13.A.i). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals ($Ar^\bullet$ and $Z^\bullet$). Note that radical reactions are presented in Chapter 14, but the coupling of an aromatic ring with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the *Suzuki Reaction* in **13-12**.

$$Ar—N{=}N—Z \rightarrow Ar^\bullet + N{\equiv}N + Z^\bullet$$

[822] See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.,* ***1986***, *15,* 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47. Also see Vernin, G.; Dou, H.J.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1972***, 1173.

[823] Beadle, J.R.; Korzeniowski, S.H.; Rosenberg, D.E.; Garcia-Slanga, B.J.; Gokel, G.W. *J. Org. Chem.* ***1984***, *49,* 1594.

[824] Kamigata, N.; Kurihara, T.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3152.

[825] For a review, see Abramovitch, R.A. *Adv. Free-Radical Chem.* ***1966***, *2,* 87.

[826] Elofson, R.M.; Gadallah, F.F. *J. Org. Chem.* ***1971***, *36*, 1769.

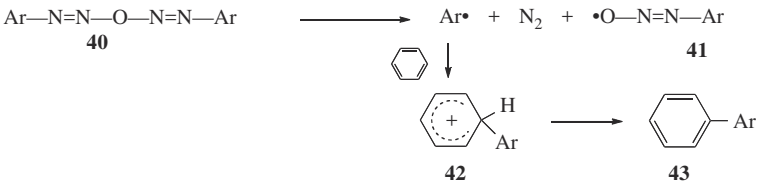
[827] Chauncy, B.; Gellert, E. *Aust. J. Chem.* ***1969***, *22,* 993. See also, Duclos, Jr., R.I.; Tung, J.S.; Rappoport, H. *J. Org. Chem.* ***1984***, *49,* 5243.

[828] Robinson, M.K.; Kochurina, V.S.; Hanna, Jr., J.M. *Tetrahedron Lett.* ***2007***, *48*, 7687.

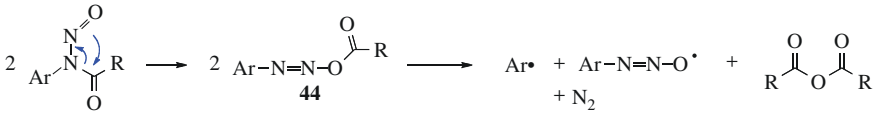
[829] See Butler, R.N.; O'Shea, P.D.; Shelly, D.P. *J. Chem. Soc. Perkin Trans. 1,* ***1987***, 1039.

[830] Fillipi, G.; Vernin, G.; Dou, H.J.; Metzger, J.; Perkins, M.J. *Bull. Soc. Chim. Fr.* ***1974***, 1075.

Under *Gomberg–Bachmann* conditions, the species that cleaves is the anhydride (**40**).[831]



The aryl radical thus formed attacks the substrate to give the aryl cation[832] intermediate **42** (see Sec. 14.A.iii), from which the radical **41** abstracts hydrogen to give the product (**43**). *N*-Nitroso amides probably rearrange to *N*-acyloxy compounds (**44**), which cleave to give aryl radicals.[833] There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.[834]



The Psc*horr reaction* can take place by two different mechanisms, depending on conditions: (1) attack by an aryl radical (as in the *Gomberg–Bachmann reaction*) or (2) attack by an aryl cation (similar to the S_N1 mechanism discussed in Sec. 13.A.ii).[835] Under certain conditions the ordinary *Gomberg–Bachmann reaction* can also involve attack by aryl cations.[836]

OS **I**, 113; **IV**, 718.

13-28 Aryl Dimerization with Diazonium Salts

De-diazonio-coupling; Arylazo-de-diazonio-substitution

$$2\,ArN_2^+ \xrightarrow[\text{or } Cu{+}H^+]{Cu^+} Ar{-}Ar + 2\,N_2 \quad \text{or} \quad Ar{-}N{=}N{-}Ar + N_2$$

When diazonium salts are treated with cuprous ion (or with Cu and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from Reaction **13-27** (and from **19-14**) in that *both* aryl groups in the product originate from ArN_2^+, that is, hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.[837]

OS **I**, 222; **IV**, 872. Also see, OS **IV**, 273.

[831] Eliel, E.L.; Saha, J.G.; Meyerson, S. *J. Org. Chem.* ***1965***, *30,* 2451.
[832] For an alternative method to generate aryl cations, see Milanesi, S.; Fagnoni, M.; Albini, A. *J. Org. Chem.* ***2005***, *70,* 603.
[833] Cadogan, J.I.G.; Murray, C.D.; Sharp, J.T. *J. Chem. Soc. Perkin Trans. 2,* ***1976***, 583, and references cited therein.
[834] Gragerov, I.P.; Levit, A.F. *J. Org. Chem. USSR* ***1968***, *4,* 7.
[835] See Gadallah, F.F.; Cantu, A.A.; Elofson, R.M. *J. Org. Chem.* ***1973***, *38,* 2386.
[836] See Burri, P.; Zollinger, H. *Helv. Chim. Acta* ***1973***, *56*, 2204; Eustathopoulos, H.; Rinaudo, J.; Bonnier, J.M. *Bull. Soc. Chim. Fr.* ***1974***, 2911; Zollinger, H. *Acc. Chem. Res.* ***1973***, *6,* 335, p. 338.
[837] See Cohen, T.; Lewarchik, R.J.; Tarino, J.Z. *J. Am. Chem. Soc.* ***1974***, *96*, 7753.

13-29 Replacement of Nitro

Alkyl-de-nitration, Hydroxy and alkoxy-de-nitration, Halo-de-nitration

$$Ar—NO_2 \rightarrow Ar—R$$

In some cases, the nitrogen group of an aromatic nitro compound can be replaced with an alkyl group. The reaction of 1,4-dinitrobenzene with potassium *tert*-butoxide in the presence of BEt_3, for example, gave 4-ethylnitrobenzene.[838]

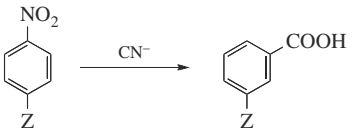
Other nucleophiles can replace a nitrogen-containing group. The reaction of hydroxide with Ar—Y, where Y = nitro,[839] azide, NR_3^+, and so on gives the corresponding phenol. This latter reaction works with alkoxide nucleophiles to give the corresponding aryl ether. The nitro can be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with fluoride ion.[840]

The reaction of vinyl nitro compounds (C=C—NO_2) and aryl iodide to give the styrene compound (C=C—Ar) was reported using BEt_3 and exposure to air.[841]

13.C.iv. REARRANGEMENTS

13-30 The von Richter Rearrangement

Hydro-de-nitro-*cine*-substitution

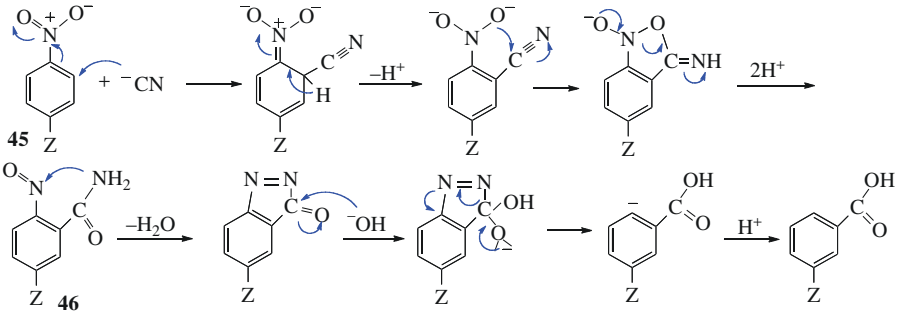


When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution (Sec. 13.A.iii), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.[842] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually <20% and never >50%.

At one time, it was believed that a nitrile (ArCN) was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (**16-4**). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut[843] demonstrated that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the *von Richter rearrangement* to give α-naphthoic acid. This proved that the nitrile could not be an intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.[844] It had

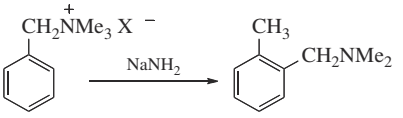
[838] Palani, N.; Jayaprakash, K.; Hoz, S. *J. Org. Chem.* ***2003***, *68*, 4388.
[839] See Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.* ***1974***, *39*, 3343.
[840] Suzuki, H.; Yazawa, N.; Yoshida, Y.; Furusawa, O.; Kimura, O. *Bull. Chem. Soc. Jpn.* ***1990***, *63,* 2010; Effenberger, F.; Streicher, W. *Chem. Ber.* ***1991***, *124*, 157.
[841] Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F. *J. Org. Chem.* ***2001***, *66*, 6021.
[842] For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 326–335.
[843] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 934, 944.
[844] Rosenblum, M. *J. Am. Chem. Soc.* ***1960***, *82*, 3796.

previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^+ is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. Rosenblum proposed a mechanism in accord with all the facts[843]:



Note that **46** is a stable compound: Hence, it should be possible to prepare it independently and to subject it to the conditions of the *von Richter rearrangement*. This was done and the correct products are obtained.[845] Further evidence is that when **45** (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, half the oxygen in the product was labeled, showing that one of the oxygen atoms of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[846]

13-31 The Sommelet–Hauser Rearrangement

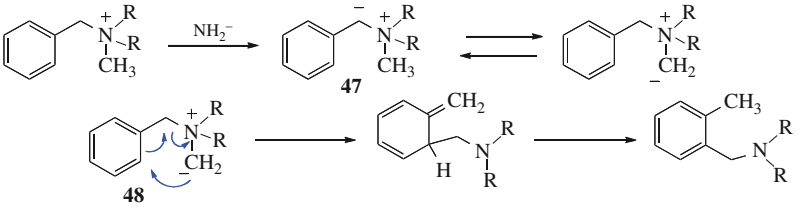


Benzylic quaternary ammonium salts, when treated with alkali metal amides, undergo a rearrangement called the *Sommelet–Hauser rearrangement*.[847] Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.[848]

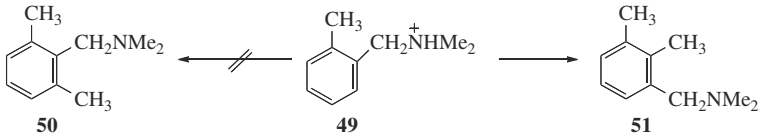
The rearrangement occurs with high yields and can be performed with various groups present in the ring.[849] The reaction is most often carried out with three methyl groups on the

[845] Ibne-Rasa, K.M.; Koubek, E. *J. Org. Chem.* ***1963***, *28*, 3240.
[846] Samuel, D. *J. Chem. Soc.* ***1960***, 1318. For other evidence, see Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* ***1961***, *39*, 144, 155, 382; Ullman, E.F.; Bartkus, E.A. *Chem. Ind. (London)* ***1962***, 93.
[847] See Pine, S.H. *Org. React.*, ***1970***, *18,* 403; Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Wittig, G. *Bull. Soc. Chim. Fr.* ***1971***, 1921; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand–Reinhold, Princeton, ***1973***, pp. 81–88; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 316–326. Also see, Klunder, J.M. *J. Heterocyclic Chem.* ***1995***, *32*, 1687.
[848] Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1960***, *25*, 334.
[849] Jones, G.C.; Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1963***, *28,* 199.

nitrogen, but other groups can also be used, though if a β-hydrogen is present, *Hofmann elimination* (Reaction **17-7**) often competes. The *Stevens rearrangement* (Reaction **18-21**) is also a competing process.[850] When both rearrangements are possible, the *Stevens rearrangement* is favored at high temperatures and the *Sommelet–Hauser* at low temperatures.[851] The mechanism is:



The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylid (**47**). However, **48**, which is present in a smaller amount, is the species that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3]-sigmatropic rearrangement (see Reaction **18-35**). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.[852] If the second mechanism were true, **49** should give **50**, but the first mechanism predicts the formation of **51**, which is what was actually obtained.[853]



The mechanism as shown can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.[854] A mechanism[855] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the *Stevens rearrangement*, Reaction **18-21**) has been invoked to explain the para products that are observed.

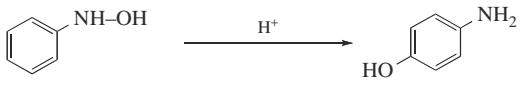
Sulfur ylids containing a benzylic group (analogous to **48**) undergo an analogous rearrangement.[856]

OS **IV**, 585.

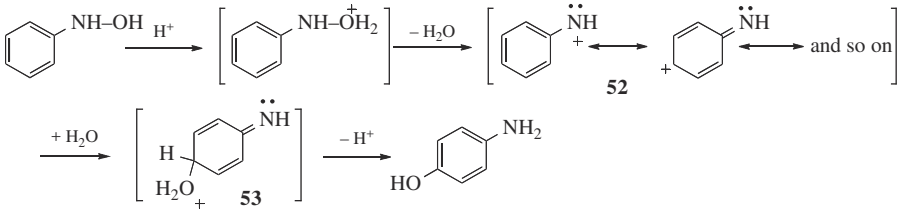
[850] See, however, Nakano, M.; Sato, Y. *J. Org. Chem.* ***1987***, *52,* 1844; Shirai, N.; Sato, Y. *J. Org. Chem.* ***1988***, *53*, 194.
[851] Wittig, G.; Streib, H. *Liebigs Ann. Chem.* ***1953***, *584,* 1.
[852] See Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1105; Pine, S.H.; Sanchez, B.L. *Tetrahedron Lett.* ***1969***, 1319; Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* ***1990***, *55*, 2767.
[853] Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* ***1951***, *73,* 4122.
[854] Pine, S.H. *Tetrahedron Lett.* ***1967***, 3393; Pine, S.H. *Org. React.* ***1970***, *18*, 403, p. 418.
[855] Bumgardner, C.L. *J. Am. Chem. Soc.* ***1963***, *85*, 73.
[856] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 118–124.

13-32 Rearrangement of Aryl Hydroxylamines

1/*C*-Hydro-5/*N*-hydroxy-interchange



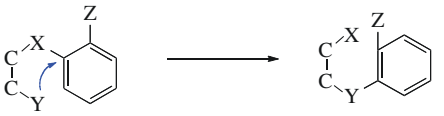
Aryl hydroxylamines treated with acids rearrange to aminophenols.[857] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to Reactions **11-28**–**11-32**, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



Among the evidence[858] for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles (e.g., *p*-ethoxyaniline) when ethanol is present, and that when the para position is blocked, compounds similar to **53** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion (**52**) was trapped, and its lifetime in solution was measured.[859] The reaction of **52** with water was found to be diffusion controlled.[860]

There is a base-mediated rearrangement of aromatic hydroxamic acids to anilines.[861] OS **IV**, 148.

13-33 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.[862] A specific example is the reaction of **54** with hydroxide to give **55**.

[857] See Shine, H.J. *Aromatic Rearrangements,* Elsevier, NY, ***1967***, pp. 182–190.

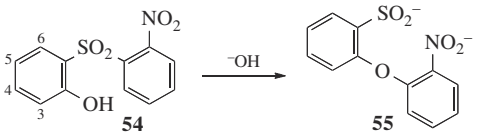
[858] Also see Kohnstam, G.; Petch, W.A.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 423; Sternson, L.A.; Chandrasakar, R. *J. Org. Chem.* ***1984***, *49*, 4295, and references cited therein.

[859] Fishbein, J.C.; McClelland, R.A. *J. Am. Chem. Soc.* ***1987***, *109,* 2824.

[860] Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1661.

[861] Hoshino, Y.; Okuno, M.; Kawamura, E.; Honda, K.; Inoue, S. *Chem. Commun* ***2009***, 2281.

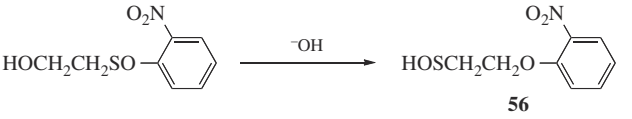
[862] See Truce, W.E.; Kreider, E.M.; Brand, W.W. *Org. React*., ***1971***, *18*, 99; Shine, H.J. *Aromatic Rearrangements,* Elsevier, NY, ***1967***, pp. 307–316; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand–Reinhold, Princeton, ***1973***, pp. 120–126.



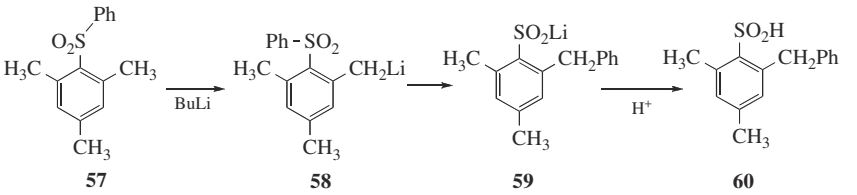
Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- is the nucleophile. The nitro group serves to activate its ortho position. Halogens also serve as activating groups.[863] The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. Here X is usually S, SO, SO_2,[864] O, or CO_2, and Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with $Y = CH_2^-$ (phenyllithium was the base here).[865]

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **54** caused the rate to be $\sim 10^5$ times faster than when the same groups were in the 4 position,[866] although electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation of the molecule can adapt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

Although the *Smiles rearrangement* is usually carried out on compounds containing two rings, this need not be the case, as in the formation of **56**.[867]



In this case the, sulfenic acid (**56**) is unstable[868] and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).



In the *Smiles rearrangement*, the nucleophile Y is most often the conjugate base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, and OR. There are few examples where Y is a

[863] Grundon, M.F.; Matier, W.L. *J. Chem. Soc., B* ***1966***, 266; Schmidt, D.M.; Bonvicino, G.E. *J. Org. Chem.* ***1984***, *49,* 1664.
[864] See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 262–274.
[865] Truce, W.E.; Robbins, C.R.; Kreider, E.M. *J. Am. Chem. Soc.* ***1966***, *88,* 4027; Drozd, V.N.; Nikonova, L.A. *J. Org. Chem*, *USSR* ***1969***, *5,* 313.
[866] Bunnett, J.F.; Okamoto, T. *J. Am. Chem. Soc.* ***1956***, *78,* 5363.
[867] Kent, B.A.; Smiles, S. *J. Chem. Soc.* ***1934***, 422.
[868] For a stable sulfenic acid, see Nakamura, N. *J. Am. Chem. Soc.* ***1983***, *105*, 7172.

carbanion, and the most common example is probably the *Truce–Smiles rearrangement,* where L—YH is an *o*-tolyl group.[869] The prototypical *Truce–Smiles rearrangement* requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement. When sulfone (**57**) was treated with butyllithium, for example, deprotonation led to the benzylic lithium compound (**58**). *Truce–Smiles rearrangement* led to **59**, and hydrolysis gave the sulfinic acid (**60**).[870] *Truce–Smiles rearrangements* with stabilized benzylic carbanions are known,[870] and rearrangements of carbanions in general fall under this category.[871] Relatively few examples have been reported, however.[872] *Truce–Smiles rearrangements* of sulfones that proceed through a six-membered transition state have been reported.[873] In another example, displacement of an activated aryl fluoride with *o*-hydroxyacetophenone gave a product that was C-arylated adjacent to the ketone.[874]

[869] Truce, W.E.; Ray, Jr., W.J.; Norman, O.L.; Eickemeyer, D.B. *J. Am. Chem. Soc.* ***1958***, *80,* 3625.
[870] Erickson, W.R.; McKennon, M.J. *Tetrahedron Lett.* ***2000***, *41,* 4541.
[871] Fukazawa, Y.; Kato, N.; Ito, S. *Tetrahedron Lett.* ***1982***, *23,* 437.
[872] Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* ***2001***, *55,* 741.
[873] Truce, W.E.; Hampton, D.C. *J. Org. Chem.* ***1963***, *28,* 2276.
[874] Mitchell, L.H.; Barvian, N.C. *Tetrahedron Lett.* ***2004***, *45*, 5669.

CHAPTER 14

Substitution Reactions: Radical

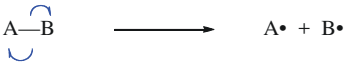
This chapter discusses many types of radical reactions, including reactions in which radicals may be intermediates. Radicals are increasingly important in organic synthesis.[1] The formation, fate, and properties of radicals were introduced in Section 5.C. Additional information concerning radicals may be found in Section 7.A, in the discussion of photochemical processes.

For the most part, this chapter discusses radical substitution reactions. Free radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. Fragmentation reactions are covered, in part, in Chapter 17. In addition, many of the oxidation–reduction reactions considered in Chapter 19 involve free radical mechanisms. Several important types of free radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book.

14.A. MECHANISMS

14.A.i. Radical Mechanisms in General[2]

A free radical process (or just a radical process) consists of at least two steps. Any radical reaction first step involve the *formation* of free radicals, usually by homolytic cleavage of a bond; that is, a cleavage in which each fragment retains one electron:



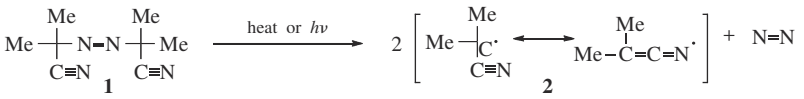
This is called an *initiation* step. It may happen spontaneously or may be induced by heat[3] or light (see the discussion in Sec. 5.C.ii), depending on the type of bond.[4] Peroxides,

[1] Rowlands, G.J. *Tetrahedron* ***2009****, 65,* 8603; ***2010****, 66*, 1593.
[2] Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radical,* Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton. J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***. See Huyser, E.S. in McManus, S.P. *Organic Reactive Intermediates,* Academic Press, NY, ***1973***, pp. 1–59; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***; Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer, NY, ***1978***; Curran, D.P. *Synthesis* ***1988***, 417, 489; Ramaiah, M. *Tetrahedron* ***1987****, 43*, 3541.
[3] See Engel, P.S.; Pan, L.; Ying, Y.; Alemany, L.B. *J. Am. Chem. Soc.* ***2001****, 123,* 3706.
[4] See Fokin, A.A.; Schreiner, P.R. *Chem. Rev.* ***2002****, 102*, 1551.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

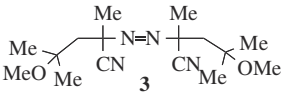
including hydrogen peroxide, dialkyl, diacyl, alkyl acyl peroxides, and peroxyacids are the most common source of free radicals. However, other organic compounds with low-energy bonds (e.g., azo compounds) are also used. Chlorine, bromine, and various ketones (see Chapter 7) are most commonly cleaved by light. Radicals can also be formed by a one-electron transfer (loss or gain) (e.g., $A^+ + e^- \rightarrow A^\bullet$). One-electron transfers usually involve inorganic ions or electrochemical processes.[5]

Dialkyl peroxides (ROOR) or alkyl hydroperoxides (ROOH) decompose to hydroxy radicals ($HO^\bullet$) or alkoxy radicals ($RO^\bullet$) when heated.[6] Cumene hydroperoxide ($PhCMe_2OOH$), bi-*tert*-butylperoxide ($Me_3COOCMe_3$),[7] and benzoyl peroxide [$(PhCO)O_2$] undergo homolytic cleavage at temperatures compatible with many organic reactions. They are also reasonably soluble in organic solvents.[8] In general, when a peroxide decomposes, the oxygen radical remains in a "cage" for $\sim 10^{-11}$ s before diffusing away. The radical can



recombine (dimerize), or react with other molecules. Azo compounds, characterized by a —N=N— bond, are free radical precursors that liberate nitrogen gas (N≡N) upon decomposition. *Azo bisi*sobutyronitrile (AIBN, **1**) is a well-known example, which decomposes to give nitrogen gas and the cyano stabilized radical (**2**).[9] Homolytic dissociation of symmetrical diazo compounds may be stepwise.[10] A derivative has been developed that decomposes at room temperature: 2,2′-*azobis*(2,4-dimethyl-4-methoxyvaleronitrile), **3**.[11] Water soluble azo compounds are known, and can be used as radical initiators.[12]

Alkyl hypochlorites (R—O—Cl) generate chlorine radicals ($Cl^\bullet$) and alkoxy radicals ($RO^\bullet$) when heated.[13] Heating *N*-alkoxydithiocarbamates is another useful source of alkoxy radicals ($RO^\bullet$).[14] Alkoxy radicals, particularly those derived from cyclic compounds, may undergo β-scission reactions to give carbonyl derivatives.[15]

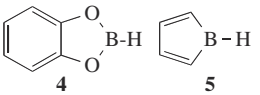


[5] For a review of bond formation and bond dissociation, see Houmam, A. *Chem. Rev.* ***2008****, 108,* 2180.
[6] For a table of approximate decomposition temperatures, see Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology* CRC Press, Washington, DC, ***1989***, p 12.
[7] Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p 13.
[8] Hydrogen bonding affects the persistency of alkyl peroxy radicals. See Mugnaini, V.; Lucarini, M. *Org. Lett.* ***2007****, 9*, 2725.
[9] Yoshino, K.; Ohkatsu, J.; Tsuruta, T. *Polym. J.* ***1977****, 9*, 275; von J. Hinz, A.; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1973***, 1975.
[10] Dannenberg, J.J.; Rocklin, D. *J. Org. Chem.* ***1982****, 47*, 4529. See also, Newman, Jr, R.C.; Lockyer, Jr, G.D. *J. Am. Chem Soc.* ***1983,*** *105*, 3982.
[11] Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* ***1997****, 38*, 3549.
[12] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H; Oshima, K. *Tetrahedron Lett.* ***1999****, 40*, 519.
[13] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer–Verlag, Berlin, ***1978***, p. 9; Chattaway, F.D.; Baekeberg, O.G. *J. Chem. Soc.* ***1923****, 123*, 2999.
[14] Kim, S.; Lim, C.J.; Song, S.-E.; Kang, H.-Y. *Synlett* ***2001***, 688.
[15] See Bietti, M.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* ***2005****, 70*, 417.

It has been known for many years that boron compounds participate in radical reactions.[16] Trialkylboranes (R_3B; see Reactions **15-27** and **12-27**), such as triethylborane (Et_3B), can be used to initiate radical reactions. Indeed, Et_3B is widely used.[17] In radical reactions, Et_3B functions as both a radical initiator and also as a chain-propagation agent.[18] Reactions are usually run in open vessels exposed to oxygen or under an oxygen atmosphere. It is known that O_2 is involved in the initiation step, as shown, in this case using an atom-transfer reaction with an alkyl iodide to give the alkyl radical, ($R^{\bullet}$). Trialkylborane/water-mediated radical reactions are also known.[19]

$$Et_3B + O_2 \rightarrow Et_2BOO^{\bullet} + Et^{\bullet} \quad \textbf{Initiation}$$
$$Et^{\bullet} + R - I \rightarrow Et - I + R^{\bullet}$$

In general, the order of reactivity is $R_3B > R_2BOR > RB(OR)_2$ where R = alkyl.[20] Boronic acids are less reactive, presumably due to π-bonding between B and O.[17] However, B-alkycatecholboranes are very reactive, and highly useful for initiating radical reactions.[21] Reaction conditions usually involve addition of catecholborane (**4**, abbreviated CatBH), and the B-alkyl derivative is presumably generated *in situ* by reaction with an alkene.[22] Note that borole derivatives (the B analogue of pyrrole, **5**) have been used to initiate radical reactions.[23]



4 **5**

Aldehydes can be a source of acyl radicals ($^{\bullet}C{=}O$) via reaction with transition metal salts (e.g., Mn(III) acetate or Fe(II) compounds).[24] α,β-Unsaturated acyl radicals are subject to an isomerization that generates α-ketenyl radicals.[25] Another useful variation employs imidoyl radicals as synthons for unstable aryl radicals.[26]

[16] See Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972****, 11,* 692; Ghosez, A.; Giese, B.; Zipse, H. Houben-Weyl, Vol. E19a, ***1989***, p. 753; Ollivier, C.; Renaud, P. *Chem. Rev.* ***2001****, 101,* 3415.

[17] Renaud, P.; Beauseigneur, A.; Brecht-Forster, A.; Becattini, B.; Darmency, V.; Kandhasamy, S.; Montermini, F.; Ollivier, C.; Panchaud, P.; Pozzi, D.; Scanlan, E.M.; Schaffner, A.-P.; Weber, V. *Pure Appl. Chem.* ***2007****, 79,* 223; Nozaki, K.; Oshima, K.; Utimoto. K. *J. Am. Chem. Soc.* ***1987****, 109,* 2547; Yorimitsu, H.; Oshima, K. in *Radicals in Organic Synthesis, Vol. 1*, Renaud, P.; Sibi, M.P. (Eds.) p. 11, Wiley–VCH, Weinheim, **2001**.

[18] See Darmency, V.; Renaud, P. in *Topics in Current Chemistry, Vol. 263* Gansaeuer, A. (Ed.), Springer, Berlin, ***2006***, p. 71.

[19] Medeiros, M.R.; Schacherer, L.N.; Spiegel, D.A.; Wood, J.L. *Org. Lett.* ***2007****, 9,* 4427.

[20] Davies, A.G.; Roberts, B.P. *Free Radicals, Vol. 1* Kochi, J.K. (Ed.), p. 457, J Wiley, NY, ***1973***, p. 457; Baban, J.A.; Goodchild, N.J.; Roberts, B.P. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 157.

[21] Ollivier, C.; Renaud, P. *Angew. Chem. Int. Ed.* ***2000****, 39,* 925; Ollivier, C.; Renaud, P. *Chem. Eur. J. 1999, 5,* 1468; Schaffner, A.-P.; Renaud, P. *Eur. J. Org. Chem.* ***2004***, 2291; Darmency, V.; Renaud, P. *Top. Curr. Chem.* ***2006****, 263*, 71.

[22] See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996****, 61,* 3224.

[23] Montgomery, I.; Parsons, A.F.; Ghelfi, F.; Roncaglia, F. *Tetrahedron Lett.* ***2008****, 49*, 628.

[24] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer–Verlag, Berlin, ***1978***, p 69; Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. *Synthesis* ***1972***, 376; Nikishin, G.I.; Vinogradov, M.G.; Verenchikov, S.P.; Kostyukov, I.N.; Kereselidze, R.V. *J. Org. Chem, USSR* ***1972****, 8*, 539 (Engl. p. 544).

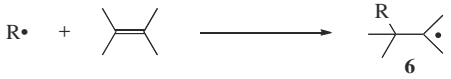
[25] Matsubara, H.; Ryu, I.; Schiesser, C.H. *J. Org. Chem.* ***2005****, 70,* 3610.

[26] Fujiwara, S.-i.; Matsuya, T.; Maeda, H.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* ***2001****, 66,* 2183.

An important step in radical reactions involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:[27]

$$A^{\bullet} + B^{\bullet} \longrightarrow A{-}B$$

This type of step is called *termination* because the product of the reaction is a neutral compound and not a radical.[28] Note that this reaction constitutes a radical coupling process. The termination step rarely follows initiation because most radicals are very reactive, and there are several radical processes that occur faster than the termination step. In the usual situation, in which the concentration of radicals is low, a radical is more likely to react with a molecule rather than another radical (i.e., the radical coupling reaction is usually slower). When a radical, which has an odd number of electrons, reacts with a molecule, which has an even number, the total number of electrons in the products must be odd. In other words, the product is another radical. When a radical



6

reacts with a π bond, for example, the product is free radical (**6**). This reaction is called a *radical addition*. Another reaction constitutes an *atom-transfer reaction*. The abstraction of an atom (e.g., hydrogen atom) from an alkyl fragment gives two particles: R—H and the new radical ($R'^{\bullet}$), as shown. This type of atom-transfer reaction is called a *hydrogen-transfer reaction*.

$$R^{\bullet} + R'H \longrightarrow RH + R'^{\bullet}$$

Once again, the product is a free radical. This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals undergo coupling and terminate the sequence. The process of initiation, propagation, and then termination constitutes what is called a *chain reaction*,[29] and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (1) cleavage of a radical into, necessarily, a radical and a molecule and (2) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive (e.g., alkyl radicals), chains are long, since reactions occur with many molecules; but with radicals of low reactivity (e.g., aryl radicals), the radical may be unable to react with anything until it meets another radical, so that chains are short. Alternatively, the reaction may be a nonchain process. In any particular chain process, there is usually a wide variety of propagation and termination steps so there may be many products. Such reaction are often difficult to treat kinetically.[30]

$$R{-}CH_2^{\bullet} + n\text{-}Bu_3Sn{-}H \longrightarrow R{-}CH_2{-}H + n\text{-}Bu_3Sn^{\bullet}$$
$$n\text{-}Bu_3Sn^{\bullet} + n\text{-}Bu_3Sn^{\bullet} \longrightarrow n\text{-}Bu_3Sn{-}Sn n\text{-}Bu_3$$

[27] For a review of stereochemistry, see Porter, N.A.; Krebs, P.J. *Top. Stereochem.* ***1988****, 18*, 97.
[28] Another type of termination step is *disproportionation* (see Sec. 5.C.ii).
[29] See Walling, C. *Tetrahedron* ***1985****, 41,* 3887.
[30] See Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 39–65.

Is it possible to terminate a radical reaction under controlled conditions? The answer is yes, using an atom-transfer reaction. When a carbon radical ($R^{\bullet}$) is generated in the presence of tributyltin hydride (n-Bu_3SnH), a hydrogen atom is transferred to the radical to give R—H and a new radical (n-$Bu_3Sn^{\bullet}$). The tin radical usually undergoes rapid coupling to another tin radical to give n-Bu_3Sn—Sn—n-Bu_3, which effectively terminates the chain-radical process. The carbon radical is *reduced* ($R^{\bullet} \rightarrow$ R—H) as a result of the hydrogen-atom transfer, and the tin dimer can be removed from the reaction. Again, hydrogen-atom transfer[31] is simply a variation of the radical reaction known as atom transfer. Silanes (e.g., triethylsilane, Et_3SiH), have also been used as an effective radical reducing agent.[32] The rate constants for the reaction of both tributytin hydride and $(Me_3Si)_3Si$—H with acyl radical have been measured and the silane quenches the radical faster than the tin hydride.[33] Thermolysis of bis(tri-n-butylstannyl)benzopinacolate has also been used as a source of n-$Bu_3Sn^{\bullet}$, used to mediate radical reactions.[34]

The following are some general characteristics of free radical reactions[35]:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, but solvation of free radicals in solution does cause some differences.[36]
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated or accelerated by typical free radical sources (e.g., the peroxides or diazo compounds) noted above, or by light. In the latter case, the concept of quantum yield applies (Sec. 7.A.viii). Quantum yields can be quite high (e.g., 1000), if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals (e.g., nitric oxide, molecular oxygen, or benzoquinone). These substances are called *inhibitors*.[37] Note that there are C-centered radicals in thermal equilibrium with their dimers that show poor reactivity with molecular oxygen, but good reactivity with peroxyl radicals.[38]

14.A.ii. Free Radical Substitution Mechanisms[39]

In a free radical substitution reaction

Step 1 R—X ⟶ R—Y

there must first be a cleavage of the substrate RX so that $R^{\bullet}$ radicals are produced. This can happen by a spontaneous cleavage,

[31] For a discussion of barriers to degenerate hydrogen transfer, see Isborn, C.; Hrovat, D.A.; Borden, W.T.; Mayer, J.M.; Carpenter, B.K. *J. Am. Chem. Soc.* ***2005****, 127,* 5794. For a discussion of hydrogen atom transfer from phenols, see Nielsen, M.F.; Ingold, K.U. *J. Am. Chem. Soc.* ***2006****, 128,* 1172.
[32] Chatgilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* ***1993****, 58*, 249.
[33] Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* ***1995****, 36*, 1299.
[34] Hart, D.J.; Krishnamurthy, R.; Pook, L.M.; Seely, F.L. *Tetrahedron Lett.* ***1993****, 34*, 7819.
[35] See Beckwith, A.L.J. *Chem. Soc. Rev.* ***1993****, 22*, 143 for a discussion of selectivity in radical reactions.
[36] See Mayo, F.R. *J. Am. Chem. Soc.* ***1967****, 89*, 2654.
[37] See Denisov, E.T.; Khudyakov, I.V. *Chem. Rev.* ***1987****, 87,* 1313.
[38] Korth, H.-G. *Angew. Chem. Int. Ed.* ***2008****, 47*, 5274.
[39] See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 113–158.

Step 2 $R—X \longrightarrow R^{\bullet} + X^{\bullet}$

or it can be caused by light or heat, or, more often, there is no actual cleavage, but $R^{\bullet}$ is produced by an *abstraction* of another atom, X by the radical $W^{\bullet}$.

Step 3 $R—X + W^{\bullet} \longrightarrow R^{\bullet} + W—X$

The radical $W^{\bullet}$ is produced by adding a compound (e.g., peroxide) that spontaneously forms free radicals. Such a compound is called an *initiator* (see above). Once $R^{\bullet}$ is formed, it can go to product in this system, by another atom abstraction, such as the reaction with A—B to form R—A and a new radical $B^{\bullet}$ (atom transfer).

Step 4 $R^{\bullet} + A—B \longrightarrow R—A + B^{\bullet}$

Another reaction is coupling with another radical to form the neutral product R—Y.

Step 5 $R^{\bullet} + Y^{\bullet} \longrightarrow B—Y$

In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called S_H1 (H for homolytic), and abstraction steps like (3) and (4) have been called S_H2; reactions can be classified as S_H1 or S_H2 on the basis of whether RX is converted to R by (2) or (3).[40] Most chain substitution mechanisms follow the pattern (3), (4), (3), (4) $\cdots$ Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse that slightly endothermic, see Sec. 14.B.i and 14.C.i). The IUPAC designation of a chain reaction that follows the pattern (3),(4) $\cdots$ is $A_rD_R + A_RD_r$ (R stands for radical).

With certain radicals the transition state in an abstraction reaction has some polar character. Consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that there is a separation of charge in the transition state, with a partial negative charge on the halogen and a partial positive charge on the carbon:

$$\overset{\delta+}{\text{PhCH}_2}\bullet\bullet\bullet\bullet\bullet\bullet\text{H}\bullet\bullet\bullet\bullet\bullet\bullet\overset{\delta-}{\text{Br}}$$

Evidence for the polar character of the transition state is that electron-withdrawing groups in the para position of toluene, which would destabilize a positive charge, decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.[41] However, substituents have a smaller effect here ($\rho \approx -1.4$) than they do in reactions where a completely ionic intermediate is involved (e.g., the S_N1 mechanism, Sec. 10.A.ii). Other evidence for polar transition states in radical abstraction reactions is mentioned in Section 14.B.i, category 4. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen-atom abstraction from ring-substituted toluenes by methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.[42] Those radicals (e.g., $Br^{\bullet}$) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step $R—X \rightarrow R^{\bullet}$ takes place at a stereogenic carbon, *racemization is almost always observed because free radicals do not retain configuration*. Exceptions

[40] Eliel, E.L. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 142–143.
[41] See Kim, S.S.; Choi, S.Y.; Kang, C.H. *J. Am. Chem. Soc.* ***1985****, 107*, 4234.
[42] See Pryor, W.A.; Tonellato, U.; Fuller, D.L.; Jumonville, S. *J. Org. Chem.* ***1969****, 34,* 2018.

to this rule are found with cyclopropyl substrates, where both inversion[43] and retention[44] of configuration have been reported, and in the reactions mentioned in Section 14.A.iv. Enantioselective radical processes have been reviewed.[45]

14.A.iii. Mechanisms at an Aromatic Substrate[46]

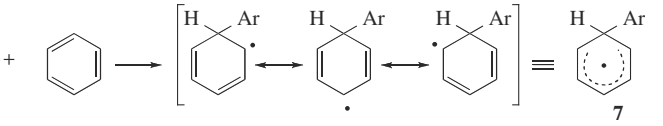
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as Reactions **13-27**, **14-17**, and **14-18**:

Step 6 $Ar^{\bullet} + ArH \longrightarrow Ar{-}Ar$

which occur in solution, the simple coupling of two rings by abstraction of an entire group (e.g., phenyl) to generate $H^{\bullet}$ by the free radical mechanism shown here is very unlikely (see Sec. 14.B.i).

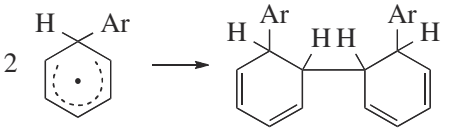
Step 7 $Ar^{\bullet} + ArH \longrightarrow Ar{-}Ar + H^{\bullet}$

The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a

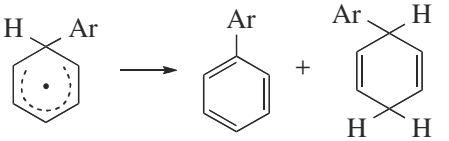
Step 8 

7

nucleophile to generate **7**. The intermediate radical (**7**) is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling to give **8**, by disproportionation to give **9**,

Step 9 

8

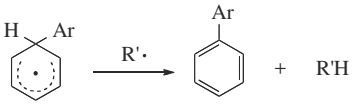
Step 10 

9

[43] Altman, L.J.; Nelson, B.W. *J. Am. Chem. Soc.* ***1969****, 91,* 5163.
[44] Jacobus, J.; Pensak, D. *Chem. Commun.* ***1969***, 400.
[45] Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* ***2003****, 103*, 3263.
[46] See Kobrina, L.S. *Russ. Chem. Rev.* ***1977****, 46,* 348; Perkins, M.J. in Kochi, J.K. *Free Radicals,* Vol. 2, Wiley, NY, ***1973***, 231–271; Bolton, R.; Williams, G.H. *Adv. Free-Radical Chem.* ***1975****, 5,* 1; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 417–469.

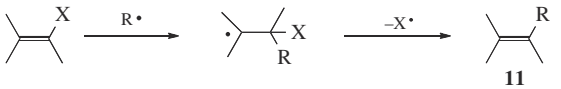
or, if a species ($R'^{\bullet}$) is present that abstracts hydrogen, by abstraction to give **10**.[47]

Step 11



10

Coupling product **8** is a partially hydrogenated *o*-quaterphenyl (an *o,o′*-diphenylbiphenyl). Of course, the coupling need not be ortho–ortho, and other isomers can also be formed. Among the evidence (9) and (10) was isolation of compounds of types **8** and **9**.[48] However, under the reaction conditions dihydrobiphenyls like **9** are normally oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **7** by CIDNP[49] and the absence of isotope effects, expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. The reaction between aromatic rings and the $HO^{\bullet}$ radical takes place by the same mechanism. Intramolecular hydrogen-transfer reactions of aryl radicals are known.[50] A similar mechanism has been shown for substitution at some vinylic[51] and acetylenic substrates, giving the substituted alkene (**11**).[52] The kinetics of radical heterolysis reactions that form alkene radical cations has been studied.[53]



11

This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (Sec. 10.F).

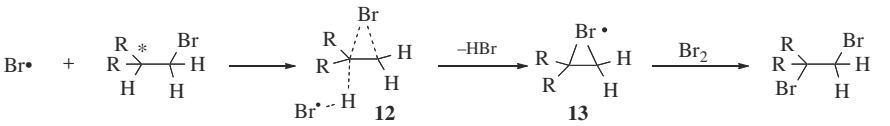
There are many transition metal mediated coupling reactions of aromatic substrates that probably proceed by radical coupling. It is likely that many of these reactions do ***not*** proceed by free radicals, but rather by metal-mediated radicals or by ligand transfer at the metal. Reactions in these categories were presented in Chapter 13 for convenient correlation with other displacement reactions of aryl halides, aryl diazonium salts, and so on.

14.A.iv. Neighboring-Group Assistance in Free Radical Reactions

In a few cases, it has been shown that cleavage steps (2) and abstraction steps (3) were accelerated by the presence of neighboring groups. Photolytic halogenation (Reaction **14-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of

[47] See Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* ***1982****, 104,* 7316.
[48] DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967****, 89,* 4051; DeTar, D. F. *J. Am. Chem. Soc.* ***1967****, 89,* 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.
[49] Fahrenholtz, S.R.; Trozzolo, A.M. *J. Am. Chem. Soc.* ***1972****, 94,* 282.
[50] Curran, D.P.; Fairweather, N. *J. Org. Chem.* ***2003****, 68,* 2972.
[51] See Bach, R.D.; Baboul, A.G.; Schlegel, H.B. *J. Am. Chem. Soc,* ***2001****, 123*, 5787.
[52] Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* ***1986****, 27,* 3479, and references cited therein.
[53] Horner, J.H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* ***2004****, 126*, 14979. See also, Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* ***2005****, 127,* 7324.

alkyl bromides gave 84–94% substitution at the carbon adjacent to the bromine already in the molecule.[54] This result may seem surprising because, as will be seen (Sec. 14.B.i, category 3), positions close to a polar group (e.g., bromine) should actually be *deactivated* by the electron-withdrawing field effect of the bromine. However, the unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom, as in **12**.[55] In the normal mechanism, $Br^{\bullet}$ abstracts a hydrogen atom from RH, leaving $R^{\bullet}$. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **13**).[56] In the final step (very similar to $R^{\bullet} + Br_2 \rightarrow RBr + Br^{\bullet}$) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: Optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.[55] Furthermore, when this reaction was carried out in



the presence of DBr, the "recovered" 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.[57] This is just what would be predicted if some of the **11** present abstracted D from DBR. There is evidence that Cl can form bridged radicals,[58] though ESR spectra show that the bridging is not necessarily symmetrical.[59] Still more evidence for bridging by Br has been found in isotope effects and other studies.[60] However, evidence from CIDNP shows that the methylene protons of the β-bromoethyl radical are not equivalent, at least while the radical is present in the radical pair [$PhCOO^{\bullet}$ $^{\bullet}CH_2CH_2Br$] within a solvent cage.[61] This evidence indicates that under these conditions $BrCH_2CH_2^{\bullet}$ is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the *Hunsdiecker reaction*[62] (**14-30**), and in abstraction of iodine atoms by the phenyl radical.[63] Participation by other neighboring groups (e.g. SR, SiR_3, SnR_3) has also been reported.[64]

[54] Thaler, W.A. *J. Am. Chem. Soc.* ***1963****, 85*, 2607. See also, Hargis, J.H. *J. Org. Chem.* ***1973****, 38*, 346.
[55] Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963****, 85*, 2849; Huyser, E.S.; Feng, R.H.C. *J. Org. Chem.* ***1971****, 36,* 731. For another explanation, see Lloyd, R.V.; Wood, D.E. *J. Am. Chem. Soc.* ***1975****, 97*, 5986. Also see, Cope, A.C.; Fenton, S.W. *J. Am. Chem. Soc.* ***1951****, 73*, 1668.
[56] See Kaplan, L. *Bridged Free Radicals*; Marcel Dekker, NY, ***1972***; Skell, P.S.; Traynham, J.G. *Acc. Chem. Res.* ***1984****, 17*, 160; Skell, P.S.; Shea, K.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 809–852.
[57] Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973****, 95,* 283.
[58] Everly, C.R.; Schweinsberg, F.; Traynham, J.G. *J. Am. Chem. Soc.* ***1978****, 100*, 1200; Wells, P.R.; Franke, F.P. *Tetrahedron Lett.* ***1979***, 4681.
[59] Cooper, J.; Hudson, A.; Jackson, R.A. *Tetrahedron Lett.* ***1973***, 831; Chen, K.S.; Elson, I.H.; Kochi, J.K. *J. Am. Chem. Soc.* ***1973****, 95*, 5341.
[60] Cain, E.N.; Solly, R.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 148; Howard, J.A.; Chenier, J.H.B.; Holden, D.A. *Can. J. Chem.* ***1977****, 55,* 1463. See, however, Tanner, D.D.; Blackburn, E.V.; Kosugi, Y.; Ruo, T.C.S. *J. Am. Chem. Soc.* ***1977****, 99*, 2714.
[61] Hargis, J.H.; Shevlin, P.B. *J. Chem. Soc., Chem. Commun.* ***1973***, 179.
[62] Applequist, D.E.; Werner, N.D. *J. Org. Chem.* ***1963****, 28,* 48.
[63] Danen, W.C.; Winter, R.L. *J. Am. Chem. Soc.* ***1971****, 93,* 716.
[64] Ingold, K.U.; Griller, D.; Nazran, A.S. *J. Am. Chem. Soc.* ***1985****, 107*, 208. See Reetz, M.T. *Angew. Chem. Int. Ed.* ***1979****, 18*, 173.

Note that a traditional explanation for the selectivity of bromine relative to chlorine is that abstraction of hydrogen by a bromine radical has a later transition state relative to abstraction of hydrogen by a chlorine radical. In a later transition state, the relative stability of the radical plays a greater role than the strength of the C—H bond. Since a tertiary radical is more stable than a secondary, which is more stable than a primary radical, bromination favors formation of the secondary radical over the primary, and a tertiary over secondary. This analysis is supported by the relative rates of hydrogen-atom abstraction by $Br^{\bullet}$ when compared to $Cl^{\bullet}$, where there is a large difference between 1°, 2°, and 3° for $Br^{\bullet}$ and a small difference for $Cl^{\bullet}$. This effect is discussed in more detail in Section 14.B.i, categories 1–5.

14.B. REACTIVITY

14.B.i. Reactivity for Aliphatic Substrates[65]

In a chain reaction, the step that determines what the product will be is most often an abstraction (atom-transfer) step. The atom abstracted by a free radical is almost never a tetra-[66] or tervalent atom[67] (except in strained systems, see Sec. 15.B.iv)[68] and seldom a divalent one.[69] Nearly always it is univalent, and for organic compounds, it is commonly hydrogen or halogen. Further, in a reaction between a chlorine radical and ethane, formation of an ethyl radical is preferred (H atom transfer) to formation of a hydrogen-atom radical (Cl atom transfer):

$$CH_3CH_3 + Cl \begin{cases} \longrightarrow & H\text{—}Cl + CH_3CH_2^{\bullet} \quad \Delta H = -3 \text{ kcal mol}^{-1}(-13 \text{ kJ/mol}) \\ \not\longrightarrow & CH_3CH_2\text{—}Cl + H^{\bullet} \quad \Delta H = +18 \text{ kcal mol}^{-1}(+76 \text{ kJ/mol}) \end{cases}$$

The principal reason for this preference is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Also, in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a C_2H_5—H bond is broken ($D = 100\,\text{kcal mol}^{-1}$, $419\,\text{kJ mol}^{-1}$, from Table 5.3) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103\,\text{kcal mol}^{-1}$, $432\,\text{kJ mol}^{-1}$) while in the latter case it is a C_2H_5—Cl bond ($D = 82\,\text{kcal mol}^{-1}$ $343\,\text{kJ mol}^{-1}$). Thus the first reaction is favored because it is exothermic by $3\,\text{kcal mol}^{-1}$ (100–103) [$13\,\text{kJ mol}^{-1}$ (419–432)], while the latter is endothermic by $18\,\text{kcal mol}^{-1}$ (100–82) [$76\,\text{kJ mol}^{-1}$ (419–343)].[70] However, the steric reason is more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.[71] *Ab initio* studies have probed the transition structures for radical hydrogen abstractions.[72]

[65] See Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982,*** *21,* 401.
[66] See Firouzbakht, M.L.; Ferrieri, R.A.; Wolf, A.P.; Rack, E.P. *J. Am. Chem. Soc.* ***1987,*** *109,* 2213.
[67] See Back, R.A. *Can. J. Chem.* ***1983***, *61*, 916.
[68] See Jackson, R.A.; Townson, M. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1452. See also, Johnson, M.D. *Acc. Chem. Res.* ***1983,*** *16,* 343.
[69] See Ingold, K.U.; Roberts, B.P. *Free-Radical Substitution Reactions*, Wiley, NY, ***1971***.
[70] The parameter ΔH for a free radical abstraction reaction can be regarded simply as the difference in D values for the bond being broken and the one formed.
[71] Giese, B.; Hartung, J. *Chem. Ber.* ***1992,*** *125*, 1777.
[72] Eksterowicz, J.E.; Houk, K.N. *Tetrahedron Lett.* ***1993,*** *34*, 427; Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* ***1993,*** *34*, 431.

TABLE 14.1 Relative Susceptibility to Attack by $Cl^{\bullet}$ of Primary, Secondary, and Tertiary Positions at 100 and 600 °C in the Gas Phase[a]

Temp (°C)	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

Reprinted with permission Hass, H.B., McBee, E.T., Weber, P. *Ind. Eng. Chem.* ***1936*** *, 28*, 333. Copyright © 1936 American Chemical Society.

[a]See Ref. 78.

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.[73] In these reactions, every hydrogen atom in the substrate is potentially replaceable and mixtures of several products may be obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. *Ab initio* studies have studied the factors controlling hydrogen abstraction by radicals.[74] For hydrogen abstraction by the *tert*-butoxy radical (*t*-Bu—$O^{\bullet}$) the factors that influence rate in their order of importance are structure of the radical > substituent effects[75] > solvent effects.[76] The position of attack will be discussed under several headings[77]:

1. *Alkanes*. If a tertiary hydrogen atoms is present in an alkane, it is preferentially abstracted by almost any radical, with secondary hydrogen atoms being next preferred. This is in the same order as *D* values for these types of C—H bonds (Table 5.3). The extent of the preference depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows[78] that at high temperatures selectivity decreases, as might be expected.[79] An example of the effect of radical selectivity is the comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H_2SO_4 with *N*-chloro-di-*tert*-butylamine and *N*-chloro-*tert*-butyl-*tert*-pentylamine, the primary hydrogen atoms are abstracted 1.7 times *faster* than the tertiary hydrogen.[80] In this case, the attacking

[73] See Hendry, D.G.; Mill, T.; Piszkiewicz, L.; Howard, J.A.; Eigenmann, H.K. *J. Phys. Chem. Ref. Data* ***1974****, 3,* 937; Roberts, B.P.; Steel, A.J. *Tetrahedron Lett.* ***1993****, 34*, 5167. See Tanko, J.M.; Blackert, J.F. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1775.

[74] Zavitsas, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 499.

[75] See Wen, Z.; Li, Z.; Shang, Z.; Cheng, J.-P. *J. Org. Chem.* ***2001****, 66*, 1466.

[76] Kim, S.S.; Kim, S.Y.; Ryou, S.S.; Lee, C.S.; Yoo, K.H. *J. Org. Chem.* ***1993****, 58*, 192.

[77] See Tedder, J.M. *Tetrahedron* ***1982****, 38,* 313; Kerr, J.A. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18, Elsevier, NY, ***1976***, pp. 39–109; Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 275–331; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1970****, 9,* 830; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969****, 1*, 79; Davidson, R.S. *Q. Rev. Chem. Soc.* ***1967****, 21*, 249; Pryor, W.A.; Fuller, D.L.; Stanley, J. P. *J. Am. Chem. Soc.* ***1972****, 94*, 1632.

[78] Hass, H.B.; McBee, E.T.; Weber, P. *Ind. Eng. Chem.* ***1936****, 28,* 333.

[79] With phenyl radicals: Kopinke, F.; Zimmermann, G.; Anders, K. *J. Org. Chem.* ***1989****, 54*, 3571.

[80] Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971****, 93,* 2065. See Dneprovskii, A.N.; Mil'tsov, S. A. *J. Org. Chem. USSR* ***1988****, 24,* 1836.

radicals (the radical ions $R_2NH^{\bullet+}$, see Reaction **14-1**) are bulky enough for steric hindrance to become a major factor.



14

Cyclopropylcarbinyl radicals (**14**) are alkyl radicals, but because of the cyclopropane ring with its relatively weak bonds, they undergo rapid ring opening to give butenyl radicals.[81] The rate constant for this process has been measured by picosecond radical kinetic techniques to be in the range of $10^7\ M^{-1}\ s^{-1}$ for the parent[82] to $10^{10}\ M^{-1}\ s^{-1}$ for substituted derivatives.[83] Cyclobutylcarbinyl radicals undergo the cyclobutylcarbinyl to 4-pentenyl radical process,[84] but examples are generally limited to the parent system and phenyl-substituted derivatives.[85] Cyclization of the 4-pentenyl radical is usually limited to systems where a stabilized radical can be formed.[86] The effect of substituents has been studied.[87] Note that 2-aziridinylmethyl radicals also undergo ring opening via C—N or C—C cleavage to give a nitrogen or carbon radical, respectively, and the ring opening is strongly influenced by substituents at C-1 rather than those on nitrogen.[88] An alkyl substituent at the C-1 substituent generally leads to C—N cleavage, whereas a carbonyl substituent at C-1 usually favors C—C cleavage.[88]

The rate of the ring-opening reaction of **5**,[89] and other substrates have been determined using an indirect method for the calibration[90] of fast radical reactions, applicable for radicals with lifetimes as short as 1 ps.[91] This 'radical clock'[92] method is based on the use of pyridine-2-thione-*N*-oxycarbonyl esters as radical precursors and radical trapping by the highly reactive thiophenol and benzeneselenol.[93] A number of radical clock substrates are known.[94] Other radical clock processes include: racemization of radicals with chiral conformations,[95] one-carbon

[81] Nonhebel, D.C. *Chem. Soc. Rev.* ***1993****, 22*, 347. For a discussion of solvent/counterion reorganization, see Tanko, J.M.; Gillmore, J.G.; Friedline, R.; Chahma, M. *J. Org. Chem.* ***2005****, 70*, 4170.

[82] Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997****, 62*, 1210.

[83] Toy, P.H.; Newcomb, M. *J. Org. Chem.* ***1998****, 63*, 8609. See Martinez, F.N.; Schlegel, H.B.; Newcomb, M. *J. Org. Chem.* ***1996****, 61*, 8547; ***1998****, 63*, 3618 for *ab initio* studies to determine rate constants.

[84] See Jin, J.; Newcomb, M. *J. Org. Chem.* ***2007****, 72*, 5098. For a discussion of ring opening versus ring expansion in bicyclic cyclocarbinyl radicals, see Shi, J.; Chong, S.-S.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* ***2008****, 73,* 974.

[85] Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000****, 65,* 4447.

[86] Cerreti, A.; D'Annibale, A.; Trogolo, C.; Umani, F. *Tetrahedron Lett.* ***2000****, 41,* 3261.

[87] Baker, J.M.; Dolbier, Jr., W.R. *J. Org. Chem.* ***2001****, 66*, 2662. See Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* ***1994****, 35*, 7217.

[88] Wang, Y.-M.; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* ***2005****, 70*, 3633.

[89] Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* ***1986****, 108,* 7981; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997****, 62,* 1210, 5656.

[90] See Hollis, R.; Hughes, L.; Bowry, V.W.; Ingold, K.U. *J. Org. Chem.* ***1992****, 57,* 4284.

[91] Newcomb, M.; Toy, P.H. *Acc. Chem. Res.* ***2000****, 33,* 449. See Horn, A.H.C.; Clark, T. *J. Am. Chem. Soc.* ***2003****, 125*, 2809.

[92] See Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980****, 13,* 317.

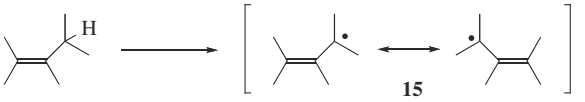
[93] Newcomb, M.; Johnson, C.C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992****, 114,* 10915; Newcomb, M.; Varick, T.R.; Ha, C.; Manek, M.B.; Yue, X. *J. Am. Chem. Soc.* ***1992****, 114,* 8158.

[94] See Kumar, D.; de Visser, S.P.; Sharma, P.K.; Cohen, S.; Shaik, S. *J. Am. Chem. Soc.* ***2004****, 126*, 1907.

[95] Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001****, 3,* 807.

ring expansion in cyclopentanones,[96] norcarane and spiro[2,5]octane,[97] α- and β-thujone radical rearrangements,[98] and cyclopropylcarbinyl radicals or alkoxycarbonyl radicals containing stabilizing substituents,[99] and cyclobutylcarbinyl radicals.[100] *Ab initio* and density functional theory have been used to study radical clock reactions.[101]

2. *Alkenes*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution, as described in Reaction **15-39**. However, for other radicals (and even for chlorine or bromine atoms when they react by hydrogen transfer) the position of attack is at the allylic carbon. Vinylic hydrogen atoms are practically never abstracted, and allylic hydrogen atoms are greatly preferred to other positions of the molecule. Allylic hydrogen abstraction from a cyclic alkene is usually faster than abstraction from an acyclic alkene.[102] This is generally attributed[103] to resonance stabilization of the allylic radical (**15**). As might be expected, allylic rearrangements (see Reaction **14-7**) are common in these cases.[104]



15

3. *Alkyl Side Chains of Aromatic Rings*. The preferential position of attack on a side chain is usually the one directly attached to the ring (the benzylic position). Both for active radicals (e.g., chlorine and phenyl) and for more selective ones (e.g., bromine), hydrogen exchange is faster than that at a primary carbon. For active radicals, hydrogen exchange at the benzylic position is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogen atoms even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:[105]

	Me—H	$MeCH_2$—H	Me_2CH—H	Me_3C—H	$PhCH_2$—H	Ph_2CH—H	Ph_3C—H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogen atoms are seldom abstracted if there are aliphatic ones to compete (note from Table 5.3, that *D* for Ph—H is higher than that for any alkyl H bond). Several

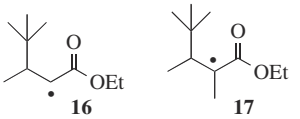
[96] Chatgilialoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* ***1998****, 63,* 1327.
[97] See Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* ***2002****, 124,* 6020.
[98] He, X.; Ortiz de Montellano, P. R. *J. Org. Chem.* ***2004****, 69,* 5684.
[99] Beckwith, A.L.J.; Bowry, V.W. *J. Am. Chem. Soc.* ***1994****, 116,* 2710. See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003****, 68,* 9441.
[100] Jin, J.; Newcomb, M. *J. Org. Chem.* ***2008****, 73*, 4740.
[101] Jäger, C.M.; Hennemann, M.; Mieszała, A.; Clark, T. *J. Org. Chem.* ***2008****, 73,* 1536.
[102] Rothenberg, G.; Sasson, Y. *Tetrahedron* ***1998****, 54*, 5417.
[103] See, however, Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L.D. *J. Org. Chem.* ***1982****, 47,* 4524.
[104] See Wilt, J.W. in Kochi, J.K. *Free Radicals, Vol. 1* Wiley, NY, ***1973***, pp. 458–466.
[105] Russell, G.A. in Kochi, J.K. *Free Radicals,* Vol. 2, Wiley, NY, ***1973***, p. 289.

$\sigma^{\bullet}$ scales (similar to the σ, σ^{+}, and σ^{-} scales discussed in Chapter 9) have been developed for benzylic radicals.[106]

4. *Compounds Containing Electron-Withdrawing Substituents.* In halogenations, electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type $Z—CH_2—CH_3$ are attacked predominantly or exclusively at the β position when Z is CO_2H, COCl, COOR, SO_2Cl, or CX_3. Compounds, such as acetic acid and acetyl chloride, are not attacked at all, in sharp contrast to electrophilic halogenations (Reactions **12-4**–**12-6**), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed in Section 14.A.ii. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogen atoms on carbon atoms next to electron-withdrawing groups have low-electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are[107]

	$CH_3—CH_2—COOH$	
Me$^{\bullet}$	1	7.8
Cl$^{\bullet}$	1	0.02

It is possible to generate radicals adjacent to electron-withdrawing groups. Radical **16** can be generated and undergoes coupling reactions with little selectivity. When **17** is generated, it rapidly disproportionates rather than couples, giving the corresponding alkene and alkane.[108] Such radicals have also been shown to have a conformational preference for orientation of the orbital containing the single electron. In such cases, hydrogen abstraction proceeds with good stereoselectivity.[109]



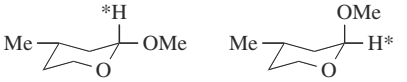
16 **17**

Some radicals (e.g., *tert*-butyl,[110] benzyl,[111] and cyclopropyl)[112] are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms).[113] The phenyl radical appears to have a very small degree of nucleophilic character.[114] For longer chains, the field effect

[106] See Fisher, T.H.; Dershem, S.M.; Prewitt, M.L. *J. Org. Chem.* ***1990****, 55*, 1040.
[107] Russell, G.A. in Kochi, J.K. *Free Radicals,* Vol. 2, Wiley, NY, ***1973***, p. 311.
[108] Porter, N.A.; Rosenstein, I.J. *Tetrahedron Lett.* ***1993****, 34*, 7865.
[109] Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* ***1992****, 33*, 1863.
[110] Pryor, W.A.; Tang, F.Y.; Tang, R.H.; Church, D.F. *J. Am. Chem. Soc.* ***1982****, 104,* 2885; Dütsch, H.R.; Fischer, H. *Int. J. Chem. Kinet.* ***1982****, 14,* 195.
[111] Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* ***1973****, 29,* 2775.
[112] Stefani, A.; Chuang, L.; Todd, H.E. *J. Am. Chem. Soc.* ***1970****, 92*, 4168.
[113] Nucleophilicity and electrophilicity indices have been developed for radicals. See De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* ***2007****, 9,* 2721.
[114] Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* ***1977****, 50,* 3324.

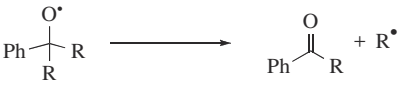
continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. Note that in Section 14.A.ii the abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the *Hammett equation*.

5. *Stereoelectronic Effects*. In Section 16.A.i, category 4, there is an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases, hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle (≈30°) with the unshared orbitals of the O or N much more easily than from those with a large angle (∼90°). For example, the starred hydrogen of **18** was abstracted about eight times faster than the starred hydrogen of **19**.[115]



18 **19**

The presence of an OR or SiR_3 substituent β- to the carbon bearing the radical accelerates the rate of halogen abstraction.[116] Tertiary arylcarbinyloxy radicals undergo β-scission to give a ketone:[117]

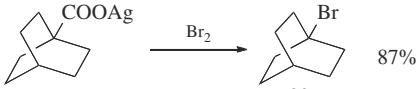


Abstraction of a halogen has been studied much less,[118] but the order of reactivity is RI > RBr > RCl ≫ RF.

There are now many cases where free radical reactions are promoted by transition metals.[119]

14.B.ii. Reactivity at a Bridgehead[120]

Many free radical reactions have been observed at bridgehead carbons, as in formation of bromide **20** (see Reaction **14-30**),[121] demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, although the bridgehead position is tertiary.[122] So, while bridgehead free radical substitution is possible, it is not preferred, presumably because of the strain involved.[123]

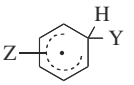


20

[115] Hayday, K.; McKelvey, R.D. *J. Org. Chem.* ***1976****, 41,* 2222. Also see Beckwith, A.L.J.; Westwood, S.W. *Aust. J. Chem.* ***1983****, 36,* 2123; Griller, D.; Bunce, N.J.; Cheung, H.K.Y.; Langshaw, J. *J. Org. Chem.* ***1986****, 51*, 5421.
[116] Roberts, B.P.; Steel, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2411.
[117] Bietti, M.; Gente, G.; Salamone, M. *J. Org. Chem.* ***2005****, 70,* 6820.
[118] See Danen, W.C. *Methods Free-Radical Chem.* ***1974****, 5,* 1.
[119] Iqbal, J.; Bhatia, B.; Nayyar, N.K. *Chem. Rev.* ***1994****, 94*, 519.
[120] See Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971****, 18,* 1, see pp. 79–81.
[121] Grob, C.A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* ***1958****, 41,* 1191.
[122] Roberts, J.D.; Urbanek, L.; Armstrong, R. *J. Am. Chem. Soc.* ***1949****, 71*, 3049. See also, Kooyman, E.C.; Vegter, G.C. *Tetrahedron* ***1958****, 4,* 382; Walling, C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1959****, 81,* 1485.
[123] See Koch, V.R.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1971****, 93*, 1657.

14.B.iii. Reactivity in Aromatic Substrates

Free radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen atom is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; that is, which position on the ring will be attacked to give the intermediate **21**.



21

The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product while that from the ortho attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, though there has been much controversy over just how meaningful such conclusions are[124]

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho–para directing; none are deactivating or (chiefly) meta directing.
3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.
4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds (XC_6H_4Y) showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).[125] The increase could be correlated with the Hammett σ_p values for X.
5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see Sec. 11.C) are not great.[126] Partial rate factors for a few groups are given in Table 14.2.[127]
6. Although hydrogen is the leaving group in most free radical aromatic substitutions, ipso attack (Sec. 11.B.iii) and ipso substitution (e.g., with Br, NO_2, or CH_3CO as the leaving group) have been found in certain cases.[128]

[124] Vidal, S.; Court, J.; Bonnier, J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 2071; Tezuka, T.; Ichikawa, K.; Marusawa, H.; Narita, N. *Chem. Lett*. ***1983***, 1013.
[125] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1970***, 2653.
[126] For a quantitative treatment, see Charton, M.; Charton, B. *Bull. Soc. Chim. Fr.* ***1988***, 199.
[127] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681.
[128] See Traynham, J.G. *J. Chem. Educ.* ***1983***, 60, 937; *Chem. Rev.* ***1979***, 79, 323; Tiecco, M. *Acc. Chem. Res.* ***1980***, 13, 51; *Pure Appl. Chem.* ***1981***, 53, 239.

TABLE 14.2 Partial Rate Factors for Attack of Substituted Benzenes by Phenyl Radicals Generated from Bz_2O_2 (Reaction 14–21)[a]

	Partial Rate Factor		
Z	*o*	*m*	*p*
H	1	1	1
NO_2	5.50	0.86	4.90
CH_3	4.70	1.24	3.55
CMe_3	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

Reproduced from Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681 with permission from the Royal Society of Chemistry

[a]See Ref. 127.

Note that interconvertible 1,4-hydrogen atom shifts are possible in radicals derived from biaryls.[129]

14.B.iv. Reactivity in the Attacking Radical[130]

As seen above, some radicals are much more selective than others (Sec. 14.B.i). The bromine atom is so selective that when only primary hydrogen atoms are available, as in neopentane or *tert*-butylbenzene, the reaction is slow; and isobutane can be selectively brominated to give *tert*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes (e.g., ethylbenzene and cumene) takes place exclusively at the α position,[131] emphasizing the selectivity of $Br^{\bullet}$. The dissociation energy (*D*) of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some radicals (e.g., triphenylmethyl) are so unreactive that they abstract hydrogen atoms very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.[132]

$$X^{\bullet} + C_2H_6 \longrightarrow X - H + C_2H_5^{\bullet} \qquad \text{Ref. 132}$$

iPr$^{\bullet}$ is $<$ $Me^{\bullet}$ and *t-Bu*$^{\bullet}$ is still less[133]

As mentioned earlier, some free radicals (e.g., chloro) are electrophilic and some (e.g., *tert*-butyl) are nucleophilic. Bear in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

[129] Peng, L.; Scott, L.T. *J. Am. Chem. Soc.* ***2005****, 127*, 16518.
[130] See Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965****, 1,* 1; Gray, P.; Herod, A.A.; Jones, A. *Chem. Rev.* ***1971****, 71*, 247.
[131] Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, p. 97.
[132] Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965****, 1,* 1.
[133] Kharasch, M.S.; Hambling, J.K.; Rudy, T.P. *J. Org. Chem.* ***1959****, 24,* 303.

TABLE 14.3 Some Common Free Radicals in Decreasing Order of Activity[5]

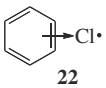
	E			E	
Radical	(kcal mol^{-1})	(kJ mol^{-1})	Radical	(kcal mol^{-1})	(kJ mol^{-1})
$F^{\bullet}$	0.3	1.3	$H^{\bullet}$	9.0	38
$Cl^{\bullet}$	1.0	4.2	$Me^{\bullet}$	11.8	49.4
$MeO^{\bullet}$	7.1	30	$Br^{\bullet}$	13.2	55.2
$CF_3^{\bullet}$	7.5	31			

[a]The *E* values represent activation energies for the reaction

[Reprinted with permission from Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965****, 1*, 1, Copyright © 1965, with permission from Elsevier Science.]

14.B.v. The Effect of Solvent on Reactivity[134]

As noted earlier, the solvent usually has little effect on free radical substitutions in contrast to ionic substitution reactions: Indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave ~60% $(CH_3)_2CHCH(CH_3)CH_2Cl$ and 40% $(CH_3)_2CHCCl(CH_3)_2$, while in aromatic solvents the ratio became 10:90.[135] This result is attributed to



22

complex formation between the aromatic solvent and the chlorine atom that makes the chlorine more selective.[136] This type of effect is not found in cases where the differences in ability to abstract the atom are caused by field effects of electron-withdrawing groups (Sec 14.B.i). In such cases, aromatic solvents make little difference.[137] Complex **22** has been detected[138] as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4.[139] Differences caused by solvents have also been reported in reactions of other radicals.[140] Some of the anomalous results obtained in the chlorination of aromatic side chains (Sec 14.B.i) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.[141] Much smaller, though real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl_4.[142] However,

[134] See Reichardt, C. *Solvent Effects in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1979***, pp. 110–123; Martin, J.C. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 493–524; Huyser, E.S. *Adv. Free-Radical Chem.* ***1965****, 1,* 77.

[135] Russell, G.A. *J. Am. Chem. Soc.* ***1958****, 80*, 4987, 4997, 5002; *J. Org. Chem.* ***1959****, 24,* 300.

[136] See also, Ingold, K.U.; Lusztyk, J.; Raner, K.D. *Acc. Chem. Res.* ***1990****, 23,* 219.

[137] Nagai, T.; Horikawa, Y.; Ryang, H.S.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 2771.

[138] See, however, Skell, P.S.; Baxter III, H.N.; Tanko, J.M.; Chebolu, V. *J. Am. Chem. Soc.* ***1986****, 108*, 6300. For arguments against this proposal, see Walling, C. *J. Org. Chem.* ***1988****, 53*, 305; Aver'yanov, V.A.; Shvets, V.F.; Semenov, A.O. *J. Org. Chem. USSR* ***1990****, 26,* 1261.

[139] Bühler, R.E. *Helv. Chim. Acta* ***1968****, 51*, 1558; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Phys. Chem.* ***1989****, 93*, 564.

[140] Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* ***1987****, 52*, 730.

[141] See Newkirk, D.D.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1974****, 96,* 3543 and reference cited therein.

[142] See Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Org. Chem.* ***1988****, 53,* 5220.

these differences are not caused by formation of a complex between $Cl^{\bullet}$ and the solvent. There are cases, however, where the rate of reaction for trapping a radical depends on the polarity of the solvent, particularly in water.[143]

14.C. REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (generally the diazonium ion); these are considered first.

14.C.i. Hydrogen as a Leaving Group

A. Substitution by Halogen

14-1 Halogenation at an Alkyl Carbon[144]

Halogenation or **Halo-de-hydrogenation**

$$R{-}H + \text{Halogenating agent} \longrightarrow R{-}X$$

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or UV light, or with heat[145] These reactions require an added chemical reagent as the radical chain initiator, or exposure to light, or higher temperatures.[146] The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: Not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen. Note that benzylic halogenation (e.g., the *Wohl–Ziegler bromination*) is discussed in Reaction **14-3**.

When functional groups are present, the principles are those outlined in Section 14.B.i. Tertiary carbons are most likely to be functionalized and primary are least likely. Favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Hydrogen atoms α to an OR group are very readily replaced. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the regioselectivity of electrophilic halogenation (Reactions **12-4**–**12-6**), which always takes place α to a carbonyl group (except when the reaction is catalyzed by $AgSbF_6$). Of course, if a *mixture* of chlorides is wanted, the reaction is usually quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen (e.g., ethane, cyclohexane, and neopentane). The most common are methylbenzenes and other substrates with methyl groups on aromatic rings,

[143] Tronche, C.; Martinez, F.N.; Horner, J.H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* ***1996****, 37*, 5845.

[144] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed, Wiley–VCH, NY, ***1999***, pp. 611–617.

[145] See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 159–229; Huyser, E.S. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 549–607; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969****, 1*, 79 (chlorination); Thaler, W.A. *Methods Free-Radical Chem.* ***1969****, 2,* 121 (bromination).

[146] Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

since few cases are known where halogen atoms substitute at an aromatic position.[147] Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (Reaction **11-10**). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2, alkenes, higher alkanes, lower alkanes, and halogen derivatives of these compounds. Solvent plays an important role in this process.[148]

The bromine atom is much more selective than the chlorine atom. As indicated in Section 14.B.iv, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (Sec 14.A.iv) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,[149] but seldom, because it is too reactive and hard to control.[150] It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations as well. Fluorination[151] has been achieved by the use of chlorine trifluoride (ClF_3) at $-75°C$.[152] For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluoroxytrifluoromethane (CF_3OF) fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.[153] For example, adamantane gave 75% 1-fluoroadamantane. Fluorine at -70 °C, diluted with N_2,[154] and bromine trifluoride at 25–35 °C[155] are also highly regioselective for tertiary positions. These reactions probably have electrophilic,[156] not free radical mechanisms. In fact, the success of the F_2 reactions depends on the suppression of free radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers. Fluorination of 1,3-dicarbonyl compounds and activated aromatic compounds was achieved under solvent-free conditions using Selectfluor™ F–TEDA–BF_4.[157]

Iodine can be used if the activating light has a wavelength of 184.9 nm,[158] but iodinations using I_2 alone are seldom attempted, largely because the HI formed reduces the alkyl iodide. The direct free radical halogenation of aliphatic hydrocarbons with iodine is significantly endothermic relative to the other halogens, and the requisite chain reaction does not occur.[159] On the other hand, when iodine ($CCl_4 \bullet 2\ AlI_3$) reacts with an alkane in

[147] Dermer, O.C.; Edmison, M.T. *Chem. Rev.* ***1957****, 57,* 77, pp. 110–112. See Kooyman, E.C. *Adv. Free-Radical Chem.* ***1965****, 1,* 137.
[148] Dneprovskii, A.S.; Kuznetsov, D.V.; Eliseenkov, E.V.; Fletcher, B.; Tanko, J.M. *J. Org. Chem.* ***1998****, 63*, 8860.
[149] Rozen, S. *Acc. Chem. Res.* ***1988****, 21*, 307; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986****, 86,* 997, pp. 1003–1005; Gerstenberger, M.R.C.; Haas, A. *Angew. Chem. Int. Ed.* ***1981****, 20,* 647; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***; pp. 67–91. For descriptions of the apparatus necessary for handling F_2, see Vypel, H. *Chimia* ***1985****, 39*, 305.
[150] See Rozhkov, I.N. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 805–825; Lagow, R.J.; Margrave, J.L. *Prog. Inorg. Chem.* ***1979****, 26*, 161. See also, Adcock, J.L.; Evans, W.D. *J. Org. Chem.* ***1984****, 49,* 2719; Huang, H.; Lagow, R.J. *Bull. Soc. Chim. Fr.* ***1986***, 993.
[151] See German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***.
[152] Brower, K.R. *J. Org. Chem.* ***1987****, 52*, 798.
[153] Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980****, 4,* 239.
[154] Rozen, S.; Gal, C. *J. Org. Chem.* ***1988****, 53,* 2803. (See Ref. 153.)
[155] Boguslavskaya, L.S.; Kartashov, A.V.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1989****, 25,* 1835.
[156] See, for example, Rozen, S.; Gal, C. *J. Org. Chem.* ***1987****, 52,* 2769.
[157] Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* ***2007****, 4*8, 2671.
[158] Gover, T.A.; Willard, J.E. *J. Am. Chem. Soc.* ***1960****, 82,* 3816.
[159] Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, R.; Minisci, F. *Chem. Commun.* ***1997***, 1501.

dibromomethane at −20 °C, good yields of the iodoalkane are obtained.[160] The reaction of an alkane with *tert*-butylhypoiodite (*t*-BuOI) at 40 °C gave the iodoalkane in good yield.[161] The reaction of alkanes with iodine and $PhI(OAc)_2$ generates the iodoalkane.[162] A radical protocol was developed using CI_4 with base. Cyclohexane could be iodinated, for example, with CI_4 in the presence of powdered NaOH.[163] The reaction led to the use of iodoform on solid NaOH as the iodination reagent of choice. A base-induced bromination has been reported. 2-Methyl butane reacts with 50% aq NaOH and CBr_4, in a phase-transfer catalyst, to give a modest yields of 2-bromo-2-methylbutane. α-Iodo ethers and α-iodolactones have been prepared from the parent ether or lactone via treatment with $Et_4N^{\bullet}4$ HF under electrolytic conditions.[164]

Many other halogenation agents have been employed, and a common reagent is sulfuryl chloride (SO_2Cl_2).[165]Among other agents used have been NBS (see Reaction **14-3**), CCl_4,[166] PCl_5,[167]*N*-haloamines, and sulfuric acid.[168] In all these cases, an initiator is required, usually peroxides or UV light.[169]

When chlorination is carried out with *N*-haloamines and sulfuric acid (catalyzed by either UV light or metal ions), selectivity is much greater than with other reagents.[168] In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the ω - 1 position).[170]Some typical selectivity values are[171]

$$\underset{1}{CH_3}-\underset{56}{CH_2}-\underset{29}{CH_2}-\underset{14}{CH_2}-CH_2-CH_2-CH_3 \qquad \text{Ref. 172}$$

$$\underset{1}{CH_3}-\underset{92}{CH_2}-\underset{3}{CH_2}-\underset{1}{CH_2}-\underset{1}{CH_2}-\underset{2}{CH_2}-\underset{0}{CH_2}-\underset{0}{CH_2}-OH \qquad \text{Ref. 173}$$

$$\underset{3}{CH_3}-\underset{72}{CH_2}-\underset{20}{CH_2}-\underset{4}{CH_2}-\underset{1}{CH_2}-\underset{0}{CH_2}-COOMe \qquad \text{Ref. 174}$$

Furthermore, di- and polychlorination are much less prevalent.Dicarboxylic acids are predominantly chlorinated in the middle of the chain,[175] and adamantane and bicyclo [2.2.2]octane at the bridgeheads[176] by this procedure. The reasons for the high ω - 1

[160] Akhrem, I.; Orlinkov, A.; Vitt, S.; Chistyakov, A. *Tetrahedron Lett.* ***2002****, 43*, 1333.
[161] Montoro, R.; Wirth, T. *Org. Lett.* ***2003****, 5*, 4729.
[162] Barluenga, J.; González-Bobes, F.; González, J.M. *Angew. Chem. Int. Ed.* ***2002****, 41*, 2556.
[163] Schreiner, P.R.; Lauenstein, O.; Butova, E.D.; Fokin, A.A. *Angew. Chem. Int. Ed.* ***1999****, 38*, 2786.
[164] Hasegawa, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* ***2002****, 43,* 1503.
[165] See Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 336–396.
[166] See Hawari, J.A.; Davis, S.; Engel, P.S.; Gilbert, B.C.; Griller, D. *J. Am. Chem. Soc.* ***1985****, 107*, 4721.
[167] Wyman, D.P.; Wang, J.Y.C.; Freeman, W.R. *J. Org. Chem.* ***1963****, 28*, 3173.
[168] See Minisci, F. *Synthesis* ***1973***, 1; Deno, N.C. *Methods Free-Radical Chem.* ***1972****, 3*, 135; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972****, 4,* 203.
[169] Schreiner, P.R.; Lauenstein, O.; Kolomitsyn, I.V.; Nadi, S.; Kokin, A.A. *Angew. Chem. Int. Ed.* ***1998****, 37*, 1895.
[170] The (ω - 1 regioselectivity diminishes when the chains are >10 carbon atoms; see Deno, N.C.; Jedziniak, E.J. *Tetrahedron Lett.* ***1976***, 1259; Konen, D.A.; Maxwell, R.J.; Silbert, L.S. *J. Org. Chem.* ***1979****, 44,* 3594.
[171] See, however, Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975****, 40*, 380.
[172] Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* ***1968***, 324. See also, Fuller, S.E.; Lindsay Smith, J.R.; Norman, R.O.C.; Higgins, R. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 545.
[173] Deno, N.C.; Billups, W.E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971****, 93*, 438.
[174] Minisci, F.; Gardini, G.P.; Bertini, F. *Can. J. Chem.* ***1970****, 48*, 544.
[175] Kämper, F.; Schäfer, H.J.; Luftmann, H. *Angew. Chem. Int. Ed.* ***1976****, 15,* 306.
[176] Smith, C.V.; Billups, W.E. *J. Am. Chem. Soc.* ***1974****, 96,* 4307.

specificity are not clearly understood.[177] Alkyl chlorides can be converted to *vic*-dichlorides by treatment with $MoCl_5$.[178] Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.[179] For regioselective chlorination at certain positions of the steroid nucleus, see Reaction **19-2**.

In almost all cases, the mechanism involves a free radical chain:

Initiation $X_2 \xrightarrow{h\nu} 2X^{\bullet}$

Propagation $RH + X^{\bullet} \longrightarrow R^{\bullet} + XH$

$R^{\bullet} + X_2 \longrightarrow RX + X^{\bullet}$

Termination $R^{\bullet} + X^{\bullet} \longrightarrow RX$

When the reagent is halogen, initiation occurs as shown above.[180] When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *tert*-butyl hypochlorite (*t*-BuOCl) have been formulated as:[181]

$$RH + t\text{-BuO}^{\bullet} \longrightarrow R^{\bullet} + t\text{-BuOH}$$

$$R^{\bullet} + t\text{-BuOCl} \longrightarrow RCl + t\text{-BuO}^{\bullet}$$

and the abstracting radicals in the case of *N*-haloamines are the aminium radical cations ($R_2NH^{\bullet+}$, Reaction **11-5**), with the following mechanism (in the case of initiation by Fe^{2+})[168]:

Initiation $R_2NCl \xrightarrow{H^+} R_2\overset{+}{N}HCl \xrightarrow{Fe^{2+}} R_2NH^{\bullet+} + \overset{+}{F}eCl$

Propagation $R_2NH^{\bullet+} + RH \longrightarrow R_2NH_2 + R^{\bullet}$

$R^{\bullet} + R_2NHCl \longrightarrow RCl + R_2NH^{\bullet+}$

This mechanism is similar to that of the *Hofmann–Löffler Reaction* (**18-40**).

The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine ($^{\bullet}H$, $^{\bullet}CH_3$, $^{\bullet}Cl$, $^{\bullet}CH_2CH_3$ in all combinations). Thus, products like H_2, higher alkanes, and higher alkyl halides can be accounted for. When methane is the substrate, the rate-determining step is

$$CH_4 + Cl^{\bullet} \rightarrow {}^{\bullet}CH_3 + HCl$$

since an isotope effect of 12.1 was observed at 0 °C.[182] For chlorinations, chains are very long, typically 10^4–10^6 propagations before a termination step takes place.

[177] See, however, Dneprovskii, A.S.; Mil'tsov, S.A.; Arbuzov, P.V. *J. Org. Chem. USSR* ***1988****, 24*, 1826. See also, Tanner, D.D.; Arhart, R.; Meintzer, C.P. *Tetrahedron* ***1985****, 41*, 4261.

[178] San Filippo, Jr., J.; Sowinski, A.F.; Romano, L.J. *J. Org. Chem.* ***1975****, 40,* 3463.

[179] Turro, N.J.; Fehlner, J.R.; Hessler, D.P.; Welsh, K.M.; Ruderman, W.; Firnberg, D.; Braun, A.M. *J. Org. Chem.* ***1988****, 53,* 3731.

[180] There is evidence radicals within a solvent cage, see Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988****, 110*, 3519; Tanko, J.M.; Anderson III, F.E. *J. Am. Chem. Soc.* ***1988****, 110,* 3525.

[181] See Walling, C.; McGuiness, J.A. *J. Am. Chem. Soc.* ***1969****, 91,* 2053. See also, Zhulin, V.M.; Rubinshtein, B.I. *Bull. Acad. Sci. USSR Div. Chem. Sci,* ***1977****, 26,* 2082.

[182] Wiberg, K.B.; Motell, E.L. *Tetrahedron* ***1963****, 19*, 2009.

TABLE 14.4 Some *D* Values[a]

	D	
Bond	(kcal mol^{-1})	(kJ mol^{-1})
H—F	136	570
H—Cl	103	432
H—Br	88	366
H—I	71	298
F—F	38	159
Cl—Cl	59	243
Br—Br	46	193
I—I	36	151
CH_3—F	108	452
CH_3—Cl	85	356
CH_3—Br	70	293
CH_3—I	57	238

Reprinted with permission from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, ***2007***, pp. 5-4–5-42. Copyright © 2007, with permission from Taylor & Francis Group LLC.

[a]See Ref. 183.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps follow:

	F_2	Cl_2	Br_2	I_2	F_2	Cl_2	Br_2	I_2
	(kcal mol^{-1})				(kJ mol^{-1})			
$CH_4 + X^{\bullet} \rightarrow CH_3^{\bullet} + HX$	−31	+2	+17	+34	−132	+6	+72	+140
$CH_4 + X_2 \rightarrow CH_3X + X^{\bullet}$	−70	−26	−24	−21	−293	−113	−100	−87

In each case, *D* for CH_3—H is 105 kcal mol^{-1} (438 kJ mol^{-1}), while *D* values for the other bonds involved are given in Table 14.4 .[183] Fluorine (F_2) is so reactive[184] that neither UV light nor any other initiation is needed (total $\Delta H = -101$ kcal mol^{-1}, -425 kJ mol^{-1})[185]; while $\mathbf{Br_2}$ and $\mathbf{I_2}$ essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br_2 and I_2. It is apparent that the most important single factor causing the order of halogen reactivity to be $\mathbf{F_2 > Cl_2 > Br_2 > I_2}$ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in *D* values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination, step 1 is exothermic for practically all substrates other than CH_4, since most other aliphatic C—H bonds are weaker than those in $\mathbf{CH_4}$.)

[183] Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, ***2007***, pp. 5-4–5-42.

[184] See Johnson, G.L.; Andrews, L. *J. Am. Chem. Soc.* ***1980****, 102,* 5736.

[185] For F_2 the following initiation step is possible: $F_2 + RH \rightarrow R\cdot + F^{\bullet} + HF$ (first demonstrated by Miller, Jr., W.T.; Koch, Jr., S.D.; McLafferty, F.W. *J. Am. Chem. Soc.* ***1956****, 78*, 4992).

Metal mediated halogenation reactions are known. Heating alkenes with bromine in the presence of MnO_2 leads to monobromination.[186] Hydrogen peroxide–HBr in water has been used for radical bromination.[187] Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.[188] Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride [PhSe(O)Cl] and $AlCl_3$ or $AlBr_3$.[189] However, while some substituted alkenes give high yields of chloro-substitution products, others (e.g., styrene) undergo addition of Cl_2 to the double bond (Reaction **15-39**).[151] Electrophilic fluorination has already been mentioned (Sec. 14.C.i).

OS **II**, 89, 133, 443, 549; **III**, 737, 788; **IV**, 807, 921, 984; **V**, 145, 221, 328, 504, 635, 825; **VI**, 271, 404, 715; **VII**, 491; **VIII**, 161.

14-2 Halogenation at Silicon

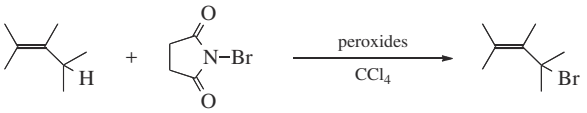
Halogenation or **Halo-de-hydrogenation**

$$R_3Si-H \longrightarrow R_3Si-X$$

Just as free radical halogenation occurs at the carbon of an alkane, via hydrogen abstraction to form the radical, a similar reaction occurs at silicon. When triisopropylsilane (iPr$_3$Si—H) reacts with *tert*-butyl hypochlorite at −10 °C, the product is triisopropylchlorosilane (iPr$_3$Si—Cl).[190]

14-3 Allylic and Benzylic Halogenation

Halogenation or **Halo-de-hydrogenation**



This reaction is a special case of Reaction **14-1**, but is important enough to be treated separately.[191] Alkenes can be brominated in the allylic position and also a benzylic position by a number of reagents, of which NBS[192] is by far the most common. When this reagent is used, the reaction is known as *Wohl–Ziegler bromination*. A nonpolar solvent is used, most often CCl_4, but the reaction has been done in an ionic liquid.[193] A variation in the reaction used NBS with 5% Yb(OTf)$_3$ and 5% ClSiMe$_3$.[194] Other *N*-bromo amides have also been used. With any reagent an initiator is needed; this is usually AIBN (**1**), a peroxide (e.g., di-*tert*-butyl peroxide) or benzoyl peroxide or, less often, UV light. Boron trifluoride has been used for benzylic bromination.[195]

[186] Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* ***2005****, 46*, 487.
[187] Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* ***2006****, 47,* 7245.
[188] Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1973****, 95*, 7686. See also, Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* ***1989****, 54*, 1463.
[189] Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* ***1988****, 44,* 449.
[190] Chawla, R.; Larson, G.L. *Synth. Commun.* ***1999****, 29*, 3499.
[191] See Nechvatal, A. *Adv. Free-Radical Chem.* ***1972****, 4*, 175.
[192] See Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 1–63.
[193] Togo, H.; Hirai, T. *Synlett* ***2003***, 702.
[194] Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetahedron Lett.* ***2002****, 43*, 2403.
[195] Chen, H.; Shen, L.; Lin, Y. *Synth. Commun.* ***2010****, 40*, 998.

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) has been used for benzylic bromination in the presence of a Lewis acid (e.g., $ZrCl_4$).[196] Similarly, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, in the presence of a Pd catalyst and microwave irradiation, led to benzylic fluorides.[197]

Allylic chlorination has also been carried out[198] with NCS and either arylselenyl chlorides (ArSeCl), aryl diselenides (ArSeSeAr), or TsNSO as catalysts. Allylic chlorination has been carried out with *tert*-butyl hypochlorite[199] or $NaClO/CeCl_3 \bullet 7H_2O$.[200]

The reaction is usually quite specific at an allylic or benzylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained (**23** and **24**). Use of the selenium catalysts produces almost entirely the allylically rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide (Cl_2O), with no catalyst, also leads to allylically rearranged chlorides in high yields.[201] A free radical mechanism is unlikely in these latter reactions.



23 **24**

When a double bond has two different allylic positions (e.g., $CH_3CH{=}CHCH_2CH_3$), a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[202] It is possible to brominate both sides of the double bond.[203] Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine. Molecules with a benzylic hydrogen (e.g., toluene) react rapidly to give α-bromomethyl benzene (e.g., $PhCH_3 \rightarrow PhCH_2Br$).

N-Bromosuccinimide is a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a C≡C triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[204]

Dauben and McCoy[205] demonstrated that the mechanism of allylic bromination is of the free radical type, showing that the reaction is very sensitive to free radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the

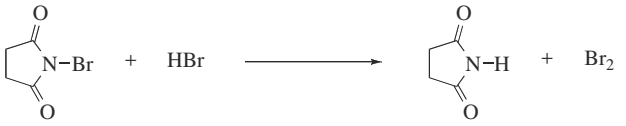
[196] Shibatomi, K.; Zhang, Y.; Yamamoto, H. *Chemistry: Asian J.* ***2008****, 3,* 1581.
[197] Hull, K.I.; Anani, W.Q.; Sanford, M.S. *J. Am. Chem. Soc.* ***2006****, 128*, 7134.
[198] Hori, T.; Sharpless, K.B. *J. Org. Chem.* ***1979****, 44,* 4204.
[199] Walling, C.; Thaler, W.A. *J. Am. Chem. Soc.* ***1961****, 83,* 3877.
[200] Moreno-Dorado, F.J.; Guerra, F.M.; Manzano, F.L.; Aladro, F.J.; Jorge, Z.S.; Massanet, G.M. *Tetrahedron Lett.* ***2003****, 44*, 6691.
[201] Torii, S.; Tanaka, H.; Tada, N.; Nagao, S.; Sasaoka, M. *Chem. Lett.* ***1984***, 877.
[202] Dauben, Jr, H.J.; McCoy, L.L. *J. Org. Chem.* ***1959****, 24,* 1577.
[203] Ucciani, E.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1962***, 871.
[204] Peiffer, G. *Bull. Soc. Chim. Fr.* ***1963***, 537.
[205] Dauben, Jr, H.J.; McCoy, L.L. *J. Am. Chem. Soc.* ***1959****, 81*, 4863.

substrate is the bromine atom. The reaction is initiated by small amounts of $Br^{\bullet}$. Once it is formed, the main propagation steps are

Step 1 $Br^{\bullet} + RH \longrightarrow R^{\bullet} + HBr$

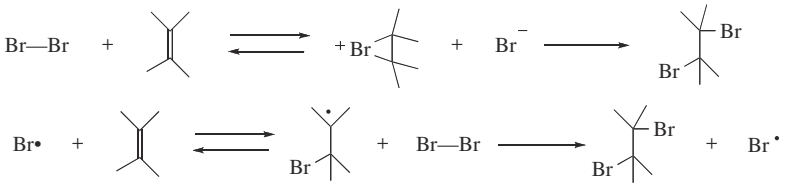
Step 2 $R^{\bullet} + Br_2 \longrightarrow RBr + Br^{\bullet}$

The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2, as shown in the reaction, in a low, steady-state concentration, which effectively uses up the HBr liberated in step 1.[206] The main evidence for this mechanism is that NBS and Br_2 show similar selectivity[207] and that the various *N*-bromo amides also show similar selectivity,[208] which is consistent with the hypothesis that the same species is abstracting in each case.[209]

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free radical mechanism (see Reaction **15-39**). Apparently, the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical:



The other bromine atom comes from another bromine-containing molecule or ion. This result is clearly not a problem in reactions with benzylic species since the benzene ring is not prone to such addition reactions. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an alkene in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is

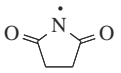
[206] See Adam, J.; Gosselain, P.A.; Goldfinger, P. *Nature (London)* ***1953****, 171*, 704; *Bull. Soc. Chim. Belg.* ***1956****, 65*, 533.

[207] Walling, C.; Rieger, A.L.; Tanner, D.D. *J. Am. Chem. Soc.* ***1963****, 85*, 3129; Russell, G.A.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963****, 85*, 3139; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963****, 85,* 3142; Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963****, 85,* 2850.

[208] Incremona, J.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1970****, 92*, 627.

[209] For other evidence, see Day, J.C.; Lindstrom, M.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1974****, 96*, 5616.

removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.[210]



25

When NBS is used to brominate non-alkenyl substrates (e.g., alkanes) another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical[211] **25** can operate.[212] This mechanism is facilitated by certain solvents (e.g., CH_2Cl_2, $CHCl_3$, or MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any $Br^{\bullet}$ that forms from the reagent. Among the evidence for the mechanism involving **25** are abstraction selectivities similar to those of $Cl^{\bullet}$ atoms and the isolation of β-bromopropionyl isocyanate ($BrCH_2CH_2CONCO$), which is formed by ring opening of **25**.

Allyl silanes react with transition metals bearing chlorine ligands to give allyl chlorides, where a chlorine replaces a Me_3Si unit.[213]

OS **IV**, 108; **V**, 825; **VI**, 462; **IX**, 191.

14-4 Halogenation of Aldehydes

Halogenation or **Halo-de-hydrogenation**

$$RCHO + Cl_2 \longrightarrow RCOCl$$

The α-halogenation reaction of carbonyl compounds was mentioned in Reaction **14-2**. A different halogenation reaction is possible in which aldehydes can be directly converted to acyl chlorides by treatment with chlorine, but the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (Reactions **14-2** and **12-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2[214] and *t*-BuOCl.[215] The mechanisms are probably of the free radical type. *N*-Bromosuccinimide, with AIBN (Sec. 14.A.i) as a catalyst, has been used to convert aldehydes to acyl bromides.[216] In the presence of benzoyl peroxide as an initiator, Br_3CCO_2Et converts aldehydes to acyl bromides under radical conditions.[217]

OS **I**, 155.

[210] McGrath, B.P.; Tedder, J.M. *Proc. Chem. Soc.* ***1961***, 80.
[211] See Chow, Y.L.; Naguib, Y.M.A. *Rev. Chem. Intermed.* ***1984****, 5*, 325.
[212] Lüning, U.; Seshadri, S.; Skell, P.S. *J. Org. Chem.* ***1986****, 51,* 2071; Zhang, Y.; Dong, M.; Jiang, X.; Chow, Y.L. *Can. J. Chem.* ***1990****, 68,* 1668.
[213] Fujii, T.; Hirao, Y.; Ohshiro, Y. *Tetrahedron Lett.* ***1993****, 34*, 5601.
[214] Arai, M. *Bull. Chem. Soc. Jpn.* ***1964****, 37*, 1280; ***1965****, 38*, 252.
[215] Walling, C.; Mintz, M.J. *J. Am. Chem. Soc.* ***1967****, 89*, 1515.
[216] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990****, 31,* 7237. For a related procedure, see Cheung, Y. *Tetrahedron Lett.* ***1979***, 3809.
[217] Kang, D.H.; Joo, T.Y.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* ***2007****, 48*, 285.

B. Substitution by Oxygen

14-5 Hydroxylation at an Aromatic Carbon[218]

Hydroxylation or **Hydroxy-de-hydrogenation**

$$ArH + H_2O_2 + FeSO_4 \longrightarrow ArOH$$

A mixture of hydrogen peroxide and ferrous sulfate,[219] called *Fenton's reagent*,[220] can be used to hydroxylate aromatic rings, although yields are usually not high.[221] Biaryls are typical side products.[222] Among other reagents used H_2O_2 and titanous ion; O_2 and Cu(I)[223] or Fe(III),[224] a mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*)[225]; O_2 and KOH in liquid NH_3[226]; and peroxyacids (e.g., peroxynitrous and trifluoroperoxyacetic acids).

Much work has been done on the mechanism of the reaction with *Fenton's reagent*, and it is known that free aryl radicals (formed by a process, e.g., $HO^{\bullet} + ArH \rightarrow AR^{\bullet} + H_2O$) are ***not*** intermediates. The mechanism is essentially that outlined in Section 14.A.iii, with $HO^{\bullet}$ as the attacking species,[227] formed by

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + HO^{\bullet}$$

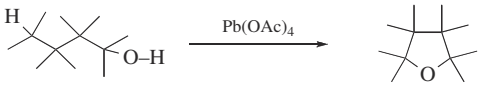
The rate-determining step is formation of $HO^{\bullet}$ and not its reaction with the aromatic substrate.

An alternative oxidation of arene to phenol was reported using $Cu(NO_3)^{\bullet}3\ H_2O$, 30% hydrogen peroxide and a phosphate buffer.[228]

See also, Reaction **11-26**

14-6 Formation of Cyclic Ethers

(5)*OC-cyclo-* Alkoxy-de-hydro-substitution



[218] See Vysotskaya, N.A. *Russ. Chem. Rev.* ***1973****, 42*, 851; Sangster, D.F. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 133–191; Metelitsa, D.I. *Russ. Chem. Rev.* ***1971****, 40*, 563; Loudon, J.D. *Prog. Org. Chem.* ***1961****, 5*, 47.

[219] See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 269–336. See also, Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press, NY, ***1981***.

[220] See Walling, C. *Acc. Chem. Res.* ***1975****, 8,* 125.

[221] Yields can be improved with phase-transfer catalysis: Karakhanov, E.A.; Narin, S.Yu.; Filippova, T.Yu.; Dedov, A.G. *Doklad. Chem.* ***1987****, 292*, 81.

[222] See the discussion of the aromatic free-radical substitution mechanism in Sec. 14.A.ii.

[223] See Cruse, R.W.; Kaderli, S.; Meyer, C.J.; Zuberbühler, A.D.; Karlin, K.D. *J. Am. Chem. Soc.* ***1988****, 110,* 5020; Ito, S.; Kunai, A.; Okada, H.; Sasaki, K. *J. Org. Chem.* ***1988****, 53,* 296.

[224] Funabiki, T.; Tsujimoto, M.; Ozawa, S.; Yoshida, S. *Chem. Lett.* ***1989***, 1267.

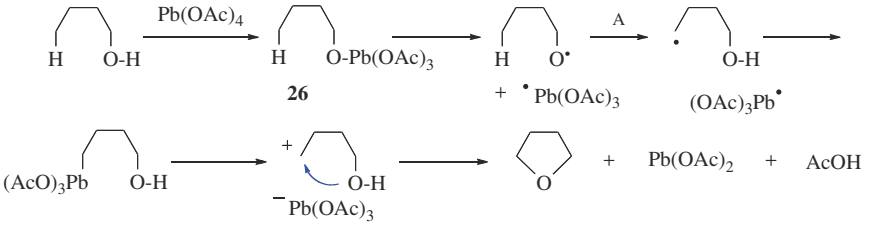
[225] Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. *J. Biol. Chem.* ***1954****, 208*, 731; Brodie, B.B.; Shore, P.A.; Udenfriend, S. *J. Biol. Chem.* ***1954****, 208,* 741. See also, Tamagaki, S.; Suzuki, K.; Tagaki, W. *Bull. Chem. Soc. Jpn.* ***1989****, 62,* 148, 153, 159.

[226] Malykhin, E.V.; Kolesnichenko, G.A.; Shteingarts, V.D. *J. Org. Chem. USSR* ***1986****, 22*, 720.

[227] Brook, M.A.; Castle, L.; Lindsay Smith, J.R.; Higgins, R.; Morris, K.P. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 687; Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* ***1986****, 108*, 6012.

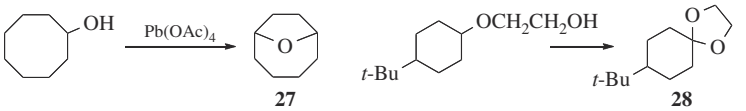
[228] Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***2000****, 32*, 373.

Alcohols with hydrogen in the δ position can be cyclized with lead tetraacetate.[229] The reaction is usually carried out at ~ 80 °C (most often in refluxing benzene), but can also be done at room temperature if the reaction mixture is irradiated with UV light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε hydrogen atoms are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),[230] with iodosobenzene diacetate and I_2,[231] and with ceric ammonium nitrate (CAN).[232] The following mechanism is likely for the lead tetraacetate reaction[233]:



although **26** has never been isolated. The step marked **A** is a 1,5-internal hydrogen abstraction. Such abstractions are well known (see Reaction **18-40**) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6-abstractions).[234]

Oxidation to the aldehyde or acid (Reactions **19-3** and **19-22**) and fragmentation of the substrate sometimes compete. When the OH group is on a ring of at least seven members, a transannular product can be formed, as in the cyclization reaction of 1-octanol to **27**.[235] β-Hydroxy ethers can give cyclic acetals (e.g., **28**).[236]



There are no references in *Organic Syntheses*, but see OS **V**, 692; **VI**, 958, for related reactions.

[229] See Mihailovic, M.Lj.; Partch, R. *Sel. Org. Transform.* ***1972****, 2,* 97; Milhailovic, M.Lj.; Cekovic, Z. *Synthesis* ***1970***, 209; Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 277–419.

[230] Roscher, N.M.; Shaffer, D.K. *Tetrahedron* ***1984****, 40*, 2643. See Kalvoda, J.; Heusler, K. *Synthesis* ***1971***, 501. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed, Wiley–VCH, NY, ***1999***, pp. 889–890.

[231] Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988****, 29*, 2215.

[232] See Doyle, M.P.; Zuidema, L.J.; Bade, T.R. *J. Org. Chem.* ***1975****, 40*, 1454.

[233] Mihailovic, M.Lj.; Cekovic, Z.; Maksimovic, Z.; Jeremic, D.; Lorenc, Lj.; Mamuzic, R.I. *Tetrahedron* ***1965****, 21,* 2799.

[234] Mihailovic, M.Lj.; Cekovic, Z.; Jeremic, D. *Tetrahedron* ***1965****, 21*, 2813.

[235] Mihailovic, M.Lj.; Cekovic, Z.; Andrejevic, V.; Matic, R.; Jeremic, D. *Tetrahedron* ***1968****, 24,* 4947.

[236] Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988****, 29*, 2215.

14-7 Formation of Hydroperoxides

Hydroperoxy-de-hydrogenation

$$RH + O_2 \longrightarrow R{-}O{-}O{-}H$$

The slow atmospheric oxidation (*slow* meaning without combustion) of C—H to C—O—O—H is called *autoxidation*.[237] The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. Most autoxidations proceed by free radical chain processes that involve peroxyl radicals.[238] To suppress autoxidation, an antioxidant can be added that will prevent or retard the reaction with atmospheric oxygen.[239] Although some lactone compounds are sold as antioxidants, many radicals derived from lactones show poor or no reactivity toward oxygen.[239] The hydroperoxides produced often react further to give alcohols, ketones, and more complicated products, so the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.[240] It is because of autoxidation that foods, rubber, paint, lubricating oils, and so on deteriorate on exposure to the atmosphere over periods of time. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes. As with other free radical reactions of C—H bonds, some bonds are attacked more readily than others,[241] and these are the ones seen before (Sec. 14.B.i), although the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), benzylic,[242] and allylic (though allylic rearrangements are common) R.[243] 2-Phenylpropane reacted with oxygen to give $PhMe_2C{-}OOH$, for example. Another susceptible position is aldehydic C—H, but the peroxyacids so produced are not easily isolated[244] since they are converted to the corresponding carboxylic acids (Reaction **19-23**). The α positions of ethers are also easily attacked by oxygen [RO—C—H → RO—C—OOH], but the resulting hydroperoxides are seldom isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.[245]

Oxygen itself (a diradical) is not reactive enough to be the species that actually abstracts the hydrogen. But if a trace of free radical (say $R'^{\bullet}$) is produced by some initiating process, *it* reacts with oxygen[246] to give $R'{-}O{-}O^{\bullet}$; since this type of radical *does* abstract

[237] The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. See Goosen, A.; Morgan, D.H. *J. Chem. Soc. Perkin Trans. 2* ***1994,*** *557*. For reviews, see Sheldon, R.A.; Kochi, J.K. *Adv. Catal.* ***1976,*** *25*, 272; Howard, W.G. in Kochi, J.K. *Free Radicals,* Vol. 2, Wiley, NY, ***1973,*** pp. 3–62; Lloyd, W.G. *Methods Free-Radical Chem.* ***1973,*** *4,* 1; Betts, J. *Q. Rev. Chem. Soc.* ***1971,*** *25,* 265; Ingold, K.U. *Acc. Chem. Res.* ***1969,*** 2, I; Mayo, F.R. *Acc. Chem. Res.* ***1968,*** *1, 193*.

[238] Ingold, K.U. *Acc. Chem. Res.* ***1969****, 2,* 1.

[239] Bejan, E.V.; Font-Sanchis, E.; Scaiano, J.C. *Org. Lett,* ***2001****, 3,* 4059.

[240] See Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 161–200.

[241] See Korcek, S.; Chenier, J.H.B.; Howard, J.A.; Ingold, K.U. *Can. J. Chem.* ***1972****, 50*, 2285, and other papers in this series.

[242] See Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* ***1989****, 30,* 4677.

[243] See Voronenkov, V.V.; Vinogradov, A.N.; Belyaev, V.A. *Russ. Chem. Rev.* ***1970****, 39*, 944.

[244] Swern, D. *Organic Peroxides,* Vol. 1, Wiley, NY, ***1970***, p. 313.

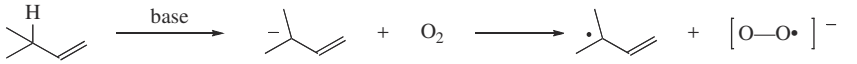
[245] For methods of detection and removal of peroxides from ether solvents, see Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, Wiley, NY, ***1972***, p. 437; Burfield, D.R. *J. Org. Chem.* ***1982****, 47*, 3821.

[246] See Schwetlick, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 2007.

hydrogen, the chain is

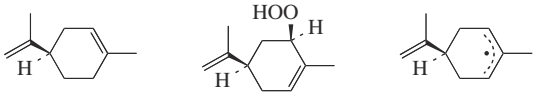
$$R'OO^{\bullet} + RH \longrightarrow R^{\bullet} + R'OOH$$
$$R^{\bullet} + O_2 \xrightarrow[\text{etc.}]{} R{-}O{-}O^{\bullet}$$

In at least some cases (in alkaline media),[247] the radical $R^{\bullet}$ can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, such as allylic radical **29**.[248] Autoxidations in alkaline media can also proceed by a different mechanism: R—H + base → R^- + O_2 → ROO^-.[249]



29

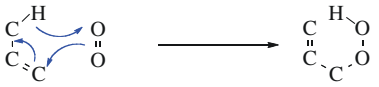
When alkenes are treated with oxygen that has been photosensitized (Sec. 7.A.vi, category 6), they are substituted by OOH in the allylic position in a synthetically useful reaction.[250] Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet), but an excited singlet state[251] (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,[252] for example, by the reaction between H_2O_2 and NaOCl[253] or between ozone and triphenyl phosphite.[254] Calcium peroxide diperoxohydrate ($CaO_2 \bullet 2H_2O_2$) has been reported as a storable compound used for the chemical generation of singlet oxygen.[255] The oxygen generated by either photochemical or nonphotochemical methods reacts with alkenes in the same way;[256] this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical



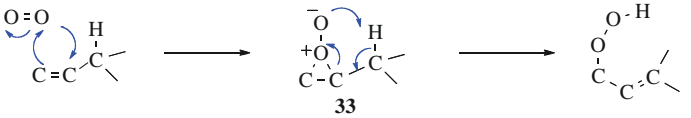
30 **31** **32**

[247] Sosnovsky, G.; Zaret, E.H. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 517–560.
[248] Barton, D.H.R.; Jones, D.W. *J. Chem. Soc.* ***1965***, 3563; Russell, G.A.; Bemis, A.G. *J. Am. Chem. Soc.* ***1966,*** *88,* 5491.
[249] Gersmann, H.R.; Bickel, A.F. *J. Chem. Soc. B* ***1971***, 2230.
[250] See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O_2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 67–91; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981****, 37,* 1825; Gollnick, K.; Kuhn, H.J. in Wasserman, H. H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 287–427; Denny, R.W.; Nickon, A. *Org. React.* ***1973****, 20,* 133; Adams, W.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1969***, pp. 65–112.
[251] See Frimer, A.A. *Singlet O_2*, 4 Vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***; Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981****, 10,* 205; Ohloff, G. *Pure Appl. Chem.* ***1975****, 43,* 481; Kearns, D.R. *Chem. Rev.* ***1971****, 71*, 395; Wayne, R.P. *Adv. PhotoChem.* ***1969****, 7*, 311.
[252] See Turro, N.J.; Ramamurthy, V. in de Mayo, P. *Rearrangements in Ground and Excited States,* Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114; Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.
[253] Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* ***1964****, 86,* 3879.
[254] See Bartlett, P.D.; Mendenhall, G.D.; Durham, D.L. *J. Org. Chem.* ***1980****, 45,* 4269.
[255] Pierlot, C.; Nardello, V.; Schrive, J.; Mabille, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem,* ***2002****, 67,* 2418.
[256] Foote, C.S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* ***1968****, 90*, 975. See also, McKeown, E.; Waters, W.A. *J. Chem. Soc. B* ***1966***, 1040.

complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free radical mechanism. Further evidence that free radicals are not involved comes from the treatment of optically active limonene (**30**) with singlet oxygen. Among other products is the optically active hydroperoxide **31**, though if **32** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.[257] In contrast, autoxidation of **30** gave optically inactive **31** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more highly substituted than with less highly substituted alkenes. The order of alkene reactivity is tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the alkene.[258] In simple trisubstituted alkenes, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.[259] With *cis*-alkenes of the form RCH=CHR′, the hydrogen is removed from the larger R group.[260] Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).[261] Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.[262]



Several mechanisms have been proposed for the reaction with singlet oxygen.[263] One of these is a pericyclic mechanism, similar to that of the ene synthesis (Reaction **15-23**) and to the first step of the reaction between alkenes and SeO_2 (Reaction **19-14**). However, there is strong evidence against this mechanism,[264] and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**33**),[265] followed by internal proton transfer.[266]



33

Still other proposed mechanisms involve diradicals or dipolar intermediates.[267]

OS **IV**, 895.

[257] See Schenck, G.O.; Neumüller, O.; Ohloff, G.; Schroeter, S. *Liebigs Ann. Chem.* ***1965****, 687*, 26.
[258] See Foote, C.S.; Denny, R.W. *J. Am. Chem. Soc.* ***1971****, 93,* 5162.
[259] Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1986****, 69*, 1638 and references cited therein.
[260] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* ***1989****, 30*, 4875.
[261] Clennan, E.L.; Chen, X.; Koola, J.J. *J. Am. Chem. Soc.* ***1990****, 112,* 5193, and references cited therein.
[262] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* ***1990****, 112*, 6417.
[263] See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O_2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 80–87; Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* ***1980****, 13*, 419; Gollnick, K.; Kuhn, H.J; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 288–341; Frimer, A.A. *Chem. Rev.* ***1979****, 79*, 359; Foote, C.S. *Pure Appl. Chem.* ***1971****, 27,* 635; Gollnick, K. *Adv. Photochem.* ***1968****, 6*, 1; Kearns, D.R. *Chem. Rev.* ***1971****, 71*, 395.
[264] Asveld, E.W.H.; Kellogg, R.M. *J. Org. Chem.* ***1982****, 47,* 1250.
[265] See Mitchell, J.C. *Chem. Soc. Rev.* ***1985****, 14,* 399, p. 401.
[266] See Wilson, S.L.; Schuster, G.B. *J. Org. Chem.* ***1986****, 51*, 2056; Davies, A.G.; Schiesser, C.H. *Tetrahedron Lett.* ***1989****, 30*, 7099; Orfanopoulos, M.; Smonou, I.; Foote, C.S. *J. Am. Chem. Soc.* ***1990****, 112,* 3607.
[267] See Jefford, C.W. *Helv. Chim. Acta* ***1981****, 64*, 2534.

14-8 Formation of Peroxides

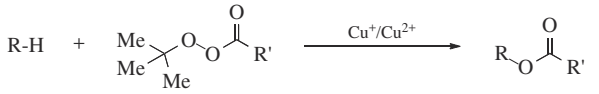
Alkyldioxy-de-hydrogenation

$$RH + R'OOH \xrightarrow{CuCl} ROOR'$$

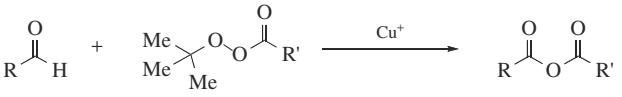
Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts (e.g., cobalt and manganese salts).[268] Very high yields can be obtained. The type of hydrogen replaced is similar to that with NBS (Reaction **14-3**); that is, mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free radical type, involving $ROO^{\bullet}$ formed from ROOH and the metal ion. The reaction can be used to demethylate tertiary amines of the form R_2NCH_3, since the product R_2NHCH_2OOR' can easily be hydrolyzed by acid (Reaction **10-6**) to give R_2NH.[269]

14-9 Acyloxylation

Acyloxylation or Acyloxy-de-hydrogenation



Susceptible positions of organic compounds can be directly acyloxylated[270] by *tert*-butyl peroxyesters, the most frequently used being acetic and benzoic ($R' = Me$ or Ph).[271] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in Reaction **14-6**: benzylic, allylic, and the α position of ethers and sulfides. Terminal alkenes are substituted almost entirely in the 3 position; that is, with only a small amount of allylic rearrangement, but internal alkenes generally give mixtures containing a large amount of allylic-shift product. If the reaction with alkenes is carried out in an excess of another acid ($R''CO_2H$), the ester produced is of *that* acid $ROCOR''$. Aldehydes give anhydrides:



Acyloxylation has also been achieved with metallic acetates (e.g., lead tetraacetate,[272] mercuric acetate,[273] and palladium(II) acetate).[274] In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those α

[268] See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 153–268. See also, Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* ***1990****, 112,* 7820; Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, p. 161.

[269] See Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* ***1988****, 110*, 8256.

[270] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed, Wiley–VCH, NY, ***1999***, pp. 1625–1630 *ff*, 1661–1663.

[271] See Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1972***, 1; Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 585–608; Doumaux Jr, A.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 141–185.

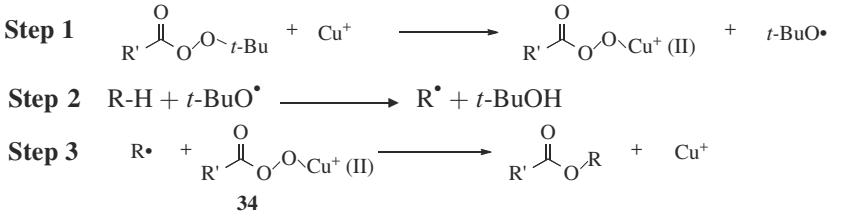
[272] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents, Vol. 3,* Wiley, NY, p. 277.

[273] Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 190–208; Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1973***, 567.

[274] Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* ***1990****, 55*, 975; Byström, S.E.; Larsson, E.M.; Åkermark, B. *J. Org. Chem.* ***1990****, 55*, 5674.

to an OR or SR group, but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those α to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases it is the enol forms that react. Ketones can be α-acyloxylated indirectly by treatment of various enol derivatives with metallic acetates (e.g., silyl enol ethers with silver carboxylates-iodine,[275] enol thioethers with lead tetraacetate,[276] and enamines[277] with lead tetraacetate).[278] Lead tetraacetate even acyloxylates alkanes, in a slow reaction (10 days–2 weeks), with tertiary and secondary positions greatly favored over primary ones.[279] α,β-Unsaturated ketones can be acyloxylated in good yields in the α′ position with manganese triacetate.[280] Palladium acetate converts alkenes to vinylic and/or allylic acetates.[281] Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.[282]

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following[283]:



34

This mechanism, involving a free radical $R^{\bullet}$, is compatible with the allylic rearrangements found.[284] The fact that *tert*-butyl peroxyesters labeled with ^{18}O in the carbonyl oxygen gave an ester with 50% of the label in each oxygen[285] is in accord with coupling of $R^{\bullet}$ with intermediate **34**, in which the Cu is ionically bound, so that the oxygen atoms are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with dienes.[286] Much less is known about the mechanisms of the reactions with other metal acetates.[287]

Free radical acyloxylation of aromatic substrates[288] has been accomplished with a number of reagents, including copper(II) acetate,[289] silver(II) complexes,[290] and cobalt(III) trifluoroacetate.[291]

[275] Rubottom, G.M.; Mott, R.C.; Juve Jr., H.D. *J. Org. Chem.* ***1981****, 46*, 2717.
[276] Trost, B.M.; Tanigawa, Y. *J. Am. Chem. Soc.* ***1979****, 101,* 4413.
[277] See Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 251–258.
[278] See Butler, R.N. *Chem. Ind. (London)* ***1976***, 499.
[279] See Mosher, M.W.; Cox, J.L. *Tetrahedron Lett.* ***1985****, 26,* 3753.
[280] Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis* ***1990***, 1119.
[281] See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 80–87; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972****, 3*, 1, pp. 44–84; Heck, R.F. *Fortschr. Chem. Forsch.* ***1971****, 16*, 221, pp. 231–237; Tsuji, J. *Adv. Org. Chem.* ***1969****, 6,* 109, pp. 132–143.
[282] See Sen, A.; Gretz, E.; Oliver, T.F.; Jiang, Z. *New J. Chem.* ***1989****, 13,* 755.
[283] Kochi, J.K.; Mains, H.E. *J. Org. Chem.* ***1965****, 30,* 1862. See also, Beckwith, A.L.J.; Zavitsas, A.A. *J. Am. Chem. Soc.* ***1986****, 108*, 8230.
[284] Goering, H.L.; Mayer, U. *J. Am. Chem. Soc.* ***1964****, 86*, 3753.
[285] Denney, D.B.; Denney, D.Z.; Feig, G. *Tetrahedron Lett.* ***1959***, no. 15, p. 19.
[286] Kochi, J.K. *J. Am. Chem. Soc.* ***1962****, 84*, 2785, 3271; Story, P.R. *Tetrahedron Lett.* ***1962***, 401.
[287] See, for example, Jones, S.R.; Mellor, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 511.
[288] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 177–180, 351–355.
[289] Takizawa, Y.; Tateishi, A.; Sugiyama, J.; Yoshida, H.; Yoshihara, N. *J. Chem. Soc., Chem. Commun.* ***1991***, 104. See also, Kaeding, W.W.; Kerlinger, H.O.; Collins, G.R. *J. Org. Chem.* ***1965****, 30*, 3754.
[290] Nyberg, K.; Wistrand, L.G. *J. Org. Chem.* ***1978****, 43,* 2613.
[291] See DiCosimo, R.; Szabo, H. *J. Org. Chem.* ***1986****, 51*, 1365.

OS **III**, 3; **V**, 70, 151; **VIII**, 137.

C. Substitution by Sulfur

14-10 Chlorosulfonation or Chlorosulfo-de-hydrogenation

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.[292] In scope and range of products obtained, the reaction is similar to **14-1**. The mechanism is also similar, except that there are two additional main propagation steps:

$$R^{\bullet} + SO_2 \longrightarrow R{-}SO_2^{\bullet}$$
$$R{-}SO_2^{\bullet} + Cl_2 \longrightarrow R{-}SO_2Cl + Cl^{\bullet}$$

Chlorosulfenation[293] can be accomplished by treatment with SCl_2 and UV light:

$$RH + SCl_2 \xrightarrow{h\nu} RSCl$$

D. Substitution by Nitrogen

14-11 The Direct Conversion of Aldehydes to Amides

Amination or **Amino-de-hydrogenation**

$$ArCHO \xrightarrow[NBS-AIBN]{NH_3} ArCONH_2$$

Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, NBS, and a catalytic amount of AIBN (Sec. 14.A.i).[294] In a reaction of more limited scope, amides are obtained from aromatic and α,β-unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.[295] Best yields (80–90%) are obtained at −25 to −20 °C. In the nickel peroxide reaction, the corresponding alcohols ($ArCH_2OH$) have also been used as substrates.

Oxidative amidation of aldehydes has been done using $AgIO_3$ in the presence of a CuI catalyst.[296] Similar oxidative amidation was accomplished using H_2O_2 and a Pd-catalyst.[297] Amides were prepared from aldehydes using NBS with a Cu catalyst.[298] Hypervalent iodine with a Fe catalyst has also been used.[299] Oxidative amidation of aromatic aldehydes using Oxone and ball milling without solvent gave the corresponding amide.[300] Amidation using nucleophilic *N*-heterocyclic carbenes leads to amidation

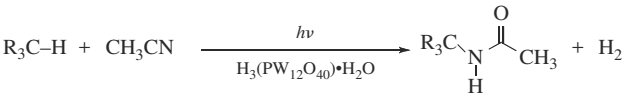
[292] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 126–131.
[293] Müller, E.; Schmidt, E.W. *Chem. Ber.* ***1964****, 97,* 2614; Kühle, E. *Synthesis* ***1970***, 561; ***1971***, 563, 617.
[294] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990****, 31*, 7237. See Ekoue-Kovi, K.; Wolf, C. *Chemistry: European J.* ***2008****, 14*, 6302.
[295] Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* ***1966***, 17.
[296] Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* ***2006****, 128*, 13064.
[297] Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* ***2008****, 49,* 5732.
[298] Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.: Eur. J.* ***2008****, 14,* 10722.
[299] Fang, C.; Qian, W.; Bao, W. *Synlett* ***2008***, 2529.
[300] Gao, J.; Wang, G.-W. *J. Org. Chem.* ***2008****, 73,* 2955.

accompanied by ring opening of proximal epoxides[301] or cyclopropane moieties.[302] Aromatic aldehydes are converted to the corresponding amide by treatment with LiN $(TMS)_2$ in the presence of $LnCl_3$, and a stoichiometric reaction was reported using $(Me_3Si)_2N]_3Ln(i\text{-}Cl)Li(THF)_3$.[303]

The reaction has been performed with MnO_2 and NaCN along with ammonia or an amine at 0 °C in isopropyl alcohol.[304] Treatment of an aldehyde with iodine in aq ammonia, followed by oxidation with aq H_2O_2 generates a primary amide.[305] Secondary amines react with aldehydes to give an amide using a Pd[306] or a Rh catalyst.[307] For an indirect way of converting aldehydes to amides, see Reaction **12-32**. Thioamides ($RCSNR'_2$) have been prepared in good yield from thioaldehydes (produced *in situ* from phosphoranes and sulfur) and secondary amines.[308]

14-12 Amidation and Amination at an Alkyl Carbon

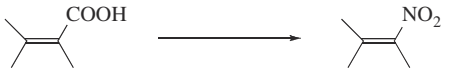
Acylamino-de-hydrogenation



When alkanes bearing a tertiary hydrogen are exposed to UV light in acetonitrile containing a heteropolytungstic acid, they are amidated.[309] The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogen atoms, alkenes are formed (by loss of two hydrogen atoms), rather than amides (Reaction **19-2**). Amidyl radicals can be generated by other means.[310]

14-13 Substitution by Nitro

Nitro-de-carboxylation



In a reaction termed a "nitro-Hunsdiecker" (see Reaction **14-30**), vinyl carboxylic acids (conjugated acids) are treated with nitric acid and a catalytic amount of AIBN (Sec. 14.A.i). The product is the vinyl nitro compound, generated via decarboxylation of a radical intermediate.[311]

Aryl halides are converted to aromatic nitro compounds via a Cu catalyzed reaction with nitrite salts ($Ar—X \rightarrow Ar—NO_2$).[312] Ceric ammonium nitrate in acetonitrile also facilitates this reaction.[313]

[301] Vora, H.U.; Rovis, T. *J. Am. Chem. Soc.* ***2007****, 129*, 13796.
[302] Bode, J.W.; Sohn, S.S. *J. Am. Chem. Soc.* ***2007****, 129*, 13798.
[303] Zhang, L.; Wang, S.; Zhou, S.; Yang, G.; Sheng, E. *J. Org. Chem.* ***2006****, 71,* 3149.
[304] Gilman, N.W. *Chem. Commun.* ***1971***, 733.
[305] Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* ***2003****, 68*, 1158.
[306] Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* ***1983***, 474.
[307] Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* ***2001***, 523.
[308] Okuma, K.; Komiya, Y.; Ohta, H. *Chem. Lett.* ***1988***, 1145.
[309] Renneke, R.F.; Hill, C.L. *J. Am. Chem. Soc.* ***1986****, 108,* 3528.
[310] Moutrille, C.; Zard, S.Z. *Chem. Commun.* ***2004***, 1848.
[311] Das, J.P.; Sinha, P.; Roy, S. *Org. Lett.* ***2002****, 4*, 3055.
[312] Saito, S.; Koizumi, Y. *Tetrahedron Lett.* ***2005****, 46,* 4715.
[313] Rao, A.S.; Srinivas, P.V.; Babu, K.S.; Rao, J.M. *Tetrahedron Lett.* ***2005****, 46*, 8141.

Conjugated amides were coupled via the γ-carbon to give good yields of the dimeric diamide, with an excess of samarium(II) iodide, and with modest enantioselectivity using a chiral additive.[314]

E. Substitution by Carbon

In these reactions, a new carbon–carbon bond is formed, and they may be given the collective title *coupling reactions*. In each case, an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or alkene to give the coupling product.[315]

14-14 Simple Coupling at a Susceptible Position

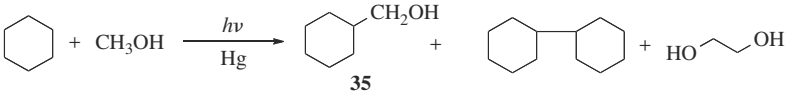
De-hydrogen-coupling

$$2\,RH \longrightarrow R{-}R$$

Alkane and alkyl substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give $R^{\bullet}$, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as *Fenton's reagent* (Reaction **14-5**). This reaction is far from general, although in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,[316] as well as those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[317] an ether group,[318] a carbonyl group,[319] a cyano group,[320] a dialkylamino group,[321] or a carboxylic ester group (either the acid or alcohol side).[322] Cross-coupling is possible in some cases. When toluene was heated with allyl bromide, in the presence of di-*tert*-butyl peroxide, 4-phenyl-1-butene was formed quantitatively.[323]

$$2\,RH \xrightarrow[Hg]{h\nu} R{-}R + H_2$$

Alkanes can be dimerized by vapor-phase mercury photosensitization[324] in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogen atoms (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary–secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., 2 EtOH → MeCH(OH)CH(OH)Me].



35

[314] Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* ***1999****, 40*, 7497.
[315] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds,* Pergamon, Elsmsford, NY, ***1986***.
[316] Meshcheryakov, A.P.; Érzyutova, E.I. *Bull. Acad. Sci. USSR Div. Chem. Sci,* ***1966***, 94.
[317] Johnston, K.M.; Williams, G.H. *J. Chem. Soc.* ***1960***, 1168.
[318] Pfordte, K.; Leuschner, G. *Liebigs Ann. Chem.* ***1961****, 643,* 1.
[319] Hawkins, E.G.E.; Large, R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 280.
[320] Kharasch, M.S.; Sosnovsky, G. *Tetrahedron* ***1958****, 3,* 97.
[321] Schwetlick, K.; Jentzsch, J.; Karl, R.; Wolter, D. *J. Prakt. Chem.* ***1964****, [4] 25,* 95.
[322] Boguslavskaya, L.S.; Razuvaev, G.A. *J. Gen. Chem. USSR* ***1963****, 33*, 1967.
[323] Tanko, J.M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* ***1999****, 38*, 159.
[324] Brown, S.H.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1989****, 111*, 2935, 2946; *J. Chem. Educ.* ***1988****, 65*, 290.

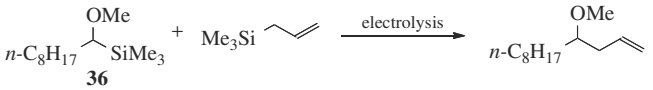
When a mixture of compounds is treated, cross-dimerization (to give **35**) and homodimerization take place statistically. Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross-coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (Reaction **10-6**) gives an aldehyde, thus achieving the conversion RH → RCHO. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals.

The reaction has been extended to ketones, carboxylic acids and esters (all of which couple α to the C=O group), and amides (which couple α to the nitrogen) by running it in the presence of H_2.[325] Under these conditions it is likely that the excited Hg abstracts $H^{\bullet}$ from H_2, and that the remaining $H^{\bullet}$ abstracts H from the substrate. Radicals have also been generated at benzylic positions and shown to couple with epoxides, forming an alcohol.[326]

OS **IV**, 367; **V**, 1026; **VII**, 482.

14-15 Coupling at a Susceptible Position via Silanes

De-silyl-coupling



Under electrochemical conditions it is possible to couple two silanes. The reaction of **36** and allyltrimethylsilane, for example, gave the corresponding homoallylic ether.[327]

14-16 Coupling of Alkynes[328]

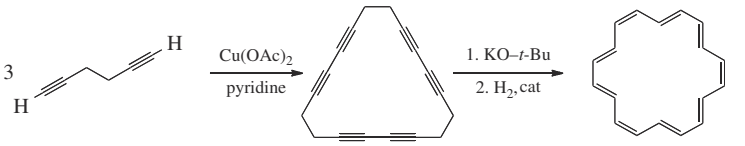
De-hydrogen-coupling

$$2\,R{-}C{\equiv}C{-}H \xrightarrow[\text{pyridine}]{CuX_2} R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.[329] The large-ring annulenes (see Sec. 2.K) were prepared by rearrangement and hydrogenation of cyclic polyynes,[330] prepared by the *Eglinton reaction* with terminal diynes to give **37**, a cyclic trimer of 1,5-hexadiyne.[331] The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers

[325] Boojamra, C.G.; Crabtree, R.H.; Ferguson, R.R.; Muedas, C.A. *Tetrahedron Lett.* ***1989****, 30*, 5583.
[326] Rawal, V.H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.* ***1993****, 34*, 2899.
[327] Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2000****, 122*, 10244.
[328] See Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem. Int. Ed.* ***2000****, 39*, 2632.
[329] See Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 529–534; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 11–31; Cadiot, P.; Chodkiewicz, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY; ***1969***, pp. 597–647.
[330] See Nakagawa, M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond,* pt. 2, Wiley, NY, ***1978***, pp. 635–712. See Sondheimer et al. in Ref. 331 also.
[331] Sondheimer, F.; Wolovsky, R. *J. Am. Chem. Soc.* ***1962****, 84,* 260; Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* ***1962****, 84*, 274.

(C_{36}) were also formed. The *Eglinton reaction* is of wide scope and many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen.



37

Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent (e.g., permanganate or hydrogen peroxide) is required in the latter procedure. This method is not satisfactory for cyclic coupling. Hydrogen peroxide, potassium permanganate, potassium ferricyanide, iodine, or Cu(II) can be used instead of oxygen as oxidants.[332] Isolation of copper acetylide during the reaction can be avoided by doing the reaction in pyridine or cyclohexylamine, in the presence of a catalytic amount of $CuCl_2$.[333] If the *Glaser reaction* is done with a *N,N,N′,N′*-tetramethylethylenediamine–CuCl complex, the reaction proceeds in good yield in virtually any organic solvent.[334] When molecular oxygen is the oxidant, this modification of the *Glaser reaction* is known as the *Hay reaction*.

A variation couples terminal alkynes using $CuCl_2$ in supercritical CO_2 (see Sec. 9.D.ii),[335] and in ionic liquids.[336] Coupling was also achieved using $CuCl_2$ on KF—Al_2O_3 with microwave irradiation.[337] A Co catalyzed *Glaser coupling* has been reported[338] and also a transition metal free coupling.[339] A modified *Glaser coupling* has been reported using KF/Alumina.[340] Coupling has been achieved under ambient conditions using cupric acetate.[341] Copper(II) promoted homocoupling of terminal alkynes has been done in supercritical CO_2.[342] Another variation is a Ni catalyzed cross-coupling.[343] Terminal alkynes give 1,3-diynes upon treatment with Cu–iodine.[344]

Unsymmetrical diynes can be prepared by *Cadiot–Chodkiewicz* coupling[345]:

$$R{-}C{\equiv}C{-}H + R'{-}C{\equiv}C{-}Br \xrightarrow{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' + HBr$$

This may be regarded as a variation of Reaction **10-74**, but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not,

[332] Gunter, H.V. *Chemistry of Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 597–647 and references cited therein.
[333] Stansbury, H.A.; Proops, W.R. *J. Org. Chem.* ***1962****, 27,* 320.
[334] Hay, A.S. *J. Org. Chem.* ***1960****, 25,* 1275; Hay, A S. *J. Org. Chem.* ***1962****, 27,* 3320.
[335] Li, J.; Jiang, H. *Chem. Commun.* ***1999***, 2369.
[336] Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Gayathri, K.U.; Prasad, A.R. *Tetrahedron Lett.* ***2003****, 44*, 6493.
[337] Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett* ***2001***, 108.
[338] Hilt, G.; Hengst, C.; Arndt, M. *Synthesis* ***2009***, 395.
[339] Yan, J.; Wang, L. *Synth. Commun.* ***2005****, 35,* 2333.
[340] Sharifi, A.; Mirzael, M.; Naimi-Jamal, M.R. *Monat. Chemie* ***2006****, 137*, 213.
[341] Balaraman, K.; Kesavan, V. *Synthesis* ***2010***, 3461.
[342] Jiang, H.-F.; Tang, J.Y.; Wang, A.-Z.; Deng, G.-H.; Yang, S.-R. *Synthesis* ***2006***, 1155.
[343] Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* ***2009****, 11*, 709.
[344] Li, D.; Yin, K.; Li, J.; Jia, X. *Tetrahedron Lett.* ***2008****, 49,* 5918.
[345] Chodkiewicz, W. *Ann. Chim. (Paris)* ***1957****, [13]* 2, 819.

which is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. One version of this reaction binds the alkynyl bromide unit to a polymer, and the di-yne is released from the polymer after the solid-state transformation.[346] Alkynes have also been coupled using CuI and a Pd catalyst.[347] A variation of the *Cadiot–Chodkiewicz method* consists of treating a haloalkyne ($R'C{\equiv}CX$) with a copper acetylide ($RC{\equiv}CCu$).[348] The *Cadiot–Chodkiewicz procedure* can be adapted to the preparation of diynes in which $R'{=}H$ by the use of $BrC{\equiv}CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.[349] This protecting group can also be used in the *Eglinton* or *Glaser* methods.[350]

The mechanism of the *Eglinton* and *Glaser reactions* probably begins with loss of a proton

$$R{-}C{\equiv}C{-}H \xrightarrow{\text{base}} R{-}C{\equiv}C^{-}$$

since there is a base present and acetylenic protons are acidic. It is known, of course, that cuprous ion can form complexes with triple bonds. The last step is probably the coupling of two radicals:

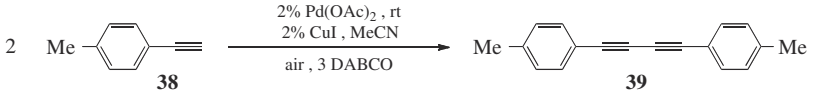
$$R{-}C{\equiv}C^{\bullet} \longrightarrow R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[351] and depend on the oxidizing agent. One proposed mechanism postulated Cu(II) as the oxidant.[352] It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines, which might be the intermediates in the *Glaser reaction* where molecular oxygen is the oxidant.[353] For the *Hay reaction*, the mechanism involves a Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytic cycle, and the key step for this reaction is the dioxygen activation during complexation of two molecules of acetylide with molecular oxygen, giving a Cu(III) complex.[354] This mechanism is supported by isolation and characterization of Cu(III) complexes formed under the conditions of the *Glaser coupling*.

Sonogashira coupling, which involves aryl halides and terminal alkynes in the presence of a Pd catalyst, has been extended to the coupling of two alkynes.[355] Indeed, the Pd catalyzed coupling of two alkynes to form a diyne[356] is often referred to as *Sonogashira cross-coupling*, or *Sonogashira-like coupling*. An example is the

[346] Montierth, J.M.; DeMario, D.R.; Kurth, M.J.; Schore, N.E. *Tetrahedron* ***1998****, 54*, 11741.
[347] Liu, Q.; Burton, D.J. *Tetrahedron Lett.* ***1997****, 38*, 4371.
[348] Curtis, R.F.; Taylor, J.A. *J. Chem. Soc. C* ***1971***, 186.
[349] Ghose, B.N.; Walton, D.R.M. *Synthesis* ***1974***, 890.
[350] Johnson, T.R.; Walton, D.R.M. *Tetrahedron* ***1972****, 28*, 5221.
[351] See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 27–31; Fedenok, L.G.; Berdnikov, V.M.; Shvartsberg, M.S. *J. Org. Chem. USSR* ***1973****, 9,* 1806; Clifford, A.A.; Waters, W.A. *J. Chem. Soc.* ***1963***, 3056.
[352] Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* ***1964****, 97*, 794.
[353] Wieghardt, K.; Chaudhuri, P. *Prog. Inorg. Chem.* ***1987****, 37,* 329.
[354] Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* ***2002****, 58*, 6741.
[355] See Henriksen, S.T.; Tanner, D.; Skrydstrup, T.; Norrby, P.-O. *Chemistry: Eur. J.* ***2010****, 16*, 9494.
[356] See Kurita, T.; Abe, M.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Synlett* ***2007***, 2521.

conversion of **38** to **39**.[357] Here rt = room temperature amd DABCO = 1,4-diazabicyclo [2.2.2]octane.



38 **39**

Terminal alkynes are not the only reaction partners. 1-Trimethylsilyl alkynes (R—C≡C—$SiMe_3$) give the diyne R—C≡C—C≡C—R) upon reaction with CuCl[358] or $Cu(OAc)_2/Bu_4NF$.[359]

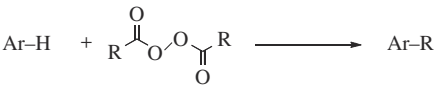
Alkynylboronates undergo homocoupling to give symmetrical 1,3-diynes in the presence of a Cu salt.[360] The Cu-catalyzed homocoupling of alkynyltrifluoroborates leads to 1,3-diynes.[361]

In related reactions, alkynyltrifluoroborates react with vinylic tellurides to give 1,3-enynes.[362] The Pd catalyzed reaction of vinyl bromides and terminal alkynes gives enynes.[363] 1,3-Dienes are prepared by the Pd catalyzed homocoupling of alkenyltrifluoroborates.[364]

OS **V**, 517; **VI**, 68, 925; **VIII**, 63.

14-17 Alkylation and Arylation of Aromatic Compounds by Peroxides

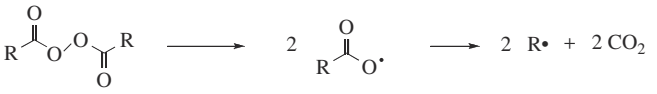
Alkylation or **Alkyl-de-hydrogenation**



This reaction is most often carried out with R = aryl, so the net result is the same as in Reaction **13-27**, though the reagent is different.[365] It is used less often than Reaction **13-27**, but the scope is similar. When R = alkyl, the scope is more limited.[366] Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

[357] Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* ***2005****, 70,* 4393.
[358] Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* ***2000,*** *65,* 1780.
[359] Heuft, M.A.; Collins, S.K.; Yap, G.P.A.; Fallis, A.E. *Org. Lett.* ***2001****, 3*, 2883.
[360] Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, K. *Tetrahedron Lett.* ***2005****, 46,* 8661.
[361] Paixão, M.W.; Weber, M.; Braga, A.L; de Azeredo, J.B.; Deobald, A.M.; Stefani, H.A. *Tetrahedron Lett.* ***2008****, 49,* 2366.
[362] Stefani, H.A.; Cella, R.; Dörr, F.A.; Pereira, C.M.P.; Zeni, G.; Gomes, Jr., M. *Tetrahedron Lett.* ***2005****, 46,* 563.
[363] Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. *Tetrahedron* ***2006****, 62,* 112.
[364] Weber, M.; Singh, F.V.; Vieira, A.S.; Stefani, H.A.; Paixão, M.W. *Tetrahedron Lett.* ***2009****, 50*, 4324.
[365] See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* ***1986****, 15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966****, 2*, 47.
[366] See Tiecco, M.; Testaferri, L. *React. Intermed. (Plenum)* ***1983****, 3,* 61.

The mechanism is as shown in Section 14.A.iii (CIDNP has been observed[367]); the radicals are produced by



Since no relatively stable free radical is present (e.g., $^{\bullet}O—N=N—Ar$ in Reaction **13-27**), most of the product arises from dimerization and disproportionation.[368] The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts a hydrogen atom and diminishes the extent of side reactions.[369] The Pd catalyzed methylation of aromatic rings in the presence of dicumyl peroxide is another variation.[370]

$$ArH + Ar^{I}Pb(OAc)_3 \longrightarrow ArAr^{I}$$

Aromatic compounds can also be arylated by aryllead tricarboxylates.[371] Best yields ($\sim$ 70–85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely. Phenols are phenylated ortho to the OH group (and enols are a phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.[372] *O*-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free radical mechanism is unlikely.[373]

OS **V**, 51. See also, OS **V**, 952; **VI**, 890.

14-18 Photochemical Arylation of Aromatic Compounds

Arylation or **Aryl-de-hydrogenation**

$$ArH + Ar^{I}I \xrightarrow{h\nu} ArAr^{I}$$

Another free radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.[374] Yields are generally higher than in Reactions **13-27** or **14-17**. The aryl iodide may contain OH or COOH groups. The coupling reaction of iodobenzene and azulene to give a phenylazulene was reported (41% conversion and 85% yield).[375] The mechanism is similar to that of Reaction **13-27**. The aryl radicals are generated by the photolytic cleavage $ArI \rightarrow AR^{\bullet} + I^{\bullet}$. The reaction has been applied to intramolecular arylation (analogous to the *Pschorr reaction*).[376] A similar reaction is photolysis of an

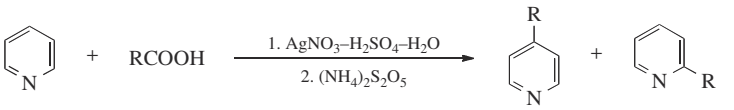
[367] Kaptein, R.; Freeman, R.; Hill, H.D.W.; Bargon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 953.
[368] The mechanism is actually more complicated. See DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967****, 89,* 4051; DeTar, D.F. *J. Am. Chem. Soc.* ***1967****, 89,* 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.
[369] Chalfont, G.R.; Hey, D.H.; Liang, K.S.Y.; Perkins, M.J. *J. Chem. Soc. B* ***1971***, 233.
[370] Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* ***2008****, 130,* 2900.
[371] Bell, H.C.; Kalman, J.R.; May, G.L.; Pinhey, J.T.; Sternhell, S. *Aust. J. Chem.* ***1979****, 32,* 1531.
[372] See Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988****, 44*, 3039, pp. 3040–3047.
[373] Barton, D.H.R.; Finet, J.; Giannotti, C.; Halley, F. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 241.
[374] See Sharma, R.K.; Kharasch, N. *Angew. Chem. Int. Ed.* ***1968****, 7*, 36.
[375] Ho, T.-I.; Ku, C.-K.; Liu, R.S.H. *Tetrahedron Lett.* ***2001****, 42,* 715.
[376] See Jeffs, P.W.; Hansen, J.F. *J. Am. Chem. Soc.* ***1967****, 89*, 2798; Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *Chem. Commun.* ***1967***, 614.

arylthallium bis(trifluoroacetate) (**12-23**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.[377] In this case, it is the C—Tl bond that is cleaved to give aryl radicals.

$$Ar^{I}Tl(OCOCF_3)_2 \xrightarrow[h\nu]{ArH} ArAr^{I}$$

14-19 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles[378]

Alkylation or **Alkyl-de-hydrogenation**, and so on

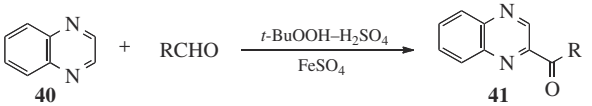


Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.[379] The R group can be primary, secondary, or tertiary. The attacking species is $R^{\bullet}$, formed by[380]

$$2\,Ag^{+} + S_2O_8^{2-} \longrightarrow 2\,Ag^{2+} + 2\,SO_4^{2-}$$
$$RCOOH + Ag^{2+} \longrightarrow RCOO^{\bullet} + H^{+} + Ag^{+}$$
$$RCOO^{\bullet} \longrightarrow R^{\bullet} + CO_2$$

A hydroxymethyl group can be introduced (ArH → $ArCH_2OH$) by several variations of this method.[381] Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and $FeSO_4$,[382] from alkyl iodides and H_2O_2—Fe(II),[383] from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.[384]

Protonated nitrogen heterocycles (e.g., quinoxaline, **40**) can be acylated by treatment with an aldehyde, *tert*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, in this case giving **41**.[385]



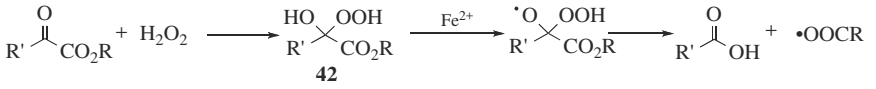
Photochemical alkylation of protonated quinoline occurred with $Ph_2Se(O_2C\text{-}c\text{-}C_6H_{11})_2$.[386]

[377] Taylor, E.C.; Kienzle, F.; McKillop, A. *J. Am. Chem. Soc.* ***1970****, 92,* 6088.
[378] See Heinisch, G. *Heterocycles* ***1987****, 26,* 481; Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* ***1989****, 28*, 489; Vorbrüggen, H.; Maas, M. *Heterocycles* ***1988****, 27*, 2659.
[379] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Tetrahedron* ***1990****, 46*, 2525.
[380] Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1970****, 92*, 1651.
[381] See Katz, R.B.; Mistry, J.; Mitchell, M.B. *Synth. Commun.* ***1989****, 19,* 317.
[382] Minisci, F.; Selva, A.; Porta, O.; Barilli, P.; Gardini, G.P. *Tetrahedron* ***1972****, 28*, 2415.
[383] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Acta Chem. Scand,* ***1989****, 43,* 995.
[384] Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M.C.N. *Tetrahedron Lett.* ***1989****, 30,* 4569.
[385] Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* ***1977****, 107*, 491.
[386] Togo, H.; Miyagawa, N.; Yokoyama, M. *Chem. Lett,* ***1992***, 1677.

Other positively charged heterocycles react as well. When *N*-fluoropyridinium triflate was treated with the enolate anion of acetone, 2-(2-oxopropyl)pyridine was formed in modest yield.[387]

These alkylation and acylation reactions are important because *Friedel–Crafts* alkylation and acylation (Reactions **11-11** and **11-17**) cannot be applied to most nitrogen heterocycles (see also, Reaction **13-17**).

Protonated nitrogen heterocycles can be carbalkoxylated[388] by treatment with esters of α-keto acids and *Fenton's reagent*. Pyridine is carbalkoxylated at C-2 and C-4, for example. The attack is by •COOR radicals generated from the esters via a hydroperoxide (**42**).



Similarly, a carbamoyl group can be introduced[389] by the use of the radicals $H_2N—\dot{C}=O$ or $Me_2N—\dot{C}=O$ generated from formamide or DMF and H_2SO_4, H_2O_2, and $FeSO_4$ or other oxidants.

14.C.ii. N_2 as Leaving Group[390]

In these reactions, diazonium salts are cleaved to aryl radicals,[391] in most cases with the assistance of copper salts. Reactions **13-27** and **13-26** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts (see Reactions **13-20**–**13-23**). Removal of nitrogen and replacement with a hydrogen atom is a reduction, found in Chapter 19.

14-20 Replacement of the Diazonium Group by Chlorine or Bromine

Chloro-de-diazoniation, and so on

$$ArN_2^+ + CuCl \longrightarrow ArCl$$

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case, the reaction is called the *Sandmeyer Reaction*.[392] The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman Reaction* (not to be confused with **11-18**). However, a Cu catalyzed *Sandmeyer bromination* reaction is known.[393] The *Sandmeyer reaction* is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is

[387] Kiselyov, A.S.; Strekowski, L. *J. Org. Chem.* ***1993****, 58*, 4476.
[388] See Heinisch, G.; Lötsch, G. *Angew. Chem. Int. Ed.* ***1985****, 24,* 692.
[389] Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* ***1985****, 41*, 4157.
[390] See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.
[391] See Galli, C. *Chem. Rev.* ***1988****, 88,* 765; Zollinger, H. *Acc. Chem. Res.* ***1973****, 6*, 355, pp. 339–341.
[392] Rate constants for this reaction have been determined. See Hanson, P.; Hammond, R.C.; Goodacre, P.R.; Purcell, J.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 691.
[393] Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovskii, P.V. *Synthesis* ***2007***, 2534.

of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is not known with certainty, but is believed to take the following course[394]:

$$ArN_2^+X^- + CuX \longrightarrow Ar^\bullet + N_2 + CuX_2$$
$$Ar^\bullet + CuX_2 \longrightarrow ArX + CuX$$

The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,[395] including treatment of the amine (1) with *tert*-butyl nitrite and anhydrous $CuCl_2$ or $CuBr_2$ at 65 °C,[396] and (2) with *tert*-butyl thionitrite or *tert*-butyl thionitrate and $CuCl_2$ or $CuBr_2$ at room temperature.[397] These procedures are, in effect, a combination of Reaction **13-19** and the *Sandmeyer Reaction*. A further advantage is that cooling to 0 °C is not needed. A mixture of Me_3SiCl and $NaNO_2$ was used to convert aniline to chlorobenzene in a related reaction.[398]

For the preparation of fluorides and iodides from diazonium salts, see Reactions **13-32** and **13-31**.

$$ArN_2^+ + CuCN \longrightarrow ArCN$$

Note that the reaction of aryl diazonium salts with CuCN to give benzonitrile derivatives is also called the *Sandmeyer Reaction*. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I**, 135, 136, 162, 170; **II**, 130; **III**, 185; **IV**, 160. Also see, OS **III**, 136; **IV**, 182. For the reaction with CuCN see OS **I**, 514.

14-21 Replacement of the Diazonium Group by Nitro

Nitro-de-diazoniation

$$ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2$$

Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the *Sandmeyer Reaction*, although, like Reaction **14-20**, it was discovered by Sandmeyer. Tetrafluoroborate (BF_4^-) is often used as the negative ion, since the diminished nucleophilicity avoids competition from the chloride ion. The mechanism is probably like that of Reaction **14-20**.[399] If electron-withdrawing groups

[394] Galli, C. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 897. See also, Hanson, P.; Jones, J.R.; Gilbert, B.C.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1009.
[395] Also see Brackman,W.; Smit, P.J. *Recl. Trav. Chim. Pays-Bas,* ***1966****, 85*, 857; Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. C* ***1966***, 1249.
[396] Doyle, M.P.; Siegfried, B.; Dellaria, Jr., J.F. *J. Org. Chem.* ***1977****, 42,* 2426.
[397] Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* ***1980****, 53*, 1065.
[398] Lee, J.G.; Cha, H.T. *Tetrahedron Lett.* ***1992****, 33*, 3167.
[399] See Singh, P.R.; Kumar, R.; Khanna, R.K. *Tetrahedron Lett.* ***1982****, 23*, 5191.

are present, the catalyst is not needed; $NaNO_2$ alone gives nitro compounds in high yields.[400]

An alternative procedure used electrolysis, in 60% HNO_3 to convert 1-aminonaphthalene to naphthalene.[401]

OS **II**, 225; **III**, 341.

14-22 Replacement of the Diazonium Group by Sulfur-Containing Groups

Chlorosulfo-de-diazoniation

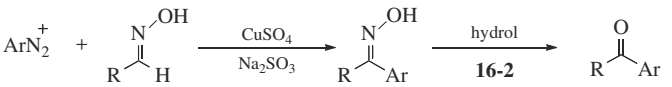
$$ArN_2^+ + SO_2 \xrightarrow[HCl]{CuCl_2} ArSO_2Cl$$

Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.[402] The use of $FeSO_4$ and copper metal instead of $CuCl_2$ gives sulfinic acids ($ArSO_2H$)[403] (see also, Reaction **13-21**).

OS **V**, 60; **VII**, 508.

14-23 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids

Acyl-de-diazoniation, and so on



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.[404] A copper sulfate–sodium sulfite catalyst is essential. In most cases, higher yields (40–60%) are obtained when the reaction is used for aldehydes rather than for ketones. In another method[405] for achieving the conversion $ArN_2^+ \rightarrow$ ArCOR, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.[406] In a different kind of reaction, silyl enol ethers of aryl ketones ($Ar'C(OSiMe_3)=CHR$) react with solid diazonium fluoroborates ($ArN_2^+ BF_4^-$) to give ketones ($ArCHRCOAr'$).[407] This is, in effect, an arylation of the aryl ketone.

Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate[408] or copper(II) chloride.[409] The mixed anhydride (ArCOOCOMe) is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.[410] An arylpalladium compound is probably an intermediate.[368]

OS **V**, 139.

[400] Bagal, L.I.; Pevzner, M.S.; Frolov, A.N. *J. Org. Chem. USSR* ***1969****, 5,* 1767.
[401] Torii, S.; Okumoto, H.; Satoh, H.; Minoshima, T.; Kurozumi, S. *SynLett,* ***1995***, 439.
[402] Gilbert, E.E. *Synthesis* ***1969***, 1, p. 6.
[403] Wittig, G.; Hoffmann, R.W. *Org. Synth.* ***V***, 60.
[404] Beech, W.F. *J. Chem. Soc.* ***1954***, 1297.
[405] See Citterio, A.; Serravalle, M.; Vimara, E. *Tetrahedron Lett.* ***1982,*** *23*, 1831.
[406] Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 1511.
[407] Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* ***1985***, 1545.
[408] Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1980****, 45,* 2365.
[409] Olah, G.A.; Wu, A.; Bagno, A.; Prakash, G.K.S. *Synlett,* ***1990***, 596.
[410] Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1981****, 46,* 4413.

14.C.iii. Metals as Leaving Groups

14-24 Coupling of Grignard Reagents

De-metallo-coupling

$$2\,RMgX \xrightarrow{M} RR$$

This organometallic coupling reaction is clearly related to the *Wurtz coupling*, discussed in Reaction **10-56**, and the coupling of other organometallic compounds is discussed in Reaction **14-25**. *Grignard reagents* can be coupled to give symmetrical dimers[411] by treatment with either thallium(I) bromide[412] or with a transition metal halide (e.g., Fe compounds,[413] $CrCl_2$, $CrCl_3$, $CoCl_2$, $CoBr_2$, or $CuCl_2$).[414] The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl *Grignard reagents* can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with ortho substituents. Aryl *Grignard reagents* can also be dimerized by treatment with 1,4-dichloro-2-butene, 1,4-dichloro-2-butyne, or 2,3-dichloropropene.[415] Vinylic and alkynyl *Grignard reagents* can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.[416] Primary alkyl, vinylic, aryl, and benzylic *Grignard reagents* give symmetrical dimers in high yield (~90%) when treated with a silver(I) salt in the presence of a nitrogen-containing oxidizing agent (e.g., lithium nitrate, methyl nitrate, or NO_2).[417] This method has been used to close rings of four, five, and six members.[418]

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (Reaction **12-36**), followed by its decomposition to free radicals.[419]

OS **VI**, 488.

14-25 Coupling of Other Organometallic Reagents[332]

De-metallo-coupling

$$R_2CuLi \xrightarrow[-78\ ^\circ C,THF]{O_2} RR$$

Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at −78 °C in THF.[420] The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents (e.g., nitrobenzene) can be used instead of O_2. Vinylic

[411] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed, Wiley–VCH, NY, ***1999***, pp. 85–88.
[412] McKillop, A.; Elsom, L.F.; Taylor, E.C. *Tetrahedron* ***1970****, 26*, 4041.
[413] Liu, W.; Lei, A. *Tetrahedron Lett.* ***2008****, 49*, 610.
[414] See Kauffmann, T. *Angew. Chem. Int. Ed.* ***1974****, 13*, 291; Elsom, L.F.; Hunt, J.D.; McKillop, A. *Organomet. Chem. Rev. Sect. A* ***1972****, 8,* 135; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B; Academic Press, NY, ***1973***, pp. 85–91. See Terao, J.; Todo, H.; Begum, S.A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* ***2007****, 46*, 2086.
[415] Cheng, J.; Luo, F. *Tetrahedron Lett.* ***1988****, 29,* 1293.
[416] Uchida, A.; Nakazawa, T.; Kondo, I.; Iwata, N.; Matsuda, S. *J. Org. Chem.* ***1972****, 37*, 3749.
[417] Tamura, M.; Kochi, J.K. *Bull. Chem. Soc. Jpn.* ***1972****, 45,* 1120.
[418] Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* ***1976****, 41*, 2882.
[419] See Kashin, A.N.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1982****, 51*, 503.
[420] Whitesides, G.M.; San Filippo Jr., J.; Casey, C.P.; Panek, E.J. *J. Am. Chem. Soc.* ***1967****, 89,* 5302. See also Bertz, S.H.; Gibson, C.P. *J. Am. Chem. Soc.* ***1986****, 108,* 8286.

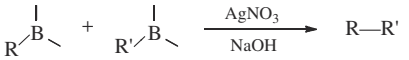
copper reagents dimerize on treatment with oxygen, or simply on standing at 0 °C for several days or at 25 °C for several hours, to yield 1,3-dienes.[421] The finding of retention of configuration for this reaction demonstrates that free radical intermediates are not involved.

The coupling reaction of *Grignard reagents* was discussed in Reaction **14-24**. There are iron-catalyzed cross-coupling reactions.[422] Lithium organoaluminates ($LiAlR_4$) are dimerized to R—R by treatment with $Cu(OAc)_2$.[423] Terminal vinylic alanes (prepared by Reaction **15-17**) can be dimerized to 1,3-dienes with CuCl in THF.[424] Symmetrical 1,3-dienes can also be prepared in high benzylic bromides to give the coupling product.[425] Coupling products are obtained by treatment of vinylic mercury chlorides[426] with LiCl and a Rh catalyst[427] and by treatment of vinylic tin compounds with a Pd catalyst.[428] Vinylic, alkynyl, and aryl tin compounds were dimerized with $Cu(NO_3)_2$.[429] Allylindium reagents were coupled to alkyl- and aryllithium compounds can be dimerized by transition metal halides in a reaction similar to Reaction **14-24**.[430]

Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents (e.g., $PhCH{=}CHHgCl + Me_2CuLi \rightarrow PhCH{=}CHMe$).[431] A radical coupling reaction has been reported, in which an aryl halide reacted with Bu_3SnH, AIBN, and benzene, followed by treatment with methyllithium to give the biaryl.[432]

14-26 Coupling of Boranes

Alkyl-de-dialkylboration

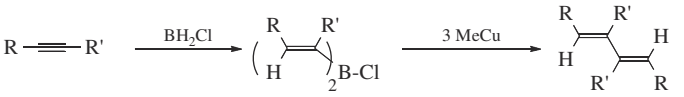


Alkylboranes can be coupled by treatment with silver nitrate and base.[433] Since alkylboranes are easily prepared from alkenes (Reaction **15-16**), this is essentially a way of coupling and reducing alkenes; in fact, alkenes can be hydroborated and coupled in the same flask. For symmetrical coupling (R = R′) yields range from 60 to 80% for terminal alkenes and from 35 to 50% for internal ones. Unsymmetrical coupling has also been

[421] Rao, S.A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 495. See also, Lambert, G.J.; Duffley, R.P.; Dalzell, H.C.; Razdan, R.K. *J. Org. Chem.* ***1982****, 47*, 3350.
[422] Fürstner, A.; Martin, R. *Chem. Lett.* ***2005****, 34,* 624.
[423] Sato, F.; Mori, Y.; Sato, M. *Chem. Lett.* ***1978***, 1337.
[424] Zweifel, G.; Miller, R.L. *J. Am. Chem. Soc.* ***1970****, 92,* 6678.
[425] Ranu, B.C.; Banerjee, S.; Adak, L. *Tetrahedron Lett.* ***2007****, 48*, 7374.
[426] See Russell, G.A. *Acc. Chem. Res.* ***1989****, 22*, 1; Larock, R.C. *Organomercury Compounds in Organic Synthesis* Springer, NY, ***1985***, pp. 240–248.
[427] Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* ***1977****, 42,* 1680; Larock, R.C.; Riefling, B. *J. Org. Chem.* ***1978****, 43*, 1468.
[428] Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Ya.L.; Spirikhin, L.V. *Synthesis* ***1989***, 633.
[429] Ghosal, S.; Luke, G.P.; Kyler, K.S. *J. Org. Chem.* ***1987****, 52*, 4296.
[430] Morizur, J. *Bull. Soc. Chim. Fr.* ***1964***, 1331.
[431] Larock, R.C.; Leach, D.R. *Organometallics* ***1982****, 1*, 74. Also see Larock, R.C.; Hershberger, S.S. *Tetrahedron Lett.* ***1981****, 22,* 2443.
[432] Studer, A.; Bossart, M.; Vasella, T. *Org. Lett.* ***2000****, 2*, 985.
[433] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 306–308.

carried out,[434] but with lower yields. Arylboranes react similarly, yielding biaryls.[435] The mechanism is probably of the free radical type.

Dimerization of two vinylborane units to give a conjugated diene can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see Reaction **15-16**) with methylcopper. (*E*,*E*)-1,3-Dienes are prepared in high yields.[436]



In a similar reaction, symmetrical conjugated diynes RC≡C—C≡CR can be prepared by reaction of lithium dialkyldialkynylborates, $Li^+ [R'_2B(C{\equiv}CR)_2]^-$, with iodine.[437]

14.C.iv. Halogen as Leaving Group

The conversion of RX to RH can occur by a free radical mechanism, but is treated at Reaction **19-53**.

14.C.v. Sulfur as Leaving Group

14-27 Desulfurization

Hydro-de-thio-substitution, and so on

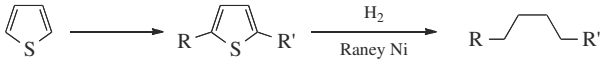
$$RSH \xrightarrow[Ni]{H_2} RH \qquad RSR' \xrightarrow[Ni]{H_2} RH + R'H$$

Thiols and thioethers,[438] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[439] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them disulfides (RSSR), thiono esters (RCSOR′),[440] thioamides (RCDNHR′), sulfoxides, and dithioacetals. The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see

[434] Brown, H.C.; Verbrugge, C.; Snyder, C.H. *J. Am. Chem. Soc.* ***1961****, 83,* 1001.
[435] Breuer, S.W.; Broster, F.A. *Tetrahedron Lett.* ***1972***, 2193.
[436] Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* ***1977****, 99*, 5652; *Bull. Chem. Soc. Jpn.* ***1977****, 50*, 3427. See Rao, V.V.R.; Kumar, C.V.; Devaprabhakara, D. *J. Organomet. Chem.* ***1979****, 179*, C7; Campbell, Jr., J.B.; Brown, H.C. *J. Org. Chem.* ***1980****, 45*, 549.
[437] Pelter, A.; Smith, K.; Tabata, M. *J. Chem. Soc., Chem. Commun.* ***1975***, 857; Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* ***1976***, 4385; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1976****, 41*, 1078.
[438] See Block, E. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.
[439] See Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962****, 12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962****, 62,* 347.
[440] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981****, 46,* 831.

Reaction **19-61**), can also give the alkene if a hydrogen atom is present.[441] In most of the examples given, R can also be aryl. Other reagents[442] have also been used,[443] including Sm in acetic acid for desulfurization of vinyl sulfones.[444]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene (see **39**), followed by reduction to the corresponding alkane.



43

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **43**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[445] It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[446] Phenyl selenides (RSePh) can be reduced to RH with Ph_3SnH[447] and with nickel boride.[448]

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free radical type.[449] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds; that is, the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.[450]

See Chapter 19 for other reduction reactions involving sulfur compounds.

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also, OS **VII**, 124, 476.

14-28 Conversion of Sulfides to Organolithium Compounds

Lithio-de-phenylthio-substitution

$$RSPh \xrightarrow[THF]{\text{Li naphthalenide}} RLi$$

Sulfides can be cleaved, with a phenylthio group replaced by a lithium,[451] by treatment with Li or lithium naphthalenide in THF.[452] Good yields have been obtained

[441] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963****, 28*, 1443.

[442] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed, Wiley–VCH, NY, ***1999***, pp. 53–60. See Luh, T.; Ni, Z. *Synthesis* ***1990***, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989****, 54,* 4848.

[443] See Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989****, 30*, 1277; Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989****, 54,* 4474.

[444] Liu, Y.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001****, 33*, 376.

[445] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972****, 2,* 415.

[446] Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 609.

[447] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* ***1978***, 41.

[448] Back, T.G. *J. Chem. Soc., Chem. Commun.* ***1984***, 1417.

[449] See Bonner, W.A.; Grimm, R.A. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. Also see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988****, 21*, 394.

[450] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962****, 40,* 941.

[451] See Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* ***1989****, 22*, 152.

[452] Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978****, 43*, 1064; ***1979****, 44*, 713.

with R = primary, secondary, or tertiary alkyl, or allylic,[453] and containing groups, such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α-lithio sulfide.[454] The reaction has also been used to prepare α-lithio ethers and α-lithio organosilanes.[451] For some of these compounds, lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.[455] The mechanism is presumably of the free radical type.

14.C.vi. Carbon as Leaving Group

14-29 Decarboxylative Dimerization: The Kolbe Reaction

De-carboxylic-coupling

$$2\,RCOO^- \xrightarrow{\text{electrolysis}} R{-}R$$

Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product R—R. This coupling reaction is called the *Kolbe Reaction* or the *Kolbe electrosynthesis*.[456] It is used to prepare symmetrical R—R, where R is straight chained, since little or no yield is obtained when there is a branching. The reaction is not successful for R = aryl. Many functional groups may be present, though many others inhibit the reaction.[456] Unsymmetrical R—R′ have been made by coupling mixtures of acid salts. The *Kolbe reaction* has been done using solid-supported bases.[457]

A free radical mechanism is involved

$$RCOO^- \xrightarrow[\text{oxidation}]{\text{electrolytic}} RCOO^\bullet \xrightarrow{-CO_2} R^\bullet \longrightarrow R{-}R$$

There is much evidence[458] for this mechanism, including side products (RH, alkenes) characteristic of free radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see Sec. 15.B.i). Other side products (ROH, RCO_2R) are sometimes found, stemming from further oxidation of the radical $R^\bullet$ to a carbocation R^+.[459]

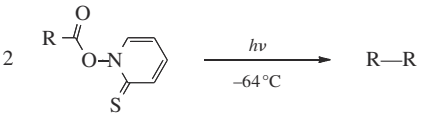
[453] See Cohen, T.; Guo, B. *Tetrahedron* ***1986****, 42,* 2803.
[454] See Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* ***1984****, 106*, 3245; Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 183.
[455] See Cohen, T.; Matz, J.R. *Synth. Commun.* ***1980****, 10,* 311.
[456] See Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. *Synthesis* ***1996***, 71; Schäfer, H.J. *Top. Curr. Chem.* ***1990****, 152,* 91; *Angew. Chem. Int. Ed.* ***1981****, 20,* 911; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed, Wiley, NY, ***1989***, pp. 238–253; Eberson, L.; Utley, J.H.P. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 435–462.
[457] Kurihara, H.; Fuchigami, T.; Tajima, T. *J. Org. Chem.* ***2008****, 73*, 6888.
[458] See Kraeutler, B.; Jaeger, C.D.; Bard, A.J. *J. Am. Chem. Soc.* ***1978****, 100*, 4903.
[459] See Corey, E.J.; Bauld, N.L.; La Londe, R.T.; Casanova Jr, J.; Kaiser, E.T. *J. Am. Chem. Soc.* ***1960****, 82,* 2645.

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:[460]

$$2\,RCOO^- + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow RCH_2CH{=}CHCH_2CH_2CH{=}CHCH_2R$$

The radical $R^\bullet$ adds to the conjugated system to give $RCH_2CH{=}CHCH_2^\bullet$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[461]

In a nonelectrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters (**44**) give dimers when irradiated at −64 °C in an Ar atmosphere:[462]



44

In another nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds ($2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$) by treatment with sodium persulfate ($Na_2S_2O_8$) and a catalytic amount of $AgNO_3$.[463] Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation.[464] Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls (Ar—Ar) by treatment with a disilane R_3SiSiR_3 and a Pd catalyst.[465]

OS **III**, 401; **V**, 445, 463; **VII**, 181.

14-30 The Hunsdiecker Reaction

Bromo-de-carboxylation

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*[466] and is a method of decreasing the length of a carbon chain by one unit.[467] The reaction is of wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not a substituted. The R group may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine, and iodine have also

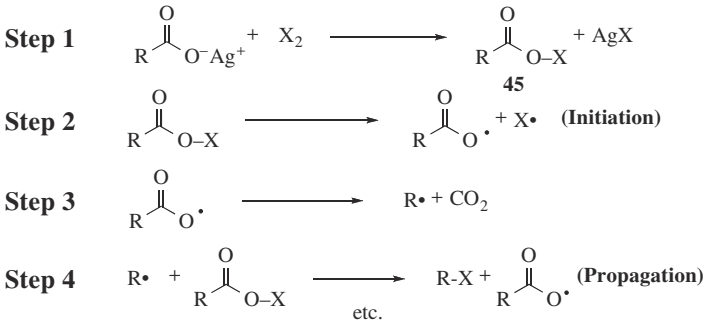
[460] Khrizolitova, M.A.; Mirkind, L.A.; Fioshin, M.Ya. *J. Org. Chem. USSR* ***1968****, 4,* 1640; Bruno, F.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1973***, 2270.
[461] See Schäfer, H.; Pistorius, R. *Angew. Chem. Int. Ed.* ***1972****, 11*, 841.
[462] Barton, D.H.R.; Bridon, D.; Fernandez-Picot, I.; Zard, S.Z. *Tetrahedron* ***1987****, 43,* 2733.
[463] Fristad, W.E.; Klang, J.A. *Tetrahedron Lett.* ***1983****, 24,* 2219.
[464] Habibi, M.H.; Farhadi, S. *Tetrahedron Lett.* ***1999****, 40*, 2821.
[465] Krafft, T.E.; Rich, J.D.; McDermott, P.J. *J. Org. Chem.* ***1990****, 55*, 5430.
[466] This reaction was first reported by the Russian composer–chemist Alexander Borodin: *Liebigs Ann. Chem.* ***1861****, 119,* 121.
[467] See Wilson, C.V. *Org. React.* ***1957****, 9*, 332; Johnson, R.G.; Ingham, R.K. *Chem. Rev.* ***1956****, 56*, 219. Also see, Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* ***1998****, 39*, 699.

been used. Catalytic Hunsdiecker reactions are known,[468] and microwave enhancement has been employed.[469]

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt/iodine gives the alkyl halide, as above. A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini Reaction* and is sometimes used to prepare carboxylic esters. The *Simonini reaction* can also be carried out with lead salts of acids.[470] A more convenient way to perform the *Hunsdiecker Reaction* is by use of a mixture of the acid and mercuric oxide instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.[471]

Other methods for accomplishing the conversion RCOOH → RX are[472] (1) treatment of thallium(I) carboxylates with bromine;[473] (2) treatment of carboxylic acids with lead tetraacetate and halide *ions* (Cl^-, Br^-, or I^-);[474] (3) reaction of the acids with lead tetraacetate and NCS, which gives tertiary and secondary chlorides in good yields, but is not good for R = primary alkyl or phenyl;[475] (4) treatment of thiohydroxamic esters with CCl_4, $BrCCl_3$ (which gives bromination), CHI_3, or CH_2I_2 in the presence of a radical initiator;[476] (5) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($RCON{=}CPh_2 \rightarrow RCl$).[477] Alkyl fluorides can be prepared in moderate-to-good yields by treating carboxylic acids (RCOOH) with XeF_2.[478] This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

The mechanism of the *Hunsdiecker reaction* is believed to be as follows:



[468] Das, J.P.; Roy, S. *J. Org. Chem.* ***2002****, 67,* 7861.
[469] Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* ***2005***, 1319.
[470] Bachman, G.B.; Kite, G.F.; Tuccarbasu, S.; Tullman, G.M. *J. Org. Chem.* ***1970****, 35,* 3167.
[471] Cristol, S.J.; Firth, W.C. *J. Org. Chem.* ***1961****, 26*, 280. See also, Meyers, A.I.; Fleming, M.P. *J. Org. Chem.* ***1979****, 44,* 3405, and references cited therein.
[472] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed, Wiley-VCH, NY, ***1999***, pp. 741–744.
[473] Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2608.
[474] Kochi, J.K. *J. Am. Chem. Soc.* ***1965****, 87,* 2500; *J. Org. Chem.* ***1965****, 30,* 3265; Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972****, 19*, 279, pp. 326–334, 390–399.
[475] Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhnen, F. *Synthesis* ***1973***, 493.
[476] Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* ***1987****, 43*, 4321; Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* ***1987****, 96*, 623; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* ***1989****, 42,* 61.
[477] Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* ***1988****, 29,* 6287.
[478] Patrick, T.B.; Johri, K.K.; White, D.H.; Bertrand, W.S.; Mokhtar, R.; Kilbourn, M.R.; Welch, M.J. *Can. J. Chem.* ***1986****, 64*, 138. For another method, see Grakauskas, V. *J. Org. Chem.* ***1969****, 34,* 2446.

The first step is not a free radical process, and its actual mechanism is not known.[479] Compound **45** is an acyl hypohalite and is presumed to be an intermediate, though it has never been isolated from the reaction mixture. Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, see Sec. 14.A.iv); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably R-R, are consistent with a free radical mechanism. There is evidence that the *Simonini reaction* involves the same mechanism as the *Hunsdiecker reaction*, but that the alkyl halide formed then reacts with excess RCOOAg (Reaction **10-17**) to give the ester[480] (see also, Reaction **19-12**).

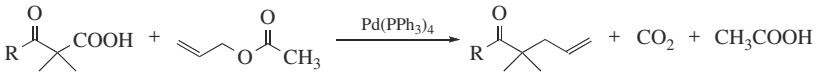
Vinyl carboxylic acids (conjugated acids) were shown to react with NBS and lithium acetate in aq acetonitrile, to give the corresponding vinyl bromide (C=C—CO_2H → C=C—Br), using microwave irradiation.[481] A similar reaction was reported using Na_2MoO_4, KBr and aq H_2O_2.[482]

A related reaction reacts the sodium salt of an alkylsulfonic acid with thionyl chloride at 100 °C, to give the alkyl chloride.[483]

OS **III**, 578; **V**, 126; **VI**, 179; **75**, 124; **X**, 237. See also, OS **VI**, 403.

14-31 Decarboxylative Allylation

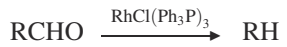
Allyl-de-carboxylation



The COOH group of a β-keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a Pd catalyst at room temperature.[484] The reaction is successful for various substituted allylic groups. The less highly substituted end of the allylic group forms the new bond. Thus, both CH_2=CHCHMeOAc and MeCH=CH-CH_2OAc gave O=C(R)-C-CH_2CH—CHMe as the product.

14-32 Decarbonylation of Aldehydes and Acyl Halides

Carbonyl-extrusion



Aldehydes, both aliphatic and aromatic, can be decarbonylated[485] by heating with a Rh catalyst[486] or other catalysts (e.g., Pd).[487] The compound $RhCl(Ph_3P)_3$ is often called

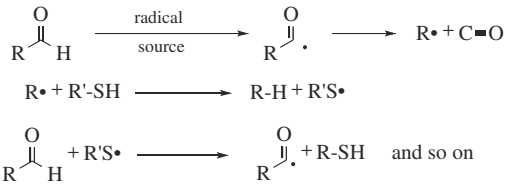
[479] When Br_2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br_2 and the silver carboxylate: see Bryce-Smith, D.; Isaacs, N.S.; Tumi, S.O. *Chem. Lett.* ***1984***, 1471.
[480] Bunce, N.J.; Murray, N.G. *Tetrahedron* ***1971***, *27*, 5323.
[481] Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* ***2000***, 1439.
[482] Sinha, J.; Layek, S.; Bhattacharjee, M.; Mandal, G.C. *Chem. Commun.* ***2001***, 1916.
[483] Carlsen, P.H.J.; Rist, Ø.; Lund, T.; Helland, I. *Acta Chem. Scand. B* ***1995***, *49*, 701.
[484] Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* ***1986***, *51*, 421.
[485] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 768–775; Baird, M.C. in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, ***1979***, pp. 825–857; Tsuji, J. in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 595–654; Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 239–247.
[486] Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* ***1968***, *90*, 99; Baird, C.W.; Nyman, C.J.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 348.
[487] Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 260–267.

Wilkinson's catalyst.[488] In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*tert*-butyl peroxide or other peroxides,[489] usually in a solution containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at ~500 °C.

Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180 °C (ArCOX → ArX).[490] This reaction has been carried out with acyl iodides,[491] bromides, and chlorides. Aliphatic acyl halides that lack a hydrogen also give this reaction,[492] but if an α hydrogen is present, elimination takes place instead (Reaction **17-17**). Aromatic acyl cyanides give aryl cyanides (ArCOCN → ArCN).[493] Aromatic acyl chlorides and cyanides can also be decarbonylated with Pd catalysts.[494]

It is possible to decarbonylate acyl halides in another way, to give alkanes (RCOCl → RH). This is done by heating the substrate with tripropylsilane (Pr_3SiH) in the presence of *tert*-butyl peroxide.[495] Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl. (See also, the decarbonylation ArCOCl → Ar—Ar mentioned in Reaction **14-29**.)

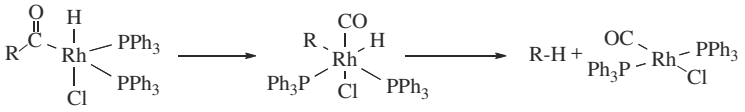
The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of thiols).[496]



The reaction of aldehydes with *Wilkinson's catalyst* goes through complexes of the form **46** and **47**, which have been trapped.[497] The reaction has been shown to give retention of configuration at a chiral R;[498] and deuterium labeling demonstrates that the reaction is

[488] For a review of this catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981****, 28,* 63.
[489] See Vinogradov, M.G.; Nikishin, G.I. *Russ. Chem. Rev.* ***1971****, 40,* 916; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group,* Vol. 1, Wiley, NY, ***1966***, pp. 711–735.
[490] Kampmeier, J.A.; Rodehorst, R.; Philip Jr., J.B. *J. Am. Chem. Soc.* ***1981****, 103,* 1847.
[491] Blum, J.; Rosenman, H.; Bergmann, E.D. *J. Org. Chem.* ***1968****, 33,* 1928.
[492] Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1966***, 4713; *J. Am. Chem. Soc.* ***1966****, 88,* 3452.
[493] Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* ***1967****, 89*, 2338.
[494] Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* ***1986****, 51,* 898.
[495] Billingham, N.C.; Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1137.
[496] Berman, J.D.; Stanley, J.H.; Sherman, V.W.; Cohen, S.G. *J. Am. Chem. Soc.* ***1963****, 85,* 4010. See Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* ***2008****, 130,* 5206.
[497] Kampmeier, J.A.; Harris, S.H.; Mergelsberg, I. *J. Org. Chem.* ***1984****, 49,* 621.
[498] Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* ***1971****, 93,* 5465. See also, Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1967***, 2173.

intramolecular: RCOD give RD.[499] Free radicals are not involved.[500] The mechanism with acyl halides appears to be more complicated.[501]



46 **47**

For aldehyde decarbonylation by an electrophilic mechanism, see Reaction **11-34**.

[499] Walborsky, H.M.; Allen, L.E. *J. Am Chem. Soc.* ***1971****, 93*, 5465. See, however, Baldwin, J.E.; Bardenm, T.C.; Pugh, R.L.; Widdison, W.C. *J. Org. Chem.* ***1987****, 52,* 3303.
[500] Kampmeier, J.A.; Harris, S.H.; Wedegaertner, D.K. *J. Org. Chem.* ***1980****, 45*, 315.
[501] Kampmeier, J.A.; Liu, T. *Organometallics* ***1989****, 8*, 2742

CHAPTER 15

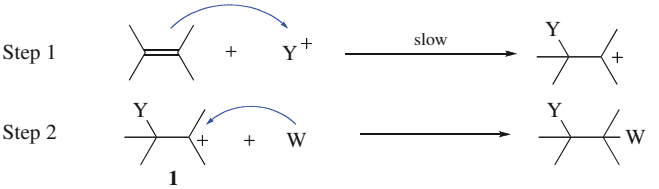
Addition to Carbon–Carbon Multiple Bonds

There are four fundamental ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, or attack upon an electrophile or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous (concerted). Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types.

15.A. MECHANISMS

15.A.i. Electrophilic Addition[1]

In this mechanism, a positive species approaches the double or triple bond and in the first step forms a bond by donation of the π pair of electrons[2] to the electrophilic species to form a σ bond:



1

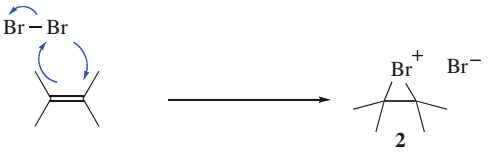
The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $Y^+ = H^+$). As in electrophilic substitution (Sec. 11.A.i), Y need not actually be a positive ion, but can be the

[1] See de la Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed., Elsevier, NY, ***1982***. For reviews, see Schmid, G.H. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 679–731; Schmid, G.H.; Garratt, D.G. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 1, pt. 2, Wiley, NY, ***1977***, pp. 725–912; Freeman, F. *Chem. Rev.* ***1975***, *75*, 439.

[2] See Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* ***2003***, *36*, 66.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

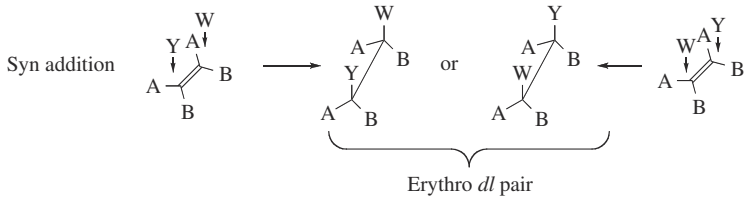
positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. The second step is a combination of **1** with a species carrying an electron pair and often bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. Not all electrophilic additions follow the simple mechanism given above. In many bromination reactions it is fairly certain that **1**, if formed at all, very rapidly cyclizes to a bromonium ion (**2**):



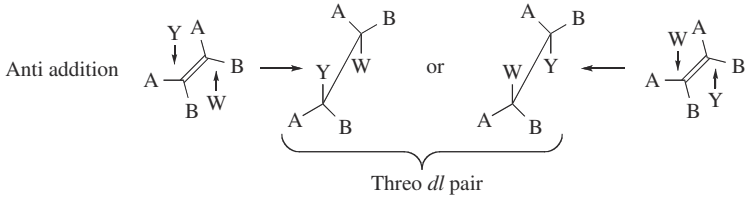
2

This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see Sec. 10.C). The attack of W: on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called Ad_E2 (electrophilic addition, bimolecular).

The most useful type of information for investigating the mechanism of addition to a double bond, is perhaps, the stereochemistry of the reaction.[3] The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (Sec. 1.D); there are thus three possibilities. Both Y and W may enter from the same side of the plane, in which case the addition is stereospecific and syn; they may enter from opposite sides for stereospecific anti addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the cis and trans isomers of an alkene of the form ABC=CBA. Using the *cis*-alkene as an example, if the addition is syn, the product will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y:



On the other hand, if the addition is anti, the threo *dl* pair will be formed:

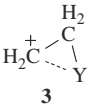


Of course, the trans isomer will give the opposite results: the threo pair if the addition is syn and the erythro pair if it is anti. These diastereomers have different physical properties. In the special case, where Y = W (as in the addition of Br_2), the "erythro pair" is a meso

[3] See Fahey, R.C. *Top. Stereochem.* ***1968****, 3,* 237; Bartlett, P.A. *Tetrahedron* ***1980****, 36,* 2, pp. 3–15.

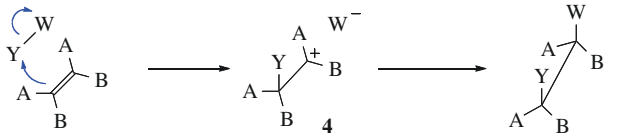
compound. In addition to triple-bond compounds of the type AC≡CA, syn addition results in a *cis*-alkene and anti addition in a *trans*-alkene. By the definition given in Section 4.N, addition to triple bonds cannot be stereospecific, although it can be, and often is, stereoselective.

It is easily seen that in reactions involving cyclic intermediates like **2**, addition must be anti, since the second step is an S_N2 step and must occur from the rear. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. In addition, the carbocation is planar, so there is no facial bias for nucleophilic attack. On the other hand, if there is some factor that maintains the configuration, the group W may come in from the same *or* the opposite side, depending on the circumstances. For example, the positive charge might be stabilized by an attraction for Y that does not involve a full bond (see **3**). In such a case, Y is said to stabilize the positive center via back-donation.



3

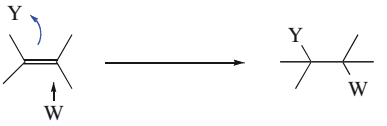
Such stabilization usually leads to anti attack of the second group. This contrasts with a circumstance that would favor syn addition: Formation of an ion pair (**4**) after the addition of Y[4]:



4

Since W is already on the same side of the plane as Y, collapse of the ion pair leads to syn addition.

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially *simultaneous*, but from opposite sides:

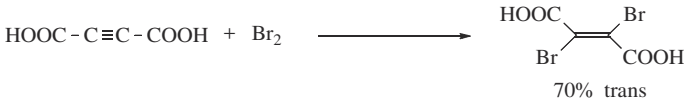


This mechanism, called the Ad_E3 mechanism (*termolecular addition*, IUPAC A_NA_E),[5] has the disadvantage that three molecules must come together in the transition state. Note that it is the reverse of the E2 mechanism for elimination, for which the transition state is known to possess this geometry (Sec. 17.A.i).

[4] Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980****, 45*, 5150.

[5] See Roberts, R.M.G. *J. Chem. Soc. Perkin Trans. 2,* ***1976***, 1374; Pasto, D.J.; Gadberry, J.F. *J. Am. Chem. Soc.* ***1978****, 100*, 1469; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978****, 111*, 2982.

There is much evidence that when an alkene attacks Br^+ (or a carrier of it), bromonium ion **2** is usually the intermediate and the addition is anti, so the reaction is diastereospecific. Such ions have also been isolated in reactions involving addition of a Br^+ species to a double bond.[6] Treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, for example, while fumaric acid (the trans isomer) gave the meso compound.[7] Many similar experiments have been performed with similar results. Bromination of dicarboxyacetylene gave 70% of the trans isomer.[8]



70% trans

There is other evidence for mechanisms involving **2**. As seen in Section 10.C, bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.[9] Similar results are found when the reaction is carried out in the presence of water (Reaction **15-40**) or of other nucleophiles.[10] *Ab initio* MO studies show that **2** is more stable than its open isomer **1** (Y = Br).[11] There is evidence that formation of **2** is reversible.[12]

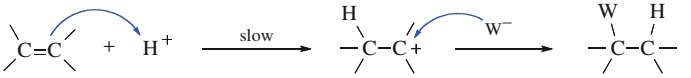
However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.[13] Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90–100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until at a dielectric constant of ~35, the addition was completely nonstereospecific.[14] Likewise in the case of triple bonds, stereoselective anti addition was found in bromination of 3-hexyne, but both cis and trans products were obtained in bromination of phenylacetylene.[15] These results indicate that a bromonium ion

[6] Slebocka-Tilk, H.; Ball, R.G.; Brown, R.S. *J. Am. Chem. Soc.* ***1985****, 107*, 4504.
[7] Fischer, E. *Liebigs Ann. Chem.* ***1911****, 386,* 374; McKenzie, A. *Proc. Chem. Soc.* ***1911***, 150; *J. Chem. Soc.* ***1912****, 101,* 1196.
[8] Michael, A. *J. Prakt. Chem.* ***1892****, 46*, 209.
[9] Francis, A.W. *J. Am. Chem. Soc.* ***1925****, 47,* 2340.
[10] See Zefirov, N.S.; Koz'min, A.S.; Dan'kov, Yu.V.; Zhdankin, V.V.; Kirin, V.N. *J. Org. Chem. USSR* ***1984****, 20,* 205.
[11] Hamilton, T.P.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1990****, 112,* 8260.
[12] Ruasse, M.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* ***1991****, 113*, 3440; Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1991****, 113,* 8012; Bennet, A.J.; Brown, R.S.; McClung, R.E.D.; Klobukowski, M.; Aarts, G.H.M.; Santarsiero, B.D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* ***1991****, 113*, 8532.
[13] Fahey, R.C.; Schneider, H. *J. Am. Chem. Soc.* ***1968****, 90,* 4429. See also, Rolston, J.H.; Yates, K. *J. Am. Chem. Soc.* ***1969****, 91,* 1469, 1477, 1483.
[14] Ruasse, M.; Dubois, J.E. *J. Am. Chem. Soc.* ***1975****, 97,* 1977; Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* ***1990****, 55,* 4094.
[15] Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970****, 48,* 3332.

is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $PhC^+HCHBrCH_3$, which is a relatively stable benzylic cation). In addition, there is probably a spectrum of mechanisms between complete bromonium ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.[16] Previously seen cases (Sec. 10.C.i, category 4) showed that cations require more stabilization from outside sources as they become intrinsically less stable themselves.[17] Further evidence for the open cation mechanism where aryl stabilization is present was reported in an isotope effect study of Br_2 addition to $ArCH{=}CHCHAr'$ ($Ar = p$-nitrophenyl, $Ar' = p$-tolyl). The ^{14}C isotope effect for one of the double-bond carbons (the one closer to the NO_2 group) was considerably larger than for the other one.[18]

When the π bond of an alkene attacks Cl^+,[19] I^+,[20] or RS^+,[21] the result is similar to that when the electrophile is Br^+; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from the discussion in Section 10.C, iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is kinetic and spectral evidence that at least in some cases (e.g., in the addition of Br_2 or ICl), the electrophile forms a π complex with the alkene before a covalent bond is formed.[22] There is evidence for β-chloro and β-bromocarbenium ions in some reactions.[23]

When the electrophile is a proton,[24] a cyclic intermediate is not possible, and the mechanism is the simple $A_H + A_N$ process shown before



This is an A-S_E2 mechanism (see Reaction **10-6**). There is a great deal of evidence[25] for it, including:

1. The reaction is general acid, not specific acid catalyzed, implying rate-determining proton transfer from the acid to the double bond.[26]

[16] Cadogan, J.I.G.; Cameron D.K.; Gosney, I.; Highcock, R.M.; Newlands, S.F. *J. Chem. Soc., Chem. Commun.* ***1985***, 1751. For a review, see Ruasse, M. *Acc. Chem. Res.* ***1990****, 23,* 87.

[17] See Naae, D.G. *J. Org. Chem.* ***1980****, 45*, 1394.

[18] Kokil, P.B.; Fry, A. *Tetrahedron Lett.* ***1986****, 27*, 5051.

[19] Fahey, R.C. *Top. Stereochem.* ***1968****, 3,* 237, pp. 273–277.

[20] Hassner, A.; Boerwinkle, F.; Levy, A.B. *J. Am. Chem. Soc.* ***1970****, 92,* 4879.

[21] Capozzi, G.; Modena, G. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 246–298; Dittmer, D.C.; Patwardhan, B.H. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 387–412; Capozzi, G.; Lucchini, V.; Modena, G.; *Rev. Chem. Intermed.* ***1979****, 2,* 347; Schmid, G.H. *Top. Sulfur Chem.* ***1977****, 3,* 102; Mueller, W.H. *Angew. Chem. Int. Ed.* ***1969****, 8,* 482. The specific nature of the three-membered sulfur-containing ring is in dispute; see Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V.; Krimer, M.Z. *Acc. Chem. Res.* ***1979****, 12*, 282; Schmid, G.H.; Garratt, D.G.; Dean, C.L. *Can. J. Chem.* ***1987****, 65*, 1172; Schmid, G.H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* ***1987****, 65,* 1945.

[22] See Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1989****, 111*, 2640.

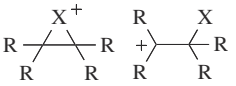
[23] Ohta, B.K.; Hough, R.E.; Jeffrey W.; Schubert, J.W. *Org. Lett.* ***2007****, 9,* 2317.

[24] See Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N. *Russ. Chem. Rev.* ***1983****, 52,* 259.

[25] Also see Hampel, M.; Just, G.; Pisanenko, D.A.; Pritzkow, W. *J. Prakt. Chem.* ***1976****, 318*, 930; Allen, A.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1983****, 104,* 3145.

[26] Schubert, W.M.; Keeffe, J.R. *J. Am. Chem. Soc.* ***1972****, 94,* 559; Chiang, Y.; Kresge, A.J. *J. Am. Chem. Soc.* ***1985****, 107*, 6363.

2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects[27] with that found in brominations, where cyclic intermediates are involved. In the latter case, substitution of alkyl groups on $H_2C{=}CH_2$ causes a cumulative rate acceleration

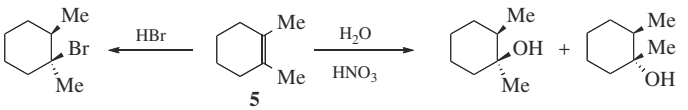


until all four hydrogen atoms have been replaced by alkyl groups, because each group helps to stabilize the positive charge.[28] In addition of HX, the effect is not cumulative. Replacement of the two hydrogen atoms on one carbon causes great rate increases (primary → secondary → tertiary carbocation), but additional substitution on the other carbon produces little or no acceleration.[29] This is evidence for open cations when a proton is the electrophile.[30]

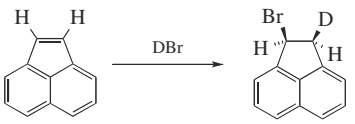
3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H_2O.[31]

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see Reaction **10-6**).

The stereochemistry of HX addition is varied. Examples are known of predominant syn, anti, and nonstereoselective addition. It was found that treatment of 1,2-dimethylcyclohexene (**5**) with HBr gave predominant anti addition,[32] while addition of water to **5** gave equal amounts of the cis and trans alcohols:[33]



On the other hand, addition of DBr to acenaphthylene and to indene and 1-phenylpropene gave predominant syn addition, as shown:[34]

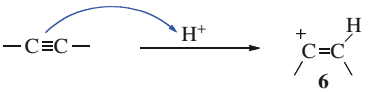


In fact, it has been shown that changing the reaction conditions can control the stereoselectivity of HCl addition. Addition of HCl to **5** in CH_2Cl_2 at −98 °C

[27] Schmid, G.H.; Garratt, D.G. *Can. J. Chem.* ***1973****, 51*, 2463.
[28] See Anantakrishnan, S.V.; Ingold, C.K. *J. Chem. Soc.* ***1935***, 1396; Swern, D. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 451–454; Nowlan, V.J.; Tidwell, T.T. *Acc. Chem. Res.* ***1977****, 10,* 252.
[29] See Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965****, 87,* 1297 and are references cited therein.
[30] See Mayr, H.; Pock, R. *Chem. Ber.* ***1986****, 119,* 2473.
[31] See Stammann, G.; Griesbaum, K. *Chem. Ber.* ***1980****, 113,* 598.
[32] Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* ***1954****, 76*, 4121; See also, Pasto, D.J.; Meyer, G.R.; Lepeska, B. *J. Am. Chem. Soc.* ***1974****, 96*, 1858.
[33] Collins, C.H.; Hammond, G.S. *J. Org. Chem.* ***1960****, 25,* 911.
[34] See Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980****, 45*, 5150.

gave predominantly syn addition, while in ethyl ether at 0 °C, the addition was mostly anti.[35]

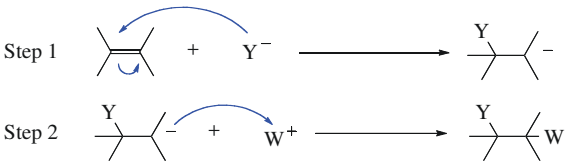
Addition of HX to triple bonds has the same mechanism, although the intermediate in this case is a vinylic cation (**6**).[36]



In all these cases (except for the Ad_E3 mechanism), it was assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate is rapid. This finding is probably true in most cases. However, some additions have been found in which the second step is rate determining.[37]

15.A.ii. Nucleophilic Addition[38]

In the first step of nucleophilic addition, a nucleophile donates a pair of electrons to one carbon atom of the double or triple bond, creating a carbanion, which reacts with a positive species in the second step:



This mechanism is the same as the simple electrophilic one shown in Section 15.A.i except that the charges are reversed (IUPAC $A_N + A_E$ or $A_N + A_H$). When the alkene contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, see Sec. 10.F).

In the special case of addition of HY to a substrate of the form —C=C—Z, where Z = CHO, COR[39] (including quinones[40]), CO_2R, $CONH_2$, CN, NO_2, SOR, 2R,[41] and so on, addition nearly always follows a nucleophilic mechanism,[42] with Y^- bonding with the carbon *away* from the Z group, for example,

[35] Becker, K.B.; Grob, C.A. *Synthesis* ***1973***, 789. See also, Marcuzzi, F.; Melloni, G.; Modena, G. *Tetrahedron Lett.* ***1974***, 413; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978****, 111*, 2982.

[36] See Rappoport, Z. *React. Intermed. (Plenum)* ***1983****, 3*, 427, pp. 428–440; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 24–151; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973****, 10*, 205; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971****, 9,* 185, pp. 187–231.

[37] See Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett.* ***1973***, 3911.

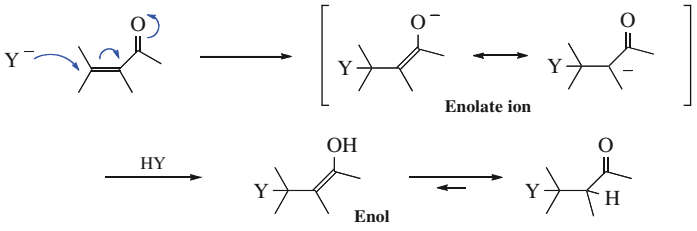
[38] Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 469–584.

[39] See in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, the articles by Boyd, G.V. pp. 281–315; Duval, D.; Géribaldi, S. pp. 355–469.

[40] See Kutyrev, A.A.; Moskva, V.V. *Russ. Chem. Rev.* ***1991****, 60*, 72; Finley, K.T. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 537–717, see pp. 539–589; Finley, K.T. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 2, Wiley, NY, ***1974***, pp. 877–1144.

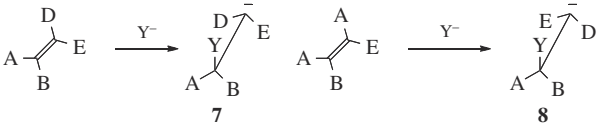
[41] See Simpkins, N.S. *Tetrahedron* ***1990****, 46*, 6951; Fuchs, P.L.; Braish, T.F. *Chem. Rev.* ***1986****, 86*, 903.

[42] See Bernasconi, C.F. *Tetrahedron* ***1989****, 45*, 4017.



After the reaction with HY, the product is a resonance-stabilized enolate anion. Subsequent protonation of the enolate ion is probably at the oxygen to give an enol, which tautomerizes to the ketone (Sec. 2.N.i). Although the net result of the reaction is addition to a carbon–carbon double bond, the *mechanism* is 1,4-nucleophilic addition to the C=C—C=O (or similar) system and is thus very similar to the mechanism of addition to carbon–oxygen double and similar bonds (see Chapter 16). This mechanism is essentially that of the *Michael reaction* discussed in Reaction **15-24**, and such reactions are often called *Michael reactions* or *Michael-type reactions*. When Z is CN or a C=O group, it is also possible for Y^- to attack C of the cyano or carbonyl, which sometimes competes. When it happens, it is called 1,2-addition (see nucleophilic acyl addition in Chapter 16). 1,4-Addition to these substrates is also known as *conjugate addition*. Attack of the Y^- ion at the 3 position is very difficult, since the resulting carbanion would have no resonance stabilization.[43] Systems of the type C=C—C=C—Z can give 1,2-, 1,4-, or 1,6-addition.[44] *Michael-type reaction*s are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to YH and CH_2=CHZ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined above for an alkene, the addition should be nonstereospecific, although it might well be stereoselective (see Sec. 4.N for the distinction). For example, the (*E*) and (*Z*) forms of an alkene ABC=CDE would give **7** and **8**. If the carbanion has



7 **8**

even a short lifetime, **7** and **8** will assume the most favorable conformation before the reaction with W. This is of course the same for both, and reaction with W will give the same product. This will be one of two possible diastereomers, so the reaction will be diastereoselective; but since the cis and trans isomers do not give rise to different isomers, it will not be diastereospecific. Unfortunately, this prediction has not been tested on open-chain alkenes. Except for *Michael-type substrates*, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the cis isomer exists. In these cases, the reaction has been shown to be stereoselective, with syn addition reported in some cases[45] and anti addition in others.[46] When the reaction is performed on a *Michael-type substrate* (C=C—Z) the hydrogen does not arrive at the carbon directly, but only

[43] See Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* ***1988****, 345,* 239.

[44] See, however, Klumpp, G.W.; Mierop, A.J.C.; Vrielink, J.J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* ***1985****, 107,* 6740.

[45] Truce, W.E.; Levy, A.J. *J. Org. Chem.* ***1963****, 28,* 679.

[46] Truce, W.E.; Levy, A.J. *J. Am. Chem. Soc.* ***1961****, 83,* 4641; Zefirov, N.S.; Yur'ev, Yu.K.; Prikazchikova, L.P.; Bykhovskaya, M.Sh. *J. Gen. Chem. USSR* ***1963****, 33*, 2100.

through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of Y. In one such case (the addition of EtOD and of Me_3CSD to *trans*-MeCH=CHCOOEt), predominant anti addition was found. There is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.[47] For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and anti,[48] although syn addition[49] and nonstereoselective addition[50] have also been reported.

15.A.iii. Free Radical Addition

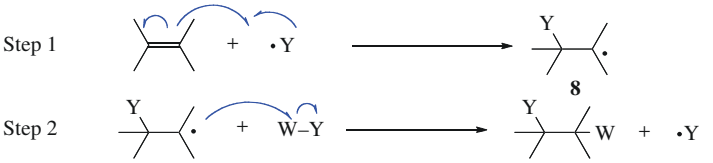
The mechanism of free radical addition[51] follows the pattern discussed in Section 14.A.i. The method of principal component analysis has been used to analyze polar and enthalpic effects in radical addition reactions.[52] A radical is generated by

$$Y-W \xrightarrow[\text{dissociation}]{h\nu \text{ or spontaneous}} Y^{\bullet} + W^{\bullet}$$

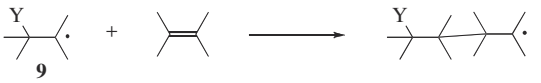
or

$$R^{\bullet} \quad (\text{from some other source}) + YW \longrightarrow RW + Y^{\bullet}$$

For subsequent reaction with an alkene, propagation occurs by

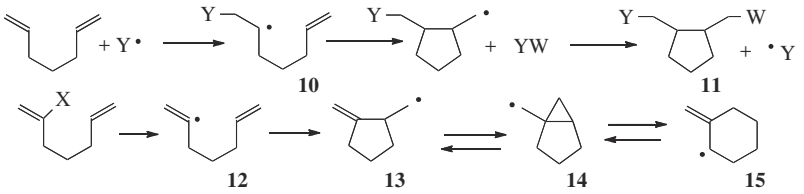


Step 2 is an abstraction (an atom transfer), so W is nearly always univalent, either hydrogen or halogen (Sec. 14.B.i). Termination of the chain can occur in any of the ways discussed in Section 14.A.i. If **9** adds to another alkene molecule, a dimer is formed. This can add to still another alkene unit, and chains, long or short, may be built up. This is the mechanism of free radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free radical addition reactions.



[47] Mohrig, J.R.; Fu, S.S.; King, R.W.; Warnet, R.; Gustafson, G. *J. Am. Chem. Soc.* ***1990****, 112,* 3665.
[48] See Truce, W.E.; Tichenor, G.J.W. *J. Org. Chem.* ***1972****, 37*, 2391.
[49] Hayakawa, K.; Kamikawaji, Y.; Wakita, A.; Kanematsu, K. *J. Org. Chem.* ***1984****, 49,* 1985.
[50] Truce, W.E.; Brady, D.G. *J. Org. Chem.* ***1966****, 31*, 3543; Prilezhaeva, E.N.; Vasil'ev, G.S.; Mikhaleshvili, I.L.; Bogdanov, V.S. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1970***, 1820.
[51] Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry* Cambridge University Press, London, ***1974***; Pyor, W.A. *Free Radicals* McGraw-Hill, NY, ***1965***. See Giese, B. *Rev. Chem. Intermed.* ***1986****, 7,* 3; *Angew. Chem. Int. Ed.* ***1983****, 22*, 753; Abell, P.I. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 63–112; Minisci, F. *Acc. Chem. Res.* ***1975****, 8*, 165.
[52] Héberger, K.; Lopata, A. *J. Chem. Soc. Perkin Trans. 2,* ***1995***, 91.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical (**10**) can add intramolecularly to the other bond, leading to a cyclic product (**11**).[53] When the radical is generated from a precursor that gives vinyl radical **12**, however, cyclization leads to **13**, which is in equilibrium with cyclopropylcarbinyl radical **14** via a 5-exo-trig reaction.[54] A 6-endo-trig reaction (Sec. 6.E) leads to **15**, but unless there are perturbing substituent effects, cyclopropanation should be the major process. Radicals of type **10**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed (Sec. 15.B.i).



The free radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **9** has any, but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed above for nucleophilic addition to alkenes. A few free radical additions are selective. For example, addition of HBr to 1-bromocyclohexene is regioselective in that it gave only *cis*-1,2-dibromocyclohexane and none of the trans isomer (anti addition),[55] and propyne (at −78 to −60 °C) gave only *cis*-1-bromopropene (anti addition), making it stereoselective.[56] Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a trans-ring closure.[57] The most important case is probably addition of HBr to 2-bromo-2-butene under free radical conditions at −80 °C. Under these conditions, the cis isomer gave 92% of the meso product, while the trans isomer gave mostly the *dl* pair.[58] This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products (∼78% of the *dl* pair and 22% of the meso compound), so the addition was still stereoselective, but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned in Section 14.A.iv:



This species is similar to the bromonium ion (**2**) that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged

[53] RajanBabu, T.V. *Acc. Chem. Res.* ***1991****, 24,* 139; Beckwith, A.L.J. Rev. *Chem. Intermed.* ***1986****, 7,* 143; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds,* Pergamon, Elmsford, NY, ***1986***, pp. 141–209; Surzur, J. *React. Intermed. (Plenum)* ***1982****, 2,* 121–295; Julia, M. Acc. *Chem. Res.* ***1972****, 4,* 386; *Pure Appl. Chem.* ***1974****, 40,* 553; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* ***1990****, 46,* 1385.

[54] Denis, R.C.; Rancourt, J.; Ghiro, E.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* ***1993****, 34*, 2091.

[55] Goering, H.L.; Abell, P.I.; Aycock, B.F. *J. Am. Chem. Soc.* ***1952****, 74,* 3588. See also, LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969****, 34,* 3112.

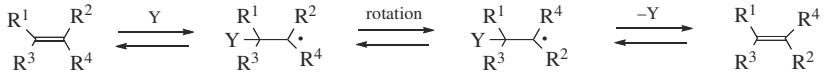
[56] Skell, P.S.; Allen, R.G. *J. Am. Chem. Soc.* ***1958****, 80*, 5997.

[57] Ogura, K.; Kayano, A.; Fujino, T.; Sumitani, N.; Fujita, M. *Tetrahedron Lett.* ***1993****, 34*, 8313.

[58] Goering, H.L.; Larsen, D.W. *J. Am. Chem. Soc.* ***1959****, 81*, 5937. Also see, Skell, P.S.; Freeman, P.K. *J. Org. Chem.* ***1964****, 29,* 2524.

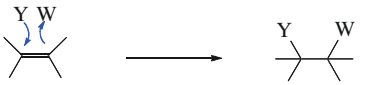
radicals was obtained by addition of $Br^{\bullet}$ to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.[59]

For many radicals, step 1 ($C{=}C + Y^{\bullet} \rightarrow {}^{\bullet}C{-}C{-}Y$) is reversible. In such cases free radicals can cause cis → trans isomerization of a double bond by the pathway[60]



15.A.iv. Cyclic Mechanisms

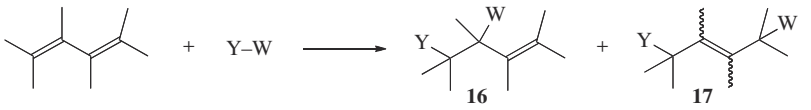
There are some addition reactions where the initial reaction is not at one carbon of the double bond, but both carbons react simultaneously. Some of these are four-center mechanisms, which follow the following pattern:



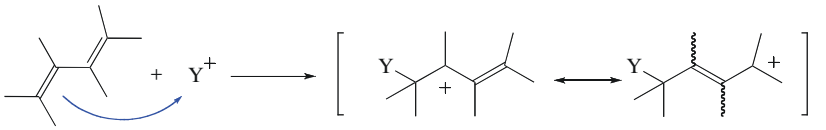
In others, there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be syn. The most important reaction of this type is the *Diels–Alder reaction* (**15-60**).

15.A.v. Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (**16**) is often obtained, but in most cases there is also a 1,4-addition product (**17**), often in larger yield:[61]



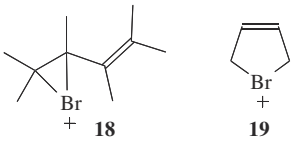
If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from attack on Y^+ is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



W^- may then be attacked by either position. The original reaction with Y^+ is always at the end of the conjugated system because reaction at a middle carbon would give a cation unstabilized by resonance. In the case of electrophiles like Br^+, which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an

[59] Abell, P.I.; Piette, L.H. *J. Am. Chem. Soc.* ***1962****, 84,* 916. See also, Leggett, T.L.; Kennerly, R.E.; Kohl, D.A. *J. Chem. Phys.* ***1974****, 60*, 3264.
[60] Golden, D.M.; Furuyama, S.; Benson, S.W. *Int. J. Chem. Kinet.* ***1969****, 1,* 57.
[61] Khristov, V.Kh.; Angelov, Kh.M.; Petrov, A.A. *Russ. Chem. Rev.* ***1991****, 60,* 39.

intermediate like **18**. Direct nucleophilic attack by W^- would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an S_N2'-type mechanism (see Sec. 10.E). Intermediates like **19** have been postulated, but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4-products.[62] If an ion like **19** were the intermediate, the 1,4-products would have to have the cis configuration.

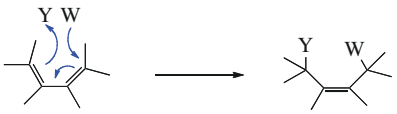


18 **19**

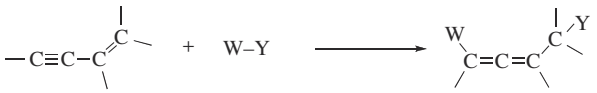
In most cases, more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic, and usually temperature dependent. In most cases, under the reaction conditions, **16** is converted to a mixture of **16** and **17** that is richer in **17**. That is, either isomer gives the same mixture of both, which contains more **17**. It was found that at low temperatures, butadiene and HCl gave only 20–25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.[63] 1,2-Addition predominated over 1,4- in the reaction between DCl and 1,3-pentadiene, where the intermediate was symmetrical (except for the D label).[64] Ion pairs were invoked to explain this result, since Cl^- would attack a free ion equally well at both positions, except for the very small isotope effect.



Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case, there is competition between 1,2- and 1,4-addition. In the case of nucleophilic or free radical attack,[65] the intermediates are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes can similarly give 1,4-addition by a cyclic mechanism:



Other conjugated systems, including trienes, enynes, diynes, and so on, have been studied much less but behave similarly. 1,4-Addition to enynes is an important way of making allenes:



Radical addition to conjugated systems is an important part of chain-propagation reactions. The rate constants for addition of cyclohexyl radical to conjugated amides

[62] Mislow, K. *J. Am. Chem. Soc.* ***1953****, 75,* 2512.
[63] Kharasch, M.S.; Kritchevsky, J.; Mayo, F.R. *J. Org. Chem.* ***1938****, 2,* 489.
[64] Nordlander, J.E.; Owuor, P.O.; Haky, J.E. *J. Am. Chem. Soc.* ***1979****, 101,* 1288.
[65] Afanas'ev, I.B.; Samokhvalov, G.I. *Russ. Chem. Rev.* ***1969****, 38,* 318.

have been measured, and shown to be faster than addition to styrene.[66] In additions to $RCH{=}C(CN)_2$ systems, where the R group has a stereogenic center, the *Felkin–Anh model* (Sec. 4.H, category 1) applies and the reaction proceeds with high selectivity.[67] Addition of some radicals [e.g., $(Me_3Si)_3Si^{\bullet}$], is reversible and this can lead to poor selectivity or isomerization.[68]

15.B. ORIENTATION AND REACTIVITY

15.B.i. Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1 and 15.2.[69] As a further illustration, the reactivity toward electrophilic addition of a group of alkenes increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[70] For nucleophilic addition, the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C{=}CF_2$[71] and $(NC)_2C{=}C(CN)_2$.[72] The effect of substituents is so great that it is possible to make the statement that *simple alkenes do not react by the nucleophilic mechanism, and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism.*[73] There are some reagents that attack only as nucleophiles (e.g., ammonia) and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $F_2C{=}CF_2$ does not react with these. In still other cases, the same reagent reacts with a simple alkene by the electrophilic mechanism and with a polyhalo alkene by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(N{\equiv}C)_2C{=}CHC{\equiv}N$ with initial attack by Cl^{-}[74] and that HF adds to $F_2C{=}CClF$ with initial attack by F^{-}.[75] Compounds that have a double bond conjugated with a Z group (as defined in Sec. 15.A.ii) nearly always react by a nucleophilic mechanism.[76] These are actually 1,4-additions, also discussed in Section 15.A.ii. A number of studies have been made of the relative activating abilities of various Z groups.[77] On the basis of these studies,

[66] Curran, D.P.; Qi, H.; Porter, N.A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* ***1993****, 34*, 4489.
[67] Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* ***1992***, 441.
[68] Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1993****, 34*, 5147.
[69] Table 15.1 is from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* ***1949****, 3,* 126, p. 145. Table 15.2 is from Dubois, J.E.; Mouvier, G. *Tetrahedron Lett.* ***1963***, 1325. See also, Grosjean, D.; Mouvier, G.; Dubois, J.E. *J. Org. Chem.* ***1976****, 41,* 3869, 3872.
[70] Shelton, J.R.; Lee, L. *J. Org. Chem.* ***1960****, 25,* 428.
[71] See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965****, 4,* 51.
[72] See Fatiadi, A.J. *Synthesis* ***1987***, 249, 749; Dhar, D.N. *Chem. Rev.* ***1967****, 67,* 611.
[73] See Olah, G.A.; Mo, Y.K.*J. Org. Chem.* ***1972****, 37,* 1028; Belen'kii, G.G.; German, L.S. *Sov. Sci. Rev. Sect. B* ***1984****, 5,* 183; Dyatkin, B.L.; Mochalina, E.P.; Knunyants, I.L. *Fluorine Chem. Rev.* ***1969****, 3*, 45.
[74] Dickinson, C.L.; Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1960****, 82*, 6132. For another example, see Atkinson, R.C.; de la Mare, P.B.D.; Larsen, D.S. *J. Chem. Soc. Perkin Trans. 2,* ***1983***, 271.
[75] Miller, Jr., W.T.; Fried, J.H.; Goldwhite, H. *J. Am. Chem. Soc.* ***1960****, 82,* 3091.
[76] Müllen, K.; Wolf, P. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 513–558.
[77] See Ring, R.N.; Tesoro, G.C.; Moore, D.R. *J. Org. Chem.* ***1967****, 32*, 1091.

TABLE 15.1 Relative Reactivity of Some Alkenes Toward Bromine in Acetic Acid at 24 °C[a]

Alkene	Relative Rate
$PhCH{=}CH_2$	Very fast
PhCH=CHPh	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
PhCH=CHBr	0.11
$CH_2{=}CHBr$	0.0011

Reproduced from de la Mare, P.B.D. *Q. Rev. Chem. Soc*. ***1949***, *3*, 126 with permission from the Royal Society of Chemistry.

[a]See Ref. 69.

TABLE 15.2 Relative Reactivity of Some Alkenes Toward Bromine in Methanol[a]

Alkene	Relative Rate
$CH_2{=}CH_2$	3.0×10^1
$CH_3CH_2CH{=}CH_2$	$2/9 \times 10^3$
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

[Reprinted with permission from Dubois, J.E. Mouvier, G. *Tetrahedron Lett*. ***1963***, 1325, Copyright © 1963, with permission from Elsevier Science].

[a]See Ref. 69.

the following order of decreasing activating ability has been suggested: $Z = NO_2$, COAr, CHO, COR, SO_2Ar, CN, CO_2R, SOAr, $CONH_2$, and CONHR.[78]

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of the double bond. Addition of electrophilic radicals to electron-rich alkenes has been reported,[79] so the reaction is possible in some cases. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.[80] There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and

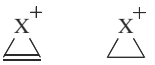
[78] Shenhav, H.; Rappoport, Z.; Patai, S. *J. Chem. Soc. B* ***1970***, 469.

[79] Curran, D.P.; Ko, S.-B. *Tetrahedron Lett*. ***1998***, *39*, 6629.

[80] See in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, the articles by Schmid, G.H. pt. 1, pp. 275–341, and by Dickstein, J.I.; Miller, S.I. pt. 2, pp. 813–955; Miller, S.I.; Winterfeldt, E. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 267–334. For comparisons of double and triple bond reactivity, see Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14,* 227; Allen, A.D.; Chiang, Y.; Kresge, A.J.; Tidwell, T.T. *J. Org. Chem.* ***1982***, *47*, 775.

yet triple bonds are *less* subject to attack at an electrophilic site and *more* subject to nucleophilic attack than double bonds.[81] This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.[82] In fact, all reagents that form bridged intermediates like **2** react faster with double than with triple bonds. On the other hand, addition of electrophilic H^+ (acid-catalyzed hydration, Reaction **15-3**; addition of hydrogen halides, Reaction **15-2**) takes place at about the same rates for alkenes as for corresponding alkynes.[83] Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene ($PhCH{=}CH_2$) was brominated 3000 times faster than PhC≡CH, the addition of a second phenyl group (PhCH=CHPh versus PhC≡CPh) lowered the rate ratio to ∼250.[84] In the case of *trans*-MeOOCCH=CHCOOMe versus MeOOCC≡CCOOMe, the triple-bond compound was actually brominated faster.[85]

As mentioned earlier, it is true that in general triple bonds are more susceptible to nucleophilic and less prone to reaction at an electrophilic site than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon–carbon distance. Thus it is harder to donate an electron pair to an electrophile. There is evidence from far-UV spectra to support this conclusion.[86] Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a π∗ orbital of bent alkynes (e.g., cyclooctyne) has a lower energy than the π^* orbital of alkenes, and it has been suggested[87] that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**20**) are more strained than the corresponding **21**. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, and so on, is slower for triple than for double bonds.[88] As might be expected, triple bonds connected to a Z group (C≡C—Z) undergo nucleophilic addition especially well.[89]



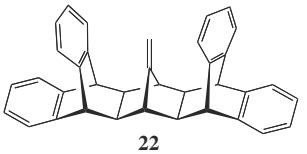
20 **21**

Although alkyl groups in general increase the rates of electrophilic addition, as mentioned in Section 15.A.i, category 1, there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.[90] Where the second step is rate

[81] See Strozier, R.W.; Caramella, P.; Houk, K.N. *J. Am. Chem. Soc.* ***1979****, 101,* 1340.
[82] Petrov, A.A. *Russ. Chem. Rev.* ***1960****, 29,* 489.
[83] Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981****, 14,* 227, p. 228.
[84] Robertson, P.W.; Dasent, W.E.; Milburn, R.M.; Oliver, W.H. *J. Chem. Soc.* ***1950***, 1628.
[85] Wolf, S.A.; Ganguly, S.; Berliner, E. *J. Am. Chem. Soc.* ***1985****, 50,* 1053.
[86] Walsh, A.D. *Q. Rev. Chem. Soc.* ***1948****, 2,* 73.
[87] Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* ***1982****, 104*, 7414.
[88] See Schmid, G.H.; Modro, A.; Lenz, F.; Garratt, D.G.; Yates, K. *J. Org. Chem.* ***1976****, 41*, 2331.
[89] See Winterfeldt, E. Angew. Chem. Int. Ed. **1967**, 6, 423; Newer Methods Prep. Org. Chem. **1971**, 6, 243.
[90] Nelson, D.J.; Cooper, P.J.; Soundararajan, R. *J. Am. Chem. Soc.* ***1989****, 111*, 1414.

determining [e.g., oxymercuration Reaction (**15-3**), hydroboration Reaction (**15-17**)], steric effects are important.[89]

Free radical additions can occur with any type of substrate. The determining factor is the presence of a reactive free radical species. Some reagents (e.g., HBr, RSH) attack by ionic mechanisms if no initiator is present, but in the presence of a free radical initiator, the mechanism changes and the addition is of the free radical type. Nucleophilic radicals (Sec. 14.A.ii) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.[91] However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,[92] which is contrary to what might have been expected.[93]

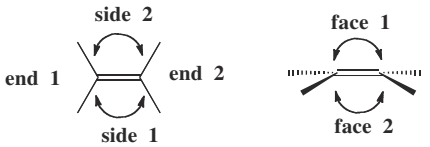


22

Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon (**22**), in which the double bond is entombed between the benzene rings, does not react with Br_2, H_2SO_4, O_3, BH_3, **:**CBr_2, or other reagents that react with most double bonds.[94] A similarly inactive compound is tetra-*tert*-butylallene $(t\text{-Bu})_2C{=}C{=}C(t\text{-Bu})_2$, which is inert to Br_2, Cl_2, O_3, and catalytic hydrogenation.[95]

15.B.ii. Orientation

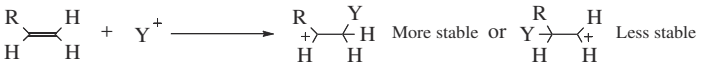
When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? In other words, what is the *regioselectivity* of the reaction? *Regioselectivity is defined as one direction of bond making or breaking that occurs preferentially over all other possible directions.* The terms side and face are arbitrary, and a simple guide is shown to help understand



the arguments used here. For reaction with an electrophile, the traditional answer is given by *Markovnikov's rule: The positive portion of the reagent goes to the side of the double or triple bond that has more hydrogen atoms*.[96] Mechanistically, regioselectivity is predicted by attack of the π bond on Y^+, forming a bond to the carbon that will give the

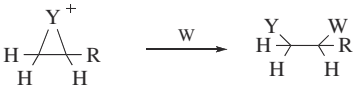
[91] See Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982****, 21*, 401.
[92] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982****, 21*, 768.
[93] See Volovik, S.V.; Dyadyusha, G.G.; Staninets, V.I. *J. Org. Chem. USSR* ***1986****, 22,* 1224.
[94] Butler, D.N.; Gupt, I.; Ng, W.W.; Nyburg, S.C. *J. Chem. Soc., Chem. Commun.* ***1980***, 596.
[95] Bolze, R.; Eierdanz, H.; Schlüter, K.; Massa, W.; Grahn, W.; Berndt, A. *Angew. Chem. Int. Ed.* ***1982****, 21*, 924.
[96] See Isenberg, N.; Grdinic, M. *J. Chem. Educ.* ***1969****, 46*, 601; Grdinic, M.; Isenberg, N. *Intra-Sci. Chem. Rep.,* ***1970****, 4,* 145–162.

more stable carbocation. For example, secondary carbocations are more stable than primary:



This mechanism is supported by evidence from core electron spectroscopy and by theoretical analysis.[97] The *Hammond postulate* is invoked to say that the lower energy carbocation is preceded by the lower energy transition state. *Markovnikov's rule* also applies for halogen substituents, and the mechanistic rationale is that the halogen stabilizes the carbocation by resonance, so the intermediate with the positive charge on the Cl bearing carbon is more stable.

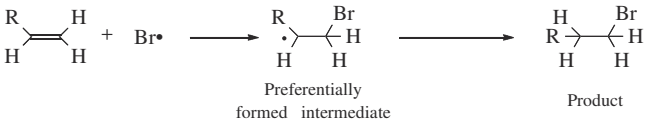
Markovnikov's rule is also followed where bromonium ions or other three-membered rings are intermediates formed in protic solvents (e.g., methanol).[98] In such a medium, attack by the nucleophile W on the three-membered ring must resemble the S_N1 (see Sec. 10.A.ii) rather than the S_N2 mechanism (and see Sec. 10.G.viii), although the overall stereospecific anti addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration. This result suggests a tight ion pair rather than a free carbocation.



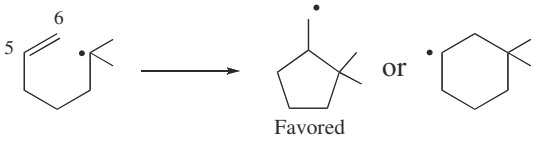
Alkenes containing strong electron-withdrawing groups may violate *Markovnikov's rule*, but formation of the more stable carbocation still controls the reaction. For example, attack at the *Markovnikov* position of Me_3N^+—CH=CH_2 would give an ion with positive charges on adjacent atoms. The compound $CF_3CH{=}CH_2$ has been reported to give electrophilic addition with acids in an *anti-Markovnikov* direction, but it has been shown[99] that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently *anti-Markovnikov* products are formed by other pathways. Molecular electrostatic potentials for the π-region of substituted alkenes were studied, with electron donating and withdrawing substituents (based on the increase or decrease in the negative character of V_{min} - most negative-valued point), and plots of V_{min} shows a good linear correlation with the *Hammett* σ_ρ *constants*, suggesting similar substituent electronic effects for substituted ethylenes and substituted benzenes.[100]

In free radical addition[101] the main effect seems to be steric.[102] All substrates $CH_2{=}CHX$ preferentially react at the CH_2, regardless of the identity of X or of the radical. With a reagent, such as HBr, which generates $Br^\bullet$ *in situ* via hydrogen-atom exchange, this means that the addition is *anti-Markovnikov*:

[97] Sæthre, L.J.; Thomas, T.D.; Svensson, S. *J. Chem. Soc. Perkin Trans. 2,* ***1997***, 749.
[98] See Dubois, J.E.; Chrétien, J.R. *J. Am. Chem. Soc.* ***1978****, 100*, 3506.
[99] Myhre, P.C.; Andrews, G.D. *J. Am. Chem. Soc.* ***1970****, 92,* 7595, 7596. See also, Newton, T.A. *J. Chem. Educ.* ***1987****, 64,* 531.
[100] Suresh, C.H.; Koga, N.; Gadre, S.R. *J. Org. Chem.* ***2001****, 66,* 6883.
[101] Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980****, 36*, 701; *Acc. Chem. Res.* ***1976****, 9*, 183. See also, Giese, B. *Rev. Chem. Intermed.* ***1986****, 7,* 3; Tedder, J.M. *J. Chem. Educ.* ***1984****, 61*, 237.
[102] See, however, Gleicher, G.J.; Mahiou, B.; Aretakis, A.J. *J. Org. Chem.* ***1989****, 54*, 308.

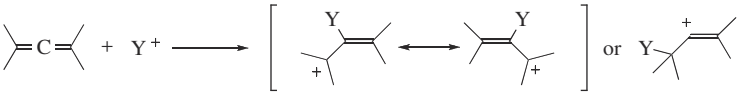


Thus the observed orientation in both kinds of HBr addition (*Markovnikov* electrophilic and *anti-Markovnikov* free radical) is caused by formation of the more stable secondary intermediate.



In *intramolecular* additions (radical cyclization, see Reaction **15-30**) of radicals containing a 5,6 double bond,[53] both five- and six-membered rings can be formed, but in most cases[103] the five-membered rings are greatly preferred kinetically, even (as in the case shown) where five-membered ring closure means generating a primary radical and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.[104] Similar behavior is found when the double bond is in other positions (from the 3,4 to the 7,8 position). In each case, the smaller ring (exo-trig addition) is preferred to the larger (endo-trig addition)[105] (see *Baldwin rules*, Sec. 6.E). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the six-membered ring is generally favored, presumably due to unfavorable steric interactions.[106]

For conjugated dienes, attack at a positive ion, by a negative ion, or reaction with a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is formed. For example, isoprene ($CH_2{=}CMeCH{=}CH_2$) treated with HCl gives only $Me_2CClCH{=}CH_2$ and $Me_2C{=}CHCH_2Cl$, with none of the product arising from attack at the other end. The compound $PhCH{=}CHCH{=}CH_2$ gives only $PhCH{=}CHCHClCH_3$ since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack that places the proton at an end of the conjugated system.



When allenes attack electrophilic reagents,[107] *Markovnikov's rule* would predict that formation of the new bond should be at the end of the system, since there are no hydrogen

[103] For an exception, see Wilt, J.W. *Tetrahedron* ***1985****, 41*, 3979.

[104] See Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* ***1985****, 41*, 3925; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987****, 52*, 959.

[105] See Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 482.

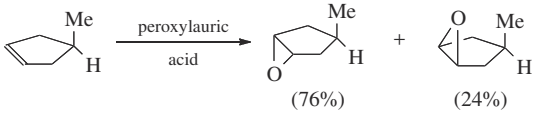
[106] See Chuang, C.; Gallucci, J.C.; Hart, D.J.; Hoffman, C. *J. Org. Chem.* ***1988****, 53*, 3218.

[107] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wiley, NY, ***1984***; Pasto, D.J. *Tetrahedron* ***1984****, 40*, 2805; Smadja, W. *Chem. Rev.* ***1983****, 83*, 263; in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, articles by Landor, S.R., Jacobs, T.L.; Hopf, H. pp. 351–577; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 152–167; Richey, Jr., H.G.; Richey, J.M. in Olah, G. A.; Schleyer, P.v.R. *Carbonium Ions,* Vol. 2, Wiley, NY, ***1970***, pp. 917–922; Taylor, D.R. *Chem. Rev.* ***1967****, 67*, 317, pp. 338–346; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1966****, 5,* 933. See Ma, S. *Pure Appl. Chem.* ***2006****, 78*,197.

atoms in the middle. Reaction at the center gives a carbocation stabilized by resonance, but not immediately. In order for such stabilization to be in effect, the three *p* orbitals must be parallel, and it requires a rotation about the C—C bond.[108] Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (Sec. 4.C, category 5). Probably because of this, reaction of the unsubstituted $CH_2{=}C{=}CH_2$ is most often at the end carbon, to give a vinylic cation, although reaction at the center carbon has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, reaction at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form $RCH{=}C{=}CH_2$ react most often at the end, but $RCH{=}C{=}CHR'$ usually gives reaction at the center carbon.[109] Free radicals[110] react with allenes most often at the end,[111] although reaction at the middle carbon has also been reported.[112] As with reactions that proceed via electrophilic intermediates and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, the presence of alkyl groups increases the extent of reaction by a radical at the middle carbon.[113]

15.B.iii. Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds steric orientation must be considered. In syn addition to an unsymmetrical cyclic alkene, the two groups can come in from the more- or from the less-hindered face of the double bond. The rule is that syn addition is usually, although not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered and 24% from the more-hindered face.[114]

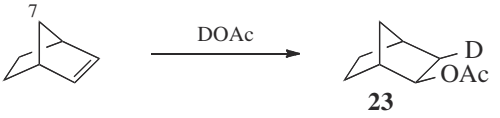


(76%) (24%)

In anti addition to a cyclic substrate, the initial reaction with the electrophile is also from the less-hindered face. However, many (although not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.[115] In these cases reaction

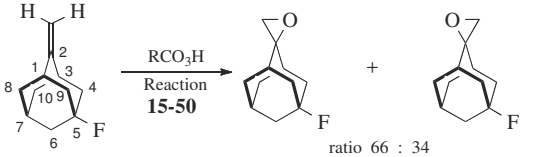
[108] See Okuyama, T.; Izawa, K.; Fueno, T. *J. Am. Chem. Soc.* ***1973****, 95*, 6749.
[109] Also see Poutsma, M.L.; Ibarbia, P.A. *J. Am. Chem. Soc.* ***1971****, 93,* 440.
[110] Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 399–415.
[111] Griesbaum, K.; Oswald, A.A.; Quiram, E.R.; Naegele, W. *J. Org. Chem.* ***1963****, 28*, 1952.
[112] See Pasto, D.J.; L'Hermine, G. *J. Org. Chem.* ***1990****, 55,* 685.
[113] See Pasto, D.J.; Warren, S.E.; Morrison, M.A. *J. Org. Chem.* ***1981****, 46,* 2837. See, however, Bartels, H.M.; Boldt, P. *Liebigs Ann. Chem.* ***1981***, 40.
[114] Henbest, H.B.; McCullough, J.J. *Proc. Chem. Soc.* ***1962***, 74.
[115] See Traylor, T.G. *Acc. Chem. Res.* ***1969****, 2,* 152.

is always from the exo side, as in formation of **23**,[116] unless the exo



23

side is blocked by substituents in the 7 position, in which case endo attack may predominate [e.g., 7,7-dimethylnorbornene undergoes syn–endo epoxidation (Reaction **15-50**) and hydroboration[117] (Reaction **15-16**)]. However, addition of DCl and F_3CCO_2D to, and oxymercuration (Reaction **15-2**) of, 7,7-dimethylnorbornene proceeds syn–exo in spite of the methyl groups in the 7 position.[118] Similarly, free radical additions to norbornene and similar molecules are often syn–exo, although anti additions and endo attacks are also known.[119]

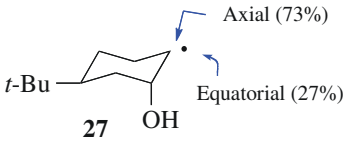


24 **25** **26**

Electronic effects can also play a part in determining which face reacts preferentially with the electrophilic species. In the adamantane derivative (**24**), steric effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene reactions (**15-64**), and hydroboration (**15-16**) all take place predominantly from the face that is syn to the electron-withdrawing fluorine.[120] In the case shown, about twice as much **25** was formed, compared to **26**. Similar results have been obtained on other substrates:[121] groups that are electron withdrawing by the field effect ($-I$) direct attack from the syn face; $+I$ groups from the anti face, for both electrophilic and nucleophilic attack. These results are attributed[122] to hyperconjugation (Sec. 2.M): For the adamantane case, there is overlap between the σ^* orbital of the newly forming bond (between the attacking species and C-2 in **24**) and the filled σ orbitals of the C_α—C_β bonds on the opposite side. This is called the *Cieplak effect*. The $LiAlH_4$ reduction of 2-axial methyl or methoxy cyclohexanones supports Cieplak's proposal.[123] In addition reactions of methanol to norbornanones, however, little evidence was found to support the Cieplak effect.[124] The four possible bonds are C-3–C-4 and C-1–C-9 on the syn side and C-3–C-10 and C-1–C-8 on the anti side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1–C-8 and C-3–C-10 bonds are more electron rich, and the group comes in on the face syn to the F.

[116] Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* ***1990****, 3,* 519.
[117] Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1973****, 95,* 2209.
[118] Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1975****, 97,* 600, 2469.
[119] See Azovskaya, V.A.; Prilezhaeva, E.N. *Russ. Chem. Rev.* ***1972****, 41,* 516.
[120] Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1987****, 109*, 5874. See also, Bodepudi, V.R.; le Noble, W.J. *J. Org. Chem.* ***1991****, 56,* 2001.
[121] Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* ***1989****, 111*, 8447.
[122] Cieplak, A.S. *J. Am. Chem. Soc.* ***1981****, 103*, 4540. See also, Jorgensen, W.L. *Chemtracts: Org. Chem.* ***1988****, 1*, 71.
[123] Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc. Perkin Trans. 2,* ***1993***, 1009.
[124] Coxon, J.M.; McDonald, D.Q. *Tetrahedron* ***1992****, 48*, 3353.

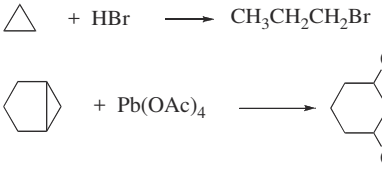
It has been mentioned that additions of Br_2 and HOBr are often anti because of formation of bromonium ions and that free radical addition of HBr is also anti. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.[125] This is so because diaxial opening of the three-membered ring preserves a maximum coplanarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.[126] However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial reaction with the radical is also usually from the axial direction,[127] resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals react has also been studied.[128] For example, when the radical (**27**) adds to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.[126]



27

15.B.iv. Addition to Cyclopropane Rings[129]

Section 4.Q.iv showed that cyclopropane rings resemble double bonds in some aspects of their reactivity.[130] It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered rings, as in the two examples shown, where Reactions **15-2** and **15-47** describe the reaction to alkene chemistry.



Reaction **15-2**

Ref. 131

Reaction **15-47**

Other examples are discussed at Reaction **15-3**, **15-15**, and **15-63**.

Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves attack on an electrophile.[132]

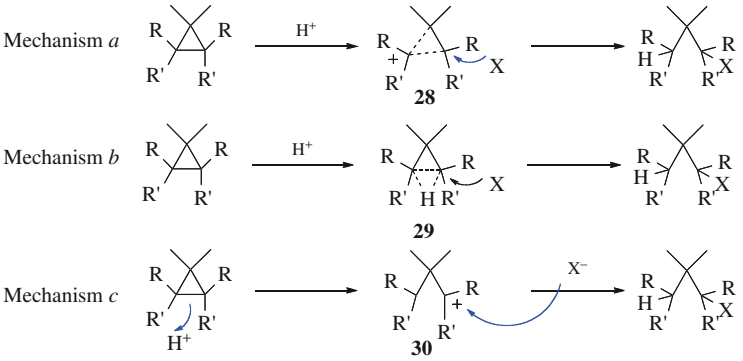
[125] Readio, P.D.; Skell, P.S. *J. Org. Chem.* ***1966****, 31,* 753, 759.
[126] See Anselmi, C.; Berti, G.; Catelani, G.; Lecce, L.; Monti, L. *Tetrahedron* ***1977****, 33*, 2771.
[127] LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969****, 34*, 3112
[128] See Giese, B. *Angew. Chem. Int. Ed.* ***1989****, 28*, 969.
[129] Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, vol 2., Wiley, NY, ***1970***, pp. 569–592; Reissig, H. *Top. Curr. Chem.* ***1988****, 144*, 73; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989****, 89,* 165.
[130] See, however, Gordon, A.J. *J. Chem. Educ.* ***1967****, 44*, 461.
[131] Moon, S. *J. Org. Chem.* ***1964****, 39,* 3456.
[132] See DePuy, C.H. *Top. Curr. Chem.* ***1973****, 40,* 73–101. For a list of references to pertinent mechanistic studies, see Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985****, 107*, 988.

For substituted cyclopropanes, these reactions usually follow *Markovnikov's rule*, although exceptions are known and the degree of regioselectivity is often small. The application of *Markovnikov's rule* to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.[133] The rule predicts that the electrophile (in this case H^+) goes to the



carbon with the most hydrogen atoms and the nucleophile goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions: the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,[134] 100% inversion,[135] and with mixtures of retention and inversion.[136] At the carbon that becomes connected to the nucleophile, the result is usually inversion, although retention has also been found,[137] and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for reaction with HX, but analogous mechanisms can be written for other electrophiles).

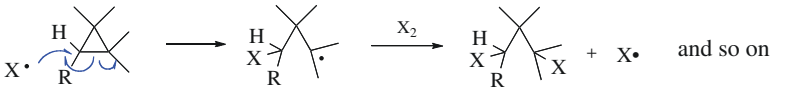


Mechanism *a* involves a corner-protonated cyclopropane[138] (**28**). Examples of such ions were seen in the 2-norbornyl and 7-norbornenyl cations (Sec. 10.C.i). Mechanism *b* involves an edge-protonated cyclopropane (**29**). Mechanism *c* consists of a one-step S_E2 type attack on H^+ to give the classical cation **30**, which then reacts with the nucleophile. Although the three mechanisms as drawn show retention of configuration at the carbon that

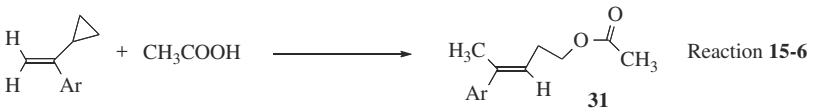
[133] Kramer, G.M. *J. Am. Chem. Soc.* ***1970****, 92,* 4344.
[134] See Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1969****, 91,* 3269.
[135] See Hogeveen, H.; Roobeek, C.F.; Volger, H.C. *Tetrahedron Lett.* ***1972***, 221; Battiste, M.A.; Mackiernan, J. *Tetrahedron Lett.* ***1972***, 4095. See also, Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1990****, 55,* 4136.
[136] DePuy, C.H.; Fünfschilling, P.C.; Andrist, A.H.; Olson, J.M. *J. Am. Chem. Soc.* ***1977****, 99,* 6297.
[137] Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1971****, 93,* 4491.
[138] Collins, C.J. *Chem. Rev.* ***1969****, 69,* 543; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970****, 7,* 129.

becomes attached to the proton, mechanisms *a* and *c* at least can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for mechanism *b* with the electrophiles Br^+ and Cl^+[139]; and for mechanism *a* with D^+ and Hg^{2+}.[140] *Ab initio* studies show that the corner-protonated **28** is slightly more stable ($\sim$1.4 kcal mol^{-1}, 6 kJ mol^{-1}) than the edge-protonated **29**.[141] There is some evidence against mechanism *c*.[142]

Free radical additions to cyclopropanes have been studied much less, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free radical mechanism in the presence of UV light. The addition follows *Markovnikov's rule*, with the initial radical reacting at the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.[143] A mechanism that accounts for this behavior is[144]



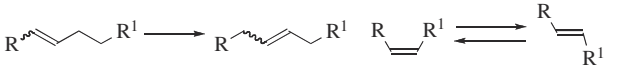
In some cases, conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is the formation of **31**.[145]



15.C. REACTIONS

15.C.i. Isomerization of Double and Triple Bonds

15-1 Isomerization



Without a transition metal catalyst, there is usually a rather high-energy barrier for the excited state required for (*E*/*Z*) isomerization.[146] The transition metal catalyzed

[139] Coxon, J.M.; Steel, P.J.; Whittington, B.I.; Battiste, M.A. *J. Org. Chem.* ***1989****, 54*, 1383; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1989****, 54*, 3702.
[140] Lambert, J.B.; Chelius, E.C.; Bible, Jr., R.H.; Hadju, E. *J. Am. Chem. Soc.* ***1991****, 113,* 1331.
[141] Koch, W.; Liu, B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1989****, 111*, 3479, and references cited therein.
[142] Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985****, 107*, 988.
[143] Maynes, G.G.; Applequist, D.E. *J. Am. Chem. Soc.* ***1973****, 95,* 856; Incremona, J.H.; Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973****, 95,* 6728; Upton, C.J.; Incremona, J.H. *J. Org. Chem.* ***1976****, 41*, 523.
[144] See Wiberg, K.B.; Waddell, S.T.; Laidig, K. *Tetrahedron Lett.* ***1986****, 27*, 1553.
[145] Sarel, S.; Ben-Shoshan, B. *Tetrahedron Lett.* ***1965***, 1053. See also, Danishefsky, S. *Acc. Chem. Res.* ***1979****, 12,* 66.
[146] Arai, T.; Takahashi, O. *J. Chem. Soc., Chem. Commun.* ***1995***, 1837.

isomerization of an alkene from (*E*) to (*Z*) or (*Z*) to (*E*) is a well-studied reaction.[147] Among the metals used, Pt is widely used, and rather selective.[148] The Pd catalyzed isomerization of (*Z*)-alkenes to (*E*)-alkenes required the presence of Bu_3SnH.[149] However, a 1:1 mixture of *cis*/*trans*-styrene derivatives was isomerized to a 90% yield of the *trans*-styrene derivatives reported using a Pd catalyst.[150] Isomerization of cyclic alkenes is difficult for rings of seven members and less, but cis/trans isomerization of cyclooctene is induced photochemically.[151] Radical-induced (*E*/*Z*) isomerization is known.[152] Isomerization of the C=C units in dienes is also induced photochemically.[153]

In a different type of reaction, isomerization of alkynes to 1,3-dienes is possible using Rh or Pd catalysts.[154]

There are several reagents that lead to isomerization of a double bond to form a new alkene. In general, there is an energetic preference of an α,β- versus β,γ-double bond.[155] Allylic arenes ($Ar—CH_2CH=CH_2$) have been converted to the corresponding (*Z*)-1-propenyl arene (Ar—CH=CHMe using an Ru catalyst[156] or a polymer-supported Ir catalyst.[157] In the presence of a Rh catalyst, certain allylic amines are converted to an enamine with high selectivity for the (*Z*) isomer.[158] Double-bond migration has been observed in sulfide photoirradiation, induced by singlet oxygen.[159] Many of these reactions were discussed in Reaction **12-2**.

For conjugated carbonyl compounds that have a hydrogen atom at the γ-position (C-4), it is possible to move a double bond *out* of conjugation. Photolysis of conjugated esters, at −40 °C in the presence of *N,N*- dimethylaminoethanol, gave the nonconjugated ester.[160] Heating an *N*-allylic amide (N—C—C=C) with $Fe(CO)_5$, neat, gave the enamide (N—C=C—C).[161] Conjugated aldehydes have been isomerized using thiourea in DMF.[162]

Double bonds of atoms other than carbon are subject to isomerization. Azobenzenes (Ar—N=N—Ar) exist as (*E*) and (*Z*) isomers, and photochemical isomerization is possible.[163]

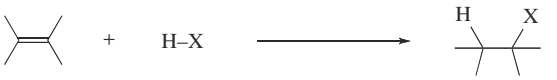
[147] See Dugave, C.; Demange, L. *Chem. Rev.* ***2003****, 103*, 2475. See Bond, G.C.; Wells, P.B. A*dv. Catal.* ***1964****, 15*, 91; Anderson, J.R.; Baker, B.G. in *Chemisorption and Reactions on Metallic Films, Vol. 2* Anderson, J.R., Ed. Academic Press, London, ***1971***, p. 63; Zaera, F. *Langmuir* ***1996****, 12*, 88.
[148] Lee, I.; Zaera, F. *J. Am. Chem. Soc.* ***2005****, 127,* 12174.
[149] Kim, I.S.; Dong, G.R.; Jung, Y.H. *J. Org. Chem.* ***2007****, 72,* 5424.
[150] Yu, J.; Gaunt, M.J.; Spencer, J.B. *J. Org. Chem.* ***2002****, 67*, 4627.
[151] Royzen, M.; Yap, G.P.A.; Fox, J.M. *J. Am. Chem. Soc.* ***2008***, *130*, 3760.
[152] Baag, Md.M.; Kar, A.; Argade, N.P. *Tetrahedron* ***2003****, 59,* 6489.
[153] Wakamatsu, K.; Takahashi, Y.; Kikuchi, K.; Miyashi, T. *J. Chem. Soc. Perkin Trans. 2,* ***1996***, 2105.
[154] Yasui, H.; Yorimitsu, H.; Oshima, K. *Synlett* ***2006***, 1783. For a review, see Kwong, C.K.-W.; Fu, M.Y.; Lam, C. S.-L.; Toy, P.H. *Synthesis* ***2008***, 2307.
[155] Lee, P.S.; Du, W.; Boger, D.L.; Jorgensen, W.L. *J. Org. Chem.* ***2004****, 69*, 5448.
[156] Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* ***1999***, 441.
[157] Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* ***2002***, 516.
[158] Alphonse, F.-A.; Yudin, A.K. *J. Am. Chem. Soc.* ***2006****, 128,* 11754. See Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* ***2004****, 45*, 5257.
[159] Clennan, E.L.; Aebisher, D. *J. Org. Chem.* ***2002****, 67,* 1036.
[160] Bargiggia, F.; Piva, O. *Tetrahedron Asymmetry* ***2001****, 12,* 1389.
[161] Sergeyev, S.; Hesse, M. *Synlett* ***2002***, 1313.
[162] Phillips, O.A.; Eby, P.; Maiti, S.N. *Synth. Commun.* ***1995****, 25*, 87.
[163] Carreño, M.C.; García, I.; Ribagorda, M.; Merino, E.; Pieraccini, S.; Spada, G.P. *Org. Lett.* ***2005****, 7,* 2869.

15.C.ii. Reactions in Which Hydrogen Adds to One Side

A. Halogen on the Other Side

15-2 Addition of Hydrogen Halides

Hydro-halo-addition



Any of the four hydrogen halides can be added to double bonds.[164] Alkenes react as Brønsted–Lowry bases with HI, HBr, and HF[165] at room temperature, but reaction with HCl is more difficult and usually requires heat.[24] Hydrogen Chloride adds easily in the presence of silica gel. However,[166] HF is difficult to handle, but a convenient method for the addition of HF involves the use of a polyhydrogen fluoride–pyridine solution in THF.[167]

The addition of hydrogen halides to simple alkenes, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with *Markovnikov's rule*.[168] In other words, the π bond of the alkenes donates two electrons to the acidic proton of H—X. The addition follows second-order kinetics.[169] When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is *anti-Markovnikov* (Sec. 15.B.i).[170] It must be emphasized that this is true *only* for HBr. Free radical addition of HF and HI has never been observed, even in the presence of peroxides; free radical addition of HCl has been observed only rarely. In the rare cases where free radical addition of HCl was noted, the orientation was still *Markovnikov*, presumably because the more stable product was formed.[171] Free radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions in Sec. 14.B.i and 14.C.i). It is known that under some conditions *anti-Markovnikov addition* of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (Reaction **14-7**). *Markovnikov addition* can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve. It is more common to add inhibitors (e.g., phenols or quinones), which suppress the free radical pathway. The presence of free radical precursors (e.g., peroxides) does not inhibit the ionic mechanism, but does inhibit the more rapid radical reaction, which is a chain process. In most cases, it is possible to control the mechanism (and hence the orientation) by adding peroxides to achieve complete free radical addition, or inhibitors to achieve complete electrophilic addition, although there are some cases where the ionic mechanism is fast enough to compete with the free radical

[164] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 633–636.
[165] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974****, 21*, 125, pp. 192–198, 212–214; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 36–41.
[166] Kropp, P.J.; Daus, K.A.; Tubergen, M.W.; Kepler, K.D.; Wilson, V.P.; Craig, S.L.; Baillargeon, M.M.; Breton, G.W. *J. Am. Chem. Soc.* ***1993****, 115*, 3071.
[167] Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979****, 44,* 3872. For a related method, see Olah, G.A.; Li, X. *Synlett* ***1990***, 267.
[168] See Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N.; *Russ. Chem. Rev.* ***1983****, 52*, 259; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964****, 3*, 245.
[169] Boregeaud, R.; Newman, H.; Schelpe, A.; Vasco, V.; Hughes, D.E.P. *J. Chem. Soc., Perkin Trans. 2,* ***2002***, 810.
[170] See Thaler, W.A. *Methods Free-Radical Chem.* ***1969****, 2,* 121, see pp. 182–195.
[171] Mayo, F.R. *J. Am. Chem. Soc.* ***1962****, 84,* 3964.

mechanism and complete control cannot be attained. *Markovnikov addition* of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase transfer catalysis.[172] For alternative methods of adding HBr (or HI) with *anti-Markovnikov orientation*, see Reaction **12-31**.

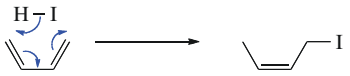
Alkynes also react as bases with acids (e.g., HX). It is possible to add 1[173] or 2 equiv of any of the four hydrogen halides to triple bonds. *Markovnikov's rule* ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of 2 equiv.

$$—C{\equiv}C— \xrightarrow{HX} —CH{=}CX— \xrightarrow{HX} —CH_2—CX_2—$$

Chlorotrimethylsilane can be added to alkenes to give alkyl chlorides. 1-Hexene reacts with Me_3SiCl in water, for example, to give 2-chlorohexane.[174] Treatment of an alkene with KHF_2 and SiF_4 leads to the alkyl fluoride,[175] and bromotrimethylsilane adds to alkynes to give the vinyl bromide.[176]

Brønsted–Lowry acids (e.g., HX) are electrophilic reagents, and many polyhalo or polycyano alkenes do not react with them in the absence of free radical conditions. Vinylcyclopropanes, however, react with opening of the cyclopropane ring to give a homoallylic chloride.[177] When such reactions do occur, however, they take place by a nucleophilic addition mechanism, that is, initial attack is by X^-. This type of mechanism also occurs with *Michael-type substrates* (C=C—Z),[178] where the orientation is always such that the halogen goes to the carbon that does not bear the Z, so the product is of the form X—C—CH—Z, even in the presence of free radical initiators.

The reaction has been carried out with conjugated dienes, where both 1,2- and 1,4-addition are possible. Hydrogen iodide adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:[179]



In a related reaction, HX can be added to ketenes[180] to give acyl halides:



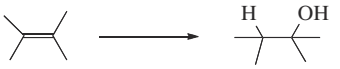
OS **I**, 166; **II**, 137, 336; **III**, 576; **IV**, 238, 543; **VI**, 273; **VII**, 59; **80**, 129.

[172] Landini, D.; Rolla, F. *J. Org. Chem.* ***1980****, 45*, 3527.
[173] See Cousseau, J. *Synthesis* ***1980***, 805; Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* ***1990***, 675.
[174] Boudjouk, P.; Kim, B.-K.; Han, B.-H. *Synth. Commun.* ***1996****, 26*, 3479.
[175] Tamura, M.; Shibakami, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1891.
[176] Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001****, 42*, 3771.
[177] Siriwardana, A.I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* ***2003****, 44*, 985.
[178] For an example, see Marx, J.N. *Tetrahedron* ***1983****, 39,* 1529.
[179] Gorton, P.J.; Walsh, R. *J. Chem. Soc., Chem. Commun.* ***1972***, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev, G.B.; Stepanov, N.F.; Leenson, I.A.; Smirnov, V. V.; Pupyshev, V.I.; Tyurina, L.A.; Mashyanov, M.N. *Tetrahedron* ***1982****, 38,* 2585.
[180] Tidwell, T.T. *Acc. Chem. Res.* ***1990****, 23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986****, 42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975****, 4*, 231.

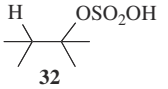
B. Oxygen on the Other Side

15-3 Hydration of Double bonds

Hydro-hydroxy-addition

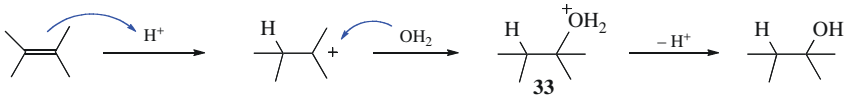


Double bonds can be hydrated by treatment with water and an acid catalyst. Sulfuric acid is a common catalyst, but other acids that have relatively non-nucleophilic counterions, such as nitric, perchloric, or more commonly sulfonic acids (*p*-toluenesulfonic acid, methanesulfonic acid, etc.) can also be used. The mechanism is electrophilic and begins with attack of the π bond on an acidic proton (Sec. 15.A.i). The resulting carbocation is then attacked by negative species (e.g., HSO_4^-, or a similar counterion in the case of other acids), to give the initial product (**32**), which can be isolated in some cases. However, such compounds are rather unstable, and



32

under the conditions of the reaction are usually hydrolyzed to the alcohol (Reaction **10-4**). Under some reaction conditions, other nucleophiles are present in the reaction, either from the solvent or from added compounds. In an aqueous medium, water is a competitive nucleophile, and attack by water forms oxonium ion **33**. Products, such as **32**, are not involved when other nucleophiles react with the carbocation, and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of El elimination of alcohols (Reaction **17-1**).[181] *The initial carbocation occasionally rearranges to a more stable one.* For example, hydration of $CH_2{=}CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. Hydration of simple alkenes leads to alcohols predicted by *Markovnikov's rule*.



33

Oxymercuration[182] (addition of oxygen and mercury) of alkenes followed by *in situ* treatment with sodium borohydride[183] (Reaction **12-24**), gives an alcohol (see example) under mild conditions, in high yields, and without rearrangement products. For example, treatment of 2-methyl-1-butene with mercuric acetate,[184] followed by $NaBH_4$, gave 2-methyl-2-butanol. Oxymercuration of alkenes has been reported in water, using cyclodextrins as phase-transfer catalysts.[185]

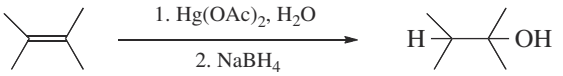
[181] See Vinnik, M.I.; Obraztsov, P.A. Russ. Chem. Rev. **1990**, 59, 63; Liler, M. *Reaction Mechanisms in Sulphuric Acid* Academic Press, NY, **1971**, pp. 210–225.

[182] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis,* Springer, NY, ***1986***; Kitching, W. *Organomet. React.* ***1972****, 3,* 319; *Organomet. Chem. Rev.* ***1968****, 3,* 61; Oullette, R.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry* pt. B, Academic Press, NY, ***1973***, pp. 140–166; House, H.O. *Modern Synthetic Reactions,* 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 387–396.

[183] Brown, H.C.; Geoghegan, Jr., P.J. *J. Org. Chem.* ***1972****, 37*, 1937; Brown, H.C.; Geoghegan Jr., P.J.; Lynch, G.J.; Kurek, J.T. *J. Org. Chem.* ***1972****, 37*, 1941; Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* ***1972***, 2016.

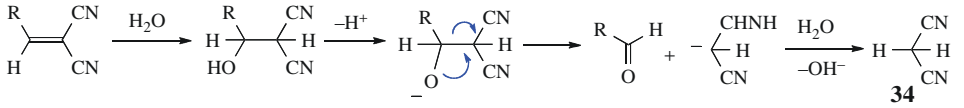
[184] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[185] Abreu, A.R.; Costa, I.; Rosa, C.; Ferreira, L.M.; Lourenço, A.; Santos, P.P. Te*trahedron* ***2005****, 61,* 11986.



This method, which is applicable to mono-, di-, tri-, and tetraalkyl, as well as phenyl-substituted alkenes, gives almost complete *Markovnikov addition*. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate, and generally do not cause difficulties.[186] When two double bonds are present in the same molecule, changing the carboxylic acid ligand of the mercuric salt allows oxymercuration of the less-substituted one without affecting the other, with ultrasound.[187] A related reaction treats an alkene with zinc borohydride on silica gel to give a 35:65 mixture of secondary/primary alcohols.[188]

With substrates of the type C=C—Z (Z is as defined in Sec.15.A.ii) the product is almost always HO—C—CH—Z and the mechanism is usually nucleophilic,[189] although electrophilic addition gives the same product[190] since a cation CH—C—Z would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the α-hydroxy compound HC—CH(OH)Z, was obtained by treatment of the substrate with O_2, $PhSiH_3$, and a manganese-complex catalyst.[191] Addition of water to RCH=CZZ′ substrates may result in cleavage of the adduct to give an aldehyde and CH_2ZZ' (**34**).[192] The cleavage step is an example of Reaction **12-41**.



For another method of *anti-Markovnikov* hydration, see hydroboration (Reaction **15-16**).

Indirect hydration, with *anti-Markovnikov* orientation, was achieved by treatment of the alkene with a 1:1 mixture of $PhCH_2NEt_3^+$ BH_4^- and Me_3SiCl, followed by addition of an aqueous solution of K_2CO_3.[193] Reaction of alkenes with $Ti(BH_4)_3$, and then aq K_2CO_3 also leads to the *anti-Markovnikov* alcohol.[194] Alkenes react with PhO_2BH and a Nb catalyst, followed by oxidation with $NaOO^-$, to give the alcohol,[195] and Cp_2TiCl_4 can also be used.[196] Conjugated alkenes also react with $PhSiH_2$ and oxygen, with a Mn catalyst, to give an α-hydroxy ketone.[197] Alkenes react with molecular oxygen in the presence of a Co porphyrin catalyst, and reduction with $P(OMe)_3$ leads to the secondary alcohol.[198] This procedure has also been used to hydrate conjugated dienes,[199] although conjugated dienes are seldom hydrated.

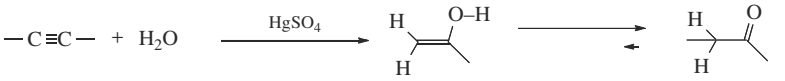
[186] See the extensive tables in Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 4–71.
[187] Einhorn, J.; Einhorn, C.; Luche, J.L. *J. Org. Chem.* ***1989****, 54,* 4479.
[188] Campelo, J.M.; Chakraborty, R.; Marinas, J.M. *Synth. Commun.* ***1996****, 26*, 1639.
[189] See Bernasconi, C.F.; Leonarduzzi, G.D. *J. Am. Chem. Soc.* ***1982****, 104,* 5133, 5143.
[190] See Noyce, D.S.; DeBruin, K.E. *J. Am. Chem. Soc.* ***1968****, 90*, 372.
[191] Magnus, P.; Scott, D.A.; Fielding, M.R. *Tetrahedron Lett.* ***2001****, 42,* 4127.
[192] Bernasconi, C.F.; Paschalis, P. *J. Am. Chem. Soc.* ***1989****, 111*, 5893, and other papers in this series.
[193] Baskaran, S.; Gupta, V.; Chidambaram, N.; Chandrasekaran, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 903.
[194] Kumar, K.S.R.; Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***1993****, 34*, 171.
[195] Burgess, K.; Jaspars, M. *Tetrahedron Lett.* ***1993****, 34,* 6813.
[196] Burgess, K.; van der Donk, W.A. *Tetrahedron Lett.* ***1993****, 34*, 6817.
[197] Magnus, P.; Payne, A.H.; Waring, M.J.; Scott, D.A.; Lynch, V. *Tetrahedron Lett.* ***2000****, 41,* 9725.
[198] Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* ***1993***, 925.
[199] Matshshita, Y.; Sugamoto, K.; Nakama, T.; Sakamoto, T.; Matsui, T.; Nakayama, M. *Tetrahedron Lett.* ***1995****, 36*, 1879.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (Reaction **10-6**). Ketenes add water to give carboxylic acids ($R_2C{=}C{=}O \rightarrow R_2CO_2H$) in a reaction catalyzed by acids[200]:

OS **IV**, 555, 560; **VI**, 766. Also see, OS **V**, 818.

15-4 Hydration of Triple Bonds

Dihydro-oxo-biaddition



The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate or even mercuric oxide) as catalysts.[201] In contrast to oxymercuration of alkenes, the organomercury intermediate from this reaction is unstable and loss of mercury *in situ* leads to an enol product. The enol tautomerizes to the ketone (see Sec. 2.N.i), so the isolated product is the ketone from either an internal or terminal alkyne (the OH unit will always be on the more substituted carbon via the more stable secondary vinyl carbocation). Only acetylene gives an aldehyde. With alkynes of the form $RC{\equiv}CR'$ both possible ketone products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid; see Sec. 5.A.ii).[202] Gold,[203] In,[204] and Ru[205] catalysts have been used to convert alkynes to the ketone. Gold(I) catalysts have also been used in the hydration of allenes.[206] Internal alkynes were treated with 2-aminophenol in refluxing dioxane using a Pd catalyst to produce the corresponding ketone.[207] Lactones have been prepared from trimethylsilyl alkenes containing a hydroxyl unit elsewhere in the molecule, when reacted with molecular oxygen, $CuCl_2$, and a Pd catalyst.[208] When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the intramolecular hydration reaction gives a γ- and/or a δ-lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double-bond shifts (Reaction **15-1**; and see **12-2**).[209] The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. The use of a chiral *Cinchonidine*

[200] See Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1485; Tidwell, T.T. *Acc. Chem. Res.* ***1990****, 23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986****, 42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975****, 4*, 231.

[201] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 123–148; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 91–95. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1217–1219.

[202] Olah, G.A.; Meidar, D. *Synthesis* ***1978***, 671.

[203] Marion, N.; Ramn, R.S.; Nolan, S.P. *J. Am. Chem. Soc.* ***2009****, 131*, 448; Leyva, A.; Corma, A. *J. Org. Chem.* ***2009****, 74*, 2067.

[204] Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* ***2006****, 62,* 2231.

[205] Alvarez, P.; Basetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* ***2001****, 42*, 8467.

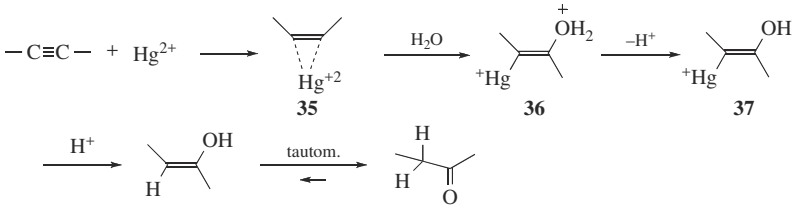
[206] Zhang, Z.; Lee, S.D.; Fisher, A.S.; Widenhoefer, R.A. *Tetrahedron* ***2009****, 65*, 1794.

[207] Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2002****, 124*, 12670.

[208] Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* ***1996****, 52*, 10405.

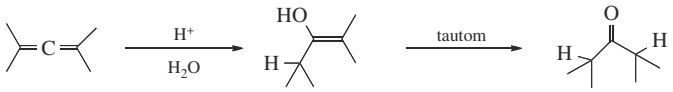
[209] See Ansell, M.F.; Palmer, M.H. *Q. Rev. Chem. Soc.* ***1964****, 18*, 211. For a Rh(I)-catalyzed reaction in ionic liquids, see Oonishi, Y.; Ogura, J.; Sato, Y. *Tetrahedron Lett.* ***2007****, 48,* 7505.

alkaloid additive leads to lactone formation with modest enantioselectivity.[210]

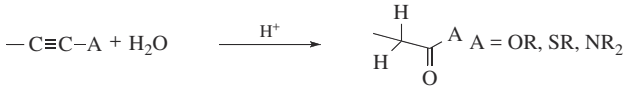


The first step of the mercury-mediated mechanism is formation of a complex (**35**). It is known that ions like Hg^{2+} form complexes with alkynes (Sec. 3.C.i). Water then attacks in an S_N2 type process to give the intermediate **36**, which loses a proton to give **37**. Hydrolysis of **37** (an example of Reaction **12-34**) gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.[211] Note that another possibility for **35** is a mercury-stabilized carbocation rather than a formal three-membered ring complex. In such a carbocation, the carbocation is stabilized by back-donation from the metal, and nucleophilic attack is more like a S_N1 type process.

Metal-free reactions are known, often using strong acids. Phenyl acetylene was converted to acetophenone [e.g., in water at 100 °C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide)], which is a very powerful acid.[212] Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.[213] Metal-free hydration of terminal alkynes occurs by reacting water, heated with microwave irradiation, to give the corresponding methyl ketone.[214] 1-Selenoalkynes (e.g., PhSe-C≡C-Ph) react with tosic acid in dichloromethane to give a seleno ester [PhSeC(=O)SH_2Ph] after treatment with water.[215] Allenes can be hydrolyzed to ketones using an acid catalyst.[216]



Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,[217] and ynamines, without a mercuric catalyst.[218]



[210] Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. *J. Org. Chem.* ***2004****, 69*, 2874.
[211] Chiang, Y.; Kresge, A.J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* ***1986****, 69*, 1331.
[212] Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* ***2000***, 1777.
[213] Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* ***1991****, 56,* 2912.
[214] Vasudevan, A.; Verzas, M.K. *Synlett* ***2004***, 631. An acid catalyst may be added, see Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* ***2006****, 47,* 5497.
[215] Sheng, S.; Liu, X. *Org. Prep. Proceed. Int.* ***2002****, 34*, 499.
[216] See Cramer, P.; Tidwell, T.T. *J. Org. Chem.* ***1981****, 46*, 2683.
[217] Braga, A.L.; Martins, T.L.C.; Silveira, C.C.; Rodrigues, O.E.D. *Tetrahedron* ***2001****, 57,* 3297. Also see Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 751–860.
[218] Arens, J.F. *Adv. Org. Chem.* ***1960****, 2*, 163; Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 774–775.

This is ordinary electrophilic addition, with rate-determining protonation as the first step.[219] Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.[220]

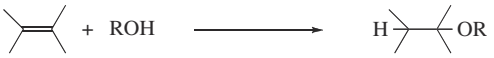
Catalysts have been developed for the *anti-Markovnikov* hydration of alkynes.[221] When 1-octyne was heated with water, isopropyl alcohol and a Ru catalyst, for example, the product was octanal.[222] The presence of certain functionality can influence the regioselectivity of hydration.

A Ni catalyzed reaction has been reported between alkynes and allyl phenyl sulfides to give thioallylation.[223]

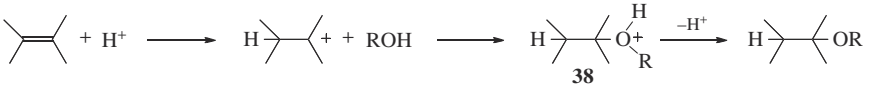
OS **III**, 22; **IV**, 13; **V**, 1024.

15-5 Addition of Alcohols and Phenols

Hydro-alkoxy-addition



Just as water adds to an alkene via hydration to form an alcohol, alcohols can also add to form an ether. Addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid catalyzed, the mechanism is electrophilic, where H^+ of the acid catalyst, is attacked by the π bond. The more stable carbocation is formed and subsequently attacked by a molecule of alcohol to give an oxonium ion (**38**).



38

The addition, therefore, follows *Markovnikov's rule*. Primary alcohols give better results than secondary, and tertiary alcohols are relatively inactive. This method is convenient for the preparation of tertiary ethers by the use of a suitable alkene (e.g., $Me_2C{=}CH_2$). Addition of alcohols to allylic systems can proceed with rearrangement, and the use of chiral additive can lead to asymmetric induction.[224] The uncatalyzed addition of alcohols occurs in supercritical alcohols.[225]

Metal-catalyzed addition to alkenes is a useful variation. The Pd catalyzed addition of alcohols to aryl alkenes gives the ether.[226] The Au(III)—$CuCl_2$ catalyzed reaction of alcohols and alkenes gives the ether.[227] Gold(I) catalyzed intermolecular addition of phenols leads to aryl ethers.[228]

[219] Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A.J. *Can. J. Chem.* ***1987****, 65*, 441.
[220] Noyce, D.S.; Schiavelli, M.D. *J. Org. Chem.* ***1968****, 33*, 845; *J. Am. Chem. Soc.* ***1968****, 90,* 1020, 1023.
[221] Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* ***2006****, 8*, 5853.
[222] Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* ***2001****, 3*, 735. Also see Grotjahn, D.B.; Lev, D.A. *J. Am. Chem. Soc.* ***2004****, 126,* 12232.
[223] Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *Org. Lett.* ***2007****, 9,* 263.
[224] See Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* ***2002****, 67*, 5124.
[225] Kamitanaka, T.; Hikida, T.; Hayashi, S.; Kishida, N.; Matsuda, T.; Harada, T. *Tetrahedron Lett.* ***2007****, 48,* 8460.
[226] Gligorich, K.M.; Schultz, M..J.; Sigman, M.S. *J. Am. Chem. Soc.* ***2006****, 128,* 2794.
[227] Zhang, X.; Corma, A. *Chem. Commun.* ***2007***, 3080.
[228] Yang, C.-G.; He, C. *J. Am. Chem. Soc.* ***2005****, 127*, 6966.

Alcohols add intramolecularly to alkenes to generate cyclic ethers, and the product often bears a hydroxyl unit,[229] but not always.[230] Cyclization is facilitated by Re,[231] Ti,[232] or Pt compounds,[233] forming functionalized tetrahydrofurans or tetrahydropyans. Intramolecular addition of alcohols to alkenes can be promoted by a Pd catalyst, but migration of the double bond in the final product is sometimes a problem.[234] Furan derivatives are available from alkene–ketones using $CuCl_2$ and a Pd[235] Cr,[236] Ag(I),[237] or lanthanide catalyst.[238] A gold catalyst was used with conjugated ketones bearing an alkyne substituent to give fused-ring furans.[239] Note that the reaction of an alkene–alcohol and NIS with a chiral Ti catalyst leads to a THF with a pendant iodoalkyl group, with modest enantioselectivity.[240]

Alcohols add to alkynes under certain conditions to give vinyl ethers. In an excess of alcohol, and in the presence of a Pt[241] or a Au catalyst,[242] internal alkynes are converted to ketals. The alcohol to alkyne addition reaction is quite useful for the preparation of heterocycles. Dihydrofurans,[243] furans,[244] benzofurans,[245] and pyran derivatives[246] have been prepared using this approach. Tetrahydrofurans bearing an exocyclic double bond (vinylidene tetrahydrofurans) were prepared from alkynyl alcohols and a silver carbonate catalyst.[247]

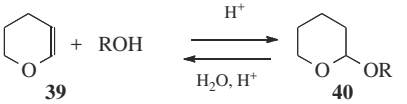
Allenes that react with alcohols and allenic alcohols have been converted to THF derivatives bearing a vinyl group at the α-position, using diphenyliodonium salts.[248] In the presence of allylic bromide and a Pd catalyst, allenic alcohols lead to allylically substituted dihydrofurans.[249] The intramolecular Au(I) catalyzed reaction of alcohols and allenes has been reported.[250] Intramolecular addition of alcohols to allenes leads to cyclic vinyl ethers.[251]

[229] Gruttadauric, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* ***2001****, 42*, 2213.
[230] Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* ***2002****, 67*, 6082; Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* ***2002****, 4*, 4451.
[231] McDonald, F.E.; Towne, T.B. *J. Org. Chem.* ***1995****, 60*, 5750.
[232] Lattanzi, A.; Della Sala, G.D.; Russo, M.; Screttri, A. *Synlett* ***2001***, 1479.
[233] Qian, H.; Han, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004****, 126*, 9536.
[234] Rönn, M.; Bäckvall, J.-E.; Andersson, P.G. *Tetrahedron Lett.* ***1995****, 36*, 7749. See Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* ***1999***, 797.
[235] Han, X.; Widenhoefer, R.A. *J. Org. Chem.* ***2004****, 69*, 1738.
[236] Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***2002****, 124*, 5260.
[237] Yang, C.-G.; Reich, N.W.; Shi, Z.; He, C. *Org. Lett.* ***2005****, 7,* 4553.
[238] Yu, X.; Seo, S.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2007****, 129,* 7244.
[239] Yao, T.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* ***2004****, 126*, 11164.
[240] Kang, S.H.; Park, C.M.; Lee, S.B.; Kim, M. *Synlett* ***2004***, 1279.
[241] Hartman, J.W.; Sperry, L. *Tetrahedron Lett.* ***2004****, 45*, 3787.
[242] Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* ***2005****, 127*, 9976; Santos, L.L.; Ruiz, V.R.; Sabater, M.J.; Corma, A. *Tetrahedron* ***2008****, 64,* 7902.
[243] Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* ***1999****, 64*, 7687.
[244] Qing, F.L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* ***2000****, 65*, 2003. See Kel'in, A.V.; Gevorgyan, V. *J. Org. Chem.* ***2002****, 67*, 95.
[245] Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* ***2000****, 2*, 297. See also, Arcadi, A.; Cacchi, S.; DiGiuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* ***2002***, 453.
[246] Davidson, M.H.; McDonald, F.E. *Org. Lett.* ***2004****, 6,* 1601.
[247] Pale, P.; Chuche, J. *Eur. J. Org. Chem.* ***2000***, 1019.
[248] The phenyl group also added to the allene. Kang, S.-K.; Baik, T.-G.; Kulak, A.N. *Synlett* ***1999***, 324.
[249] Ma, S.; Gao, W. *J. Org. Chem.* ***2002****, 67*, 6104.
[250] Zhang, Z.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* ***2007****, 46,* 283.
[251] Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* ***2004****, 69,* 6867.

Functionalized ethers can be formed in the presence of other reagents. In methanol with a R—Se—Br reagent, alkenes are converted to selenoalkyl ethers (MeO—C—C—SeR).[252]

Base-catalyzed reactions are known. For those substrates more susceptible to nucleophilic attack, for example, polyhalo alkenes and alkenes of the type C=C—Z, it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[253] The reactions with C=C—Z are of the *Michael type*, and OR goes to the side away from the Z.[254]

Since triple bonds are more susceptible to nucleophilic attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction.[255] Because enol ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to enol ethers can also be catalyzed by acids.[256] One utilization of this reaction



39 **40**

involves the compound dihydropyran (**39**), which is often used to protect the OH groups of primary and secondary alcohols[257] and phenols.[258] When the desired reactions are completed, **40** is easily cleaved by treatment with dilute acids (Reaction **10-6**). In base-catalyzed addition to triple bonds, the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions.

Photochemical addition of alcohols to certain double-bond compounds (cyclohexenes, cycloheptenes) is possible[259] in the presence of a photosensitizer (e.g., benzene). The mechanism is electrophilic and *Markovnikov* orientation is found. The alkenes react in their first excited triplet states.[260]

The oxymercuration–demercuration procedure mentioned in Reaction **15-3** can be adapted to the preparation of ethers in what is known as *alkoxymercuration–demercuration* (*Markovnikov* orientation), if the reaction is carried out in an alcohol (ROH) solvent.[261] For example, oxymercuration of 2-methyl-1-butene in ethanol gives $EtMe_2COEt$.[262] Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols, it is necessary to use mercuric trifluoroacetate.[263] However, even this reagent fails where the product would be a ditertiary ether. It is possible to combine the alcohol reactant with another reagent. The reaction of an alkene with iodine and allyl alcohol, in the presence of HgO, gave the *vic*-iodo ether.[264] Alkene-alcohols react with mercuric trifluoroacetate and the aq KBr (with $LiBH_4/BEt_3$) to

[252] Back, T.G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* ***2002****, 67,* 499.
[253] See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965****, 4*, 51, pp. 53–61.
[254] See Farnsworth, M.V.; Cross, M.J.; Louie, J. *Tetrahedron Lett.* ***2004****, 45*, 7441.
[255] Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968****, 37*, 907.
[256] See Kresge, A.J.; Yin, Y. *J. Phys. Org. Chem.* ***1989****, 2,* 43.
[257] See Bolitt, V.; Mioskowski, C.; Shin, D.; Falck, J.R. *Tetrahedron Lett.* ***1988****, 29,* 4583.
[258] See Johnston, R.D.; Marston, C.R.; Krieger, P.E.; Goem G.L. *Synthesis* ***1988***, 393.
[259] See Wan, P.; Yates, K. *Rev. Chem. Intermed.* ***1984****, 5,* 157.
[260] Marshall, J.A. *Acc. Chem. Res.* ***1969****, 2,* 33.
[261] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 162–345.
[262] Brown, H.C.; Rei, M. *J. Am. Chem. Soc.* ***1969****, 91,* 5646.
[263] Brown, H.C.; Kurek, J.T.; Rei, M.; Thompson, K.L. *J. Org. Chem.* ***1984****, 49*, 2551; ***1985****, 50*, 1171.
[264] Talybov, G.M.; Mekhtieva, V.Z.; Karaev, S.F. *Russ. J. Org. Chem.* ***2001****, 37*, 600.

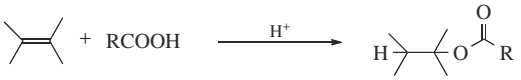
give a THF derivative bearing an iodoalkyl substituent [—O—C—CH(I)R].[265] Alkynes generally react under the same conditions to give acetals. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with $NaBH_4$) is an alkyl peroxide (*peroxy-mercuration*).[266] This can be done intramolecularly.[267]

Both alcohols and phenols add to ketenes to give carboxylic esters [$R_2C{=}C{=}O + ROH \rightarrow R_2CHCO_2R$].[268] This has been done intramolecularly (with the ketene end of the molecule generated and used *in situ*) to form medium- and large-ring lactones.[269] In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates. 1,4-Asymmetric induction is possible when chiral alcohols add to ketenes.[270]

OS **III**, 371, 774, 813; **IV**, 184, 558; **VI**, 916; **VII**, 66, 160, 304, 334, 381; **VIII**, 204, 254; **IX**, 472.

15-6 Addition of Carboxylic Acids to Form Esters

Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to alkenes, a reaction that is usually acid catalyzed (by Brønsted–Lowry or Lewis acids[271]) and similar in mechanism to Reaction **15-5**. Since *Markovnikov's rule* is followed, hard-to-get esters of tertiary alcohols can be prepared from alkenes of the form $R_2C{=}CHR$.[272] Carboxylic esters have also been prepared by the acyloxymercuration–demercuration of alkenes (similar to the procedures mentioned in Reactions **15-3** and **15-4**).[273] Addition of carboxylic acids to alkenes to form esters or lactones is catalyzed by Pd compounds.[274] Thallium acetate also promotes this cyclization reaction.[275] Diene carboxylic acids have been cyclized using acetic acid and a Pd catalyst to form lactones that have an allylic acetate moiety elsewhere in the molecule.[276]

[265] Kang, S.H.; Kim, M. *J. Am. Chem. Soc.* ***2003****, 125*, 4684. For an enantioselective example, see Kang, S.H.; Lee, S.B.; Park, C.M. *J. Am. Chem. Soc.* ***2003****, 125*, 15748.
[266] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 346–366.
[267] Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, F. *Tetrahedron Lett.* ***1995****, 36*, 463.
[268] Quadbeck, G. *Newer Methods Prep. Org. Chem.* ***1963****, 2,* 133–161. See Tidwell, T.T. *Acc. Chem. Res.* ***1990****, 23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986****, 42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975****, 4*, 231.
[269] Boeckman, Jr., R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* ***1989****, 111*, 8286.
[270] Cannizzaro, C.E.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* ***2001****, 123*, 2668.
[271] See Ballantine, J.A.; Davies, M.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 8.
[272] See Peterson, P.E.; Tao, E.V.P. *J. Org. Chem.* ***1964****, 29,* 2322.
[273] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis* Springer, NY, ***1986***, pp. 367–442.
[274] Larock, R.C.; Hightower, T.R. *J. Org. Chem.* ***1993****, 58*, 5298; Annby, U.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* ***1993****, 34*, 8545.
[275] Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* ***1992****, 22*, 399.
[276] Verboom, R.C.; Persson, B.A.; Bäckvall, J.-E. *J. Org. Chem.* ***2004****, 69*, 3102.

Triple bonds can give enol esters[277] or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts,[278] and vinylmercury compounds ($RO_2C—C=C—HgX$) are intermediates,[279] but Ru complexes have also been used.[280] Terminal alkynes ($RC\equiv CH$) react with CO_2, a secondary amine (R'_2NH), and a Ru complex catalyst, to give enol carbamates [$RCH=CHOC(=O)NR$].[281] This reaction has also been performed intramolecularly, to produce unsaturated lactones.[282] Cyclic unsaturated lactones (internal vinyl esters) have been generated from alkyne-carboxylic acids using a Pd[283] or a Ru catalyst.[284] Carboxylic esters can also be obtained by the addition to alkenes of diacyl peroxides.[285] These reactions are catalyzed by Cu and are free radical processes.

Allene carboxylic acids have been cyclized to butenolides with copper(II) chloride.[286] Allene esters were converted to butenolides by treatment with acetic acid and LiBr.[287] Cyclic carbonates can be prepared from allene alcohols using carbon dioxide and a Pd catalyst.[288] Carboxylic acids react with ketenes to give anhydrides[289] and acetic anhydride is prepared industrially in this manner [$CH_2=C=O + MeCO_2H \rightarrow (MeC=O)_2O$].

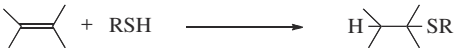
Sulfonic acids add to alkenes and alkynes. The reaction of an alkyne with *p*-toluenesulfonic acid and treatment with silica gives the vinyl sulfonate ($C=C—OSO_2Tol$).[290] Cyclic sulfonates can be generated by the reaction of an allylic sulfonate salt ($C=C—C—OSO_3^-$) with silver nitrate in acetonitrile containing an excess of bromine and a catalytic amount of water.[291] Sultones are formed when alkenes react with PhIO and 2 equiv of Me_2SiSO_3Cl.[292]

OS **III**, 853; **IV**, 261, 417, 444; **V**, 852, 863; **VII**, 30, 411. Also see, OS **I**, 317.

C. Sulfur on the Other Side

15-7 Addition of H_2S and Thiols

Hydro-alkylthio-addition



[277] Goossen, L.J.; Paetzold, J.; Koley, D. *Chem. Commun.* ***2003***, 706. See Hua, R.; Tian, X. *J. Org. Chem.* ***2004***, *69*, 5782.
[278] See Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P.H. *Organometallics* ***1990***, *9*, 1155.
[279] Bassetti, M.; Floris, B. *J. Chem. Soc. Perkin Trans. 2,* ***1988***, 227; Grishin, Yu.K.; Bazhenov, D.V.; Ustynyuk, Yu.A.; Zefirov, N.S.; Kartashov, V.R.; Sokolova, T.N.; Skorobogatova, E.V.; Chernov, A.N. *Tetrahedron Lett.* ***1988***, *29*, 4631.
[280] Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* ***1987***, *52*, 2230
[281] Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* ***1989***, *54,* 1518.
[282] See Sofia, M.J.; Katzenellenbogen, J.A. *J. Org. Chem.* ***1985***, *50*, 2331. For a list of other examples, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 1895.
[283] Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* ***1995***, *60*, 3711
[284] Jiménez-Tenorio, M.; Puerta, M.C.; Valerga, P.; Moreno-Dorado, F.J.; Guerra, F.M.; Massanet, G.M. *Chem. Commun.* ***2001***, 2324.
[285] Kharasch, M.S.; Fono, A. *J. Org. Chem.* ***1959***, *24*, 606; Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 1572.
[286] Ma, S.; Wu, S. *J. Org. Chem.* ***1999***, *64*, 9314.
[287] Ma, S.; Li, L.; Wei, Q.; Xie, H.; Wang, G.; Shi, Z.; Zhang, J. *Pure. Appl. Chem.* ***2000***, *72*, 1739.
[288] Uemura, K.; Shiraishi, D.; Noziri, M.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1063.
[289] See Blake, P.G.; Vayjooee, M.H.B. *J. Chem. Soc. Perkin Trans. 2,* ***1976***, 1533.
[290] Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 371.
[291] Steinmann, J.E.; Phillips, J.H.; Sanders, W.J.; Kiessling, L.L. *Org. Lett.* ***2001***, *3,* 3557.
[292] Bassindale, A.R.; Katampe, I.; Maesano, M.G.; Patel, P.; Taylor, P.G. *Tetrahedron Lett.* ***199***, *40*, 7417.

Hydrogen sulfide (H_2S) and thiols add to alkenes to give alkyl thiols or sulfides by electrophilic, nucleophilic, or free radical mechanisms.[293] In the absence of initiators, the addition to simple alkenes is by an electrophilic mechanism, similar to that in Reaction **15-5**, and *Markovnikov's rule* is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless a Brønsted–Lowry or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated H_2SO_4[294] or with the addition of $AlCl_3$.[295] In the presence of free radical initiators, H_2S and thiols add to double and triple bonds by a free radical mechanism and the orientation is *anti-Markovnikov*.[296] *Anti-Markovnikov* addition of thiols to vinyl ethers occurs under solvent- and catalyst-free conditions,[297] and is promoted by water.[298]

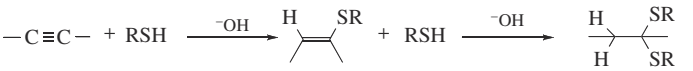
Additives can influence the regioselectivity. Styrene reacts with thiophenol to give primarily the *anti-Markovnikov* product, whereas addition of thiophenol in the presence of Montmorillonite K-10 clay gives primarily the *Markovnikov addition* product.[299] The addition of thiophenol to an alkene with a zeolite, however, leads to the *anti-Markovnikov* sulfide.[300] In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free radical addition can be done with H_2S, RSH (R may be primary, secondary, or tertiary), ArSH, or RCOSH.[301] The R group may contain various functional groups. The alkenes may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, CO_2H, CO_2R, NO_2, RSO_2, and so on. Addition of Ph_3SiSH to terminal alkenes under radical conditions also leads to the primary thiol.[302]

Alkynes react with thiols to give vinyl sulfides. With alkynes it is possible to add 1 or 2 molar equivalents of RSH, giving a vinyl sulfide[303] or a dithioketal, respectively. Thiols also add to alkynes with a Pd catalyst to give vinyl sulfides.[304] Thiols add to alkenes under photochemical conditions to form thioethers, and the reaction can be done intramolecularly to give cyclic thioethers.[305] Thiocarbonates function as thiol surrogates, converting alkenes to alkyl thiols in the presence of $TiCl_4$ and CuO.[306] Sulfonic acids add to alkynes to give vinyl sulfonates in the presence of a Au catalyst.[307] A cesium carbonate catalyzed reaction

[293] See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 169–178.
[294] Shostakovskii, M.F.; Kul'bovskaya, N.K.; Gracheva, E.P.; Laba, V.I.; Yakushina, L.M. *J. Gen. Chem. USSR* ***1962****, 32*, 707.
[295] Belley, M.; Zamboni, R. *J. Org. Chem.* ***1989****, 54*, 1230.
[296] See Voronkov, M.G.; Martynov, A.V.; Mirskova, A.N. *Sulfur Rep.,* ***1986****, 6,* 77; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1970****, 9,* 273; Oswald, A.A.; Griesbaum, K. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds, Vol. 2*, Pergamon, Elmsford, NY, ***1966***, pp. 233–256; Stacey, F.W.; Harris, Jr., J.F. *Org. React.* ***1963****, 13*, 150, pp. 165–196, 247–324.
[297] Lou, F.-W.; Xu, J.-M.; Liu, B.-K.; Wu, Q.; Pan, Q.; Lin, X.-F. *Tetrahedron Lett.* ***2007****, 48,* 8815. For a solvent free, Ce(III)-promoted reaction, see Silveira, C.C.; Mendes, S.R.; Líbero, F.M. *Synlett* ***2010***, 790.
[298] Ranu, B.C.; Mandal, T. *Synlett* ***2007****, 9*25; Ranu, B.C. *Can. J. Chem.* ***2009****, 87*, 1605.
[299] Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.* ***2001****, 42,* 3791.
[300] Kumar, P.; Pandey, R.K.; Hegde, V.R. *Synlett* ***1999***, 1921.
[301] Janssen, M.J. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 720–723.
[302] Haché, B.; Gareau, Y. *Tetrahedron Lett.* ***1994****, 35,* 1837.
[303] See Arjona, O.; Medel, R.; Rojas, J.; Costa, A.M.; Vilarrasa, J. *Tetrahedron Lett.* ***2003****, 44*, 6369.
[304] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* ***1992****, 114*, 5902.
[305] Kirpichenko, S.V.; Tolstikova, L.L.; Suslova, E.N.; Voronkov, M.G. *Tetrahedron Lett.* ***1993****, 34*, 3889.
[306] Mukaiyama, T.; Saitoh, T.; Jona, H. *Chem. Lett.* ***2001***, 638.
[307] Cui, D.-M.; Meng, Q.; Zheng, J.-Z.; Zhang , C. *Chem. Commun.* ***2009***, 1577.

gives the vinyl sulfide with good (*Z*)-selectivity.[308] The Rh^{-}[309] In^{-},[310] organoactinide^{-},[311] organozirconium-,[312] or Pt catalyzed[313] reaction of alkynes with thiols gives the corresponding vinyl sulfide. Similar results were obtained under solvent-free conditions using an alumina–KF system.[314] Alternative preparations are available, as in the reaction of a terminal alkyne with $Cp_2Zr(H)Cl$ followed by PhSCl to give the vinyl sulfide with the SPh unit at the less substituted position (PhCH=CHSPh).[315] The intramolecular addition of a thiol to an ene–yne, with a Pd catalyst, leads to substituted thiophene derivatives.[316] Alkenes react with diphenyl disulfide in the presence of $GaCl_3$ to give the product with two phenylthio units (PhS—C—C—SPh).[317] The reaction of an alkyne with diphenyl disulfide and a Pd catalyst leads to the bis(vinyl) sulfide (PhS—C=C—SPh).[318]

When thiols are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the *Michael type*[319] or may be polyhalo alkenes or alkynes.[255] As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



By any mechanism, the initial product of addition of H_2S to a double bond is a thiol, which is capable of adding to a second molecule of alkene, so that sulfides are often produced: C=C → H—C—C—S—C—C—H. As with alcohols, ketenes add thiols to give thiol esters [$R_2C{=}C{=}O + RSH \rightarrow R_2CHCOSR$].[320]

Selenium compounds (RSeH) add in a similar manner to thiols.[321] Vinyl selenides can be prepared from alkynes using diphenyl diselenide and sodium borohydride.[322] A Pd(II) catalyzed reaction of PhSeH with alkynes, in pyridine, also gives the corresponding vinyl selenide.[323]

The conjugate addition of thiols to α,β-unsaturated carbonyl derivatives is discussed in Reaction **15-31**.

OS **III**, 458; **IV**, 669; **VIII**, 302. See also, OS **VIII**, 458.

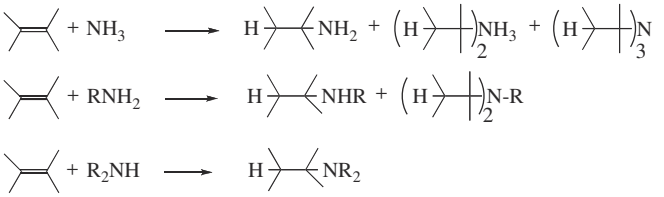
[308] Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* ***2005****, 70,* 6468.
[309] Cao, C.; Fraser, L.R.; Love, J.A. *J. Am. Chem. Soc.* ***2005****, 127*, 17614; Yang, J.; Sabarre, A.; Fraser, L.R.; Patrick, B.O.; Love, J.A. *J. Org. Chem.* ***2009****, 74*, 182.
[310] Yadav, J.S.; Subba Reddy, B.V.; Raju, A.; Ravindar, K.; Baishya, G. *Chem. Lett.* ***2007****, 36,* 1474
[311] Weiss, C.J.; Wobser, S.D.; Marks, T.J. *J. Am. Chem. Soc.* ***2009****, 131,* 2062.
[312] Weiss, C.J.; Marks, T.J. *J. Am. Chem. Soc.* ***2010****, 132*, 10533.
[313] Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* ***2008****, 10,* 101.
[314] Silva, M.S.; Lara, R.G.; Marczewski, J.M.; Jacob, R.G.; Lenardão, E.J.; Perin, G. *Tetrahedron Lett.* ***2008****, 49, 19*27.
[315] Huang, X.; Zhong, P.; Guo, W.-r. *Org. Prep. Proceed. Int.* ***1999****, 31,* 201.
[316] Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* ***2000****, 2*, 351.
[317] Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004****, 6*, 601.
[318] Ananikov, V.P.; Beletskaya, I.P. *Org. Biomol. Chem.* ***2004****, 2*, 284.
[319] See Gassman, P.G.; Gilbert, D.P.; Cole, S.M. *J. Org. Chem.* ***1977****, 42,* 3233.
[320] See Blake, A.J.; Friend, C.L.; Outram, R.J.; Simpkins, N.S.; Whitehead, A.J. *Tetrahedron Lett.* ***2001****, 42,* 2877.
[321] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett.* ***1992****, 33*, 5525.
[322] Dabdoub, M.J.; Baroni, A.C.M.; Lenardão, E.J.; Gianeti, T.R.; Hurtado, G.R. *Tetrahedron* ***2001****, 57*, 4271.
[323] Kamiya, I.; Nishinaka, E.; Ogawa, A. *J. Org. Chem.* ***2005****, 70*, 696.

D. Nitrogen or Phosphorus on the Other Side

15-8 Addition of Ammonia and Amines, Phosphines, and Related Compounds[324]

Hydro-amino-addition

Hydro-phosphino-addition



Ammonia and primary and secondary amines add to alkenes *in some cases*.[325] Ammonia and amines are much weaker acids than water, alcohols, and thiols (see Reactions **15-3**, **15-5**, and **15-7**) and since acids turn NH_3 into the weak acid, the ammonium ion (NH_4^+), this reaction does not occur by an electrophilic mechanism. The reaction tends to give very low yields, if any, with ordinary alkenes, unless extreme conditions are used (e.g., 178–200 °C, 800–1000 atm, and the presence of metallic Na, for the reaction between NH_3 and ethylene[326]). There is, however, a proton-catalyzed hydroamination reaction in which aniline derivatives add to alkenes in the presence of anilinium salts, in 20–90% yield depending on the alkene.[327]

There are many examples of transition-catalyzed addition of nitrogen compounds to alkenes, alkynes,[328] and so on. Amines can be added to certain nonactivated alkenes using Pd,[329] Rh,[330] In,[331] Ti,[332] Fe,[333] Ta,[334] Au,[335] Y,[336] Mo,[337] and various lanthanide catalysts.[338] 1,3-Dienes,[339] and also allenes,[340] undergo hydroamination in the presence

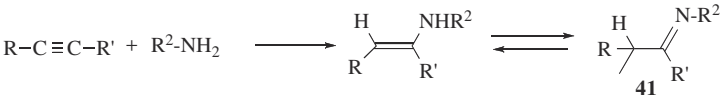
[324] Müller, T.E.; Hultzsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* ***2008****, 108*, 3795.
[325] See Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983****, 39*, 703; Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds* Academic Press, NY, ***1977***, pp. 423–454; Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C.G.; Seayad, J.; Thiel, O.R.; Tillack, A.; Trauthwein, H. *Synlett* ***2002***, 1579. For selectivity, see Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* ***2004****, 45*, 8875.
[326] Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954****, 76*, 1899.
[327] Anderson, L.L.; Arnold, J.; Bergman, R.G. *J. Am. Chem. Soc.* ***2005****, 127*, 14542.
[328] For a review, see Doye, S. *Synlett* ***2004***, 1653.
[329] See Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983****, 39*, 703; Bäckvall, J. *Adv. Met.-Org. Chem.* ***1989****, 1*, 135. Also see Rogers, M.M.; Kotov, V.; Chatwichien, J.; Stahl, S.S. *Org. Lett.* ***2007****, 9,* 4331. See also Singer, R.A.; Doré, M.; Sieser, J.E.; Berliner, M.A. *Tetrahedron Lett.* ***2006****, 47,* 3727.
[330] The anti-Markovkinov amine is produced: Utsonomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2004****, 126*, 2702; Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* ***2005****, 46,* 7401. For mechansitic studies, see Takaya, J.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2005****, 127,* 5756.
[331] Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett* ***2007****, 48*, 3375.
[332] Kaspar, L.T.; Fingerhut, B.; Ackermann, L. *Angew. Chem. Int. Ed.* ***2005****, 44,* 5972.
[333] Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* ***2007***, 2601.
[334] Herzon, S.B.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007****, 129*, 6690.
[335] Hesp, K.D.; Stradiotto, M. *J. Am. Chem. Soc.* ***2010****, 132,* 18026.
[336] O'Shaughnessy, P.N.; Scott, P. *Tetrahedron Asymmetry* ***2003****, 14,* 1979.
[337] Srivastava, R.S.; Nicholas, K.M. *Chem. Commun.* ***1996***, 2335.
[338] Hultzsch, K.C. Org. Biomol. Chem. **2005**, 3, 1819; Yin, P.; Loh, T.-P. Org. Lett. **2009**, 11, 3791. See Reznichenko, A.L.; Nguyen, H.N.; Hultzsch, K.C. Angew. Chem. Int. Ed. **2010**, 49, 8984.
[339] Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* ***2006****, 45*, 1744.
[340] Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* ***2006****, 45*, 3314.

of an Au catalyst. Complexation with the metal lowers the electron density of the double bond, facilitating nucleophilic attack.[341] *Markovnikov* orientation is observed and the addition is anti.[342] Aniline reacts with dienes and a Pd catalyst to give allylic amines.[343] Diene amines react with Sm catalysts to give 2-alkenyl pyrrolidines.[344] The mechanism of the Au(I) catalyzed hydroamination reaction of alkenes has been studied.[345] It is believed to involve a ligand substitution reaction in the active Au species followed by nucleophile attack of the N-nucleophile on the activated double bond, which is followed by proton transfer from the NH_2 group to the unsaturated carbon atom.

Cyclization reactions are useful variations of this reaction. An intramolecular addition of an amine unit to an alkene to form a pyrrolidine was reported using a Pd[346] Rh,[347] Sc,[348] Sm,[349] Ti,[350] Zr,[351] or a Lu catalyst.[352] as well as a lanthanide reagent,[353] or a Y reagent.[354] An intramolecular Ca mediated reaction of amino alkenes leads to cyclic amines.[355] Alkenyl amines give cyclic amines as the major product, in good yield, when treated with *n*-butyllithium.[356] Reaction of a secondary amine with butyllithium generates an amide base, which reacts with alkenes to give alkyl amines,[357] and can add intramolecularly to an alkene to form a pyrrolidine.[358] Pyrroles can be generated in this manner.[359]

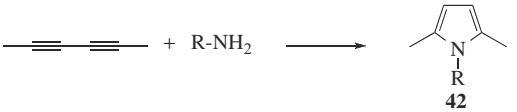
Other nitrogen compounds, among them hydroxylamine and hydroxylamines,[360] hydrazines, and amides (Reaction **15-9**), also add to alkenes. Tertiary amines (except those that are too bulky) add to *Michael-type* substrates (C=C—Z) in a reaction that is catalyzed by acids like HCl or HNO_3 to give the corresponding quaternary ammonium salts (R_3N^+—C—C—Z).[361] The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine). The reaction of NaOH with an amine containing two distal alkene units, followed by addition of a neodymium catalyst, leads to a bicyclic amine.[362]

[341] See Hegedus, L.S.; Åkermark, B.; Zetterberg, K.; Olsson, L.F. *J. Am. Chem. Soc.* ***1984****, 106,* 7122.
[342] See Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003****, 125*, 14286.
[343] Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* ***2001****, 40*, 4501.
[344] Hong, S.; Marks, T.J. *J. Am. Chem. Soc.* ***2002****, 124,* 7886.
[345] Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* ***2008****, 130,* 853.
[346] Ney, J.E.; Wolfe, J.P. J. *Am. Chem. Soc.* ***2005****, 127*, 8644. See also, Sakai, N.; Ridder, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006****, 128,* 8134; Rogers, M.M.; Wendlandt, J.E.; Guzei, I.A.; Stahl, S.S. *Org. Lett.* ***2006****, 8,* 2257.
[347] Takemiya, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006****, 128,* 6042; Liu, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2008****, 130,* 1570.
[348] Kim, J.Y.; Livinghouse, T. *Org. Lett.* ***2005****, 7*, 4391.
[349] Quinet, C.; Ates, A.; Markó, I.E. *Tetrahedron Lett.* ***2008****, 49,* 5032.
[350] Müller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* ***2006***, 2499.
[351] Kim, H.; Lee, P.H.; Livinghouse, T. *Chem. Commun.* ***2005***, 5205; Yang, L.; Xu, L.-W.; Zhou, W.; Gao, Y.-H.; Sun, W.; Xia, C.-G. *Synlett* ***2009***, 1167.
[352] Gribkov, D.V.; Hultzsch, K.C.; Hampel, F. *J. Am. Chem. Soc.* ***2006****, 128*, 3748.
[353] Ryu, J.-S.; Marks, T.J.; McDonald, F.E. *Org. Lett.* ***2001****, 3*, 3091. See Hong, S.; Tian, S.; Metz, M.V.; Marks, T. J. *J. Am. Chem. Soc.* ***2003****, 125*, 14768.
[354] Kim, Y.K.; Livinghouse, T.; Bercaw, J.E. *Tetrahedron Lett.* ***2001****, 42*, 2933.
[355] Crimmin, M.R.; Casely, I.J.; Hill, M.S. *J. Am. Chem. Soc.* ***2005****, 127,* 2042.
[356] Ates, A.; Quinet, C. *Eur. J. Org. Chem.* ***2003***, 1623.
[357] Hartung, C.G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* ***2000****, 56*, 5157.
[358] Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* ***1992****, 33*, 6359.
[359] Dieter, R.K.; Yu, H. *Org. Lett.* ***2000****, 2,* 2283.
[360] Singh, S.; Nicholas, K.M. *Synth. Commun.* ***2001****, 31*, 3087.
[361] Le Berre, A.; Delacroix, A. *Bull. Soc. Chim. Fr.* ***1973***, 640, 647. See also, Vogel, D.E.; Büchi, G. *Org. Synth., 66,* 29.
[362] Molander, G.A.; Pack, S.K. *J. Org. Chem.* ***2003****, 68*, 9214.



41

Primary amines add to triple bonds[363] to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize (Sec. 2.N.ii, category 4) to the more stable imines (**41**).[364] The reaction has been done with a Pd,[365] a Ti,[366] a Ta,[367] a Cu,[368] or an Au catalyst.[369] An intramolecular addition of amines to an alkyne unit in the presence of a Pd catalyst generated heterocyclic or cyclic amine compounds.[370] A variation treats an alkynyl imine with CuI to form pyrroles.[371] *N,N*-Diphenylhydrazine reacts with diphenyl acetylene and a Ti catalyst to give indole derivatives.[372] Treatment of an imine of 2-alkynyl benzaldehyde with iodide gave a functionalized isoquinoline.[373] When ammonia is used instead of a primary amine, the corresponding $R_2C{=}NH$ imine product is not stable enough for isolation, but polymerizes. Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles (**42**).[374] *Anti-Markovnikov* addition of alkynes is possible using a Cu catalyst.[375]

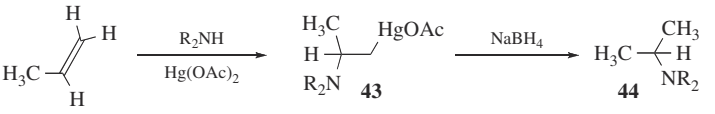


42

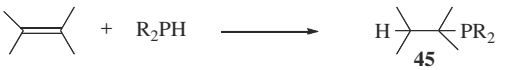
A related reaction of amines and alkynes, in supercritical CO_2, leads to amides.[376]

Allenes are reaction partners,[377] and amines add to allenes in the presence of a catalytic amount of CuBr,[378] Au,[379] or Pd compounds.[380] Intramolecular reaction of allene amines leads to dihydropyrroles, using a Au catalyst.[381] Cyclic imines can be prepared from allene amines using a Ti catalyst.[382]

[363] See Chekulaeva, I.A.; Kondrat'eva, L.V. *Russ. Chem. Rev.* ***1965****, 34,* 669; Hartung, C.G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* ***2001****, 66*, 6339.
[364] See Kruse, C.W.; Kleinschmidt, R.F. *J. Am. Chem. Soc.* ***1961****, 83,* 213, 216.
[365] Patil, N.T.; Lutete, L.M.; Wu, H.; Pahadi, N.K.; Gridnev, I.D.; Yamamoto, Y. *J. Org. Chem.* ***2006****, 71,* 4270.
[366] Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* ***2003****, 5*, 4767; Tillack, A.; Castro, I.G.; Hartung, C.G.; Beller, M. *Angew. Chem. Int. Ed.* ***2002****, 41*, 2541; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* ***2001***, 4411.
[367] Anderson, L.L.; Arnold, J.; Bergman R.G. *Org. Lett.* ***2004****, 6,* 2519; Cao, C.; Li, Y.; Shi, Y.; Odom, A.L. *Chem. Commun.,* ***2004***, 2002.
[368] Shanbhag, G.V.; Kumbar, S.M.; Joseph, T.; Halligudi, S.B. *Tetrahedron Lett.* ***2006****, 47,* 141.
[369] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* ***2003****, 5,* 3349.
[370] MülHiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* ***2004****, 6,* 2953; Lutete, L.M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2004****, 126*, 1622. See also, Karur, S.; Kotti, S.R.S.S.; Xu, X.; Cannon, J.F.; Headley, A.; Li, G. *J. Am. Chem. Soc.* ***2003****, 125*, 13340.
[371] Kel'in, A.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2001****, 123,* 2074.
[372] Ackermann, L.; Born, R. *Tetrahedron Lett.* ***2004****, 45*, 9541. For a different approach using hypervalent iodine, see Barluenga, J.; Trincado, M.; Rubio, E.; González, J.M. *Angew. Chem. Int. Ed.* ***2003****, 42,* 2406.
[373] Huang, Q.; Hunter, J.A.; Larock, R.C *J. Org. Chem.* ***2002****, 67,* 3437.
[374] Schult, K.E.; Reisch, J.; Walker, H. *Chem. Ber.* ***1965****, 98,* 98.
[375] Zhou, L.; Bohle, D.S.; Jiang, H.-F.; Li, C.-J. *Synlett* ***2009***, 937.
[376] Mak, X.Y.; Ciccolini, R.P.; Robinson, J.M.; Tester, J.W.; Danheiser, R.L. *J. Org. Chem.* ***2009****, 74,* 9381.
[377] Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* ***1998****, 39*, 5421.
[378] Geri, R.; Polizzi, C.; Lardicci, L.; Caporusso, A.M. *Gazz. Chim. Ital.,* ***1994****, 124*, 241.
[379] Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* ***2009****, 11,* 3166.
[380] Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* ***1993***, 85.
[381] Morita, N.; Krause, N. *Org. Lett.* ***2004****, 6,* 4121.
[382] Ackermann, L.; Bergman, R.G.; Loy, R.N. *J. Am. Chem. Soc.* ***2003****, 125,* 11956.



A NH_2 or NR_2 unit can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (Reaction **15-16**) followed by treatment with NH_2Cl or NH_2OSO_2OH (Reaction **12-32**). This produces a primary amine with *anti-Markovnikov* orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration to give **43**, followed by reduction (see Reaction **15-3** for the analogous *oxymercuration–demercuratio*n procedure) to give amine **44**.[383] The addition of a secondary amine produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows *Markovnikov's rule*. For conversion of **43** to other products, see Reaction **15-53**.



Phosphines add to alkenes to give alkyl phosphines (**45**) and to alkynes to give vinyl phosphines. A Pd catalyzed reaction of alkenes and triarylphosphines gives alkyltriarylphosphonium salts.[384] Alkenes also react with diarylphosphines and a Ni catalyst to give the alkyl phosphine.[385] Silylphosphines ($R_3Si—PAr_2$) react with alkenes and Bu_4NF to give the *anti-Markovnikov* allyl phosphine.[386] Phosphine oxides can be prepared by the reaction of an aryl substituted alkene and diphenylphosphine oxide, $Ph_2P(=O)H$.[387] Phosphonate esters were similarly prepared from alkenes and diethyl phosphite [$(EtO)_2P(=O)H$] and an Mn catalyst in a reaction exposed to oxygen.[388] Similar addition was observed in the reaction of an alkene with NaH_2PO_2 to give the phosphinate [$RCH=CH_2 \rightarrow RCH_2CH_2PH(=O)ONa$].[389] Palladium catalysts were used for the preparation of similar compounds from alkenes[390] and the reaction of terminal alkynes with dimethyl phosphite and a Ni catalyst gave the *Markovnikov* vinyl phosphonate ester.[391]

In the presence of an Yb catalyst, diphenylphosphine added to diphenyl acetylene to give the corresponding vinyl phosphine.[392] A Pd catalyst was used for the addition of diphenylphosphine to terminal alkynes, giving the *anti-Markovnikov* vinyl phosphine, but a Ni catalyst led to the *Markovnikov* vinyl phosphine.[393] A Co catalyst has also been used.[394] Diphenylphosphine oxide also reacted with terminal alkynes to give the

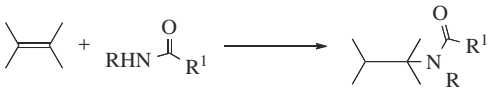
[383] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 443–504. See also, Barluenga, J.; Perez-Prieto, J.; Asensio, G. *Tetrahedron* ***1990***, *46,* 2453.
[384] Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2006***, *128,* 50. See Kawaguchi, S.-i.; Nagata, S.; Nomoto, A.; Sonoda, M.; Ogawa, A. *J. Org. Chem.* ***2008***, *73,* 7928.
[385] Shulyupin, M.O.; Kazankova, M.A.; Beletskaya, I.P. *Org. Lett.. 2002, 4*, 761.
[386] Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* ***2004***, *45,* 9167.
[387] Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* ***2004***, *69*, 4595.
[388] Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69,* 5494.
[389] Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* ***2001***, *66*, 6745.
[390] Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9386.
[391] Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* ***2004***, *126*, 5080.
[392] Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* ***2003***, *68*, 6554.
[393] Kazankova, M.A.; Efimova, I.V.; Kochetkov, A.N.; Atanas'ev, V.V.; Beletskaya, I.P.; Dixneuf, P.H. *Synlett* ***2001***, 497.
[394] Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* ***2005***, *44,* 2368.

anti-Markovnikov vinyl phosphine oxide using an Rh catalyst.[395] Other phosphites were added to dienes to give an allylic phosphonate ester using a Pd catalyst.[396] Diarylphosphines react with vinyl ethers and a Ni catalyst to give α-alkoxy phosphonate esters.[397]

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **VI**, 75, 943; **VIII**,188, 190, 536; **80**, 75. See also, OS **VI**, 932.

15-9 Addition of Amides

Hydro-amido-addition



Under certain conditions, primary and secondary amides can add directly to alkenes to form *N*-alkylated amides. Sulfonamides react in a similar manner. Alkenes react with amides and related compounds in the presence of certain transition metals. The Ti catalyzed reaction of alkenyl *N*-tosylamines gives *N*-tosyl cyclic amines.[398]

The reaction can be done intramolecularly. 3-Pentenamide cyclized to 5-methyl-2-pyrrolidinone by treatment with trifluorosulfonic acid.[399] *N*-Benzyl pent-4-ynamide reacted with tetrabutylammonium fluoride to an alkylidene lactam.[400] Acyl hydrazine derivatives also cyclize in the presence of hypervalent iodine reagents to give lactams.[401] Treatment of triflamide alkenes with triflic acid gives the corresponding *N*-triflyl cyclic amine.[402] Intramolecular cyclization of sulfamate esters, catalyzed by a Rh complex, leads to cyclic sulfamates.[403]

Alkynes and allenes also react with amides. A Ru/In catalyzed addition of sulfonamides to alkynes leads to cyclic *N*-sulfonyl derivatives.[404] Palladium-catalyzed reactions give similar results,[405] and Bi and Hf have been used as catalysts.[406] Phenylthiomethyl alkynes were converted to *N*-Boc-*N*-phenylthio allenes with Boc azide and an iron catalyst.[407] Enamides are prepared by the Re[408] or Ru catalyzed[409] hydroamidation of terminal alkynes with amides. The Pd catalyzed reaction of an allene amide, with iodobenzene, leads to *N*-sulfonyl aziridines having an allylic group at C-1.[410] Other allene *N*-tosylamines similarly give *N*-tosyl tetrahydropyridines.[411]

[395] Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* ***2001****, 66*, 5929.
[396] Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* ***2001****, 42*, 297.
[397] Kazankova, M.A.; Shulyupin, M.O.; Beletskaya, I.P. *Synlett* ***2003***, 2155.
[398] Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* ***2000****, 2*, 385.
[399] Marson, C.M.; Fallah, A. *Tetrahedron Lett.* ***1994****, 35*, 293.
[400] Jacobi, P.A.; Brielmann, H.L.; Hauck, S.I. *J. Org. Chem.* ***1996****, 61*, 5013.
[401] Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* ***1992****, 33*, 5717.
[402] Schlummer, B.; Hartwig, J.F. *Org. Lett.* ***2002****, 4*, 1471; Haskins, C.M.; Knight, D.W. *Chem. Commun.* ***2002***, 2724.
[403] Zalatan, D.N.; Du Bois, J. *J. Am. Chem. Soc.* ***2008****, 130,* 9220.
[404] Trost, B.M.; Maulide, N.; Livingston, R.C. *J. Am. Chem. Soc.* ***2008****, 130,* 16502.
[405] Bajracharya, G.B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* ***2005****, 70*, 4883; Patil, N.T.; Huo, Z.; Bajracharya, G.B.; Yamamoto, Y. *J. Org. Chem.* ***2006****, 71,* 3612; Narsireddy, M.; Yamamoto, Y. *J. Org. Chem.* ***2008****, 73,* 9698.
[406] Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chemistry: Asian J.* ***2007****, 2,* 150.
[407] Bacci, J.P.; Greenman, K.L.; van Vranken, D.L. *J. Org. Chem.* ***2003*** *68*, 4955.
[408] Yudha S., S.; Kuninobu, Y.; Takai, K. *Org. Lett.* ***2007****, 9,* 5609.
[409] Gooßen, L.J.; Salih, K.S.M.; Blanchot, M. *Angew. Chem. Int. Ed.* ***2008****, 47*, 8492.
[410] Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* ***1999****, 64*, 2992.
[411] Na, S.; Yu, F.; Gao, W. *J. Org. Chem.* ***2003****, 68,* 5943; Ma, S.; Gao, W. *Org. Lett.* ***2002****, 4*, 2989.

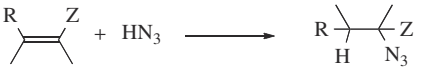
N-Bromocarbamates also add to alkenes, in the presence of $BF_3 \cdot OEt_2$ to give a *vic*-bromo *N*-Boc amine.[412] When a carbamate was treated with Bu_3SnH, and AIBN, addition to an alkene led to a bicyclic lactam.[413] Alkenyl amides and carbamates react with transition metal catalysts to form lactams or cyclic carbamates. Similar addition of a tosylamide–alkene, with a Pd catalyst, led to a vinyl *N*-tosyl pyrrolidine.[414] Both Pd[415] and Au[416] catalyzed cyclization reactions of carbamates are known, and Os compounds have been used.[417] Ionic liquids have been used to catalyze these reactions.[418]

Imides can also add to alkenes or alkynes. Phthalimide reacts with an alkene in the presence of a Pd catalyst.[419] Ethyl 2-propynoate reacted with phthalimide, in the presence of a Pd catalyst, to give ethyl 2-phthalimido-2-propenoate.[420]

Nickel-catalyzed hydrophosphinylation reactions are known, such as the reaction of an alkyne with an alkyl phosphinate to give a vinyl phosphinate ester.[421] Both H-phosphinates and secondary phosphine oxides add to alkenes in an *anti-Markovnikov* manner, induced by air in what is likely a radical reaction.[422]

15-10 Addition of Hydrazoic Acid

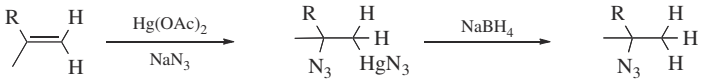
Hydro-azido-addition



Hydrazoic acid (HN_3) can be added to certain Michael-type substrates (Z is as defined in Sec. 15.A.ii) to give β-azido compounds.[423] The reaction apparently fails if R is phenyl. Hydrazoic acid also adds to enol ethers $CH_2{=}CHOR$ to give $CH_3{-}CH(OR)N_3$, and to silyl enol ethers,[424] but it does not add to ordinary alkenes unless a Lewis acid catalyst (e.g., $TiCl_4$) is used, in which case good yields of azide can be obtained.[424]

[412] Sliwnska, A.; Zwierzak, A. *Tetrahedron* ***2003****, 59*, 5927.
[413] Callier, A.-C.; Quiclet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* ***1994****, 35*, 6109.
[414] Larock, R.C.; Hightower, T.R.; Hasvold, L.A.; Peterson, K.P. *J. Org. Chem.* ***1996****, 61*, 3584. See also, Pinho, P.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* ***2003****, 5*, 259. For an electrochemical variation, see Xu, H.-C; Moeller, K. D. *J. Am. Chem. Soc.* ***2008****, 130,* 13542.
[415] Alexanian, E.J.; Lee, C.; Sorensen, E.J. *J. Am. Chem. Soc.* ***2005****, 127*, 7690; Michael, F.E.; Cochran, B.M. *J. Am. Chem. Soc.* ***2006****, 128,* 4246. For a related reaction, see Zabawa, T.P.; Kasi, D.; Chemler, S.R. *J. Am. Chem. Soc.* ***2005****, 127,* 11250.
[416] Zhang, Z.; Liu, C.; Kinder, R.E.; Han, X.; Qian, H.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2006****, 128,* 9066; LaLonde, R.L.; Sherry, B.D.; Kang, E.J.; Toste, F.D. *J. Am. Chem. Soc.* ***2007****, 129,* 2452; Han, X.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* ***2006****, 45,* 1747.
[417] Donohoe, T.J.; Chughtai, M.J.; Klauber, D.J.; Griffin, D.; Campbell, A.D. *J. Am. Chem. Soc.* ***2006****, 128,* 2514.
[418] Yang, L.; Xu, L.-W.; Xia, C.-G. *Synthesis* ***2009***, 1969.
[419] Brice, J.L.; Harang, J.E.; Timokhin, V.I.; Anastasi, N.R.; Stahl, S.S. *J. Am. Chem. Soc.* ***2005****, 127,* 2868; Liu, G.; Stahl, S.S. *J. Am. Chem. Soc.* ***2006****, 128,* 7179; Qian, H.; Widenhoefer, R.A. *Org. Lett.* ***2005****, 7,* 2635.
[420] Trost, B.M.; Dake, G.R. *J. Am. Chem. Soc.* ***1997****, 119*, 7595.
[421] Ribière, P,; Bravo-Altamirano, K.; Antczak, M.I.; Hawkins, J.D.; Montchamp, J.-L. *J. Org. Chem.* ***2005****, 70,* 4064.
[422] Hirai, T.; Han, L.-B. *Org. Lett.* ***2007****, 9,* 53.
[423] Harvey, G.R.; Ratts, K.W. *J. Org. Chem.* ***1966****, 31,* 3907. See Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 120–136.
[424] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984****, 49,* 4237.

Hydrazoic acid can also be added indirectly to ordinary alkenes by azidomercuration, followed by demercuration,[425] analogous to the

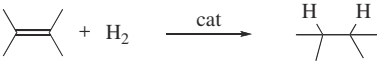


similar procedures mentioned in Reactions **15-3**, **15-5**, **15-6**, and **15-8**. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene), but fails for unstrained internal alkenes. A variation is the hydroazidation reaction of alkenes using a Co catalyst and *tert*-BuOOH to give the alkyl azide.[426]

E. Hydrogen on Both Sides

15-11 Hydrogenation of Double and Triple Bonds[427]

Dihydro-addition



Most carbon–carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.[428] However, a transition metal catalyst is required to break apart H_2 into metal-bound hydrogen atoms before reaction can occur with the alkene. Almost all known alkenes added hydrogen at temperatures between 0 and 275 °C. The catalysts used can be divided into two broad classes, both of which mainly consist of transition metals and their compounds: (1) Catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,[429] Pd-on-charcoal (perhaps the most common),[430] $NaBH_4$ reduced nickel[431] (also called nickel boride), Pt metal or its oxide, Rh, Ru, and zinc oxide,[432] (2) Catalysts soluble in the reaction medium

[425] Heathcock, C.H. *Angew. Chem. Int. Ed.* ***1969****, 8,* 134. See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 522–527.
[426] Waser, J.; Nambu, H.; Carreira, E.M. *J. Am. Chem. Soc.* ***2005****, 127,* 8294.
[427] See Mitsui, S.; Kasahara, A. in Zabicky, J. *The Chemistry of Alkenes,* Vol. 2, Wiley, NY, ***1970***, pp. 175–214. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 422–438.
[428] See Rylander, P.N. *Hydrogenation Methods* Academic Press, NY, **1985**; *Catalytic Hydrogenation in Organic Synthesis* Academic Press, NY, ***1979***; Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis* Wiley, NY, ***1978***; *Practical Catalytic Hydrogenation* Wiley, NY, **1971**; Augustine, R.L. *Catalytic Hydrogenation* Marcel Dekker, NY, **1965**; Parker, D. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond, Vol. 4,* Wiley, NY, ***1987***, pp. 979–1047.
[429] Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 175–311; Pojer, P.M. *Chem. Ind. (London)* ***1986***, 177.
[430] See Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004****, 45*, 2421.
[431] See Ganem, B.; Osby, J.O. *Chem. Rev.* ***1986****, 86,* 763.
[432] See Minachev, Kh.M.; Khodakov, Yu.S.; Nakhshunov, V.S. *Russ. Chem. Rev.* ***1976****, 45,* 142.

(*homogeneous catalysts*).[433] An important example is chlorotris(triphenylphosphine) rhodium [$RhCl(Ph_3P)_3$],[434] **46**, *Wilkinson's catalyst*),[435] which catalyzes the hydrogenation of many alkenyl compounds without disturbing such groups as CO_2R, NO_2, CN, or COR present in the same molecule.[436] Even unsaturated aldehydes can be reduced to saturated aldehydes,[437] although in this case decarbonylation (Reaction **14-32**) may be a side reaction. In general, for catalytic hydrogenation many functional groups may be present in the molecule, for example, OH, COOH, NR_2 (including NH_2), and N(R)COR′ (including carbamates),[438] CHO, COR, CO_2R, or CN. Vinyl esters can be hydrogenated using homogeneous Rh catalyst.[439] Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively[440] (see Table 19.2). Controlling the solvent allows catalytic hydrogenation of an alkene in the presence of an aromatic nitro group.[441]

Modification of the catalyst includes a polymer bound Ru catalyst,[442] and a polymer incarcerated Pd catalyst.[443] A nanoparticulate Pd catalyst in an ionic liquid has been used for the hydrogenation of alkenes.[444]

Homogeneous catalysts have the advantages of better catalyst reproducibility and better selectivity. Apart from *Wilkinson's catalyst* (**46**), chlorotris(triphenylphosphine)hydridoruthenium(II) [$(Ph_3P)_3RuClH$][445] is an important homogeneous catalyst that is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all). Homogeneous catalysts are also less susceptible to catalyst poisoning.[446] Heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by thiols and sulfides.[447] Note that heterogeneous catalysts are usually easier to separate from a reaction mixture.

Using soluble, homogeneous catalysts, unfunctionalized alkenes are hydrogenated with good diastereoselectivity and enantioselectivity[448] using various metal catalysts

[433] James, B.R. *Homogeneous Hydrogenation* Wiley, NY, ***1973***; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA ***1987***, pp. 523–564; Birch, A.J.; Williamson, D.H. *Org. React.* ***1976****, 24,* 1; James, B.R. *Adv. Organomet. Chem.* ***1979****, 17*, 319; Harmon, R.E.; Gupta, S.K.; Brown, D.J. *Chem. Rev.* ***1973****, 73,* 21; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts* Academic Press, NY, ***1973***, pp. 60–76.

[434] See van Bekkum, H.; van Rantwijk, F.; van de Putte, T. *Tetrahedron Lett.* ***1969***, 1.

[435] See Jardine, F.H. *Prog. Inorg. Chem.* ***1981****, 28,* 63–202.

[436] Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoolenberg, J. *J. Org. Chem.* ***1969****, 34*, 3684. See also, Mohrig, J.R.; Dabora, S.L.; Foster, T.F.; Schultz, S.C. *J. Org. Chem.* ***1984****, 49,* 5179.

[437] Jardine, F.H.; Wilkinson, G. *J. Chem. Soc. C* ***1967***, 270.

[438] Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* ***2000****, 56*, 8433.

[439] Tang, W.; Liu, D.; Zhang, X *Org. Lett.* ***2003****, 5*, 205.

[440] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 59–120. Also see, Hudlicky, M. *Reductions in Organic Chemistry* Ellis Horwood Ltd., Chichester ***1984***.

[441] Jourdant, A.; González-Zamora, E.; Zhu, J. *J. Org. Chem.* ***2002****, 67*, 3163.

[442] Taylor, R.A.; Santora, B.P.; Gagné, M.R. *Org. Lett.* ***2000****, 2,* 1781.

[443] Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* ***2004****, 69*, 2871. See also, Bremeyer, N.; Ley, S.V.; Ramarao, C.; Shirley, I.M.; Smith, S.C. *Synlett* ***2002***, 1843.

[444] Huang, J.; Jiang, T.; Han, B.; Gao, H.; Chang, Y.; Zhao, G.; Wu, W. *Chem. Commun.* ***2003***, 1654.

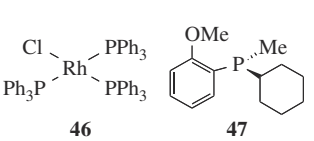
[445] Hallman, P.S.; McGarvey, B.R.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 3143; Jardine, F.H.; McQuillin, F.J. *Tetrahedron Lett.* ***1968***, 5189.

[446] Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1967***, 1935.

[447] Barbier, J.; Lamy-Pitara, E.; Marecot, P.; Boitiaux, J.P.; Cosyns, J.; Verna, F. *Adv. Catal.* ***1990****, 37,* 279–318.

[448] Cui, X.; Burgess, K. *Chem. Rev.* ***2005****, 105,* 3272.

(e.g., Ir,[449] Pd,[450] or Zr,[451] and chiral ligands).[452] The chiral transition metal catalyst (Rh and Ru are probably the most common) is usually prepared with suitable chiral ligands prior to addition to the reaction. Alternatively, an achiral catalyst (e.g., *Wilkinson's catalyst*, **46**), is simply added along with a chiral ligand. With monophosphine chiral ligands, [453] the phosphorous may be chiral, as in **47** (called R-camp)[454] or bis(phosphine) **48** (called dipamp),[455] but pyramidal inversion at elevated temperatures (see Sec. 4.C) limits the utility of such ligands. The alternative is to prepare phosphines that contain a chiral carbon, as in **49** (known as Chiraphos),[456] but there are many variations of chiral bis(phosphine) ligands.[457] Chiral poisoning has been used as a strategy for asymmetric catalysis.[458]



46 **47** **48** **49**

Hydrogenations are carried out at room temperature and just above atmospheric pressure, in most cases, but some double bonds are more resistant and require higher temperatures and pressures. The poor reactivity is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25 °C and 100 atm, while tetrasubstituted double bonds may require 275 °C and 1000 atm. Among the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in steroid **49**. Hydrogenations, even at about atmospheric pressure, are often performed in a special hydrogenator, but this is not always necessary. Indeed, placing a hydrogen-filled balloon over the reaction flask is common for small-scale hydrogenations that do not require heat or

[449] Roseblade, S.J.; Pfaltz, A. *Acc. Chem. Res.* ***2007****, 40,* 1402; Källström, K.; Andersson, P.G. *Tetrahedron Lett.* ***2006****, 47,* 7477; Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* ***2007****, 48,* 3915; Özkar, S.; Finke, R.G. *J. Am. Chem. Soc.* ***2005****, 127,* 4800; Schrems, M.G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed.* ***2007****, 46,* 8274; Källström, K.; Munslow, I.; Andersson, P.G. *Chemistry: European J.* ***2006****, 12,* 3194.

[450] Callis, N.M.; Thiery, E.; Le Bras, J.; Muzart, J. *Tetrahedron Lett.* ***2007****, 48*, 8128. See Brunel, J.M. *Tetrahedron* ***2007****, 63,* 3899.

[451] Troutman, M.V.; Appella, D.H.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999****, 121*, 4916.

[452] Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* ***2005****, 127,* 11934; Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L.K.; Andersson, P.G. *J. Am. Chem. Soc.* ***2006****, 128,* 2995. See McIntosh, A.I.; Watson, D.J.; Burton, J.W.; Lambert, R.M. *J. Am. Chem. Soc.* ***2006****, 128,* 7329; Diguez, M.; Mazuela, J.; Pmies, O.; Verendel, J.J.; Andersson, P.G. *J. Am. Chem. Soc.* ***2008****, 130,* 7208; Chen, W.; Roberts, S.M.; Whittall, J. *Tetrahedron Lett.* ***2006****, 47,* 4263; Tang, W.-J.; Huang, Y.-Y.; He, Y.-M.; Fan, Q.-H. *Tetrahedron Asymmetry* ***2006****, 17,* 536; Tang, W.; Qu, B.; Capacci, A.G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N.K.; Krishnamurthy, D.; Chris H.; Senanayake, C.H. *Org. Lett.* ***2010****, 12*, 176; Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed.* ***2010****, 49*, 6421.

[453] Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* ***2004****, 69*, 2355; Hua, Z.; Vassar, V.C.; Ojima, I. *Org. Lett.* ***2003****, 5*, 3831. For a review, see Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* ***2004****, 15*, 2101.

[454] Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. *Adv. Chem. Ser* ***1974****, 132*, 274.

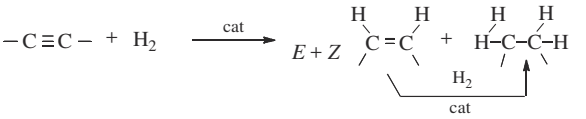
[455] Brown, J.M.; Chaloner, P.A. *J. Chem. Soc., Chem. Commun.* ***1980***, 344; ***1978***, 321; *J. Am. Chem. Soc.* ***1980****, 102*, 3040.

[456] See Chan. A.S.C.; Halpern, J. *J. Am. Chem. Soc.* ***1980****, 102,* 838; Chua, P.S.; Roberts, N.K.; Bosnich, B.; Okrasinski, S.J.; Halpern, J. *J. Chem. Soc. Chem. Commun.* ***1981***, 1278.

[457] See Tang, W.; Zhang, X. *Chem. Rev.* ***2003****, 103,* 3029.

[458] Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* ***1993****, 115*, 804.

pressure. The great variety of catalysts available often allows an investigator to find one that is highly selective. For example, the catalyst Pd(salen) encapsulated in zeolites permitted the catalytic hydrogenation of 1-hexene in the presence of cyclohexene.[459] It has been shown that the pressure of the reaction can influence enantioselectivity in asymmetric catalytic hydrogenations.[460]

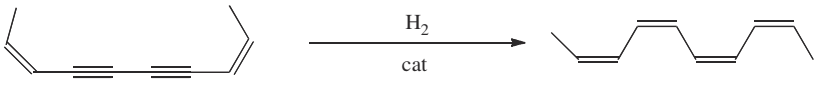


Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned in the following two sections. The comparative reactivity of triple and double bonds depends on the catalyst. *With most catalysts (e.g., Pd), triple bonds are hydrogenated more easily*, and therefore it is usually possible to add just 1 equiv of hydrogen and reduce a triple to a double bond or to reduce a triple bond without affecting a double bond present in the same molecule.[461] A particularly good catalyst for this purpose is the *Lindlar catalyst* (Pd—$CaCO_2$—PbO),[462] which gives rather lean syn addition, and a (*Z*)-alkene. An alternative catalyst used for selective hydrogenation to *cis*-alkenes is the Pd on a barium sulfate ($BaSO_4$) catalyst, poisoned with quinoline[463] (sometimes called the *Rosenmund catalyst*). Palladium on calcium carbonate in PEG has also been used as a recyclable catalyst system.[464] Catalytic hydrogenation of alkynes leads to *cis*-alkenes with a Pd catalyst and DMF/KOH was found to be an efficient transfer-hydrogen source.[465] Hydrogenation of a C≡C unit occurs in the presence of other functional groups, including NR_2 including NH_2,[466] and sulfonyl.[467]

Conjugated dienes can add hydrogen by 1,2- or 1,4-addition. Selective 1,4-addition can be achieved by hydrogenation in the presence of CO, with bis(cyclopentadienyl)chromium as catalyst.[468] With allenes,[469] catalytic hydrogenation usually reduces both double bonds. Hydrogenation of functionalized alkenes is possible. The Rh catalyzed hydrogenation of enamines leads to amines,[470] for example. Hydrogenation of fluorinated alkenes has been reported using an Ir catalyst.[471] The hydrogenation of conjugated alkenes is discussed in Reaction **15-14**.

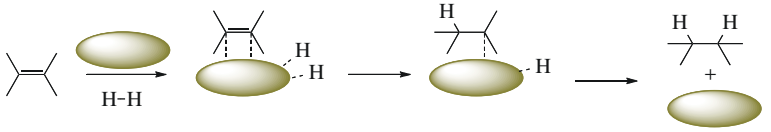
[459] Kowalak, S.; Weiss, R.C.; Balkus Jr., K.J. *J. Chem. Soc., Chem. Commun.* ***1991***, 57.
[460] Sun, Y.; Landau, R.N.; Wang, J.; LeBlond, C.; Blackmond, D.G. *J. Am. Chem. Soc.* ***1996****, 118*, 1348.
[461] See Hutchins, R.O.; Hutchins, M.G.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wley, NY, ***1983***, pp. 571–601; Marvell, E.N.; Li, T. *Synthesis* ***1973***, 457; Gutmann, H.; Lindlar, H. in Viehe, H.G. *Acetylenes,* Marcel Dekker, NY, ***1969***, pp. 355–363.
[462] Lindlar, H.; Dubuis, R. *Org. Synth.* ***V***, 880. See also, Rajaram, J.; Narula, A.P.S.; Chawla, H.P.S.; Dev, S. *Tetrahedron* ***1983****, 39*, 2315; McEwen, A.B.; Guttieri, M.J.; Maier, W.F.; Laine, R.M.; Shvo, Y. *J. Org. Chem.* ***1983****, 48*, 4436.
[463] Cram, D.J.; Allinger, N.L. *J. Am. Chem. Soc.* ***1956****, 78*, 2518; Rosenmund, K.W. *Ber.* ***1918****, 51*, 585; Mosettig, E.; Mozingo, R. *Org. React.* ***1948****, 4,* 362.
[464] Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004****, 45*, 2421.
[465] Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* ***2010****, 75,* 2966.
[466] Campos, K.R.; Cai, D.; Journet, M.; Kowal, J.J.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* ***2001****, 66*, 3634.
[467] Zhong, P.; Huang, X.; Ping-Guo, M. *Tetrahedron* ***2000****, 56*, 8921.
[468] Miyake, A.; Kondo, H. *Angew. Chem. Int. Ed.* ***1968****, 7,* 631. For other methods, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 403–404.
[469] See Schuster, H.F.; Coppola, G.M. *Allenes in Organoic Synthesis* Wiley, NY, ***1984***, pp. 57–61.
[470] Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2006****, 128*, 11774.
[471] Engman, M.; Diesen, J.S.; Paptchikhine, A.; Andersson, P.G. *J. Am. Chem. Soc.* ***2007****, 129*, 4536.

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be mostly syn, with the hydrogen atoms incorporated from the less-hindered side of the molecule.[472] This selectivity depends in large part of how well the reactive intermediates are bound to the metal, and isomerization of the double bond is possible. Stereospecificity can be investigated only for tetrasubstituted alkenes (except when the reagent is D_2), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80–100% syn, although some of the anti-addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the *cis*-alkene (usually at least 80%), even when it is thermodynamically less stable. For example, **50** gave **51**, even though the steric hindrance is such that a planar molecule is impossible.[473] This is



50 **51**

thus a useful method for preparing *cis*-alkenes.[474] However, when steric hindrance is too great, the *trans*-alkene may be formed. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogen atoms takes place, as can be shown by hydrogenation with deuterium.[475] Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and ethanes (even C_2H_6), as well as HD.[476] With 2-butene, it was found that double-bond migration, cis–trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur (e.g., $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst).[477] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,[478] and even without deuterium (e.g., $CH_4 + CD_4 \rightarrow CHD_3 + CH_3D$ in the gas phase), with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.



The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.[479] Because the reaction is heterogeneous, kinetic data, although easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties

[472] See Brown, J.M. *Angew. Chem. Int. Ed.* ***1987****, 26*, 190.
[473] Holme, D.; Jones, E.R.H.; Whiting, M.C. *Chem. Ind. (London)* ***1956***, 928.
[474] See Burch, R.R.; Muetterties, E.L.; Teller, R.G.; Williams, J.M. *J. Am. Chem. Soc.* ***1982****, 104*, 4257.
[475] See Gudkov, B.S. *Russ. Chem. Rev.* ***1986****, 55*, 259.
[476] Turkevich, J.; Schissler, D.O.; Irsa, P. *J. Phys. Chem.* ***1951****, 55,* 1078.
[477] Wilson, J.N.; Otvos, J.W.; Stevenson, D.P.; Wagner, C.D. *Ind. Eng. Chem.* ***1953****, 45,* 1480.
[478] See Gudkov, B.S.; Balandin, A.A. *Russ. Chem. Rev.* ***1966****, 35,* 756. For an intramolecular exchange, see Lebrilla, C.B.; Maier, W.F. *Tetrahedron Lett.* ***1983****, 24*, 1119. See also, Poretti, M.; Gäumann, T. *Helv. Chim. Acta* ***1985****, 68,* 1160.
[479] See Webb, G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20; Elsevier, NY, ***1978***, pp. 1–121; Clarke, J.K.A.; Rooney, J.J. *Adv. Catal.* ***1976****, 25*, 125–183.

caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.[480] According to this, the alkene is adsorbed onto the surface of the metal, although the nature of the actual bonding is unknown,[481] despite many attempts to elucidate it.[482] In the 1934 work, the metallic site was indicated by an asterisk, but here  is used. For steric reasons it is apparent that adsorption of the alkene takes place with its less-hindered side attached to the catalyst surface, probably as an η^2 complex (Sec. 3.C.i). The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the alkene. It is likely that as the H_2 molecule is adsorbed on (coordinated to) the metal catalyst, cleavage occurs to give η^1-coordinated hydrogen atoms (Sec. 3.C.i). Note that this model suggests a single metal particle for coordination of the alkene and the hydrogen atoms, but the hydrogen atoms and the alkene could be coordinated to different metal particles. It has been shown that Pt catalyzes homolytic cleavage of hydrogen molecules.[483] In the second step, one of the adsorbed (η^1-coordinated) hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical, which is still bound to the catalyst although only by one bond, probably η^1-coordination. Transfer of a hydrogen atom to carbon opens a site on the metal catalyst for coordination to additional hydrogen atoms. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and the metal catalyst that is now available for coordination of additional hydrogen atoms and/or alkenes. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process.[484] Although this mechanism is satisfactory as far as it goes,[485] there are still questions it does not answer, among them questions[486] that involve the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.[487]

Another problem with any study of heterogeneous catalysis is that it occurs at the surface, and different types of metal particles are exposed to the medium and reactants. Maier[488] suggested the presence of **terrace-**, **step-,** and **kink**-type atoms (in Fig. 15.1)[488] on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors, which correspond to different transition metal fragments, as well as to different coordination states of that metal.[489] A terrace-type atom (A in Fig. 15.1) typically has eight or nine neighbors and corresponds to a geometry shown for the ML_5 particle. The step type of atom (B) usually has seven neighbors and can

[480] Horiuti, I.; Polanyi, M. *Trans. Faraday Soc.* ***1934****, 30,* 1164.
[481] See Burwell, Jr., R.L.; Schrage, K. *J. Am. Chem. Soc.* ***1965****, 87*, 5234.
[482] See Bautista, F.M.; Campelo, J.M.; Garcia, A.; Guardeño, R.; Luna, D.; Marinas, J.M. *J. Chem. Soc. Perkin Trans. 2,* ***1989***, 493.
[483] Krasna, A.I. *J. Am. Chem. Soc.* ***1961****, 83*, 289.
[484] Smith, G.V.; Burwell, Jr., R.L. *J. Am. Chem. Soc.* ***1962****, 84,* 925.
[485] A different mechanism has been proposed by Zaera, F.; Somorjai, G.A. *J. Am. Chem. Soc.* ***1984****, 106,* 2288, but there is evidence against it: Beebe, Jr., T.P.; Yates, Jr., J.T. *J. Am. Chem. Soc.* ***1986****, 108*, 663. See also, Thomson, S.J.; Webb, G. *J. Chem. Soc., Chem. Commun.* ***1976***, 526.
[486] See Augustine, R.L.; Yaghmaie, F.; Van Peppen, J.F. *J. Org. Chem.* ***1984****, 49*, 1865; Maier, W.F. *Angew. Chem. Int. Ed.* ***1989****, 28,* 135.
[487] See Schlögl, R.; Noack, K.; Zbinden, H.; Reller, A. *Helv. Chim. Acta* ***1987****, 70,* 627.
[488] Maier, W.F. *Angew. Chem. Int. Ed.* ***1989****, 28*, 135.
[489] Maier, W.F. in Rylander, P.N.; Greenfield, H.; Augustine, R.L. *Catalysis of Organic Reactions*, Marcel Dekker, NY, ***1988***, pp 211–231, Cf. p. 220.

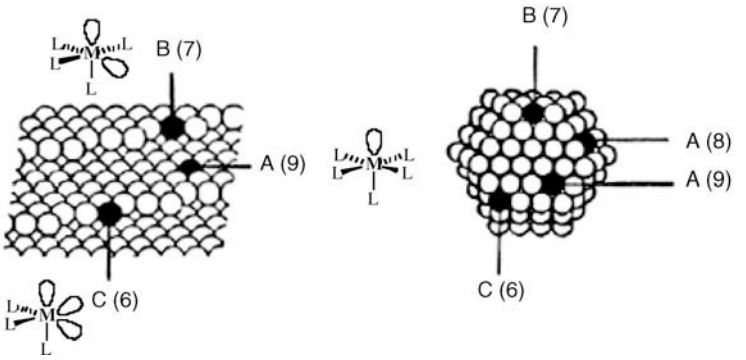
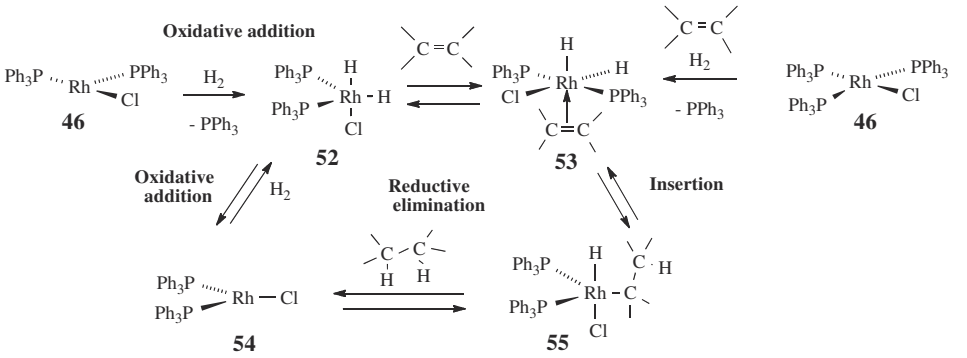


FIG. 15.1. The principal surface and particle sites for heterogeneous catalysts. [Reprinted with permission from Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, 135, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***1989*** by Wiley-VCH Verlag]

be correlated with the geometry shown for the ML_4 particle. Finally, the kink-type atom (C) has six neighbors and corresponds to geometry shown for the ML_3 particle. In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms.



The mechanism of homogeneous hydrogenation[490] catalyzed by $RhCl(Ph_3P)_3$ (**46**, *Wilkinson's catalyst*)[491] involves reaction of the catalyst with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**52**).[492] Replacement of a triphenylphosphine ligand with two toms of hydrogen constitutes an oxidative addition. After coordination of the alkene to form **53**, transfer of hydrogen to carbon is an insertion process, presumably generating **55**, and a second insertion liberates the hydrogenated compound, and Rh species **54**, which adds hydrogen by oxidative addition to give **55**. In a different study of Pd catalyzed hydrogenations, a palladium hydride species was detected.[493] Alternatively, replacement of triphenylphosphine can lead to **53**, with two hydrogen atoms and a η^2 alkene complex. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and nondeuterated

[490] See Crabtree, R.H. *Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 190–200; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 1049–1071.
[491] Koga, N.; Daniel, C.; Han, J.; Fu, X.Y.; Morokuma, K. *J. Am. Chem. Soc.* ***1987****, 109,* 3455.
[492] Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. *J. Am. Chem. Soc.* ***1976****, 96*, 2762.
[493] López-Serrano, J.; Duckett, S.B.; Lledós, A. *J. Am. Chem. Soc.* ***2006****, 128,* 9596.

compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one alkene molecule and that no exchange takes place.[491] Although conversion of **53** to the products takes place in two steps,[494] the addition of H_2 to the double bond is syn, although bond rotation in **55** can lead to stereochemical mixtures.

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding D_2 to a double or triple bond in a regioselective or stereospecific manner. However, this objective can be achieved (with syn addition) by a homogeneous catalytic hydrogenation, which usually adds D_2 without scrambling[495] or by the use of one of the diimide methods (Reaction **15-12**). Deuterium can also be regioselectively added by the hydroboration–reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 794; **IV**, 298, 304, 408; **V**, 16, 96, 277; **VI**, 68, 459; **VII**, 226, 287; **VIII**, 420. 609; **IX**, 169, 533.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880; **VI**, 1007.

15-12 Other Reductions of Double and Triple Bonds



Although catalytic hydrogenation is the method most often used, double or triple bonds can be reduced by other reagents as well. These include sodium in ethanol, sodium and *tert*-butyl alcohol in HMPA,[496] lithium in aliphatic amines[497] (see also, Reaction **15-13**), zinc and acids, and $(EtO)_3SiH—Pd(OAc)_2$.[498] Trialkylsilanes (R_3SiH) in conjunction with an acid will reduce double bonds.[499] When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the *Birch reduction* (Reaction **15-13**).[500] The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.[289] In accord with this mechanism, the reaction can be applied only to those alkenes that when protonated can form a tertiary carbocation or one stabilized in some other way (e.g., by a OR substitution).[501] It has been

[494] Smith, G.V.; Shuford, R.J. *Tetrahedron Lett.* ***1970***, 525; Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970****, 48*, 3580.

[495] Morandi, J.R.; Jensen, H.B. *J. Org. Chem.* ***1969****, 34,* 1889. See, however, Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970****, 48*, 3580.

[496] Whitesides, G.M.; Ehmann, W.J. *J. Org. Chem.* ***1970****, 35,* 3565.

[497] Benkeser, R.A.; Schroll, G.; Sauve, D.M. *J. Am. Chem. Soc.* ***1955****, 77,* 3378.

[498] Tour, J.M.; Pendalwar, S.L. *Tetrahedron Lett.* ***1990****, 31*, 4719.

[499] Masuno, M.N.; Molinski, T.F. *Tetrahedron Lett.* ***2001****, 42*, 8263; Kursanov, D.N.; Parnes, Z.N.; Kalinkin, M.I.; Loim, N.M. *Ionic Hydrogenation and Related Reactions* Harwood Academic Publishers, Chur, Switzerland, ***1985***.

[500] See Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1987***, 893–901; Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 471–512.

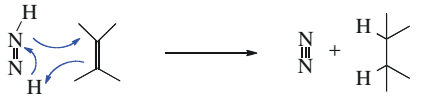
[501] Parnes, Z.N.; Bolestova, G.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972****, 21*, 1927.

shown, by the detection of CIDNP, that reduction of α-methylstyrene by hydridopentacarbonylmanganese(I), $[HMn(CO)_5]$, involves free radical addition.[502]

Triethylamine reduces alkynes in the presence of a Pd catalyst.[503] Samarium iodide in water and a triamine additive led to reduction of alkenes.[504] Similar reduction was reported using $Co_2(CO)_8$ and an excess of water in dimethoxyethane.[505]

Another hydrogenation method is called *transfer hydrogenation*.[506] In this method, the hydrogen atom comes from another organic molecule, and that molecule is oxidized. A transition metal catalyst, heterogeneous or homogeneous, is frequently employed. A common reducing agent is cyclohexene, which, when a Pd catalyst is used, is oxidized to benzene, losing 2 molar equivalents of hydrogen. Nickel nanoparticles reduce alkenes by transfer hydrogenation using 2-propanol.[507]

Diimide (NH=NH) is a reducing agent for simple alkenes, formed *in situ* from N_2H_4 from the reaction of a mixture of hydrazine and hydroxylamine.[508] The rate of this reaction has been studied.[509] Diimide is also generated from hydrazine using a flavin catalyst in an oxygen atmosphere.[510] Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,[511] at least in part by a cyclic mechanism:[512]



The addition is stereospecifically syn[513] and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, although not much discrimination in this respect is observed where the difference in bulk effects is small.[514] Diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N) and are not useful for those inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation at ordinary temperatures, although it has been prepared[515] as a yellow solid at −196°C.

An indirect method[516] of double-bond reduction involves formation of an alkylborane from an alkene, followed by hydrolysis of the borane (prepared by Reaction **15-16**).

[502] Sweany, R.L.; Halpern, J. *J. Am. Chem. Soc.* ***1977****, 99,* 8335. See also, Bullock, R.M.; Samsel, E.G. *J. Am. Chem. Soc.* ***1987****, 109*, 6542.
[503] Luo, F.; Pan, C.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron* ***2010****, 66*, 1399. See Han, J.W.; Hayashi, T. *Tetrahedron Asymm.* ***2010****, 21*, 2193.
[504] Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2003****, 44*, 2661.
[505] Lee, H.-Y.; An, M. *Tetrahedron Lett.* ***2003****, 44*, 2775.
[506] Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* ***1985****, 85*, 129; Brieger, G.; Nestrick, T.J. *Chem. Rev.* ***1974****, 74*, 567.
[507] Alonso, F.; Riente, P.; Yus, M. *Tetrahedron* ***2009****, 65*, 10637.
[508] See Pasto, D.J.; Taylor, R.T. *Org. React.* ***1991****, 40,* 91; Hünig, S.; Müller, H.R.; Thier, W. *Angew. Chem. Int. Ed.* ***1965****, 4*, 271.
[509] Nelson, D.J.; Henley, R.L.; Yao, Z.; Smith, T.D. *Tetrahedron Lett.* ***1993****, 34*, 5835.
[510] Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* ***2005****, 127,* 14544.
[511] Aylward, F.; Sawistowska, M.H. *J. Chem. Soc.* ***1964***, 1435.
[512] Willis, C.; Back, R.A.; Parsons, J.A.; Purdon, J.G. *J. Am. Chem. Soc.* ***1977****, 99,* 4451.
[513] Corey, E.J.; Pasto, D.J.; Mock, W.L. *J. Am. Chem. Soc.* ***1961****, 83*, 2957.
[514] van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* ***1962****, 84,* 1067.
[515] Wiberg, N.; Fischer, G.; Bachhuber, H. *Angew. Chem. Int. Ed.* ***1977****, 16,* 780. See also, Craig, N.C.; Kliewer, M.A.; Shih, N.C. *J. Am. Chem. Soc.* ***1979****, 101*, 2480.
[516] See Zweifel, G. *Intra-Sci. Chem. Rep.* ***1973****, 7(2)*, 181–189.

Trialkylboranes can be hydrolyzed by heating to reflux with carboxylic acids,[517] while monoalkylboranes (RBH_2) can be hydrolyzed with base.[518] A mild procedure involves treatment of the alkene with 2 molar equivalents of catecholborane, a catalytic amount of $MeCONMe_2$, followed by reduction of the organoborane with 4 molar equivalents of MeOH and then treatment with air.[519] Triple bonds can be similarly reduced to *cis*-alkenes.[520] Further reduction is also possible. When an alkyne was treated with decaborane and Pd/C in methanol, 2 equiv of hydrogen are transferred to give the alkane.[521] Reduction of alkenes occurs with *tert*-butylamine • borane complex in methanol with 10% Pd/C.[522] In a related reaction, reduction occurs *in situ* when an alkene is treated with $NaBH_4$, $NiCl_2 \cdot 6 H_2O$ with moist alumina.[523] Hydrogenation with Ni_2B on borohydride-exchange resin (BER) has also been used.[524]

Metallic hydrides (e.g., lithium aluminum hydride and sodium borohydride) do not typically reduce carbon–carbon double bonds, although in special cases where the double bond is polar, as in 1,1-diarylethenes[525] and in enamines,[526] reduction can occur. Note that both $LiAlH_4$ and $NaBH_4$, as well as NaH, reduce ordinary alkenes and alkynes when complexed with transition metal salts (e.g., $FeCl_2$ or $CoBr_2$).[527] Lithium aluminum hydride reduces cyclopropenes with a pendant alcohol in the allylic position to the corresponding cyclopropane.[528] Transition metals catalyze the reduction of alkenes using $NaBH_4$. Among the metals used for this purpose are Pd,[529] and Ru.[530] A mixture of $NaBH_4$ and $BiCl_3$ also reduced certain alkenes.[531] Zinc metal catalyzes the reduction of alkenes in water in the presence of a Rh complex.[532]

The fact that ordinary double bonds are inert toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without disturbing a double bond in the same molecule (see Chap 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds,[533] although it does reduce alkynes, allenes, conjugated dienes,[534] and aromatic rings (Reaction **15-13**).

[517] Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986****, 42,* 5497; Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1979****, 44,* 4185.
[518] Weinheimer, A.J.; Marisco, W.E. *J. Org. Chem.* ***1962****, 27,* 1926.
[519] Pozzi, D.; Scanlan, E.M.; Renaud, P. *J. Am. Chem. Soc.* ***2005****, 127,* 14204.
[520] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959****, 81,* 1512.
[521] Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* ***2000****, 41*, 887.
[522] Couturier, M.; Andresen, B.M.; Tucker, J.L.; Dubé, P.; Brenek, S.J.; Negri, J.J. *Tetrahedron Lett.* ***2001****, 42*, 2763.
[523] Yakabe, S.; Hirano, M.; Morimoto, T. *Tetrahedron Lett.* ***2000****, 41*, 6795.
[524] Choi, J.; Yoon, N.M. *Synthesis* ***1996***, 597.
[525] See Granoth, I.; Segall, Y.; Leader, H.; Alkabets, R. *J. Org. Chem.* ***1976****, 41*, 3682.
[526] Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985****, 17*, 317; Nilsson, A.; Carlson, R. *Acta Chem. Scand. Sect. B* ***1985****, 39*, 187.
[527] See Ashby, E.C.; Lin, J.J. *J. Org. Chem.* ***1978****, 43*, 2567; Chung, S. *J. Org. Chem.* ***1979****, 44,* 1014. See also, Osby, J.O.; Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1986****, 108,* 67.
[528] Zohar, E.; Marek, I. *Org. Lett.* ***2004****, 6*, 341.
[529] Tran, A.T.; Huynh, V.A.; Friz, E.M.; Whitney, S.K.; Cordes, D.B. *Tetrahedron Lett.* ***2009****, 50*, 1817.
[530] Adair, G.R.A.; Kapoor, K.K.; Scolan, A.L.B.; Williams, J.M.J. *Tetrahedron Lett.* ***2006****, 47*, 8943.
[531] Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1996****, 26*, 763.
[532] Sato, T.; Watanabe, S.; Kiuchi, H.; Oi, S.; Inoue, Y. *Tetrahedron Lett.* ***2006****, 47*, 7703.
[533] There are some exceptions. Butler, D.N. *Synth. Commun.* ***1977****, 7,* 441, and references cited therein.
[534] See Caine, D. *Org. React.* ***1976****, 23*, 1–258.

Enantioselective reduction of certain alkenes has also been achieved by reducing with baker's yeast.[535]

Catalytic hydrogenation of triple bonds and the reaction with Dibal-H (diisobutylaluminum hydride) usually give the *cis*-alkene (Reaction **15-11**). Most of the other methods of triple-bond reduction lead to the more thermodynamically stable *trans*-alkene. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or NH_2OSO_3H, which also give the cis products.

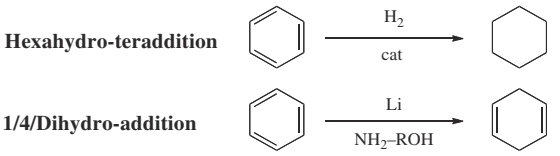
Triple bonds can also be selectively reduced to double bonds with Dibal-H,[536] with activated zinc (see Reaction **12-38**),[537] or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.[538] Terminal alkynes are not reduced by the Na—NH_3 procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the Na—NH_2 solution of $(NH_4)_2SO_4$, which liberates the free ethynyl group.[539] The reaction of a terminal alkyne with lithium naphthalenide and $NiCl_2$ effectively reduced the alkyne unit.[540] This reagent is also effective for the reduction of simple alkenes.[541]

Alkynes are converted to *trans*-alkenes with siloxanes [$(RO)_3SiH$] [542] and a Ru catalyst, followed by treatment with AgF, or silanes[543] and a Ru catalyst, followed by treatment with CuI and Bu_4NF. Reduction of an alkyne to an alkene can be done via an organometallic, by heating the alkyne with In metal in aq ethanol.[544] Alkynes are reduced with palladium acetate and sodium ethoxide. In methanol, the product is the alkane, whereas in THF the product is the *cis*-alkene.[545]

Reduction of just one double bond of an allene, to give an alkene, has been accomplished by treatment with Na—NH_3[546] or with Dibal-H,[547] and by hydrogenation with $RhCl(PPh_3)_3$ as catalyst.[548]

Reductions of double and triple bonds are found at OS **III**, 586, 742; **IV**, 136, 302, 887; **V**, 281, 993; **VII**, 524; **80**, 120.

15-13 Hydrogenation of Aromatic Rings



[535] See Ferraboschi, P.; Reza-Elahi, S.; Verza, E.; Santaniello, E. *Tetrahedron Asymmetry* ***1999****, 10*, 2639. For reviews of baker's yeast, see Csuk, R.; Glänzer, B.I. *Chem. Rev.* ***1991****, 91,* 49; Servi, S. *Synthesis* ***1990***, 1.
[536] Ulan, J.G.; Maier, W.F.; Smith, D.A. *J. Org. Chem.* ***1987****, 52*, 3132.
[537] Chou, W.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* ***1991****, 32*, 299. See Kaufman, D.; Johnson, E.; Mosher, M.D. *Tetrahedron Lett.* ***2005****, 46*, 5613.
[538] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 405–410.
[539] Henne, A.L.; Greenlee, K.W. *J. Am. Chem. Soc.* ***1943****, 65,* 2020.
[540] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1997****, 38*, 149.
[541] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1996****, 37*, 6925.
[542] Fürstner, A.; Radkowski, K. *Chem. Commun.* ***2002***, 2182.
[543] Trost, B.M.; Ball, Z.T.; Jöge, T. *J. Am. Chem. Soc.* ***2002****, 124*, 7922.
[544] Ranu, B.C.; Dutta, J.; Guchhait, S.K. *J. Org. Chem.* ***2001****, 66*, 5624.
[545] Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* ***2003****, 44*, 1979.
[546] Vaidyanathaswamy, R.; Joshi, G.C.; Devaprabhakara, D. *Tetrahedron Lett.* ***1971***, 2075.
[547] Montury, M.; Goré, J. *Tetrahedron Lett.* ***1980****, 21*, 51.
[548] Bhagwat, M.M.; Devaprabhakara, D. *Tetrahedron Lett.* ***1972***, 1391.

Aromatic rings can be reduced by catalytic hydrogenation,[549] but higher temperatures (100–200 °C) are required than for double bonds in alkenes.[550] Although the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.[551] Hydrogenations using phase transfer catalysts often proceed under mild conditions.[552] Hydrogenation in ionic liquids is known,[553] and also hydrogenation in supercritical ethane containing water.[554] Many functional groups (e.g., OH, O^-, CO_2H, CO_2R, NH_2) do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (Reaction **19-54**). Phenols may be reduced to cyclohexanones, presumably through the enol. A computational study of the mechanism of hydrogenation of aromatic compounds has been reported, and it was shown that the barrier for uncatalyzed 1,4-hydrogenation is substantially lower than that for 1,2-hydrogenation, despite similar reaction enthalpies.[555]

It is usually impossible to stop the reduction of benzene rings after only one or two bonds have been reduced, since alkenes are more easily reduced than aromatic rings.[556] Thus, 1 molar equivalent of benzene, treated with 1 molar equivalent of hydrogen, gives no cyclohexadiene or cyclohexene, but one-third equivalent of cyclohexane and two-thirds equivalent of recovered benzene. This is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (Sec. 2.I.i). Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.[557] Hydrogenation of toluene in an ionic liquid using a Ru catalyst gave methylcyclohexane.[558]

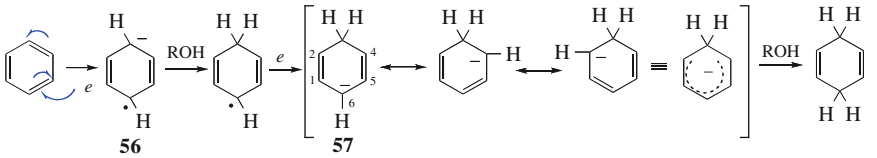
Heterocyclic compounds are often reduced by hydrogenation.[559] Furan gives THF, pyrroles[560] give pyrrolidines, and pyridines[561] give piperidines. The nitrogen-containing ring of quinolines is reduced by hydrogenation using iodine and an Ir catalyst.[562] Catalytic hydrogenation of the five-membered ring in indole derivatives using a chiral Rh catalyst gave hydroindoles with excellent enantioselectivity.[563]

When aromatic rings are reduced by Li (or K or Na) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *tert*-butyl alcohol), 1,4-addition of hydrogen takes place and

[549] See Karakhanov, E.A.; Dedov, A.G.; Loktev, A.S. *Russ. Chem. Rev.* ***1985****, 54,* 171.
[550] See Timmer, K.; Thewissen, D.H.M.W.; Meinema, H.A.; Bulten, E.J. *Recl. Trav. Chim. Pays-Bas* ***1990****, 109*, 87.
[551] Muetterties, E.L.; Bleeke, J.R. *Acc. Chem. Res.* ***1979****, 12*, 324. See also, Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. *Tetrahedron Lett.* ***2000****, 41,* 5865.
[552] Januszkiewicz, K.R.; Alper, H. *Organometallics* ***1983****, 2,* 1055.
[553] Dyson, P.J.; Ellis, D.J.; Parker, D.G.; Welton, T. *Chem. Commun.* ***1999***, 25. Rhodium nanoparticles are used as a catalyst: Mu, X.-d.; Meng, J.-q.; Li, Z.-C.; Kou, Y. *J. Am. Chem. Soc.* ***2005****, 127,* 9694.
[554] Bonilla, R.J.; James, B.R.; Jessop, P.G. *Chem. Commun.* ***2000***, 941.
[555] Zhong, G.; Chan, B.; Radom, L. *J. Am. Chem. Soc.* ***2007****, 129*, 924.
[556] For an indirect method of hydrogenating benzene to cyclohexene, see Harman, W.D.; Taube, H. *J. Am. Chem. Soc.* ***1988****, 110*, 7906.
[557] Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* ***1992****, 65*, 824.
[558] Boxwell, C.J.; Dyson, P.J.; Ellis, D.J.; Welton, T. *J. Am. Chem. Soc.* ***2002****, 124*, 9334.
[559] Zhou, Y.-G. *Acc. Chem. Res.* ***2007****, 40,* 1357.
[560] Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* ***2008****, 130,* 808.
[561] Piras, L.; Genesio, E.; Ghiron, C.; Taddei, M. *Synlett* ***2008***, 1125.
[562] Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* ***2003****, 125*, 10536.
[563] Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* ***2004****, 6*, 2213. See Kim, J.T.; Gevorgyan, V. *J. Org. Chem.* ***2005****, 70,* 2054.

nonconjugated cyclohexadienes are produced.[564] This reaction is called the *Birch reduction*.[565] Heterocycles (e.g., pyrroles,[566] furans,[567] pyridines,[568] and indolones[569]) can be reduced using *Birch reduction*. Ammonia obtained commercially often has iron salts as impurities that lower the yield in the *Birch reduction*. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the *Birch reduction*, electron-donating groups (e.g., alkyl or alkoxyl) decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups (e.g., COOH or $CONH_2$) increase the reaction rate and are found on the reduced positions of the product.[570] The regioselectivity of the reaction has been examined.[571] The mechanism involves solvated electrons,[572] which are transferred from the metal to the solvent, and hence to the ring:[573]

The sodium becomes oxidized to Na^+ and creates a radical ion (**56**).[574] There is a great deal of evidence from ESR spectra for these species.[575] The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **57** accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of **56** are frequently obtained. There is evidence[576] at least with some substrates (e.g., biphenyl) that the radical ion corresponding to **56** is converted to the carbanion corresponding to **56** by a different pathway, in which the order of the steps is reversed: First a second electron is gained to give a dianion,[573] which then acquires a proton, producing the intermediate (e.g., **56**).



56 **57**

Ordinary alkenes are usually unaffected by *Birch-reduction* conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However,

[564] See Brandsma, L.; van Soolingen, J.; Andringa, H. *Synth. Commun.* ***1990****, 20*, 2165. Also see, Weitz, I.S.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 1,* ***1993***, 117.

[565] Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds* Plenum, NY, ***1972***; Birch, A.J. *Pure Appl. Chem.* ***1996****, 68*, 553; Rabideau, P.W. *Tetrahedron* ***1989****, 45,* 1579; Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* ***1972****, 8,* 1; Kaiser, E.M. *Synthesis* ***1972***, 391.

[566] Donohoe, T.J.; House, D. *J. Org. Chem.* ***2002****, 67*, 5015.

[567] Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocyclic Chem.* ***1996****, 33*, 1313.

[568] Donohoe, T.J.; McRiner, A.J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1435.

[569] Guo, Z.; Schultz, A.G. *J. Org. Chem.* ***2001****, 66*, 2154.

[570] See Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1990****, 112*, 1280; Rabideau, P.W.; Karrick, G.L. *Tetrahedron Lett.* ***1987****, 28,* 2481.

[571] Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1993****, 115*, 2205.

[572] For reviews of solvated electrons and related topics, see Dye, J.L. *Prog. Inorg. Chem.* ***1984****, 32*, 327–441; Alpatova, N.M.; Krishtalik, L.I.; Pleskov, Y.V. *Top. Curr. Chem.* ***1987****, 138*, 149–219.

[573] Birch, A.J.; Nasipuri, D. *Tetrahedron* ***1959****, 6,* 148.

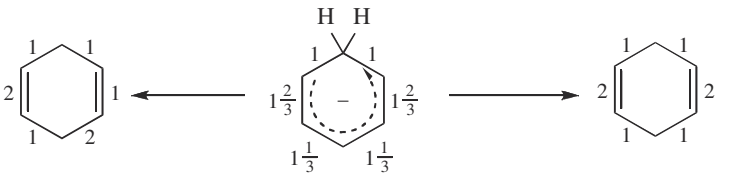
[574] See Holy, N.L. *Chem. Rev.* ***1974****, 74*, 243.

[575] See Jones, M.T. in Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***, pp. 245–274; Bowers, K.W. *Adv. Magn. Reson.,* ***1965****, 1,* 317; Carrington, A. *Q. Rev. Chem. Soc.* ***1963****, 17,* 67.

[576] Rabideau, P.W.; Peters, N.K.; Huser, D.L. *J. Org. Chem.* ***1981****, 46*, 1593.

phenylated alkenes, internal alkynes (Reaction **15-12**),[577] and conjugated alkenes (with C=C or C=O) are reduced under these conditions.

Note that **56** is a resonance hybrid; that is, two additional canonical forms can be written. The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?[578] An answer to this question has been proposed by Hine,[579] who suggested that this case is an illustration of the operation of the *principle of least motion*. According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[578] The principle can be applied to the case at hand in the following manner (simplified): The valence bond bond orders (Sec. 2.A) for the six carbon–carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3}+\frac{1}{3}+\frac{1}{3}+\frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3}+\frac{2}{3}+\frac{2}{3}+\frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ^{13}C NMR spectrum of **111** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.[580]

Reduction of aromatic rings with Li[581] or Ca[582] in amines (instead of ammonia: called *Benkeser reduction*) proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.[583] Lithium triethylborohydride ($LiBEt_3H$) has also been used, to reduce pyridine derivatives to piperidine derivatives.[584]

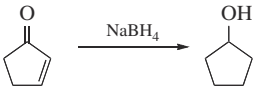
Transition metals and metal compounds can reduce aromatic rings in the proper medium. Indium metal reduces the pyridine ring in quinoline in aq ethanol solution,[585] as well as the C=C unit in the five-membered ring of indole derivatives.[586] Samarium

[577] See Brandsma, L.; Nieuwenhuizen, W.F.; Zwikker, J.W.; Mäeorg, U. *Eur. J. Org. Chem.* ***1999***, 775.
[578] See Rabideau, P.W.; Huser, D.L. *J. Org. Chem.* ***1983***, *48,* 4266.
[579] Hine, J. *J. Org. Chem.* ***1966***, *31,* 1236; Hine, J. *Adv. Phys. Org. Chem.* ***1977***, *15,* 1. See also, Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem. Int. Ed.* ***1980***, *19,* 495.
[580] Bates, R.B.; Brenner, S.; Cole, C.M.; Davidson, E.W.; Forsythe, G.D.; McCombs, D.A.; Roth, A.S. *J. Am. Chem. Soc.* ***1973***, *95,* 926.
[581] Benkeser, R.A.; Agnihotri, R.K.; Burrous, M.L.; Kaiser, E.M.; Mallan, J.M.; Ryan, P.W. *J. Org. Chem.* ***1964***, *29,* 1313; Kwart, H.; Conley, R.A. *J. Org. Chem.* ***1973***, *38*, 2011.
[582] Benkeser, R.A.; Belmonte, F.G.; Kang, J. *J. Org. Chem.* ***1983***, *48,* 2796. See also, Benkeser, R.A.; Laugal, J.A.; Rappa, A. *Tetrahedron Lett.* ***1984***, *25*, 2089.
[583] See Keay, J.G. *Adv. Heterocycl. Chem.* ***1986***, *39,* 1.
[584] Blough, B.E.; Carroll, F.I. *Tetrahedron Lett.* ***1993***, *34*, 7239.
[585] Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1029.
[586] Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 955.

iodide (SmI_2) reduces pyridine in aq THF[587] and phenol in MeOH/KOH.[588] Ammonium formate and a Pd—C catalyst reduces pyridine *N*-oxide to piperidine in methanol.[589] The nitrogen-containing ring of quinolines is reduced with an In catalyst in isopropyl alcohol.[590]

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

15-14 Reduction of the Double or Triple Bonds Conjugated to Carbonyls, Cyano, Nitro, and so on



(100%)

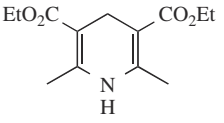
Reduction of only the C=C bond of conjugated C=C—C=O and C=C—C≡N systems[591] has been achieved by many reducing agents,[592] including catalytic hydrogenation with a Rh,[593] a Ru,[594] a Pd,[595] or an Ir catalyst,[596] and with Raney nickel alone.[597] Reagents, such as SmI_2[598] and catecholborane,[599] are effective. Conjugated ketones react with 2 equiv of Cp_2TiCl in THF/MeOH to give the corresponding saturated ketone.[600] Zinc and acetic acid has been used for the conjugate reduction of dihydropyridin-4-ones.[601] Formic acid with a Pd catalyst reduced conjugated carboxylic acids.[602] A zinc–titanocene protocol has been developed for conjugate reductions.[603] Both $NaBH_4$ in MeOH—THF[604] and $NaCNBH_3$ on a zeolite[605] reduce α,β-unsaturated nitro compounds to nitroalkanes.

In certain cases,[606] metallic hydride reagents may selectively reduce double bonds that are in conjugation with C=O bonds,[607] although the C=O bonds are also reduced in many

[587] Kamochi, Y.; Kudo, T. *Heterocycles* ***1993****, 36*, 2383.
[588] Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* ***1994****, 35*, 4169.
[589] Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* ***2001****, 66*, 5264.
[590] Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* ***2004****, 45*, 3215.
[591] See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022.; Augustine, R.L. *Adv. Catal.* ***1976****, 25,* 56.
[592] See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 13–27.
[593] Cabello, J.A.; Campelo, J.M.; Garcia, A.; Luna, D.; Marinas, J.M. *J. Org. Chem.* ***1986****, 51,* 1786.
[594] Wang, C.-J.; Tao, H.; Zhang, X. *Tetrahedron Lett.* ***2006****, 47,* 1901.
[595] Nagano, H.; Yokota, M.; Iwazaki, Y. *Tetrahedron Lett.* ***2004****, 45*, 3035.
[596] Yue, T.-Y.; Nugent, W.A. *J. Am. Chem. Soc.* ***2002****, 124*, 13692;
[597] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***1999***, 1663; Wang, H.; Lian, H.; Chen, J.; Pan, Y.; Shi, Y. *Synth. Commun.* ***1999****, 29,* 129.
[598] Cabrera, A.; Alper, H. *Tetrahedron Lett.* ***1992****, 33*, 5007. See also, Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* ***2007****, 129*, 3402.
[599] Evans, D.A.; Fu, G.C. *J. Org. Chem.* ***1990****, 55*, 5678.
[600] Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* ***2002****, 43*, 2013.
[601] Comins, D.L.; Brooks, C.A.; Ingalls, C.L. *J. Org. Chem.* ***2001****, 66*, 2181.
[602] Arterburn, J.B.; Pannala, M.; Gonzlez, A.M.; Chamberlin, R.M. *Tetrahedron Lett.* ***2000****, 41*, 7847.
[603] Kosal, A.D.; Ashfeld, B.L. *Org. Lett.* ***2010****, 12,* 44.
[604] Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985****, 15,* 151.
[605] Gupta, A.; Haque, A.; Vankar, Y.D. *Chem. Commun.* ***1996***, 1653.
[606] See Meyer, G.R. *J. Chem. Educ.* ***1981****, 58,* 628.
[607] For a discussion of hydride affinity with respect to hydride reducing agents, see Zhu, X.-Q.; Zhang, M.; Liu, Q.-Y.; Wang, X.-X.; Zhang, J.-Y.; Cheng, J.-P. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3954; Vianello, R.; Peran, N.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2007***, 5296.

cases, as in the conversion of cyclopentenone to cyclopentanol.[608] The reagent $NaBH_4$ has a greater tendency than $LiAlH_4$ to effect this double reduction, although even with $NaBH_4$ the product of 1,2-reduction (of the C=O bond) is usually formed in larger amount than the doubly reduced product. The C=C unit proximal to the carbonyl in dienyl amides is selectively reduced with $NaBH_4/I_2$.[609] Mixed hydride reducing agents (e.g., $NaBH_4$—$BiCl_3$,[610] $NaBH_4$—$InCl_3$,[611] and Dibal-H–$Co(acac)_2$)[612] have been used. The $InCl_3$—$NaBH_4$ reagent was used to covert conjugated diene ketones (C=C—C=C—C=O) selectively to the nonconjugated alkenyl ketone (C=C—CH_2CH_2—C=O).[613] Lithium aluminum hydride also reduces the double bonds of allylic alcohols.[614]

Transfer hydrogenation can be applied to the reduction of conjugated alkenes. Reduction of the C=C unit of conjugated aldehydes is accomplished with an imidazolidinone catalyst[615] or an amino ester[616] in the presence of a *Hantzch ester* (e.g., **58**). Nitroalkenes are hydrogenated using a thiourea catalyst in the presence of **58**.[617] Palladium/carbon with microwave heating is used for the transfer hydrogenation of conjugated carboxylic acids, using 1,4-cyclohexadiene as the hydrogen-transfer agent.[618] Solvent-free transfer hydrogenation is possible using a Ru complex, with formic acid or water[619] as the hydrogen donor.[620] Palladium—P(*t*-Bu)$_3$ has been used as a mild catalyst for transfer hydrogenation.[621] Titanium-catalyzed reductions are also known.[622]

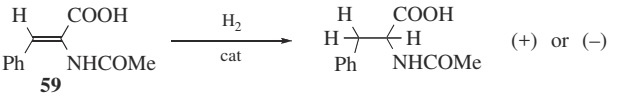


58

Silanes reduce the C=C unit in conjugated systems in the presence of Cu species.[623] An asymmetric CuH catalyzed hydrosilation reaction is known.[624] Phenylsilane ($PhSiH_3$) and

[608] Brown, H.C.; Hess, H.M. *J. Org. Chem.* ***1969****, 34,* 2206. For other methods of reducing both double bonds, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 1096.
[609] Das, B.; Kashinatham, A.; Madhusudhan, P. *Tetrahedron Lett.* ***1998****, 39*, 677.
[610] Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1995****, 25*, 3395.
[611] Ranu, B.C.; Samanta, S. *Tetrahedron Lett.* ***2002****, 43*, 7405.
[612] Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* ***1999***, 96.
[613] Ranu, B.C.; Samanta, S. *J. Org. Chem.* ***2003****, 68*, 7130.
[614] See Blunt, J.W.; Hartshorn, M.P.; Soong, L.T.; Munro, M.H.G. *Aust. J. Chem.* ***1982****, 35,* 2519; Vincens, M.; Fadel, R.; Vidal, M. *Bull. Soc. Chim. Fr.* ***1987***, 462.
[615] Ouellet, S.G.; Tuttle, J.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2005****, 127,* 32; Tuttle, J.B.; Ouellet, S.G.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2006****, 128*, 12662; Adolfsson, H. *Angew. Chem. Int. Ed.* ***2005****, 44,* 3340.
[616] Martin, N.J.A.; List, B. J. *Am. Chem. Soc.* ***2006****, 128*, 13368.
[617] Martin, N.J.A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* ***2007****, 129*, 8976.
[618] Quinn, J.F.; Razzano, D.A.; Golden, K.C.; Gregg, B.T. *Tetrahedron Lett.* ***2008****, 49*, 6137.
[619] Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* ***2010****, 75,* 2981.
[620] Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* ***2007****, 48,* 465.
[621] Brunel, J.M. *Synlett* ***2007***, 330.
[622] Che, J.; Lam, Y. *Synlett* ***2010***, 2415.
[623] Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, R. *Chem. Commun.* ***1997***, 2159; Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* ***1999****, 55*, 4573.
[624] Huang, S.; Voigtritter, K.R.; Unger, J.B.; Lipshutz, B.H. *Synlett* ***2010***, 2041.

a Ni catalyst,[625] CuCl,[626] a Mn catalyst[627] or a Mo[628] catalyst have been used for hydrosilation reactions. Triphenylsilane was also used for the asymmetric reduction of nitro alkenes ($C{=}C{-}NO_2$).[629] Poly(methylhydrosiloxane) with a chiral Cu catalyst gave conjugate reduction of conjugated esters to give the saturated derivative with high enantioselectivity.[630] Polymethylhydrosiloxane, in the presence of a Co-catalyst reduces conjugated nitriles.[631] A β-bromo conjugated lactone was reduced to the β-bromolactone with modest enantioselectivity using an excess of Ph_3SiH and a CuCl catalyst with a chiral ligand.[632] Tributyltin hydride, in the presence of $MgBr_2 \cdot OEt_2$ gave 1,4-reduction of conjugated esters.[633]



59

Optically active homogeneous hydrogenation catalysts have been used to achieve the enantioselective hydrogenation[634] of many prochiral conjugated substrates.[635] For example,[636] hydrogenation of **59** with a suitable catalyst gives the (+) or (−) amino ester (depending on which enantiomer of the catalyst is used) with an ee as high as 96%.[637] Prochiral substrates that give such high optical yields generally contain functional groups (e.g., a carbonyl group,[638] amide groups, cyano groups) or combinations of such groups as in **58**.[639] The catalyst in such cases[640] is usually a Ru[641] or Rh complex[642]with chiral

[625] Boudjouk, P.; Choi, S.-B.; Hauck, B.J.; Rajkumar, A.B. *Tetrahedron Lett.* ***1998****, 39*, 3951.
[626] Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* ***1997****, 38*, 8887.
[627] Magnus, P.; Waring, M.J.; Scott, D.A. *Tetrahedron Lett.* ***2000****, 41,* 9731.
[628] Keinan, E.; Perez, D. *J. Org. Chem.* ***1987****, 52,* 2576.
[629] Czekelius, C.; Carreira, E.M. *Org. Lett.* ***2004****, 6*, 4575.
[630] See Jurkauskas, V.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002****, 124*, 2892; Lipshutz, B.H.; Servesko, J.M.; Taft, B.R. *J. Am. Chem. Soc.* ***2004****, 126*, 8352.
[631] Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* ***2005***, 1755.
[632] Hughes, G.; Kimura, M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003****, 125*, 11253.
[633] Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* ***2004****, 45*, 2207.
[634] See Gridnev, I.D.; Imamoto, T. *Acc. Chem. Res.* ***2004****, 37*, 633.
[635] Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989****, 45*, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis* VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983****, 16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983****, 22*, 897; Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* ***1981***, 85. See also, Wroblewski, A. E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J. G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144; Knowles, W.S. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1999.
[636] See Ashby, M.T.; Halpern, J. *J. Am. Chem. Soc.* ***1991****, 113*, 589; Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* ***1991****, 2*, 51; Burk, M.J. *J. Am. Chem. Soc.* ***1991****, 113*, 8518.
[637] Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, p. 74.
[638] Reetz, M.T.; Mehler, G. *Angew. Chem. Int. Ed.* ***2000****, 39,* 3889.
[639] Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 83–101.
[640] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 8–12. See Izumi, Y. *Adv. Catal.* ***1983****, 32*, 215; Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* ***1987***, 631.
[641] Wu, H.-P.; Hoge, G. *Org. Lett.* ***2004****, 6*, 3645; Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* ***2003****, 125*, 9570.
[642] Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-i.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chemistry: European J.* ***2006****, 12*, 63.

phosphine ligands.[643] Good asymmetric induction[644] has been achieved using chiral Rh complexes with other chiral additives.[645] Iridium complexes have been used with excellent enantioselectivity.[646] The role of solvent has been examined.[647] A pressure-dependent enantioselective hydrogenation has been reported.[648] Asymmetric catalytic hydrogenation has been reported for conjugated carboxylic acids[649] and conjugated ketones.[650] Asymmetric hydrogenation of conjugated carboxylic acids in an ionic liquid is known using a chiral Ru complex[651]

See Reaction **19-36** for methods of reducing C=O bonds in the presence of conjugated C=C bonds.

The C=C unit of conjugated aldehydes has been reduced using $AlMe_3$ with a catalytic amount of CuBr[652] and with ammonium formate/Pd—C.[653] Polymer-supported formate has been used for the 1,4-reduction of conjugated ketones[654] and for conjugated acids using an Rh catalyst and microwave irradiation.[655] Isopropyl alcohol and an Ir catalyst gives conjugate reduction of conjugated ketones.[656] The reaction of conjugated ketones with aluminum chlorides, followed by treatment with water generates the saturated ketone.[657]

Enzymatic reduction of conjugated systems requires the reactivity with certain purified or whole cell enzymes. Baker's yeast reduces conjugated nitro compounds to nitroalkanes[658] and also the C=C unit of conjugated ketones.[659] Other enzymatic reductions are possible. A reductase from *Nicotiana tabacum* reduced a conjugated ketone to the

[643] Pagenkopf, B.L. *J. Org. Chem.* ***2004****, 69*, 4177; Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* ***2004****, 69,* 4648; Yi, B.; Fan, Q.-H.; Deng, G.-J.; Li, Y.-M.; Qiu, L.-Q.; Chan, A.S.C. *Org. Lett.* ***2004****, 6*, 1361.; Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A.J.; de Vries, J.G.; Feringa, B.L. *Org. Lett.* ***2004****, 6*, 1433; Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* ***2004****, 69,* 8157; Hoge, G.; Wu, H.-P.; Kissel, W.S.; Pflum, D.A.; Greene, D.J.; Bao, J. *J. Am. Chem. Soc.* ***2004****, 126*, 5966; Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* ***2004****, 126*, 10331; Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron Asymmetry* ***2004****, 15*, 2011; Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. J. *Am. Chem. Soc.* ***2007****, 129,* 12930.

[644] Zhu, G.; Zhang, X. *J. Org. Chem.* ***1998****, 63*, 9590; Burk, M.J.; Casy, G.; Johnson, N.B. *J. Org. Chem.* ***1998****, 63*, 6084; Burk, M.J.; Allen, J.G.; Kiesman, W.F. *J. Am. Chem. Soc.* ***1998****, 120*, 657.

[645] Noyori, R.; Hashiguchi, S. *Accts. Chem. Res.* ***1997****, 30*, 97.

[646] Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2008****, 130*, 8584; Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed.* ***2008****, 47,* 10133.

[647] Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem. Int. Ed.* ***2002****, 41*, 777.

[648] Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* ***2001****, 66*, 6816.

[649] Suárez, A.; Pizzano, A. *Tetrahedron Asymmetry* ***2001****, 12,* 2501. See Okano, T.; Kaji, M.; Isotani, S.; Kiji, J. *Tetrahedron Lett.* ***1992****, 33*, 5547 for the influence of water on the regioselectivity of this reduction.

[650] Yamaguchi, M.; Nitta, A.; Reddy, R.S.; Hirama, M. *Synlett* ***1997***, 117.

[651] Brown, R.A.; Pollet, P.; McKoon, E.; Eckert, C.A.; Liotta, C.L.; Jessop, P.G. *J. Am. Chem. Soc.* ***2001****, 123*, 1254.

[652] Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* ***1994***, 679.

[653] Ranu, B.C.; Sarkar, A. *Tetrahedron Lett.* ***1994****, 35*, 8649.

[654] Basu, B.; Bhuiyan, Md.M.H.; Das, P.; Hossain, I. *Tetrahedron Lett.* ***2003****, 44*, 8931.

[655] Desai, B.; Danks, T.N. *Tetrahedron Lett.* ***2001****, 42,* 5963.

[656] Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* ***2001****, 66,* 4710.

[657] Koltunov, K.Yu.; Repinskaya, I.B.; Borodkin, G.I. *Russ. J. Org. Chem.* ***2001****, 37,* 1534.

[658] Kawai, Y.; Inaba, Y.; Tokitoh, N. *Tetrahedron Asymmetry* ***2001****, 12*, 309.

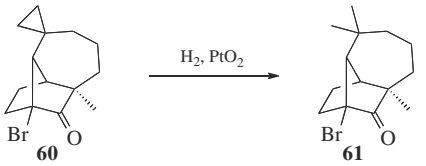
[659] Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2001****, 12,* 847; Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Asymmetry* ***2001****, 12,* 3007.

saturated ketone, with excellent enantioselectivity.[660] Enzyme YNAR-I and NADP-H reduces conjugated nitro compounds to nitroalkanes.[661] Conjugated nitro compounds are reduced in the presence of *Clostridium sporogenes*.[662]

15-15 Reductive Cleavage of Cyclopropanes



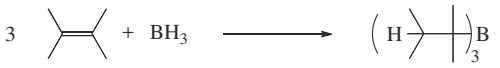
Cyclopropanes can be cleaved by catalytic hydrogenolysis.[663] Among the catalysts used have been Ni, Pd, Rh,[664] and Pt. The reaction can often be run under mild conditions.[665] Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,[666] can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.[667] Similar reduction has been accomplished photochemically in the presence of $LiClO_4$.[668] This reaction is an excellent way to introduce a *gem*-dimethyl unit into a molecule. Hydrogenation of the cyclopropane ring in **60**, for example, gave the *gem*-dimethyl unit in **61** using PtO_2 (*Adam's catalyst*).[669]



60 **61**

F. A Metal on the Other Side

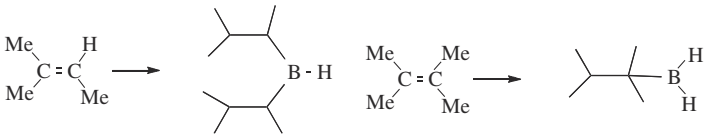
15-16 Hydroboration



When alkenes are treated with borane[670] in ether solvents, BH_3 adds across the double bond.[671] The alkene reacts as a base with the boron essentially reacting as a Lewis acid. Borane cannot be prepared as a stable pure compound[672] (it dimerizes to diborane, B_2H_6),

[660] Shimoda, K.; Kubota, N.; Hamada, H. *Tetrahedron Asymmetry* ***2004****, 15*, 2443.
[661] Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* ***2001****, 42*, 3367.
[662] Fryszkowska, A.; Fisher, K.; Gardiner, J.M.; Stephens, G.M. *J. Org. Chem.* ***2008****, 73*, 4295.
[663] See Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 588–592; Newham, J. *Chem. Rev.* ***1963****, 63*, 123; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals* Academic Press, *NY,* ***1967***, pp. 469–474.
[664] Bart, S.C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2003****, 125,* 886.
[665] See Woodworth, C.W.; Buss, V.; Schleyer, P.v.R. *Chem. Commun.* ***1968***, 569.
[666] See Walborsky, H.M.; Aronoff, M.S.; Schulman, M.F. *J. Org. Chem.* ***1970****, 36,* 1036.
[667] For a review, see Staley, S.W. *Sel. Org. Transform.* ***1972****, 2*, 309.
[668] Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993****, 34*, 8107.
[669] Karimi, S.; Tavares, P. *J. Nat. Prod.* ***2003****, 66,* 520.
[670] See Lane, C.F. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 1–191.
[671] See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, *Organic Syntheses Via Boranes Wiley*, NY, ***1975***; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***; Matteson, D.S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 307–409, pp. 315–337; Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986****, 130*, 23.
[672] Fehlner, T.P. *J. Am. Chem. Soc.* ***1971****, 93*, 6366.

but it is commercially available in the form of "ate" complexes with THF, Me_2S,[673] phosphines, or tertiary amines. The alkenes can be treated with a solution of one of these complexes. Tetrahydrofuran–BH_3 reacts at 0 °C and is the most convenient to use and $R_3N—BH_3$ generally require temperatures of ~100 °C. The latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture in air) or with a mixture of $NaBH_4$ and BF_3 etherate, which generates borane *in situ*.[674] Pyridine–borane can be used for the hydroboration of alkenes at room temperature.[675] With relatively unhindered alkenes, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH, which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane (R_3B). The reaction can be performed on alkenes with one to four substituents, including cyclic alkenes, but when the alkene is moderately hindered, the product *is* the dialkylborane (R_2BH) or even the monoalkylborane (RBH_2).[676] For example, **62** (*disiamylborane*) and **63** (*thexylborane*)[677] have been prepared in this manner. Monoalkylboranes (RBH_2), which can be prepared from hindered alkenes, (as above) and dialkylboranes (R_2BH) also add to alkenes, to give the mixed trialkylboranes (RR'_2B and $R_2R'B$), respectively. Surprisingly, when methylborane ($MeBH_2$),[678] which is not a bulky molecule, adds to alkenes in the solvent THF, the reaction can be stopped with one addition to give dialkylboranes (RMeBH).[679] Reaction of this with a second alkene produces the trialkylborane (RR′MeB).[680] Other monoalkylboranes (*i*$PrBH_2$, *n*-$BuBH_2$, *s*-$BuBH_2$, and *t*-$BuBH_2$), behave similarly with internal alkenes, but not with alkenes of the type $RCH=CH_2$.[681]

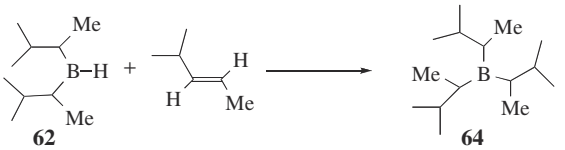


Disiamylborane **62** Thexylborane **63**

In all cases, the boron goes to the side of the double bond that has more hydrogen atoms (less substituted), whether the substituents are aryl or alkyl.[682] Technically, this follows *Markovnikov's rule*, since boron is more positive than hydrogen. The regioselectivity is caused mostly by steric factors, although electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of

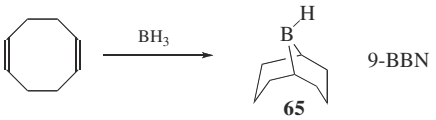
[673] See Hutchins, R.O.; Cistone, F. *Org. Prep. Proced. Int.* ***1981****, 13*, 225; Cadot, C.; Dalko, P.I.; Cossy, J. *Tetrahedron Lett.* ***2001****, 42*, 1661.
[674] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1005–1009.
[675] Clay, J.M.; Vedejs, E. *J. Am. Chem. Soc.* ***2005****, 127,* 5766.
[676] Unless coordinated with a strong Lewis base, such as a tertiary amine, mono- and dialkylboranes actually exist as hydrogen-bridged dimers: Brown, H.C.; Klender, G.J. *Inorg. Chem.* ***1962****, 1*, 204.
[677] See Negishi, E.; Brown, H.C. *Synthesis* ***1974***, 77.
[678] See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986****, 51,* 4925.
[679] Srebnik, M.; Cole, T.E.; Brown, H.C. *J. Org. Chem.* ***1990****, 55,* 5051.
[680] See Kulkarni, S.U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H.C. *Organometallics* ***1982****, 1,* 212.
[681] Srebnik, M.; Cole, T.E.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* ***1989****, 54,* 6085.
[682] Cragg, G.M.L. *Organoboranes in Organic Synthesis* Marcel Dekker, NY, ***1973***, pp. 63–84, 137–197; Brown, H.C.; Vara Prasad, J.V.N.; Zee, S. *J. Org. Chem.* ***1986****, 51*, 439.

substituted styrenes showed that the reaction with boron and the alkene has electrophilic character.[683] When both sides of the double bond are monosubstituted or disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large borane molecule. For example, treatment of *i*PrCH=CHMe with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **62** gave 95% **64** and only 5% of the other isomer.[684]



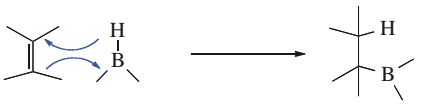
62 **64**

Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN, **65**), which is prepared by hydroboration of 1,5-cyclooctadiene,[685] and has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and preferentially react at the less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one alkene in the presence of a less reactive alkene.[686] For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a *cis*-alkene can be selectively hydroborated in a mixture of the cis and trans isomers.



65

For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.[687] Note that organoboranes can be analyzed using ^{11}B NMR.[688] The mechanism[689] may be a cyclic four-center one:[690]



[683] Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966****, 88,* 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967****, 7,* 377. See also, Marshall, P.A.; Prager, R.H. *Aust. J. Chem.* ***1979****, 32,* 1251; Mo, Y.; Jiao, H.; Schleyer, P.v.R. *J. Org. Chem.* ***2004****, 69*, 3493.

[684] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961****, 83,* 1241.

[685] See Brown, H.C.; Chen, J.C. *J. Org. Chem.* ***1981****, 46,* 3978; Soderquist, J.A.; Brown, H.C. *J. Org. Chem.* ***1981****, 46*, 4599.

[686] Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966****, 88,* 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967****, 7,* 377.

[687] Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1978****, 43,* 1567.

[688] Medina, J.R.; Cruz, G.; Cabrera, C.R.; Soderquist, J.A. *J. Org. Chem.* ***2003****, 68*, 4631.

[689] See Nelson, D.J.; Cooper, P.J. *Tetrahedron Lett.* ***1986****, 27,* 4693; Brown, H.C.; Chandrasekharan, J. *J. Org. Chem.* ***1988****, 53*, 4811.

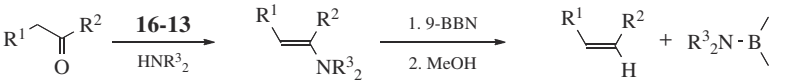
[690] Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1857. See, however, Jones, P.R. *J. Org. Chem.* ***1972****, 37,* 1886.

When the substrate is an allylic alcohol or amine, the addition is generally anti,[691] although the stereoselectivity can be changed to syn by the use of catecholborane and Rh complexes.[692] Because the mechanism is different, use of this procedure can result in a change in regioselectivity as well (e.g., styrene, $PhCH{=}CH_2$, gave $PhCH(OH)CH_3$).[693]

Monochloroborane[694] (BH_2Cl) coordinated with DMS shows greater regioselectivity than BH_3 for terminal alkenes or those of the form $R_2C{=}CHR$, and the hydroboration product is a dialkylchloroborane (R_2BCl).[695] For example, 1-hexene gave 94% of the *anti-Markovnikov* product (the boron is on the less substituted carbon) with BH_3—THF, but 99.2% with $BH_2Cl^-SMe_2$. Treatment of alkenes with dichloroborane–DMS ($BHCl_2$—SMe_2) in the presence of BF_3[696] or with BCl_3 and Me_3SiH[697] gives alkyldichloroboranes ($RBCl_2$). Extensions of this basic approach are possible with dihalo alkylboranes. The reaction of an alkene with allyl dibromoborane, incorporated an allyl group and the boron on adjacent carbons.[698]

An important use of the hydroboration reaction is oxidation of an organoborane to alcohols with H_2O_2 and NaOH (see Reaction **12-27**). The synthetic result is an indirect way of adding H_2O across a double bond in an *anti-Markovnikov* manner. However, boranes undergo many other reactions as well. Among other things, they react with α-halo carbonyl compounds to give alkylated products (Reaction **10-73**), with α,β-unsaturated carbonyl compounds to give *Michael-type* addition of R and H (Reaction **15-27**), with CO to give alcohols and ketones (Reactions **18-23**–**18-24**); they can be reduced with carboxylic acids (Reaction **15-11**), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones[699] or aldehydes (from terminal alkenes),[700] dimerized with silver nitrate and NaOH (Reaction **14-26**), isomerized (Reaction **18-11**), or converted to amines (Reaction **12-32**), halides (Reaction **12-31**), or carboxylic acids.[701] They are thus useful intermediates for the preparation of a wide variety of compounds. Intramolecular hydroboration reactions are possible.[702]

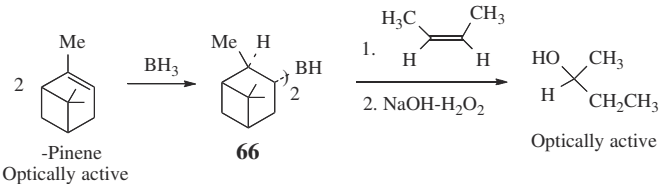
Such functional groups as OR, OH, NH_2, SMe, halogen, and CO_2R may be present in the molecule,[703] but not groups that are reducible by borane (e.g., COOH). Hydroboration of enamines with 9-BBN provides an indirect method for reducing an aldehyde or ketone to an alkene, for example,[704]



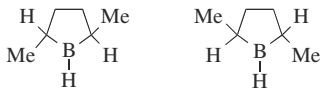
[691] See Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* ***1983****, 105,* 2487.
[692] See Burgess, K.; Cassidy, J.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991****, 56,* 1020; Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991****, 56,* 1027.
[693] Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* ***1991****, 56*, 1670.
[694] See Brown, H.C.; Kulkarni, S.U. *J. Organomet. Chem.* ***1982****, 239*, 23.
[695] Brown, H.C.; Ravindran, N.; Kulkarni, S.U. *J. Org. Chem.* ***1979****, 44,* 2417.
[696] Brown, H.C.; Racherla, U.S. *J. Org. Chem.* ***1986****, 51*, 895.
[697] Soundararajan, R.; Matteson, D.S. *J. Org. Chem.* ***1990****, 55,* 2274.
[698] Frantz, D.E.; Singleton, D.A. *Org. Lett.* ***1999****, 1*, 485.
[699] Parish, E.J.; Parish, S.; Honda, H. *Synth. Commun.* ***1990****, 20,* 3265.
[700] Brown, H.C.; Kulkarni, S.U.; Rao, C.G.; Patil, V.D. *Tetrahedron* ***1986****, 42,* 5515.
[701] Soderquist, J.A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* ***2004****, 45,* 5541.
[702] See Shapland, P.; Vedejs, E. *J. Org. Chem.* ***2004****, 69*, 4094.
[703] See Brown, H.C.; Unni, M.K. *J. Am. Chem. Soc.* ***1968****, 90*, 2902; Brown, H.C.; Gallivan, Jr., R.M. *J. Am. Chem. Soc.* ***1968****, 90*, 2906; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1968****, 90*, 2915.
[704] Singaram, B.; Rangaishenvi, M.V.; Brown, H.C.; Goralski, C.T.; Hasha, D.L. *J. Org. Chem.* ***1991****, 56,* 1543.

The presence of certain functional groups has directing effects on hydroboration reactions. Amides direct hydroboration reactions in alkenyl amides, for example.[705] Intramolecular hydroboration is directed by amine groups in alkenyl amines.[706] Alkenyl alcohols or ethers also undergo hydroboration, where delivery of boron is directed by the oxygen.[707]

Use of the reagent diisopinocampheylborane (**66**, prepared by treating optically active α-pinene with BH_3) results in enantioselective hydroboration–oxidation.[708] Since both (+) and (−) α-pinene are readily available, both enantiomers can be prepared. Alcohols with moderate-to-excellent enantioselectivities have been obtained



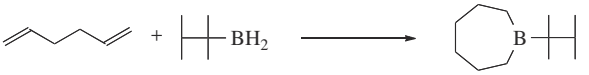
in this way.[709] However, **66** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane[710] although optical yields are lower. Limonylborane,[711] 2- and 4-dicaranylboranes,[712] a myrtanylborane,[713] and dilongifolylborane[714] have also been used. Other new asymmetric boranes have also been developed. The chiral cyclic boranes *trans*-2,15-dimethylborolanes (**67** and **68**) also add enantioselectively to alkenes (except alkenes of the form $RR'C{=}CH_2$) to give boranes of high optical purity.[715] When chiral boranes are added to trisubstituted alkenes of the form $RR'C{=}CHR''$, two new chiral centers are created, and, with **67** or **68**, only one of the four possible diastereomers is predominantly produced, in yields >90%.[715] This has been called *double-asymmetric synthesis*.[716] An alternative asymmetric synthesis of alcohols involves the reaction of catechol borane with an alkene in the presence of a chiral Rh catalyst, giving the alcohol enantioselectivity after the usual oxidation.[717]



(*R*, *R*) **67** (*S*, *S*) **68**

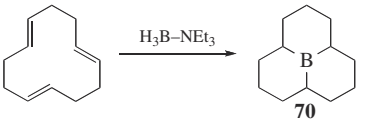
[705] Smith, S.M.; Thacker, N.C.; Takacs, J.M. *J. Am. Chem. Soc.* ***2008****, 130*, 3734.
[706] Scheideman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* ***2008****, 130,* 8669.
[707] Rarig, R.-A.F.; Scheideman, M.; Vedejs, E. *J. Am. Chem. Soc.* ***2008****, 130*, 9182.
[708] Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* ***1986****, 108*, 2049.
[709] Brown, H.C.; Singaram, B. *Acc. Chem. Res.* ***1988****, 21*, 287; Srebnik, M.; Ramachandran, P.V. *Aldrichimica Acta* ***1987****, 20,* 9; Brown, H.C.; Jadhav, P.K. in Morrison, J.D. *Asymmetric Synthesis* Vol. 2, Academic Press, NY, ***1983***, pp. 1–43. For a study of electronic effects, see Garner, C.M.; Chiang, S.; Nething, M.; Monestel, R. *Tetrahedron Lett.* ***2002****, 43*, 8339.
[710] Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* ***1982****, 47*, 5074. See also, Brown, H.C.; Weissman, S. A.; Perumal, P.T.; Dhokte, U.P. *J. Org. Chem.* ***1990****, 55*, 1217. For the crystal structure of this adduct, see Soderquist, J.A.; Hwang-Lee, S.; Barnes, C.L. *Tetrahedron Lett.* ***1988****, 29*, 3385.
[711] Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* ***1982****, 18,* 169.
[712] Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. *J. Org. Chem.* ***1988****, 53,* 2911.
[713] Kiesgen de Richter, R.; Bonato, M.; Follet, M.; Kamenka, J. *J. Org. Chem.* ***1990****, 55,* 2855.
[714] Jadhav, P.K.; Brown, H.C. *J. Org. Chem.* ***1981****, 46*, 2988.
[715] Masamune, S.; Kim, B.M.; Petersen, J.S.; Sato, T.; Veenstra, J.S.; Imai, T. *J. Am. Chem. Soc.* ***1985****, 107,* 4549. See Thomas, S.P.; Aggarwal, V.K. *Angew. Chem. Int. Ed.* ***2009****, 48,* 1896.
[716] For another enantioselective hydroboration method, see Reaction **15-16**.
[717] Demay, S.; Volant, F.; Knochel, P. *Angew. Chem. Int. Ed.* ***2001****, 40*, 1235.

The double bonds in a conjugated diene are hydroborated separately; that is, there is no 1,4-addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. Thexylborane[677] (**63**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated, as in the formation of **69**.[718]



63 **69**

Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.[719] One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene (**70**).[720]



70

Boronate esters are prepared from alkenes. The reaction of an alkene with pyridine iodoborane, followed by treatment with pinacol and NaOH, for example, leads to the pinacol boronate ester.[721]

Triple bonds[722] can be monohydroborated to give vinylic boranes, which can be reduced with carboxylic acids to *cis*-alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed in Reaction **15-4**. However, terminal alkynes give vinylic boranes[723] (and hence aldehydes) only when treated with a hindered borane (e.g., **62**, **63**, or catecholborane, Reaction **12-31** and Sec. 14.A.i),[724] or with $BHBr_2—SMe_2$.[725] The reaction between terminal alkynes and BH_3 produces 1,1-dibora compounds, which can be oxidized either to primary alcohols (with $NaOH—H_2O_2$) or to carboxylic acids (with *m*-chloroperoxybenzoic acid).[726] Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.[727] On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.[728] Furthermore, it is often

[718] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1972****, 94,* 3567.
[719] Cyclic hydroboration: see Brown, H.C.; Negishi, E. *Tetrahedron* ***1977****, 33,* 2331. See also, Brown, H.C.; Pai, G.G.; Naik, R.G. *J. Org. Chem.* ***1984****, 49*, 1072.
[720] Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985****, 50*, 520.
[721] Karatjas, A.G.; Vedejs, E. *J. Org. Chem.* ***2008****, 73*, 9508.
[722] See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbn–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 203–219.
[723] Brown, H.C.; Campbell, Jr., J.B. *Aldrichimica Acta* ***1981****, 14,* 1.
[724] Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1975****, 97*, 5249. See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996****, 61*, 3224.
[725] Brown, H.C.; Campbell Jr., J.B. *J. Org. Chem.* ***1980****, 45,* 389.
[726] Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* ***1967****, 89,* 291.
[727] Brown, H.C.; Coleman, R.A. *J. Org. Chem.* ***1979****, 44,* 2328.
[728] Pelter, A.; Singaram, S.; Brown, H.C. *Tetrahedron Lett.* ***1983****, 24,* 1433.

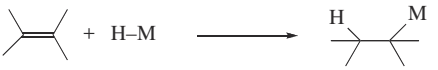
possible to hydroborate selectively one particular double bond of a nonconjugated diene.[729] A triple bond can be hydroborated in the presence of a ketone, and treatment with acetic acid reduces the C≡C unit to a *cis*- alkene (see Reaction **15-12**).[730] When the reagent is catecholborane, hydroboration is catalyzed by Rh complexes,[731] (e.g., *Wilkinson's catalyst*, **46**,[732] by SmI_2,[733] or lanthanide reagents).[734] Enantioselective hydroboration–oxidation has been achieved by the use of optically active Rh complexes.[735]

A chain extension variation involved the reaction of styrene with catecholborane and then Me_3SiCHN_2.[736] Subsequent oxidation with $NaOH/H_2O_2$ and the reaction with Bu_4NF gave 3-phenyl-1-propanol.

OS **VI**, 719, 852, 919, 943; **VII**, 164, 339, 402, 427; **VIII**, 532.

15-17 Other Hydrometalation

Hydro-metallo-addition



Metal hydrides of Groups 13 and 14 of the periodic table (e.g., AlH_3, GaH_3), as well as many of their alkyl and aryl derivatives (e.g., R_2AlH and Ar_3SnH) add to double bonds to give organometallic compounds.[737] In each case, the alkene reacts with the Lewis acid. The hydroboration reaction (**15-16**) is the most important example but, as mentioned, other important metals in this reaction are Al,[738] Sn,[739] and Zr[740] (a Group 4 metal). Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.[741] Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl),[742] known as *Schwartz's reagent*. The mechanism with Group 13 hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with Group 14 hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesium reagents have been obtained by adding MgH_2 to double bonds.[743]

[729] See Gautam, V.K.; Singh, J.; Dhillon, R.S. *J. Org. Chem.* ***1988****, 53*, 187. See also, Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986****, 130*, 23.

[730] Kabalka, G.W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* ***1997****, 38*, 7681.

[731] Burgess, K.; van der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T. ; Calabrese, J.C. *J. Am. Chem. Soc.* ***1992****, 114*, 9350; Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1992****, 114*, 6671.

[732] Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.* ***1991****, 91*, 1179.

[733] Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* ***1993****, 58*, 5307.

[734] Harrison, K.N.; Marks, T.J. *J. Am. Chem. Soc.* ***1992****, 114*, 9220.

[735] Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1990****, 31,* 231; Brown, J.M.; Lloyd-Jones, G.C. *Tetrahedron: Asymmetry* ***1990****, 1,* 869.

[736] Goddard, J.-P.; LeGall, T.; Mioskowski, C. *Org. Lett.* ***2000****, 2*, 1455.

[737] Negishi, E. *Adv. Met.-Org. Chem.* ***1989****, 1*, 177; Eisch, J.J. *The Chemistry of Organometallic Compounds*; Macmillan, NY, ***1967***, pp. 107–111; Eisch, J.J.; Fichter, K.C. *J. Organomet. Chem.* ***1983****, 250,* 63.

[738] See Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1990****, 59,* 1157; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1988****, 44,* 5001.

[739] See Negishi, E. *Organometallics in Organic Synthesis* Vol. 1, Wiley, NY, ***1980***, pp. 45–48, 357–363, 406–412; Speier, J.L. *Adv. Organomet. Chem.* ***1979****, 17*, 407; Andrianov, K.A.; Soucek, J.; Khananashvili, L.M. *Russ. Chem. Rev.* ***1979****, 48,* 657.

[740] Negishi, E.; Takahashi, T. *Synthesis* ***1988***, 1; Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *J. Organomet. Chem.* ***1986****, 304,* 17. Also see, Hoveyda, A.H.; Morken, J.P. *J. Org. Chem.* ***1993****, 58*, 4237.

[741] Doyle, M.P.; High, K.G.; Nesloney, C.L.; Clayton, Jr., T.W.; Lin, J. *Organometallics* ***1991****, 10,* 1225.

[742] Lipshutz, B.H.; Keil, R.; Ellsworth, E.L. *Tetrahedron Lett.* ***1990****, 31*, 7257.

[743] See Bogdanovic, B. *Angew. Chem. Int. Ed.* ***1985****, 24,* 262.

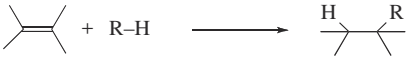
With some reagents triple bonds[744] can add 1 or 2 equiv.[745] When 2 molar equivalents are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydroboration), while free radical addition usually gives the 1,2-dimetallic products.

OS **VII**, 456; **VIII**, 268, 295, 507; **80**, 104. See also, OS **VIII**, 277, 381.

G. Carbon or Silicon on the Other Side

15-18 Addition of Alkanes

Hydro-alkyl-addition



There are two important ways of adding alkanes to alkenes: direct heating, and acid catalysis.[746] Both give mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method, the reactants are heated to high temperatures (~500 °C) at high pressures (150–300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[747] The mechanism is undoubtedly of a free radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:

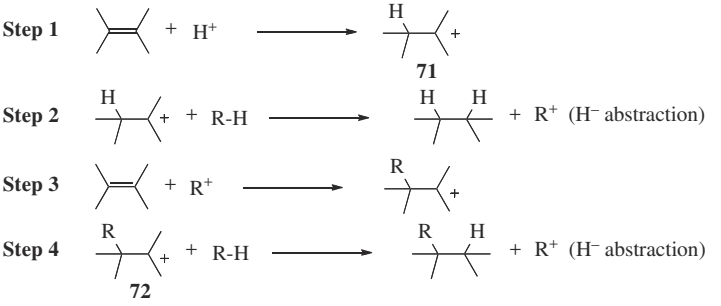
Step 1 $CH_3CH_2CH_3 + CH_2{=}CH_2 \xrightarrow{\Delta} CH_3{-}\dot{C}H{-}CH_3 + CH_3CH_2^{\bullet}$

Step 2 $CH_3{-}\dot{C}H{-}CH_3 + CH_2{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CH_2^{\bullet}$

Step 3 $(CH_3)_2CHCH_2CH_2^{\bullet} + CH_3CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 + CH_3\dot{C}HCH_3$

There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps[748] (the opposite of disproportionation, see Sec. 5.C.ii).

In the acid-catalysis method, a protonic or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between –30 and 100 °C. This is a *Friedel–Crafts* process that proceeds via a carbocation mechanism[749] (illustrated for a proton acid catalyst):



[744] See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond,* pt. 1, Wiley, NY, ***1978***, pp. 219–232.

[745] Eisch, J.J.; Kaska, W.C. *J. Am. Chem. Soc.* ***1966,*** *88*, 2213; Eisch, J.J.; Rhee, S. *Liebigs Ann. Chem.* ***1975***, 565.

[746] See Shuikin, N.I.; Lebedev, B.L. *Russ. Chem. Rev.* ***1966,*** *35,* 448; Schmerling, L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1075–1111, 1121–1122.

[747] Frey, E.J.; Hepp, H.J. *Ind. Eng. Chem.* ***1936,*** *28,* 1439.

[748] Metzger, J.O. *Angew. Chem. Int. Ed.* ***1983,*** *22,* 889; Hartmanns, J.; Klenke, K.; Metzger, J.O. *Chem. Ber.* ***1986,*** *119*, 488.

[749] See Mayr, H. *Angew. Chem. Int. Ed.* ***1990,*** *29*, 1371.

Carbocation **72** often rearranges before a hydride is transferred, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. Instead of abstracting a hydride, it is also possible for **71** (or **72**) to add to another molar equivalent of alkene, so that not only rearrangement products, but also dimeric and polymeric products, are frequent. If the tri- or tetrasubstituted alkenes are treated with Me_4Si, HCl, and $AlCl_3$, protonation gives a tertiary carbocation, which reacts with the Me_4Si to give a product that is the result of addition of H and Me to the original alkene.[750] (For a free radical hydro-methyl addition, see Reaction **15-28**.) An intramolecular cyclization of 1-dodecene to cyclododecane was reported using aluminum chloride in an ionic liquid.[751]

Alkanes add to alkynes under photolysis conditions to give an alkene.[752] Tetrahydrofuran adds to alkynes to give the alkene with microwave irradiation.[753]

The reaction can also be base catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.[754] Carbanions most often used are those stabilized by one or more α-aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:[755]

$$PhCH_3 \xrightarrow{Na} Ph\overset{+}{C}H_2 + PhCH{=}CH_2 \longrightarrow Ph\overset{+}{C}H{-}CH_2CH_2Ph \xrightarrow{solvent} PhCH_2CH_2CH_2Ph$$

Conjugated dienes give 1,4-addition.[756] This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids[757] (see also, Reaction **10-59**).

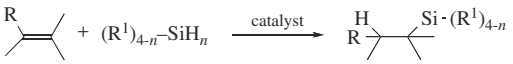
$$CH_3COOK \xrightarrow{NaNH_2} {}^{-}CH_2COOK + CH_2{=}CH_2 \longrightarrow {}^{-}CH_2{-}CH_2CH_2COOK$$

There are transition metal catalyzed addition reactions of alkyl units to alkenes,[758] often proceeding with metal hydride elimination to form an alkene. An intramolecular cyclization reaction of an *N*-pyrrolidino amide alkene was reported using an iridium catalyst for addition of the carbon α to nitrogen at the alkene unit.[759]

OS **I**, 229; **IV**, 665; **VII**, 479.

15-19 Addition of Silanes (Hydrosilation)

Silyl-hydro-addition



[750] Bolestova, G.I.; Parnes, Z.N.; Kursanov, D.N. *J. Org. Chem. USSR* ***1983****, 19,* 2175.
[751] Qiao, K.; Deng, Y. *Tetrahedron Lett.* ***2003****, 44,* 2191.
[752] Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.* ***2001****, 42*, 3211.
[753] Zhang, Y.; Li, C.-J. *Tetrahedron Lett.* ***2004****,45*, 7581.
[754] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 240–422; Pines, H. *Acc. Chem. Res.* ***1974****, 7,* 155.
[755] Pines, H.; Wunderlich, D. *J. Am. Chem. Soc.* ***1958****, 80,* 6001.
[756] Eberhardt, G.G.; Peterson, H.J. *J. Org. Chem.* ***1965****, 30*, 82; Pines, H.; Stalick, W.M. *Tetrahedron Lett.* ***1968***, 3723.
[757] Schmerling, L.; Toekelt, W.G. *J. Am. Chem. Soc.* ***1962****, 84,* 3694.
[758] Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* ***2002****, 35*, 826.
[759] DeBoef, B.; Pastine, S.J.; Sames, D. *J. Am. Chem. Soc.* ***2004****, 126*, 6556.

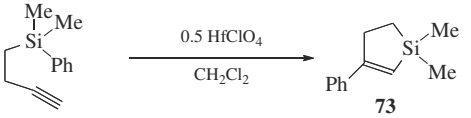
Although silanes bearing at least one Si—H unit do not generally react with alkenes or alkynes, addition occurs to give the corresponding alkyl or vinyl silane in the presence of transition metal catalysts.[760] This reaction is known as hydrosilation. The reaction of an alkylsilane and an alkene with a Ru,[761] Rh,[762] Pd,[763] Re,[764] La,[765] Y,[766] Pt[767] Cu,[768] or Sm[769] catalyst leads to addition with high *anti-Markovnikov* selectivity. Silanes add to dienes with a Pd catalyst, and asymmetric induction is achieved by using a chiral binapthyl additive.[770] Alkenes react with Li metal and t-Bu_2SiCl_2 to give a three-membered ring silane.[771]

Dienes react with zirconium compounds and silanes to produce cyclic compounds in which the silyl group has also added to one C=C unit.[772] With an Y catalyst, $PhSiH_3$ reacts with nonconjugated dienes to give cyclic alkenes with a pendant CH_2SiH_2Ph group.[773] Rhodium compounds allow silanes to add to enamides to give the α-silylamide.[774] Formation of silanes via reaction with alkenes can be followed by reaction with fluoride ion and then oxidation to give an alcohol[775] (see Reaction **10-16**; *Tamao–Fleming oxidation*). A variation of this reaction generated allylic silanes from terminal alkenes and a dianion-type zincate using a Ti catalyst.[776]

In the presence of BEt_3, silanes add to alkenes to give the alkylsilane with *anti-Markovnikov* selectivity,[777] or to alkynes to give the corresponding vinyl silane.[778] Similar selectivity was observed when a silylated zinc reagent was added to a terminal alkyne.[779] Hydrosilation of alkynes is accomplished using transition metal catalysts (e.g., Ru[780] Pt,[781] Ti,[782] or Ir).[783] Organocatalyts have been used as well.[784] Siloxanes [e.g., $(RO)_3SiH$] add to alkynes with a Ru catalyst to give the corresponding vinyl silane.[785] The reaction of Cl_2MeSiH and terminal alkynes, in ethanol–triethylamine with a Ru catalyst, to give

[760] Buch, F.; Brettar, J.; Harder, S. *Angew. Chem. Int. Ed.* ***2006****, 45*, 2741.
[761] Glaser, P.B.; Tilley, T.D. *J. Am. Chem.Soc.* ***2003****, 125*, 13640.
[762] See Tsuchiya, Y.; Uchimura, H.; Kobayashi, K.; Nishiyama, H. *Synlett* ***2004***, 2099.
[763] Motoda, D.; Shinokubo, H.; Oshima, K. *Synlett* ***2002***, 1529.
[764] Zhao, W.-G.; Hua, R. *Eur. J. Org. Chem.* ***2006***, 5495.
[765] Takaki, K.; Sonoda, K.; Kousaka, T.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* ***2001****, 42*, 9211.
[766] Molander, G.A.; Julius, M. *J. Org. Chem.* ***1992****, 57*, 6347.
[767] See Sabourault, N.; Mignani, G.; Wagner, A.; Mioskowski, C. *Org. Lett.* ***2002****, 4*, 2117.
[768] Nakamura, S.; Uchiyama, M. *J. Am. Chem. Soc.* ***2007****, 129*, 28; Lipshutz, B.H.; Lower, A.; Kucejko, R.J.; Noson, K. *Org. Lett.* ***2006****, 8,* 2969.
[769] Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* ***2001****, 123*, 9216.
[770] Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* ***1994****, 35*, 7981.
[771] Driver, T.G.; Franz, A.K.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2002****, 124*, 6524.
[772] Molander, G.A.; Corrette, C.P. *Tetrahedron Lett.* ***1998****, 39*, 5011.
[773] Muci, A.R.; Bercaw, J.E. *Tetrahedron Lett.* ***2000****, 41*, 7609.
[774] Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* ***1994***, 2143.
[775] Jensen, J.F.; Svendsen, B.H.; la Cour, T.V.; Pedersen, H.L.; Johannsen, M. *J. Am. Chem. Soc.* ***2002****, 124*, 4558.
[776] Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* ***2005****, 127*, 13116.
[777] Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* ***2002****, 67*, 1936.
[778] Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1993****, 66*, 2356.
[779] Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* ***2004****, 126*, 11146.
[780] Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2005****, 127*, 17644; Maifeld, S.V.; Tran, M.N.; Lee, D. *Tetrahedron Lett.* ***2005****, 46,* 105.
[781] Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Synthesis* ***2007***, 2025.
[782] Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* ***2003****, 5*, 3479.
[783] Miyake, Y.; Isomura, E.; Iyoda, M. *Chem. Lett.* ***2006****, 35*, 836.
[784] Berthon-Gelloz, G.; Schumers, J.-M.; De Bo, G.; Markó, I.E. *J. Org. Chem.* ***2008****, 73,* 4190.
[785] Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2001****, 123*, 12726.

primarily the *Markovnikov* vinyl silane.[786] However, Et_3SiH adds to terminal alkynes with a Rh[787] or a Pt[788] catalyst to give the *anti-Markovnikov* vinyl silane. Using a 0.5 molar equivalent of $HfClO_4$ with alkynes bearing a dimethylphenylsilyl unit gave a cyclic vinyl silane with transfer of the phenyl group to carbon (see **73**).[789]



73

Silanes add to alkenes under radical conditions (using AIBN) with high *anti-Markovnikov* selectivity.[790] An alternative route to alkylsilanes reacted an alkene with Li metal in the presence of 3 equiv of chlorotrimethylsilane, giving bis-1,2-trimethylsilyl compounds after treatment with water.[791] Silanes also add to alkenes to form the *anti-Markovnikov* alkylsilane ($R_3Si—C—C—R'$) in the presence of a hyponitrite.[792]

In a reaction more related to those in Reaction **15-24**, vinyl silanes add to conjugated carbonyl compounds in the presence of a Ru catalyst,[793] or to acrylonitriles with a Co catalyst.[794] Silyl phosphines react with conjugated ynones directly to give an enone with an α-trimethylsilyl and a β-phosphine group.[795] Siloxanes of the type $(RO)_3SiH$ add to the α-carbon of enamines in the presence of a dirhodium catalyst.[796] The uncatalyzed reaction of trimethylsilyl cyanide and ynamines, however, gave an enamine with a β-trimethylsilyl and an α-cyano group.[797]

bis(Silanes) add to alkylidene malonate derivatives (see Reaction **15-24**) in the presence of a Cu catalyst to give β-silyl malonates [$RCH(SiR_3)CH(CO_2Me)_2$].[798] Alkylsilane units add using bis(trialkylsilyl)zinc reagents with a CuCN catalyst.[799] Trimethylsilyl cyanide (Me_3SiCN) adds a cyano group to α,β-unsaturated amines with a specialized Al(salen)-Y catalyst.[800]

15-20 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

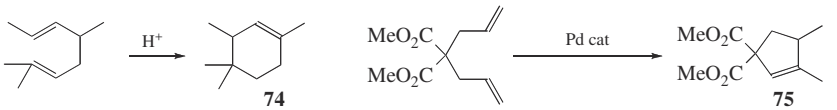
Hydro-alkenyl-addition

$$CH_2{=}CH_2 + CH_2{=}CH_2 \xrightarrow{H^+} CH_2{=}CHCH_2CH_3$$

[786] Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* ***2002****, 4*, 2825.
[787] Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004****, 6*, 2217.
[788] Wu, W.; Li, C.-J. *Chem. Commun.* ***2003***, 1668.
[789] Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2001****, 123*, 10899. See also, Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* ***2000****, 65*, 8919.
[790] Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* ***1992****, 57*, 3994.
[791] Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* ***2001****, 57*, 10119.
[792] Dang, H.-S.; Roberts, B.P. *Tetrahedron Lett.* ***1995****, 36*, 2875.
[793] Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* ***1995***, 679; Trost, B.M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* ***1995****, 117*, 5371.
[794] Tayama, O.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Eur. J. Org. Chem.* ***2003***, 2286.
[795] Reisser, M.; Maier, A.; Maas, G. *Synlett* ***2002***, 1459.
[796] Hewitt, G.W.; Somers, J.J.; Sieburth, S.Mc.N. *Tetrahedron Lett.* ***2000****, 41*, 10175.
[797] Lukashev, N.V.; Kazantsev, A.V.; Borisenko, A.A.; Beletskaya, I.P. *Tetrahedron* ***2001****, 57*, 10309.
[798] Clark, C.T.; Lake, J.F.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004****, 126*, 84.
[799] Oestreich, M.; Weiner, B. *Synlett* ***2004***, 2139.
[800] See Sammis, G.M.; Danjo, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004****, 126*, 9928.

With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.[801] A catalyst comprised of a combination of Zn and a $CoCl_2$ accomplished this type of coupling.[802] One alkene adds to another in the presence of a Ni catalyst.[803] α-Alkenes add to dienes in a 1,4-manner in the presence of an Fe catalyst.[804]

This reaction is more often carried out internally, as in the formation of cyclohexene (**74**). A Pd catalyzed cyclization is known, in which dienes are converted to cyclopentene derivatives (e.g., **75**).[805]

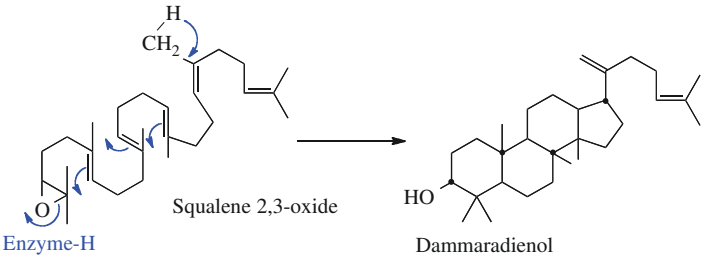


74 **75**

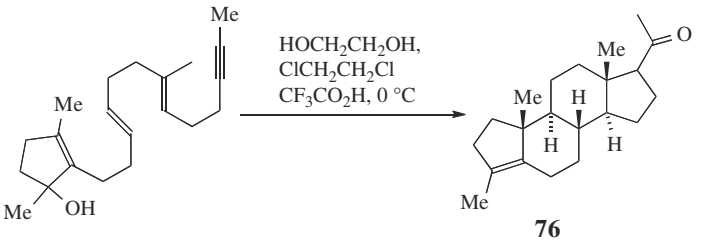
Ring-forming reactions are possible. A Ru catalyzed version of this reaction gave the five-membered ring with an exocyclic double bond.[806] Carbocyclization of an alkene unit to another alkene unit was reported using a Y,[807] or a Ti catalyst.[808] In some cases, internal coupling of two alkenes can form larger rings.[809] Carbocyclization was reported using Pd,[810] Rh,[811] Ru,[812] Ir,[813] or a Zr catalyst.[814] Alkene allene substrates were cyclized to form cyclic products with an exocyclic double bond using a Pd catalyst.[815] An interesting variation adds a silyl enol ether to an alkyne using $GaCl_3$ to give an unconjugated ketone (O=C—C—C=C).[816] Alkenes and alkynes can also add to each other to give cyclic products in other ways (see Reaction **15-63** and **15-65**).

Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymatic catalysis to dammaradienol. The squalene → lanosterol biosynthesis, which is a key step in the biosynthesis of cholesterol, is similar. The idea that the biosynthesis of

[801] See Onsager, O.; Johansen, J.E. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 205–257.
[802] Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* ***2004****, 45,* 6203.
[803] Ng, S.-S.; Ho, C.-Y.; Schleicher, K.D.; Jamison, T.F. *Pure Appl. Chem.* ***2008****, 80*, 929.
[804] Moreau, B.; Wu, J.Y.; Ritter, T. *Org. Lett.* ***2009****, 11*, 337.
[805] Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2001****, 66*, 635.
[806] Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* ***2003****, 125*, 5606; Michaut, M.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* ***2003****, 44*, 2157.
[807] Molander, G.A.; Dowdy, E.D.; Schumann, H. *J. Org. Chem.* ***1998****, 63*, 3386.
[808] Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* ***2000****, 122*, 1223. See Hart, D.J.; Bennett, C.E. *Org. Lett.* ***2003****, 5*, 1499.
[809] Toyota, M.; Majo, V.J.; Ihara, M. *Tetrahedron Lett.* ***2001****, 42*, 1555.
[810] Kende, A.S.; Mota Nelson, C.E.; Fuchs, S. *Tetrahedron Lett.* ***2005****, 46*, 8149.
[811] Wender, P.A.; Dyckman, A.J. *Org. Lett.* ***1999****, 1*, 2089; Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* ***2000****, 122,* 6490; Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* ***2000****, 39*, 4104.
[812] Fernández-Rivas, C.; Méndez, M.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2000****, 122*, 1221.
[813] Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* ***2001****, 66*, 4433.
[814] Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1996****, 37*, 9059. Also see, Maye, J.P.; Negishi, E. *Tetrahedron Lett.* ***1993****, 34*, 3359.
[815] See Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* ***2004****, 69*, 4541.
[816] Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* ***1999****, 121*, 4074.



such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork–Eschenmoser hypothesis*.[817] Such reactions can also be carried out in the laboratory, without enzymes.[818] By putting cation-stabilizing groups at positions at which positive charges develop, Johnson and co-workers[819] have been able to close as many as four rings stereoselectively and in high yield, in one operation. An example is formation of **76**,[820] by what is known as the *Johnson polyene cyclization*.[821] Lewis acids can be used to initiate this cyclization,[822] including $EtAlCl_2$ used for the coupling of an alkyne and an alkene.[823] A Pd catalyst has been used for a similar cyclization reaction.[824] A radical cyclization approach (Reaction **15-30**) to polyene cyclization using a seleno–ester anchor gave a tetracyclic system.[825]



76

The addition of alkenes to alkenes[826] can also be mediated by bases.[827] Coupling reactions can occur using transition metal catalyst systems[828] (e.g., alkylaluminum

[817] Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* ***1955****, 77,* 5068; Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* ***1955****, 38*, 1890.

[818] Gnonlonfoun, N. *Bull. Soc. Chim. Fr.* ***1988***, 862; Johnson, W.S. *Angew. Chem. Int. Ed.* ***1976****, 15*, 9; *Acc. Chem. Res.* ***1968****, 1,* 1; van Tamelen, E.E. *Acc. Chem. Res.* ***1975****, 8,* 152. See Bartlett, P.A. in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, ***1985***, pp. 341–409.

[819] Guay, D.; Johnson, W.S.; Schubert, U. *J. Org. Chem.* ***1989****, 54,* 4731 and references cited therein.

[820] Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* ***1971****, 93*, 4332.

[821] Johnson, W.S. *Acc. Chem. Res.* ***1968****, 1*, 1; Kametani T.; Fukumoto, K. *Synthesis* ***1972***, 657.

[822] Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1999****, 121*, 4906.

[823] Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1999****, 121*, 3797.

[824] Mullen, C.A.; Gagné, M.R. *J. Am. Chem. Soc.* ***2007****, 129*, 11880.

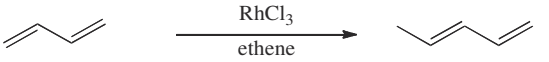
[825] Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* ***1994****, 35*, 2593.

[826] Fel'dblyum, V.Sh.; Obeshchalova, N.V. *Russ. Chem. Rev.* ***1968****, 37*, 789.

[827] For a review, see Pines, H. *Synthesis* ***1974***, 309.

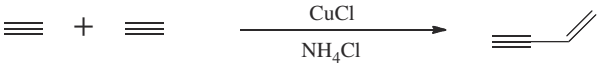
[828] Pillai, S.M.; Ravindranathan, M.; Sivaram, S. *Chem. Rev.* ***1986****, 86*, 353; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972****, 3,* 1, p. 117; Heck, R.F. *Organotransition Metal Chemistry* Academic Press, NY, ***1974***, pp. 84–94, 150–157. Also see, Kaur, G.; Manju, K.; Trehan, S. *Chem. Commun.* ***1996***, 581.

compounds, known as *Ziegler catalysts*),[829] Rh,[830] Fe,[831] or Ni[832] catalysts. The 1,4-addition of alkenes to conjugated dienes to give nonconjugated dienes[833] occurs with various transition metal catalysts, as does the dimerization of 1,3-butadienes to octatrienes.[834] A



molecule containing two distal conjugated diene units was cyclized to give a bicyclic molecule with an exocyclic double bond using a Pd catalyst.[835] A Ni catalyst converted a similar system to a saturated five-membered ring containing an allylic and a vinyl group.[836] Ethylene adds to alkenes to form a new alkene in the presence of a Ni[837] or a Zr catalyst,[838] and to alkynes in the presence of a Ru catalyst[839] to form a diene. Allenes add to alkynes to give a diene with a Ti catalyst.[840]

In the presence of cuprous chloride and ammonium chloride, acetylene undergoes self-coupling to give vinylacetylene. Alkynes are coupled to dienes to give enynes in the presence of a Ni catalyst.[841]

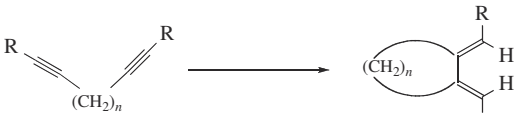


Another type of alkyne dimerization is the reductive coupling in which two molecules of alkyne, the same or different, give a 1,3-diene, as shown.[842] In this method, one alkyne is treated with *Schwartz's reagent* (see Reaction **15-17**) to produce a vinylic zirconium intermediate. Addition of MeLi or MeMgBr, followed by the second alkyne, gives another intermediate, which, when treated with aq acid, gives the diene in moderate-to-good yields.[843]If the second intermediate is treated with I_2 instead of aq acid, the 1,4-diiodo-1,3-diene is obtained, in comparable yield and isomeric purity. The reaction of an alkyne with a *Grignard reagent*, followed by an Fe complex and then an alkene leads to enynes.[844] A Rh catalyzed coupling reaction of alkenes and electron-deficient internal alkynes leads to 1,3-dienes.[845] A combination of Zr and Cr reagents allows the coupling of alkynes to form

[829] See Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed.* ***1973****, 12*, 943.
[830] Takahashi, N.; Okura, I.; Keii, T. *J. Am. Chem. Soc.* ***1975****, 97,* 7489.
[831] Takacs, J.M.; Myoung, Y.C. *Tetrahedron Lett.* ***1992****, 33*, 317.
[832] Zhang, A.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***2006****, 128,* 54.
[833] Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem. Int. Ed.* ***2001****, 40*, 387. For a review see Su, A.C.L. *Adv. Organomet. Chem.* ***1979****, 17,* 269.
[834] See Denis, P.; Jean, A.; Croizy, J.F.; Mortreux, A.; Petit, F. *J. Am. Chem. Soc.* ***1990****, 112*, 1292.
[835] Takacs, J.M.; Leonov, A.P. *Org. Lett.* ***2003****, 5*, 4317.
[836] Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* ***2004****, 126*, 5956.
[837] Nomura, N.; Jin, J.; Park, H.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***1998****, 120*, 459.
[838] Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* ***1997****, 119*, 4561.
[839] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* ***1997****, 119*, 12388.
[840] Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* ***1997****, 119*, 11295.
[841] Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* ***2008****, 130,* 5410.
[842] Buchwald, S.L.; Nielsen, R.B. *J. Am. Chem. Soc.* ***1989****, 111*, 2870.
[843] Ryan, J.; Micalizio, G.C. *J. Am. Chem. Soc.* ***2006****, 128,* 2764; Kanno, K.-i.; Igarashi, E.; Zhou, L.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* ***2008****, 130,* 5624.
[844] Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T.; Nakamura, M. *Org. Lett.* ***2008****, 10*, 5341.
[845] Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* ***2008****, 10*, 2829; Katagiri, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Commun.* ***2008***, 3405.

linear polyenes.[846] Alkynes can also be coupled to allylic silyl ethers with a Ru catalyst to give dienes.[847] Other alkyne–allylic coupling reactions are known to give dienes.[848]

This reaction can also be done intramolecularly, as in the cyclization of diyne **77** to (*E*, *E*)-exocyclic dienes (**78**) by treatment with a Zr,[849] Rh,[850] Ru,[851] Au,[852] or Pt complex.[853] A similar reaction was reported using a Ti catalyst from a diyne amide.[854] Rings of four, five, and six members were obtained in high yield; seven-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **78** are formed using various catalysts, but with only one double bond[855] Larger rings can be formed from the appropriate enyne, including forming cyclohexadiene compounds.[856] Spirocyclic compounds can be prepared from enynes in this manner using formic acid and a Pd catalyst.[857]

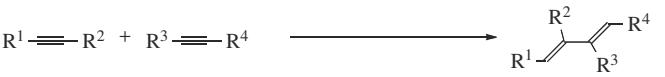


77 **78**

The Rh catalyzed cyclization of 1,6-enynes, triggered by arylboronic acids, leads to rings with an exocyclic alkylidene group.[858] Alkynes are coupled to give enynes using Ni,[859] Pd,[860] Lu,[861] and Ru[862] catalysts. Similar products are obtained by cross-coupling terminal alkynes with an allene, using a combination of Pd and CuI catalysts.[863] The reaction has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.[864] Diynes have also been cyclized to form cyclic enynes (an endocyclic double bond) using a diruthenium catalyst with ammonium tetrafluoroborate in methanol.[865] Enynes are similarly cyclized to cyclic alkenes with an endocyclic

[846] Takahashi, T.; Liu, Y.; Iesato, A.; Chaki, S.; Nakajima, K.; Kanno, K.-i. *J. Am. Chem. Soc.* ***2005****, 127*, 11928.
[847] Trost, B.M.; Surivet, J.-P.; Toste, F.D. *J. Am. Chem. Soc.* ***2001****, 123*, 2897.
[848] Giessert, A.J.; Snyder, L.; Markham, J.; Diver, S.T. *Org. Lett*. ***2003****, 5*, 1793.
[849] Nugent, W.A.; Thorn, D.L.; Harlow, R.L. *J. Am. Chem. Soc.* ***1987****, 109*, 2788. See Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* ***1988****, 110,* 7255; Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* ***1989****, 111*, 6478.
[850] Jang, H.-Y.; Krische, M.J. *J. Am. Chem. Soc.* ***2004****, 126*, 7875.
[851] Varela, J.A.; Rubín, S.G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* ***2006****, 128,* 9263.
[852] Zhang, C.; Cui, D.-M.; Yao, L.-Y.; Wang, B.-S.; Hu, Y.-Z.; Hayashi, T. *J. Org. Chem.* ***2008****, 73,* 7811.
[853] Méndez, M.; Muñoz, M.P. ; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2001****, 123*, 10511; Wang, X.; Chakrapani, H.; Madine, J.W.; Keyerleber, M.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2002****, 67*, 2778. See also, Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* ***2001****, 123*, 11863.
[854] Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* ***2000****, 2,* 3481.
[855] Chakrapani, H.; Liu, C.; Widenhoefer, R.A. *Org. Lett*. ***2003****, 5*, 157; Lee, P.H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett*. ***2004****, 6*, 4825.
[856] Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* ***2004****, 69*, 6697.
[857] Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* ***2003****, 125*, 4704.
[858] Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* ***2005****, 127,* 1094.
[859] Ogoshi, S.; Ueta, M.; Oka, M.-a.; Kurosawa, H. *Chem. Commun.* ***2004***, 2732.
[860] Rubina, M.; Gevergyan, V. *J. Am. Chem. Soc.* ***2001****, 123*, 11107; Yang, C.; Nolan, S.P. *J. Org. Chem.* ***2002****, 67*, 591.
[861] Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* ***2003****, 125*, 1184.
[862] Bassetti, M.; Pasquini, C.; Raneri, A.; Rosato, D. *J. Org. Chem.* ***2007****, 72*, 4558.
[863] Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R.K.; Korn, S.; Del Cierva, C.O.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* ***2003****, 44*, 8669.
[864] Trost, B.M.; Matusbara, S.; Carninji, J.J. *J. Am. Chem. Soc.* ***1989****, 111*, 8745.
[865] Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem. Int. Ed.* ***2000****, 39,* 2909.

C=C unit using a dicobalt catalyst.[866]



Enynes can also be converted to cyclic and bicyclic compounds using a Au[867] Rh,[868] Fe,[869] or Pd[870] catalyst. Enynes having a conjugated alkene unit also undergo this reaction in the presence of $ZnBr_2$.[871] Using mercury(II) triflate in water, cyclization leads to five-membered rings having an exocyclic double bond, and a pendant alcohol group.[872] Enynes give cyclic compounds with an endocyclic double bond conjugated to another alkene unit (a conjugated diene) when treated with $GaCl_3$[873] or a Pt catalyst in an ionic liquid.[874] Allene–alkenes give a similar product with a Pd[875] or a Ru catalyst,[876] as do alkyne–allenes with a dirhodium catalyst.[877]

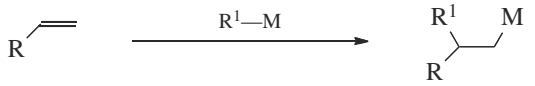
There are many useful variations. Internal coupling of an alkyne with a vinyl halide, using triethylsilane and a Pd catalyst, gave the saturated cyclic compound with two adjacent exocyclic double bonds (a 2,3-disubstituted diene).[878] Alkynes are added to propargyl acetates using Pd catalyst to give an alkyne–allene.[879] Alkyne–alkenes were formed by coupling terminal alkynes and allenes in the presence of a Pd catalyst.[880] An alkyne was coupled internally to give an allene using a Pd catalyst, to give an product that has an exocyclic methylene group and a vinyltin derivative.[881] A similar process occurred with $RhCl(PPh_3)_3$ to incorporate a vinyl chloride.[882] Allene–allylic halide systems reacted with phenylboronic acid and a Pd catalyst to give cyclopentane rings with two pendant vinyl groups, one of which contained a phenyl group.[883]

OS **VIII**, 190, 381, 505; **IX**, 310.

[866] Ajamian, A.; Gleason, J.L. *Org. Lett.* ***2003****, 5*, 2409.
[867] Luzung, M.R.; Markham, J.P.; Toste, F.D. *J. Am. Chem. Soc.* ***2004****, 126*, 10858; Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2005****, 127,* 6962.
[868] Kim, H.; Lee, C. *J. Am. Chem. Soc.* ***2005****, 127,* 10180. With $AgBF_4$, Evans, P.A.; Lai, K.W.; Sawyer, J.R. *J. Am. Chem. Soc.* ***2005****, 127,* 12466; Kim, H.; Lee, C. *J. Am. Chem. Soc.* ***2006****, 128,* 6336. See Denmark, S.E.; Liu, J. H.-C. *J. Am. Chem. Soc.* ***2007****, 129,* 3737.
[869] Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* ***2005****, 127*, 12236.
[870] Ma, S.; Gu, Z. *J. Am. Chem. Soc.* ***2005****, 127,* 6182; Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* ***2007****, 129,* 2764.
[871] Yamazaki, S.; Yamada, K.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* ***2002****, 67*, 2889.
[872] Nishizawa, M.; Yadav, V.K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003****, 5*, 1609.
[873] Chatani, N.; Inoue, H.; Kotsuma, T.; Morai, S. *J. Am. Chem. Soc.* ***2002****, 124*, 10294.
[874] Miyanohana, Y.; Inoue, H.; Chatani, N. *J. Org. Chem.* ***2004****, 69*, 8541.
[875] Frazén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***2002****, 124*, 11246.
[876] Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* ***2002****, 43*, 6693.
[877] Brummond, K.M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* ***2002****, 124*, 15186. See also, Candran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* ***2004****, 126*, 3408.
[878] Oh, C.H.; Park, S.J. *Tetrahedron Lett.* ***2003****, 44*, 3785.
[879] Condon-Gueugnot, S.; Linstrumelle, G. *Tetrahedron* ***2000****, 56,* 1851.
[880] Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D.J.; Gevorgyan, V. *J. Org. Chem.* ***2003****, 68*, 6251.
[881] Shin, S.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***2001****, 123*, 8416.
[882] Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* ***2003****, 125*, 6370.
[883] Zhu, G.; Zhang, Z. *Org. Lett.* ***2004****, 6*, 4041.

15-21 Addition of Organometallics to Double and Triple Bonds Not Conjugated to Carbonyls

Hydro-alkyl-addition



Neither *Grignard reagents* nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds in the absence of a transition metal catalyst.[884] *Grignard reagents* usually add only to double bonds susceptible to nucleophilic attack (e.g., fluoroalkenes and tetracyanoethylene).[885] However, active *Grignard reagents* (benzylic, allylic) also add to the double bonds of allylic amines,[886] and of allylic and homoallylic alcohols,[887] as well as to the triple bonds of propargyl alcohols and certain other alkynols.[888] Transition metal complexes facilitate the addition of *Grignard reagents* to alkenes. Examples include Ti,[889] Mn,[890] Zr,[891] Ni,[892] Fe,[893] and Cu compounds.[894] Cyclopropenes are an exception, and an excess of a Grignard reagent will add at low temperatures.[895] Cyclopropene derivatives also react with CuI and then allyl bromide.[896]

Benzylic alkenes react with silylmethyl *Grignard reagents* in the presence of oxygen.[897] It is likely that cyclic intermediates are involved in these cases, in which the Mg coordinates with the heteroatom. Allylic, benzylic, and tertiary alkyl *Grignard reagents* also add to 1-alkenes and strained internal alkenes (e.g., norbornene), if the reaction is carried out in a hydrocarbon solvent (e.g., pentane) rather than ether, or in the alkene itself as solvent, heated, under pressure if necessary, to 60–130 °C.[898] Yields are variable.

Intramolecular addition of RMgX to completely unactivated double and triple bonds has been demonstrated.[899] The reaction of tosylates bearing a remote alkene unit and a *Grignard reagent* leads to cyclization when a Zr catalyst is used.[900] The intramolecular

[884] Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, *Vol. 2,* Wiley, NY, ***1985***, pp. 219–338, pp. 268–296.
[885] Gardner, H.C.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976****, 98,* 558.
[886] Richey Jr., H.G.; Moses, L.M.; Domalski, M.S.; Erickson, W.F.; Heyn, A.S. *J. Org. Chem.* ***1981****, 46,* 3773.
[887] Kang, J. *Organometallics* ***1984****, 3*, 525.
[888] Eisch, J.J.; Merkley, J.H. *J. Am. Chem. Soc.* ***1979****, 101,* 1148; Miller, R.B.; Reichenbach, T. *Synth. Commun.* ***1976****, 6,* 319. See also, Duboudin, J.G.; Jousseaume, B. *J. Organomet. Chem.* ***1979****, 168,* 1; *Synth. Commun.* ***1979****, 9*, 53.
[889] See Sato, F. *J. Organomet. Chem.* ***1985****, 285,* 53–64.; Dzhemilev, U.M.; D'yakonov, V.A.; Khafizova, L.O.; Ibragimov, A.G. *Russ. J. Org. Chem.* ***2005****, 41,* 352.
[890] Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***1998***, 11.
[891] de Armas, J.; Hoveyda, A.H. *Org. Lett.* ***2001****, 3*, 2097.
[892] Pellet-Rostaing, S.; Saluzzo, C.; Ter Halle, R.; Breuzard, J.; Vial, L.; LeGuyader, F.; Lemaire, M. *Tetrahedron Asymmetry* ***2001****, 12*, 1983.
[893] Zhang, D.; Ready, J.M. *J. Am. Chem. Soc.* ***2006****, 128, 1*5050.
[894] Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* ***2005****, 127,* 17164.
[895] Liu, X.; Fox, J.M. *J. Am. Chem. Soc.* ***2006****, 128*, 5600,
[896] Yan, N.; Liu, X.; Fox, J.M. *J. Org. Chem.* ***2008****, 73*, 563.
[897] Nobe, Y.; Arayama, K.; Urabe, H. *J. Am. Chem. Soc.* ***2005****, 127,* 18006.
[898] Lehmkuhl, H.; Janssen, E. *Liebigs Ann. Chem.* ***1978***, 1854. This is actually a type of ene reaction, see Oppolzer, W. *Angew. Chem. Int. Ed.* ***1989****, 28*, 38.
[899] Felkin, H.; Umpleby, J.D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* ***1972***, 2285; Hill, E.A.; Myers, M.M. *J. Organomet. Chem.* ***1979****, 173*, 1. See also, Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* ***2001****, 123*, 8612.
[900] Cesati III, R.R.; de Armas, J.; Hoveyda, A.H. *Org. Lett.* ***2002****, 4*, 395.

addition of a CH_2Br unit to the C=C unit of an allylic ether was accomplished using PhMgBr and a Co catalyst, give a functionalized THF and incorporation of the phenyl group on the C=C unit as well.[901]

In a useful variation, vinyl epoxides react with *Grignard reagents* and CuBr to give an allylic alcohol via reaction at the C=C unit and concomitant opening of the epoxide.[902] Conjugated dienes react with arylmagnesium halides, Ph_3SiCl, and a Pd catalyst to give a coupling product involving the reaction of 2 equiv of the diene and incorporation of two $SiPh_3$ units.[903] The Cr catalyzed formation of arylmagnesium compounds[904] and the Rh catalyzed hydroarylation[905] of alkynes are also known. The Pd catalyzed hydroarylation[906] of alkynes is possible using arenediazonium salts[907] as substrates or hydroarylation of 1,3-dienes with boronic acids.[908]

Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) add to the double and triple bonds of allylic and propargylic alcohols,[909] (tetramethylethylenediamine is a catalyst) and also to certain other alkenes containing hetero groups (e.g., OR, NR_2, or SR). Mixing an organolithium reagent with transition metal compounds [e.g., $CeCl_3$[910] or $Fe(acac)_3$][911] leads to addition of the alkyl group. Cyclopropane derivatives have been formed in this manner.[912] The organolithium reagents can contain heteroatoms (e.g., nitrogen) elsewhere in the molecule, and the organolithium species can be generated from an intermediate organotin derivative.[913] Organolithium reagents add to the less substituted C=C unit of conjugated dienes.[914] Addition of butyllithium to alkenes has been observed with good enantioselectivity when sparteine was added.[915]

The intramolecular addition of RLi and R_2CuLi has been reported.[916] Organolithium reagents containing an alkene[917] or alkyne[918] unit cyclize[919] at low temperatures and

[901] Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2001****, 123*, 5374.
[902] Taber, D.F.; Mitten, J.V. *J. Org. Chem.* ***2002****, 67*, 3847.
[903] Terao, J.; Oda, A.; Kambe, N. *Org. Lett.* ***2004****, 6,* 3341.
[904] Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2007****, 9,* 1569.
[905] Schipper, D.J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* ***2010****, 132*, 6910.
[906] The mechanism of the phosphine free Pd catalyzed reaction has been studied. See Ahlquist M.; Fabrizi, G.; Sandro Cacchi,, S.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2006****, 128*, 12785.
[907] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Persiani, D. *Org. Lett.* ***2008****, 10,* 1597.
[908] Liao, L.; Sigman, M.S. *J. Am. Chem. Soc.* ***2010****, 132,* 10209.
[909] See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11; VCH, NY, ***1988***, pp. 129–142; García, G.V.; Budelman, N.S. *Org. Prep. Proceed. Int.* ***2003****, 35*, 445.
[910] Bartoli, G.; Dalpozzo, R.; DeNino, A.; Procopio, A.; Sanbri, L.; Tagarelli, A. *Tetrahedron Lett.* ***2001****, 42*, 8823.
[911] Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* ***2001****, 40*, 621.
[912] Gandon, V.; Laroche, C.; Szymoniak, J. *Tetrahedron Lett.* ***2003****, 44*, 4827.
[913] Coldham, I.; Hufton, R.; Rathmell, R.E. *Tetrahedron Lett.* ***1997****, 38*, 7617; Coldham, I.; Lang-Anderson, M.M.S.; Rathmell, R.E.; Snowden, D.J. *Tetrahedron Lett.* ***1997****, 38*, 7621.
[914] Norsikian, S.; Baudry, M.; Normant, J.F. *Tetrahedron Lett.* ***2000****, 41*, 6575.
[915] Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J.F. *J. Org. Chem.* ***1997****, 62,* 4898.
[916] Wender, P.A.; White, A.W. *J. Am. Chem. Soc.* ***1988****, 110*, 2218; Bailey, W.F.; Nurmi, T.T.; Patricia, J.J.; Wang, W. *J. Am. Chem. Soc.* ***1987****, 109*, 2442.
[917] Bailey, W.F.; Khanolkar, A.D. *J. Org. Chem.* ***1990****, 55,* 6058 and references cited therein; Bailey, W.F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* ***2003****, 68*, 1334. Also see, Fretwell, P.; Grigg, R.; Sansano, J.M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* ***2000****, 56*, 7525.
[918] Bailey, W.F.; Ovaska, T.V. *J. Am. Chem. Soc.* ***1993****, 115*, 3080, and references cited therein. See Funk, R.L.; Bolton, G.L.; Brummond, K.M.; Ellestad, K.E.; Stallman, J.B. *J. Am. Chem. Soc.* ***1993****, 115*, 7023.
[919] A conformational radical clock has been developed to evaluate organolithium-mediated cyclization reactions. See Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001****, 3*, 807.

quenching with methanol replaces the new C—Li bond with C—H. Tandem cyclization is possible with dienes and enynes to form more than one ring,[920] including bicyclic compounds.[921] Tandem cyclization is possible with alkyne iodides[922] or alkynes with a homoallylic CH_2Li unit.[923] The organolithium compound can be generated *in situ* by reaction of an organotin compound with butyllithium, allowing cyclization to occur upon treatment with an excess of LiCl.[924]

Unactivated alkenes or alkynes[925] react with other organometallic compounds under certain conditions. The Pt catalyzed addition to alkynes leads to functionalized alkenes.[926] Phenylboronic acids add to alkynes in the presence of a Co[927] or a Pd catalyst.[928] Trimethylaluminum reacts with 4-methyl-1-pentene, in the presence of Cl_2ZrCp_2, for example, and subsequent reaction with molecular oxygen leads to (2*R*),4-dimethyl-1-pentanol in good yield and 74% ee.[929] These reagents also add to alkynes.[930] Ruthenium catalysts have been used to mediate the addition of allylic alcohols to alkynes.[931] Samarium iodide (SmI_2) induces cyclization of a halide moiety to an alkyne unit[932] or an alkene unit[933] to form cyclized products. Copper complexes can catalyze similar cyclization to alkenes, even when an ester unit is present in the molecule.[934] Allyl manganese compounds add to allenes to give nonconjugated dienes.[935]

Organomanganese reagents add to alkenes.[936] Manganese triacetate [$Mn(OAc)_3$], in the presence of cupric acetate, facilitates intramolecular cyclization of a halide unit to an alkene.[937] Alkynes react with In reagents [e.g., $(allyl)_3In_2I_3$] to form dienes (allyl substituted alkenes from the alkyne).[938] Allylic halides add to propargyl alcohols using In metal to form the aryl organometallic *in situ*.[939] Allyltin reagents add to alkynes in a similar manner in the presence of $ZrCl_4$.[940] Alkylzinc reagents add to alkynes to give substituted alkenes in the presence of a Pd catalyst.[941] Allylzinc reagents add to alkynes in

[920] Bailey, W.F.; Ovaska, T.V. *Chem. Lett.* ***1993***, 819.
[921] Bailey, W.F.; Khanolkar, A.D.; Gavaskar, K.V. *J. Am. Chem. Soc.* ***1992****, 114*, 8053.
[922] Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett*. ***2000****, 2,* 1855.
[923] Wei, X.; Taylor, R.J.K. *Angew. Chem. Int. Ed.* ***2000****, 39*, 409.
[924] Komine, N.; Tomooka, K.; Nakai, T. *Heterocycles* ***2000****, 52,* 1071.
[925] See Trost, B.M.; Ball, Z.T. *Synthesis* ***2005***, 853.
[926] Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2005****, 127*, 15022; Fürstner, A.; Davies, P.W. *J. Am. Chem. Soc.* ***2005****, 127,* 15024.
[927] Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chemistry: European J.* ***2008****, 14*, 11296;
[928] Gupta, A.K.; Kim, K.S.; Oh, C.H. *Synlett* ***2005***, 457.
[929] Kondakov, D.Y.; Negishi, E. *J. Am. Chem. Soc.* ***1995****, 117*, 10771. Also see, Shibata, K.; Aida, T.; Inoue, S. *Tetrahedron Lett.* ***1993****, 33*, 1077.
[930] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* ***1993****, 32*, 1068.
[931] Trost, B.M.; Indolese, A.F.; Müller, T.J.J.; Treptow, B. *J. Am. Chem. Soc.* ***1995****, 117*, 615.
[932] Zhou, Z.; Larouche, D.; Bennett, S.M. *Tetrahedron* ***1995****, 51*, 11623.
[933] Fukuzawa, S.; Tsuchimoto, T. *Synlett* ***1993***, 803.
[934] Pirrung, F.O.H.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Schoemaker, H.E. *Tetrahedron* ***1994****, 50*, 12415.
[935] Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett*. ***2003****, 5*, 4623.
[936] Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1997****, 62*, 1910.
[937] Snider, B.B.; Merritt, J.E. *Tetrahedron* ***1991****, 47*, 8663.
[938] Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* ***1999****, 64*, 4095.
[939] Klaps, E.; Schmid, W. *J. Org. Chem.* ***1999****, 64*, 7537.
[940] Asao, N.; Matsukawa, Y.; Yamamoto, Y. *Chem. Commun.* ***1996***, 1513.
[941] Luo, F.-T.; Fwu, S.-L.; Huang, W.-S. *Tetrahedron Lett.* ***1992****, 33*, 6839.

the presence of a Co catalyst.[942] A vinyltellurium reagent adds to alkynes in the presence of $CuI/PdCl_2$.[943]

Ketones with an α-hydrogen add to alkenes intramolecularly when heated in a sealed tube with $CuCl_2$ and a Pd catalyst.[944] A similar reaction was reported using $Yb(OTf)_3$ and a Pd catalyst[945] or an In catalyst.[946] Keto esters add to alkynes using 10% benzoic acid and a Pd catalyst,[947] or an In catalyst.[948] 1,3-Diketones add to dienes (1,4-addition) using a Pd catalyst,[949] a $AuCl_3/AgOTf$ catalyst,[950] and this addition has been done intramolecularly using 2.4 molar equivalents of $CuCl_2$ and a Pd catalyst.[951] The intermolecular addition of diesters (e.g., malonates) to alkynes was accomplished in acetic acid and a Pd catalyst under microwave irradiation.[952] The enolate anion derived from the reaction of a nitrile with potassium *tert*-butoxide added to the less substituted carbon of the C=C unit of styrene in DMSO.[953] Silyl enol ethers add to alkynes using a W catalyst.[954] Malonate derivatives add to alkenes in the presence of an $Al(OR)_3$ catalyst.[955] 1,3-Dicarbonyl compounds add to allenes in the presence of a Pd catalyst.[956]

Aryl iodides add to alkynes using a Pt complex in conjunction with a Pd catalyst.[957] A Pd catalyst has been used alone for the same purpose,[958] and the intramolecular addition of a arene to an alkene was accomplished with a Pd[959] or a $GaCl_3$ catalyst.[960] Alkyl iodides add intramolecularly to alkenes with a Ti catalyst,[961] or to alkynes using In metal and additives.[962] The latter cyclization of aryl iodides to alkenes was accomplished with In and I_2[963] or with SmI_2.[964]

Aromatic hydrocarbons (e.g., benzene) add to alkenes using a Ru catalyst[965] a catalytic mixture of $AuCl_3/AgSbF_6$,[966] or a Rh catalyst,[967] and Ru complexes catalyze the addition

[942] Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* ***2004***, 1573.
[943] Zeni, G.; Nogueira, C.W.; Pena, J.M.; Pialssa, C.; Menezes, P.H.; Braga, A.L.; Rocha, J.B.T. *Synlett* ***2003***, 579.
[944] Wang, X.; Pei, T.; Han, X.; Widenhoefer, R.A. *Org. Lett.* ***2003****, 5*, 2699.
[945] Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* ***2003****, 5*, 2869.
[946] Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2008****, 130,* 17161.
[947] Patil, N.T.; Yamamoto, Y. *J. Org. Chem.* ***2004****, 69*, 6478.
[948] Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* ***2003****, 125*, 13002.
[949] Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J.F. *J. Org. Chem.* ***2004****, 69*, 7552.
[950] Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* ***2004****, 126*, 6884.
[951] Pei, T.; Wang, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2003****, 125*, 648.
[952] Patil, N.T.; Khan, F.N.; Yamamoto, Y. *Tetrahedron Lett.* ***2004****, 45*, 8497.
[953] Rodriguez, A.L.; Bunlaksananusorn, T.; Knochel, P. *Org. Lett.* ***2000****, 2*, 3285.
[954] Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P.H. *Org. Lett.* ***2002****, 4*, 4463.
[955] Black, P.J.; Harris, W.; Williams, J.M.J. *Angew. Chem. Int. Ed.* ***2001****, 40*, 4475.
[956] Trost, B.M.; Simas, A.B.C.; Plietker, B.; Jäkel, C.; Xie, J. *Chemistry: European J.* ***2005****, 11*, 7075.
[957] Denmark, S.E.; Wang, Z. *Org. Lett.* ***2001****, 3*, 1073.
[958] Havránek, M.; Dvorák, D. *J. Org. Chem.* ***2002****, 67*, 2125. See also, Lee, K.; Seomoon, D.; Lee, P.H. *Angew. Chem. Int. Ed.* ***2002****, 41*, 3901.
[959] Huang, Q.; Fazio, A.; Dai, G.; Campo, M.A.; Larock, R.C. *J. Am. Chem. Soc.* ***2004****, 126*, 7460.
[960] Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* ***2002****, 67,* 1414.
[961] Zhou, L.; Hirao, T. *J. Org. Chem.* ***2003****, 68*, 1633.
[962] Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* ***2004****, 69*, 2417; Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* ***2004****, 6*, 2825.
[963] Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemoto, Y. *Tetrahedron Lett.* ***2004****, 45*, 2331.
[964] Dahlén, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* ***2003****, 1*, 2423.
[965] Lail, M.; Arrowood, B.N.; Gunnoe, T.B. *J. Am. Chem. Soc.* ***2003****, 125*, 7506.
[966] Reetz, M.T.; Sommer, K. *Eur. J. Org. Chem.* ***2003***, 3485.
[967] Thalji, R.K.; Ellman, J.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***2004****, 126*, 7192.

of heteroaromatic compounds (e.g., pyridine) to alkynes.[968] Such alkylation reactions are clearly reminiscent of the *Friedel–Crafts* reaction (**11-11**). Palladium catalysts can also be used for the addition of aromatic compounds to alkynes,[969] and Rh catalysts for addition to alkenes (with microwave irradiation).[970] Note that vinylidene cyclopropanes react with furans and a Pd catalyst to give allylically substituted furans.[971]

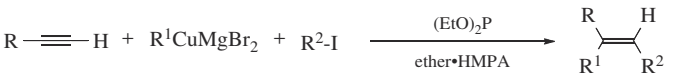
Arylboronic acids (see Reaction **13-13**) add to alkynes to give the substituted alkene using a Rh catalyst.[972] Allenes react with phenylboronic acid and an aryl iodide, in the presence of a Pd catalyst, to give a substituted alkene.[973] 2-Bromo-1,6-dienes react with phenylboronic acid with a Pd catalyst to give a cyclopentane with an exocyclic double bond and a benzyl substituent.[974]

An indirect addition converts alkynes to an organozinc compound using a Pd catalyst, which then reacts with allylic halides.[975] Similarly, the reaction of an alkyne with $Ti(OiPr)_4$/2 *i*PrMgCl followed by addition of an alkyne leads to a conjugated diene.[976]

OS 81, 121.

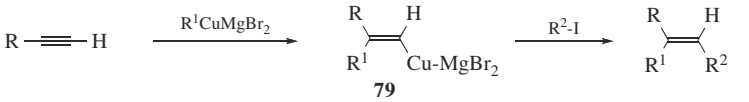
15-22 The Addition of Two Alkyl Groups to an Alkyne

Dialkyl-addition



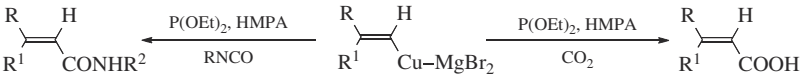
Two different alkyl groups can be added to a terminal alkyne[977] in one laboratory step by treatment with an alkylcopper–magnesium bromide reagent (called *Normant reagents*)[978] and an alkyl iodide in ether–HMPA containing triethylphosphite.[979] The groups add stereoselectively syn. The reaction, which has been applied to primary[980] R′ and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R′, involves initial addition of an intermediate alkylcopper reagent,[981] followed by a coupling reaction (**10-57**):

[968] See Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* ***2004****, 104*, 3079.
[969] Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* ***2003****, 125*, 12102.
[970] Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I.-J.; Chang, D.-H.; Jun, C.-H. *Tetrahedron* ***2004****, 60*, 5539.
[971] Nakamura, I.; Siriwardana, A.I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* ***2002****, 67*, 3445.
[972] Lautens, M.; Yoshida, M. *J. Org. Chem.* ***2003****, 68*, 762; Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* ***2004****, 45*, 4157.
[973] Yoshida, M.; Gotou, T.; Ihara, M. *Chem. Commun.* ***2004***, 1124.
[974] Oh, C.H.; Sung, H.R.; Park, S.J.; Ahn, K.H. *J. Org. Chem.* ***2002****, 67*, 7155.
[975] Matsubara, S.; Ukai, K.; Toda, N.; Utimoto, K.; Oshima, K. *Synlett* ***2000***, 995.
[976] Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* ***2003****, 5*, 67.
[977] Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 159–306, 233–248; Normant, J.F.; Alexakis, A. *Synthesis* ***1981***, 841; Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 233–238. See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 452–460.
[978] See Ashby, E.C.; Goel, A.B. *J. Org. Chem.* ***1983****, 48,* 2125.
[979] Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* ***1985****, 41,* 5887 and references cited therein. For an extensive list of references, see Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org. Chem.* ***1979****, 44,* 3888.
[980] See Rao, S.A.; Periasamy, M. *Tetrahedron Lett.* ***1988****, 29,* 4313.
[981] See Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1981****, 100*, 98, and references cited therein.



79

Acetylene itself (R = H) undergoes the reaction with R_2CuLi instead of the *Normant reagent*.[982] The use of R′ containing functional groups has been reported.[983] If the alkyl iodide is omitted, the vinylic copper intermediate (**79**) can be converted to a carboxylic acid by the addition of CO_2 (see Reaction **16-30**) or to an amide by the addition of an isocyanate, in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.[984] The use of I_2 results in a vinylic iodide.[985]



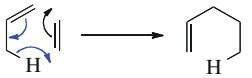
Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes (R_3Al) and zirconium complexes as catalysts.[986] Internal alkynes undergo bis(allylation) using a Ni catalysts and triallylindium.[987] Allyl ethers and iodobenzene have also been added using a Zr complex.[988] Similarly, allyl ethers and allyl chlorides have been added.[989]

Arylboronic acids (see Reaction **13-13**) react with alkynes and 1 equiv of an aryl iodide, with a Pd catalyst, to add two aryl groups across the triple bond.[990]

OS **VII**, 236, 245, 290.

15-23 The Ene Reaction

Hydro-allyl-addition

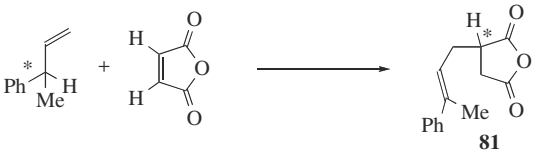


80

An interesting addition of RH to a double bond involves the reaction of alkenes with an alkene having an allylic hydrogen (**80**), and is called the *ene reaction* or the *ene synthesis*.[991] The reaction proceeds without a catalyst, but one of the components must

[982] Furber, M.; Taylor, R.J.K.; Burford, S.C. *J. Chem. Soc. Perkin Trans. 1,* ***1986***, 1809.
[983] Rao, S.A.; Knochel, P. *J. Am. Chem. Soc.* ***1991****, 113*, 5735.
[984] Normant, J.F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1973****, 54*, C53.
[985] Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* ***VII***, 290.
[986] See Negishi, E. *Acc. Chem. Res.* ***1987****, 20*, 65; *Pure Appl. Chem.* ***1981****, 53*, 2333; Negishi, E.; Takahashi, T. *Aldrichimica Acta* ***1985****, 18*, 31.
[987] Hirashita, T.; Akutagawa, K.; Kamei, T.; Araki, S. *Chem. Commun.* ***2006***, 2598.
[988] Hara, R.; Nishihara, Y.; Landré, P.D.; Takahashi, T. *Tetrahedron Lett.* ***1997****, 38*, 447.
[989] Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* ***1994****, 35*, 5685.
[990] Zhou, C.; Emrich, D.E.; Larock, R.C. *Org. Lett.* ***2003****, 5*, 1579; Zhou, C.; Larock, R.C. *J. Org. Chem.* ***2005****, 70,* 3765; Zhou, C.; Larock, R.C. *Org. Lett.* ***2005****, 7,* 259.
[991] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, ***1990***; Boyd, G.V. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups,* Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 477–525; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1969****, 8,* 556. For reviews of intramolecular ene reactions see Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions* Springer, NY, ***1984***; pp. 61–94; Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* ***1978****, 17,* 476–486; Conia, J.M.; Le Perchec, P. *Synthesis* ***1975****,* 1. See Desimoni, G.; Faita, G.; Righetti, P.P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* ***1994****, 50,* 1821 for solvent effects in the ene reaction.

be a reactive dienophile (reacts with a diene; see Reaction **15-60** for a definition of this word), such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene (e.g., propene) as long as there is an allylic hydrogen atom. Rather high reaction temperatures (250–450 °C) are common unless the substrates are very activated, but steric acceleration of the uncatalyzed ene reaction is known.[992] The reaction is compatible with a variety of functional groups that can be appended to the ene and dienophile. N,N-Diallyl amides give an ene cyclization, for example.[993] There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise mechanisms have been suggested. The mechanism of the ene reaction of singlet ($^1\Delta_g$) oxygen with simple alkenes was found to involve two steps, with no intermediate.[994] A retro-ene reaction is known with allylic dithiocarbonate.[995] An intramolecular ene reaction between oxazolones and enol ethers leads to functionalized oxazolones.[996] The reaction between maleic anhydride and optically active PhCHMeCH=CH_2 gave an optically active product (**81**),[997] which is strong evidence for a concerted rather than a stepwise mechanism.[998] The reaction can be highly stereoselective.[999]



81

The reaction can be extended to less-reactive enophiles by the use of Lewis acid catalysts, especially alkylaluminum halides.[1000] Titanium catalysts,[1001] Sc,[1002] $LiClO_4$[1003] Y,[1004] In,[1005] Pd,[1006] Co,[1007] Ni catalysts,[1008] as well as a combination of Ag and Au catalysts[1009] have also been used. A magnesium–ene cyclization stereochemically directed by an allylic oxyanionic group has been reported.[1010] The Lewis acid catalyzed reaction

[992] Choony, N.; Kuhnert, N.; Sammes, P.G.; Smith, G.; Ward, R.W. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1999.
[993] Cossy, J.; Bouzide, A. *Tetrahedron* ***1997****, 53*, 5775; Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* ***1993****, 76,* 2329; Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* ***1994****, 35*, 7939.
[994] Singleton, D.A.; Hang, C.; Szymanski, M.J.; Meyer, M.P.; Leach, A.G.; Kuwata, K.T.; Chen, J.S.; Greer, A.; Foote, C.S.; Houk, K.N. *J. Am. Chem. Soc.* ***2003****, 125,* 1319.
[995] Eto, M.; Nishimoto, M.; Kubota, S.; Matsuoka, T.; Harano, K. *Tetrahedron Lett.* ***1996****, 37*, 2445.
[996] Fisk, J.S.; Tepe, J.J. *J. Am. Chem. Soc.* ***2007****, 129,* 3058.
[997] Nahm, S.H.; Cheng, H.N. *J. Org. Chem.* ***1986****, 51*, 5093.
[998] See Jenner, G.; Salem, R.B.; El'yanov, B.; Gonikberg, E.M. *J. Chem. Soc. Perkin Trans. 2,* ***1989***, 1671; Thomas IV, B.E.; Loncharich, R.J.; Houk, K.N. *J. Org. Chem.* ***1992****, 57*, 1354.
[999] Ooi, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1994****, 50*, 6505; Thomas IV, B.E.; Houk, K.N. *J. Am. Chem. Soc.* ***1993****, 115*, 790; Also see, Masaya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* ***1994****, 35*, 7965.
[1000] See Chaloner, P.A. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond,* Vol. 4, Wiley, NY, ***1987***, pp. 456–460; Snider, B.B. *Acc. Chem. Res.* ***1980****, 13*, 426.
[1001] Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999****, 121*, 1976.
[1002] Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998****, 39*, 1997.
[1003] Davies, A.G.; Kinart, W.J. *J. Chem. Soc. Perkin Trans. 2,* ***1993***, 2281.
[1004] Molander, G.A.; Corrette, C.P. *J. Org. Chem.* ***1999****, 64,* 9697.
[1005] Hatakeyama, S. *Pure Appl. Chem.* ***2009****, 81*, 217.
[1006] Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* ***2005****, 127,* 17168.
[1007] Hilt, G.; Treutwein, J. *Angew. Chem. Int. Ed.* ***2007****, 46*, 8500.
[1008] Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* ***2001****, 3*, 2065.
[1009] Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2004****, 126*, 4526.
[1010] Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* ***2001****, 123,* 30.

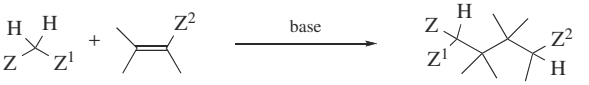
probably has a stepwise mechanism.[1011] An Ir catalyzed ene reaction has been done in an ionic liquid.[1012] An ene reaction of arynes with alkynes leads to aryl allenes.[1013] An *aza–ene reaction*[1014] has been used in a synthesis of enantioenriched piperidines, using two different imines as starting materials.[1015] Ene reactions of imines are sometimes called *imino–ene reactions*.[1016]

The *carbonyl–ene reaction*[1017] is also very useful, and often gives synthetically useful yields of products when catalyzed by Lewis acids.[1018] Scandium triflate[1019] and chromium complexes[1020] are useful Lewis acids in this reaction. Asymmetric catalysts[1021] for enantioselective carbonyl ene reactions have been reported using chiral Sc catalysts[1022] In,[1023] or chiral Ni catalysts.[1024] Ketoester ene reactions with silyl enol ethers occurs in the presence of Pd and Ag catalysts.[1025] Carbonyl–ene cyclization has been reported on silica gel at high pressure (15 kbar).[1026] Ene reactions with imines,[1027] nitrile oxides,[1028] as well as nitroso–ene reactions are known.[1029] Vinyl boronates have been prepared via a Ru catalyzed ene reaction.[1030]

OS **IV**, 766; **V**, 459. See also, OS **VIII**, 427.

15-24 The Michael Reaction

Hydro-bis(ethoxycarbonyl)methyl-addition, and so on



Compounds containing electron-withdrawing groups (Z is defined in Sec. 15.A.ii as an electron-withdrawing group) add to alkenes of the form C=C—Z in the presence of bases.[1031] This is called the *Michael reaction* and is formally a conjugate addition.[1032] The

[1011] See Snider, B.B.; Ron E. *J. Am. Chem. Soc.* ***1985****, 107,* 8160.
[1012] Shibata, T.; Yamasaki, M.; Kadowaki, S.; Takagi, K. *Synlett* ***2004***, 2812.
[1013] Jayanth, T.T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* ***2006****, 128,* 2232.
[1014] See Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* ***2006****, 45*, 2254.
[1015] Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* ***2007****, 129*, 10336.
[1016] See Pandey, M.K.; Bisai, A.; Pandey, A.; Singh, V.K. *Tetrahedron Lett.* ***2005****, 46,* 5039.
[1017] For a review, see Clarke, M.L.; France, M.B. *Tetrahedron* ***2008****, 64,* 9003.
[1018] See Achmatowicz, O.; Bialeck-Florjanczyk, E. *Tetrahedron* ***1996****, 52*, 8827; Marshall, J.A.; Andersen, M.W. *J. Org. Chem.* ***1992****, 57*, 5851 for mechanistic discussions of this reaction.
[1019] See Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998****, 39*, 1997.
[1020] Ruck, R.T.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002****, 124*, 2882.
[1021] Grachan, , M.L.; Tudge, M.T.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2008****, 47,* 1469.
[1022] Evans, D.A.; Wu, J. *J. Am. Chem. Soc.* ***2005****, 127*, 8006.
[1023] Zhao, J.-F.; Tsui, H.-Y.; Wu, P.-J.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2008****, 130,* 16492.
[1024] Zheng, K.; Shi, J.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* ***2008****, 130,* 15770.
[1025] Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* ***2007****, 129,* 12950.
[1026] Dauben, W.G.; Hendricks, R.T. *Tetrahedron Lett.* ***1992****, 33*, 603.
[1027] Yamanaka, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* ***2000****, 2*, 159.
[1028] See Yu, Z.-X.; Houk, K.N. *J. Am. Chem. Soc.* ***2003****, 125*, 13825.
[1029] Lu, X. *Org. Lett.* ***2004****, 6,* 2813. See also, Leach, A.G.; Houk, K.N. *J. Am. Chem. Soc.* ***2002****, 124*, 14820; Adam, W.; Krebs, O. *Chem. Rev.* ***2003****, 103*, 4131.
[1030] Hansen, E.C.; Lee, D. *J. Am. Chem. Soc.* ***2005****, 127,* 3252.
[1031] See Myers, M.C.; Bharadwaj, A.R.; Milgram, B.C.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2005****, 127,* 14675.
[1032] See Yanovskaya, L.A.; Kryshtal, G.V.; Kulganek, V.V. *Russ. Chem. Rev.* ***1984****, 53*, 744; Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* ***1959****, 10*, 179;. For a review of α-substitution versus conjugate addition, see Lewandowska, E. *Tetrahedron* ***2007****, 63,* 2107.

product formed, RCH_2Z or $RCHZZ'$, can include aldehydes,[1033] ketones,[1034] esters,[1035] diesters,[1036] diketones,[1037] keto-esters,[1038] carboxylic acids, dicarboxylic acids,[1039] nitriles,[1040] vinyl sulfones,[1041] nitro compounds (see below),[1042] and others of the form ZCH_3, ZCH_2R, $ZCHR_2$, and $ZCHRZ'$. [1043] In the most common examples, a base removes the acidic proton from the substrate adding to C=C—Z and the mechanism is as outlined in Section 15.A.ii. *Michael addition* is known to be catalyzed by phosphines,[1044] as well as other organocatalysts.[1045] Catalysts are known that are compatible with an aqueous medium.[1046] A double *Michael* process is possible, where conjugate addition to an alkynyl ketone is followed by an intramolecular *Michael reaction* to form a functionalized ring.[1047] Vinylogous *Michael* reactions are well known, using a variety of nucleophilic species[1048] (see Sec. 6.B for vinylogy). 1,6-Additions are also known.[1049] Arylsilanes add to conjugated esters and amides in the presence of a Rh catalyst.[1050] Nitro compounds add to conjugated ketones via *Michael addition*.[1051] Niroalkenes are *Michael* acceptors[1052] for the enolate anions of β-keto esters[1053] or malonate derivatives with a Ni catalyst[1054] or

[1033] Willis, M.C.; McNally, S.J.; Beswick, P.J. *Angew. Chem. Int. Ed.* ***2004****, 43*, 340; Chi, Y.; Gellman, S.H. *Org. Lett.* ***2005****, 7,* 4253.
[1034] Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* ***2003****, 5*, 2559; Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003****, 125*, 2582.
[1035] Kim, S.-G.; Ahn, K.H. *Tetrahedron Lett.* ***2001****, 42*, 4175.
[1036] Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2003****, 42*, 661.
[1037] da silva, F.M.; Gomes, A.K.; Jones Jr., J. *Can. J. Chem.* ***1999****, 77* , 624.
[1038] Suzuki, T.; Torii, T. *Tetrahedron Asymmetry* ***2001****, 12*, 1077; García-Gómez, G.; Moretó, J.M. *Eur. J. Org. Chem.* ***2001***, 1359; Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* ***2001****, 41*, 247.
[1039] Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* ***2002****, 43*, 5301.
[1040] Wolckenhauer, S.A.; Rychnovsky, S.D. *Org. Lett.* ***2004****, 6*, 2745; Fleming, F.F.; Wang, Q. *Chem. Rev.* ***2003****, 103*, 2035.
[1041] Zhu, Q.; Lu, Y. *Org. Lett.* ***2008****, 10,* 4803.
[1042] Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* ***2004****, 126*, 11790. See Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Froment, F.; Corset, J. *Tetrahedron Lett.* ***1994****, 35*, 3935.
[1043] Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2003****, 125*, 11204.
[1044] Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R.M.; Vallribera, A. *Tetrahedron* ***2005****, 61,* 8598.
[1045] Almaşi, D.; Alonso, D.A.; Nájera, C. *Tetrahedron Asymmetry* ***2007****, 18*, 299; Vicario, J.L.; Badía, D.; Carrillo, L. *Synthesis* ***2007***, 2065.
[1046] Chen, X.; She, J.; Shang, Z.; Wu, J.; Zhang, P. *Synthesis* ***2008***, 3931.
[1047] Holeman, D.S.; Rasne, R.M.; Grossman, R.B. *J. Org. Chem.* ***2002****, 67*, 3149.
[1048] Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* ***2001****, 42*, 8471.
[1049] Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2007****, 129,* 5772.
[1050] Oi, S.; Taira, A.; Honma, Y.; Sato, T.; Inoue, Y. *Tetrahedron Asymmetry* ***2006****, 17,* 598.
[1051] Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* ***2005****, 105,* 933; Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* ***2008****, 73,* 3475; Prieto, A.; Halland, N.; Jørgensen, K.A. *Org. Lett.* ***2005****, 7,* 3897.
[1052] See Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985****, 18*, 284; Baer, H.H.; UrBas L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 130–148. See Thayumanavan, R.; Tanaka, F.; Barbas, III, C.F. *Org. Lett.* ***2004****, 6*, 2527; Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* ***2004****, 126*, 9558; Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* ***2004****, 126*, 9906; Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2004****, 126*, 11148.
[1053] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* ***2005****, 127,* 119.
[1054] Evans, D.A.; Seidel, D. *J. Am. Chem. Soc.* ***2005****, 127,* 9958; Evans, D.A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* ***2007****, 129,* 11583.

an organocatalyst.[1055] Other substrates have been added to nitroalkenes via *Michael addition*.[1056] Malonate derivatives also add to conjugated ketones,[1057] and keto esters add to conjugated esters.[1058] Vinyl sulfones undergo *Michael addition*.[1059]

It is known that 1,2-addition (to the C=O or C≡N group) often competes and sometimes predominates (Reaction **16-38**).[1060] In particular, α,β-unsaturated *aldehydes* seldom give 1,4-addition.[1061] The *Michael reaction* generally gives better yields with fewer side reactions by conversion of the nucleophile to its enolate form (a *preformed enolate*).[1062] Phase-transfer catalysts have been used,[1063] and ionic liquids have been used in conjunction with phase-transfer catalysis.[1064] Transition metal compounds Ce,[1065] Yb,[1066] Bi,[1067] Fe,[1068] Ni,[1069] Cu,[1070] La,[1071] Ru,[1072] or Sc[1073] also induce the reaction Conjugate addition has also been promoted by Y-zeolite,[1074] and water-promoted *Michael additions* have also been reported.[1075] Acylsilanes, when treated with fluoride ion, add to conjugated amides under certain conditions.[1076] Addition to the meta-position of phenolic compounds leads to bicyclic ketones.[1077] Conjugate addition of nitrones using SmI_2 has

[1055] Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* ***2006****, 128*, 1454; Xu, D.-Q.; Wang, B.T.; Luo, S.-P.; Yue, H.-D.; Wang, L.-P.; Xu, Z.-Y. *Tetrahedron Asymmetry* ***2007****, 18,* 1788; Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron Asymmetry* ***2007****, 18,* 2086; Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3093.

[1056] See Mattson, A.E.; Zuhl, A.M.; Reynolds, T.E.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2006****, 128,* 4932; Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* ***2006****, 128,* 4966; Huang, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2006****, 128,* 7170; Pansare, S.V.; Pandya, K. *J. Am. Chem. Soc.* ***2006****, 128,* 9624; Chi, Y.; Guo, L.; Kopf, N.A.; Gellman, S.H. *J. Am. Chem. Soc.* ***2008****, 130,* 5608; Wiesner, M.; Revell, J.D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* ***2008****, 130,* 5610; Malerich, J.P.; Hagihara, K.; Rawal, V.H. *J. Am. Chem. Soc.* ***2008****, 130,* 14416.

[1057] Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* ***2004***, 61.

[1058] Yadav, J.S.; Geetha, V.; Reddy, B.V.S. *Synth. Commun.* ***2002****, 32*, 3519.

[1059] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* ***2005****, 127,* 8948.

[1060] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989****, 19,* 227, pp. 232–236.

[1061] See, however, Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* ***1991***, 1088.

[1062] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1991****, 20*, 87; ***1989****, 19,* 227.

[1063] Kim, D.Y.; Huh, S.C. *Tetrahedron* ***2001****, 57*, 8933.

[1064] Kotrusz, P.; Toma, S.; Schamlz, H.-G.; Adler, A. *Eur. J. Org. Chem.* ***2004***, 1577.

[1065] Bartoli, G.; Bosco, M.; Bellucci, M.C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* ***1999***, 617.

[1066] Ding, R.; Katebzadeh, K.; Roman, L.; Bergquist, K.-E.; Lindström, U.M. *J. Org. Chem.* ***2006****, 71*, 352.

[1067] Varala, R.; Alam, M.M.; Adapa, S.R. *Synlett* ***2003***, 720.

[1068] For a review, see Christoffers, J. *Synlett* ***2001***, 723.

[1069] For a discussion of *Heck coupling* versus *Michael addition*, see Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chemistry: Asian J.* ***2007****, 2,* 1409.

[1070] Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* ***2003***, 1040; Meyer, O.; Becht, J.-M.; Helmchen, G. *Synlett* ***2003***, 1539. For a discussion of the mechanism, see Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R.M.; Vallribera, A. *J. Org. Chem.* ***2004****, 69*, 6834.

[1071] Kim, Y.S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000****, 122*, 6506.

[1072] Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2003****, 125*, 7508; Wadsworth, K.J.; Wood, F.K.; Chapman, C.J.; Frost, C.G. *Synlett* ***2004***, 2022; Hayashi, T.; Yamasaki, K. *Chem. Rev.* ***2003****, 103*, 2829.

[1073] Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetahedron Lett.* ***2000****, 41*, 3107.

[1074] Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* ***1997****, 38*, 6557.

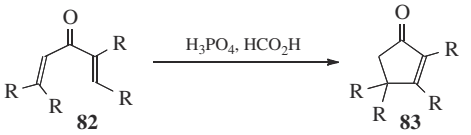
[1075] Lubineau, A.; Augé, J. *Tetrahedron Lett.* ***1992****, 33*, 8073.

[1076] Nahm, M.R.; Potnick, J.R.; White, P.S.; Johnson, J.S. *J. Am. Chem. Soc.* ***2006****, 128,* 2751.

[1077] Vo, N.T.; Pace, R.D.M.; O'Hara, F.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2008****, 130*, 404.

been reported.[1078] Cyanide ion adds to *Michael* acceptors, and TMSCN also adds in a *Michael reaction*.[1079]

Intramolecular versions of *Michael addition* are known.[1080] The intramolecular *Michael addition* of an α-chloro ketone enolate anion, formed *in situ* using DABCO, leads to formation of a bicyclo[4.1.0] diketone.[1081]

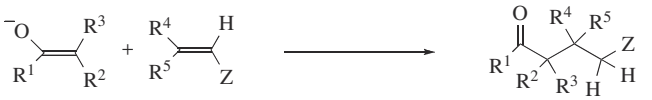


82 **83**

An important cyclization procedure involves the acid-catalyzed addition of dieneketones (e.g., **82**), where one conjugated alkene adds to the other conjugated alkene to form cyclopentenones (**83**). This is called the *Nazarov cyclization*.[1082] While it may be categorized in Reaction **15-20** because one alkene unit adds to another, the addition is formally a *Michael addition*, and so is placed here. Structural variations are possible that prepare a variety of cyclopentenones. The steric influence of substituents has been discussed,[1083] and the rate-accelerating influence observed in N- and S-heterocycles.[1084] Substituents on the C=C units lead to cyclopentenones that bear those substituents. Gold[1085] and V catalyzed[1086] cyclizations have been reported, as well as a Sc catalyzed cyclization in water.[1087] Heating dienones in DME or an ionic liquid has been shown to give the *Nazarov* product without addition of a Lewis acid.[1088] Allenes participate in *Nazarov cyclization* reactions.[1089] A vinylogous *Nazarov reaction* is involved in the cyclization of cross-conjugated trienes[1090] (see Sec. 6.B for vinylogy). The use of a chiral ligand gave the cyclopentenone with modest enantioselectivity.[1091] Reductive cyclization can also give the nonconjugated five-membered ring.[1092] Note that a *retro*-Nazarov is possible with α-bromocyclopentanones.[1093] In one variation using an Al complex, a

[1078] Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* ***2003****, 42*, 2265.
[1079] Yang, J.; Wang, Y.; Wu, S.; Chen, F.-X. *Synlett* ***2009***, 3365; Yang, J.; Shen, Y.; Chen, F.-X. *Synthesis* ***2010***, 1325.
[1080] Fonseca, M.T.H.; List, B. *Angew. Chem. Int. Ed.* ***2004****, 43*, 3958.
[1081] Bremeyer, N.; Smith, S.C.; Ley, S.V.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2004****, 43*, 2681.
[1082] Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk,* ***1942***, 200; Pellissier, H. *Tetrahedron* ***2005****, 61,* 6479; Frontier, A.J.; Collison, C. *Tetrahedron* ***2005****, 61,* 7577; Tius, M.A. *Eur. J. Org. Chem.* ***2005***, 2193. See Smith, D.A.; Ulmer II, C.W. *J. Org. Chem.* ***1993****, 58*, 4118 for a discussion of torquoselectivity and hyperconjugation in this reaction.
[1083] Marcus, A.P.; Amy, S.; Lee, A.S.; Davis, R.L.; Tantillo, D.J.; Sarpong, R. *Angew. Chem. Int. Ed.* ***2008****, 47,* 6379.
[1084] Cavalli, A.; Pacetti, A.; Recanatini, M.; Prandi, C.; Scarpi, D.; Occhiato, E.G. *Chemistry: European J.* ***2008****, 14, 9*292.
[1085] Zhang, L.; Wang, S. *J. Am. Chem. Soc.* ***2006****, 128,* 1442.
[1086] Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* ***2007***, 2650.
[1087] Kokubo, M.; Kobayashi, S. *Chemistry: Asian J.* ***2009****, 4*, 526.
[1088] Douelle, F.; Tal, L.; Greaney, M.F. *Chem. Commun.* ***2005***, 660.
[1089] Banaag, A.R.; Tius, M.A. *J. Am. Chem. Soc.* ***2007****, 129,* 5328; Banaag, A.R.; Tius, M.A. *J. Org. Chem.* ***2008****, 73,*8133.
[1090] Rieder, C.J.; Winberg, K.J.; West, F.G. J. *Am. Chem. Soc.* ***2009****, 131,* 7504.
[1091] Aggarwal, V.K.; Belfield, A.J. *Org. Lett.* ***2003****, 5*, 5075.
[1092] Giese, S.; West, F.G. *Tetrahedron Lett.* ***1998****, 39*, 8393; Giese, S.; West, F.G. *Tetrahedron* ***2000****, 56*, 10221.
[1093] Harmata, M.; Lee, D.R. *J. Am. Chem. Soc.* ***2002****, 124*, 14328. For a discussion of the scope and mechanism of the retro-Nazarov reaction, see Harmata, M.; Schreiner, P.R.; Lee, D.R.; Kirchhoefer, P.L. *J. Am. Chem. Soc.* ***2004****, 126*, 10954. For a torquoselective retro-Nazarov, see Harmata, M.; Lee, D.R.; Barnes, C.L. *Org. Lett.* ***2005****, 7,* 1881.

cyclohexenone was formed.[1094] There is a so-called interrupted *Nazarov*, in which an amine is trapped after cyclization to give an α-amino conjugated cyclopentenone.[1095] Spirocycles have been prepared via a tandem *Nazarov–Wagner–Meerwein* sequence.[1096]



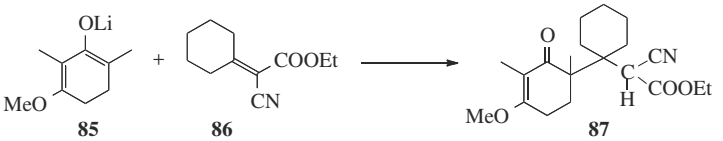
84

In a *Michael reaction* with suitably different R groups, two new stereogenic centers may be created (see **84**). In a diastereoselective process, one of the two pairs is formed exclusively or predominantly as a racemic mixture.[1097] When either or both of the reaction components have a chiral substituent, the reaction can be enantioselective (only one of the four diastereomers formed predominantly).[1098] There are many examples of catalytic enantioselective Michael additions,[1099] often by the use of a chiral catalyst[1100] or by using optically active enamines instead of enolates.[1101] Common chiral catalysts used with carbonyl substrates include Ru,[1102] Ni,[1103] Sr,[1104] and Al(salen) complexes.[1105] Chiral organocatalysts[1106] (e.g., oxazolidinones)[1107] have been developed and chiral imines have also been used.[1108] Certain antibodies have been used to facilitate chiral, intramolecular *Michael addition* reactions.[1109] Enzymes have been used as for asymmetric *Michael reactions*.[1110] Addition of chiral additives to the reaction (e.g., metal–salen complexes,[1111] proline derivatives,[1112] or (−)-sparteine[1113]) lead to product formation with good-to-excellent asymmetric induction. Ultrasound has been used to promote

[1094] Magomedev, N.A.; Ruggiero, P.L.; Tang, Y. *Org. Lett.* ***2004****, 6*, 3373.
[1095] Dhoro, F.; Tius, M.A. *J. Am. Chem. Soc.* ***2005****, 127,* 12472; Dhoro, F.; Kristensen, T.E.; Stockmann, V.; Yap, G.P.A.; Tius, M.A. *J. Am. Chem. Soc.* ***2007****, 129,* 7256. See also, Grant, T.N.; Rieder, C.J.; West, F.G. *Chem. Commun.* ***2009***, 5676.
[1096] Huang, J.; Frontier, A.J. *J. Am. Chem. Soc.* ***2007****, 129*, 8060.
[1097] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989****, 19,* pp. 237.
[1098] See Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* ***1995****, 36*, 5951; Enders, D.; Demir, A.S.; Rendenbach, B.E.M. *Chem. Ber.* ***1987****, 120,* 1731; Hawkins, J.M.; Lewis, T.A. *J. Org. Chem.* ***1992****, 57*, 2114.
[1099] See Krause, N.; Hoffmann-Röder, A. *Synthesis* ***2001***, 171.
[1100] Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* ***1990****, 46*, 2927.
[1101] See d'Angelo, J.; Revial, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* ***1988****, 29,* 4427.
[1102] Guo, R.; Morris, R.H.; Song, D. *J. Am. Chem. Soc.* ***2005****, 127*, 516.
[1103] Evans, D.A.; Thomson, R.J.; Franco, F. *J. Am. Chem. Soc.* ***2005****, 127,* 10816.
[1104] Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2008****, 130*, 2430.
[1105] Taylor, M.S.; Zalatan, D.N.; Lerchner, A.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2005****, 127,* 1313.
[1106] Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* ***2005****, 127,* 16028; Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* ***2006****, 128,* 12652; Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* ***2006****, 45,* 4966; Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem. Int. Ed. 2007, 46,* 8431.
[1107] Peelen, T.J.; Chi, Y.; Gellman, S.H. *J. Am. Chem. Soc.* ***2005****, 127*, 11598.
[1108] d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron Asymmetry* ***1992****, 3*, 459.
[1109] Weinstain, R.; Lerner, R.A.; Barbas, III, C.F.; Shabat, D. *J. Am. Chem. Soc.* ***2005****, 127,* 13104.
[1110] Svedendahl, M.; Hult, K.; Berglund, P. *J. Am. Chem. Soc.* ***2005****, 127*, 17988.
[1111] Jha, S.C.; Joshi, N.N. *Tetrahedron Asymmetry* ***2001****, 12*, 2463.
[1112] Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* ***1996****, 61*, 3520.
[1113] Xu, F.; Tillyer, R.D.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Assymetry* ***1998****, 9*, 1651.

asymmetric *Michael reactions*.[1114] In reactions of enolate anions, both the enolate anion and substrate can exist as (*Z*) or (*E*) isomers. With enolates derived from ketones or carboxylic esters, the (*E*) enolates gave the syn pair of enantiomers (Sec. 4.G), while (*Z*) enolates gave the anti pair.[1115]

When the substrate contains *gem*-Z groups, (e.g., **86**), bulky groups can be added, if the reaction is carried out under aprotic conditions. For example, addition of enolate **85** to **86** gave **87** in which two adjacent quaternary centers have been formed.[1116]



85 **86** **87** (98%)

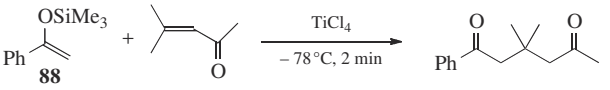
In certain cases, *Michael reactions* can take place under acidic conditions.[1117] *Michael-type* addition of radicals to conjugated carbonyl compounds is also known.[1118] Radical addition can be catalyzed by $Yb(OTf)_3$,[1119] but radicals add under standard conditions as well, even intramolecularly.[1120] Electrochemical-initiated Michael additions are known.

Alkynes are reactive, and *Michael reactions* are sometimes applied to substrates of the type C≡C—Z, where the coproducts are conjugated systems of the type C=C—Z.[1121] Terminal alkynes add to conjugated systems.[1122] Due to the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes (e.g., acetylene), to be substrates in this reaction.[1123]

Silyl enol ethers (e.g., **88**) add to α,β-unsaturated ketones and esters when catalyzed[1124] by $TiCl_4$[1125] or $InCl_3$.[1126] Aluminum compounds also catalyze this reaction[1127] and the reaction has been done in neat tri-*n*-propylaluminum.[1128] A solid-state version of the reaction used alumina•$ZnCl_2$.[1129] Tin-enolates have been used.[1130] This reaction has been performed with good diastereoselectivity,[1131] and silyl enol ethers have been used

[1114] Mirza-Aghayan, M.; Etemad-Moghadam, G.; Zaparucha, A.; Berlan, J.; Loupy, A.; Koenig, M. *Tetrahedron Asymmetry* ***1995****, 6*, 2643.
[1115] See Oare, D.A.; Heathcock, C.H. *J. Org. Chem.* ***1990****, 55,* 157.
[1116] Holton, R.A.; Williams, A.D.; Kennedy, R.M. *J. Org. Chem.* ***1986****, 51*, 5480.
[1117] See Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974****, 39,* 1612; *Org. Synth.* ***VII***, 363.
[1118] Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* ***1999****, 40*, 3169.
[1119] Sibi, M.P.; Jasperse, C.P.; Ji, J. *J. Am. Chem. Soc.* ***1995****, 117*, 10779. See Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* ***1995****, 117*, 11029 for a related reaction.
[1120] Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* ***1995****, 60*, 4850.
[1121] Rudorf, W.-D.; Schwarz, R. *Synlett* ***1993***, 369.
[1122] Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* ***2010****, 132*, 10275.
[1123] See Makosza, M. *Tetrahedron Lett.* ***1966***, 5489.
[1124] See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1576–1582; Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* ***1990****, 382*, 39.
[1125] Matsuda, I. *J. Organomet. Chem.* ***1987****, 321*, 307; Narasaka, K. *Org. Synth,. 65,* 12. See also, Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985****, 18*, 284.
[1126] Loh, T.-P.; Wei, L.-L. *Tetrahedron* ***1998****, 54*, 7615.
[1127] Tucker, J.A.; Clayton, T.L.; Mordas, D.M. *J. Org. Chem.* ***1997****, 62*, 4370.
[1128] Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* ***1995****, 51*, 743.
[1129] Ranu, B.C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* ***1993****, 34*, 1989.
[1130] Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* ***2003****, 125*, 7291.
[1131] See Heathcock, C.H.; Uehling, D.E. *J. Org. Chem.* ***1986****, 51,* 279; Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* ***1986***, 1017, 1817, 1821; ***1987***, 743.

in conjunction with chiral additives.[1132]

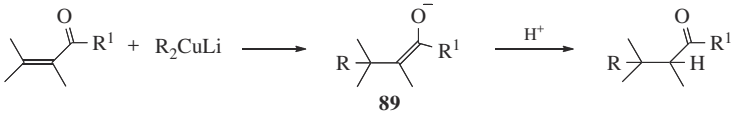


The reaction of C=C—Z compounds with enamines (**10-69**) can also be considered a Michael reaction.

OS **I**, 272; **II**, 200; **III**, 286; **IV**, 630, 652, 662, 776; **V**, 486, 1135; **VI**, 31, 648, 666, 940; **VII**, 50, 363, 368, 414, 443; **VIII**, 87, 210, 219, 444, 467; **IX**, 526. See also, OS **VIII**, 148.

15-25 1,4-Addition of Organocuprates and Other Organometallic Compounds to Activated Double Bonds

Hydro-alkyl-addition



Lithium dialkylcopper reagents (R_2CuLi reagents,[1133] also known as *Gilman reagents*, see Reaction **10-57**) add to α,β-unsaturated aldehydes[1134] and ketones (R′ = H, R, Ar) and other systems of the form C≡C—C=O[1135] to give conjugate addition products[1136] in a reaction closely related to the *Michael reaction*. α,β-Unsaturated esters are less reactive,[1137] and the corresponding acids do not react at all. The R group can be primary alkyl, vinylic,[1138] or aryl. If Me_3SiCl is present, the reaction takes place much faster and in higher yield; in the example given, the product is the silyl enol ether of **89** (see Reaction **12-17**).[1139] The use of Me_3SiCl also permits good yields with allylic R groups.[1140] Conjugated alkynyl-ketones also react via 1,4-addition to give substituted alkenyl-ketones.[1141] Solvent effects are important for the reactivity of organocuprates,[1142] which

[1132] Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* ***2004****, 6*, 4877.

[1133] Anderson, R.J.; Corbin, V.L.; Cotterrell, G.; Cox, G.R.; Henrick, C.A.; Schaub, F.; Siddall, J.B. *J. Am. Chem. Soc.* ***1975****, 97*, 1197.

[1134] Alexakis, A.; Chuit, C.; Commerçon-Bourgain, M.; Foulon, J.P.; Jabri, N.; Mangeney, P.; Normant, J.F. *Pure Appl. Chem.* ***1984****, 56,* 91.

[1135] For reactions with conjugated enynes, see Miginiac, L. *J. Organomet. Chem.* ***1982****, 238,* 235.

[1136] See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1599–1613, 1814–1824; Posner, G.H. *Org. React.* ***1972****, 19*, 1; House, H.O. *Acc. Chem. Res.* ***1976****, 9*, 59; Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* ***2004****, 126*, 6287; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 10–67.

[1137] See Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* ***1985****, 26,* 657.

[1138] Bennabi, S.; Narkunan, K.; Rousset, L.; Bouchu, D.; Ciufolini, M.A. *Tetrahedron Lett.* ***2000****, 41*, 8873.

[1139] Matsuza, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* ***1989****, 45,* 349; Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* ***1989****, 30*, 7087; Linderman, R.J.; McKenzie, J.R. *J. Organomet. Chem.* ***1989****, 361,* 31; Bertz, S.H.; Smith, R.A.J. *Tetrahedron* ***1990****, 46*, 4091. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1491–1492.

[1140] Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H.; Smith , R.A.J. *J. Am. Chem. Soc.* ***1990****, 112*, 4404; Lipshutz, B.H.; James, B. *Tetrahedron Lett.* ***1993****, 34*, 6689.

[1141] Degl'Innocenti, A.; Stucchi, E.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A. *Synlett* ***1992***, 329, 332.

[1142] See also Yangand, J.; Dudley, G.B. *Tetrahedron Lett.* ***2007****, 48*, 7887.

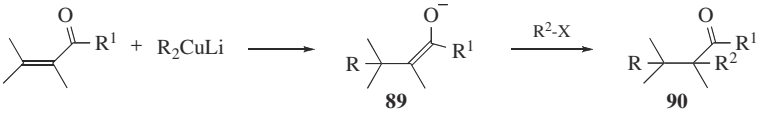
influence aggregation and aggregation state of the dialkyl cuprate.[1143] Organocuprate reactions have been shown to undergo oscillations in complexation.[1144]

An excess of the cuprate reagent relative to the conjugated substrate is often required. In general, only one of the R groups of R_2CuLi adds to the substrate; the other is wasted with respect to the conjugated substrate. This can be a limitation where the precursor (RLi or RCu, see Reaction **12-36**) is expensive or available in limited amounts, particularly if an excess of the reagent is required. The difficulty of group transfer can be overcome by using one of the mixed reagents [R(R′C≡C)CuLi,[1145] R(O-*t*-Bu)CuLi,[1146] R(PhS)CuLi[1147] each of which transfers only the R group. Mixed reagents are easily prepared by the reaction of RLi with R′C≡CCu (R′ = *n*-Pr or *t*-Bu), *t*-BuOCu, or PhSCu, respectively. A further advantage of the mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagents R(CN)CuLi[1148] (prepared from RLi and CuCN) and $R_2Cu(CN)Li_2$[1149] also selectively transfer the R group.[1150] With mixed cuprates, one of the ligands may be less prone to transfer than the other, as $R(R'Se)Cu(CN)Li_2$, leading to selective transfer of the R group.[1151] This less transferable ligand is sometimes referred to as a "dummy ligand". The selectivity of ligand transfer depends on two factors, thermodynamics of groups (e.g., alkyl or thioalkyl) and kinetic reactivity of groups (e.g., silylalkyl or vinyl).[1152] The selectivity arises in the Cu(III) intermediate formed by complexation of the cuprate and the unsaturated carbonyl compound.[1150,1153] A Cu(III) complex has been detected using rapid injection NMR.[1154]

Various functional groups (e.g., OH and unconjugated C=O groups) may be present in the substrate when organocuprates are employed.[1155] There is generally little or no competition from 1,2-addition (to the C=O). However, when R is allylic, 1,4-addition is observed with some substrates and 1,2-addition with others.[1156] The R_2CuLi group also adds to α,β-unsaturated sulfones,[1157] but not to simple α,β-unsaturated nitriles.[1158] Organocopper reagents (RCu) as well as certain R_2CuLi add to α,β-unsaturated and acetylenic sulfoxides.[1159] The reaction has been carried out[1160] with α,β-acetylenic ketones,[1161] esters, and nitriles. Conjugate addition to α,β-unsaturated and acetylenic

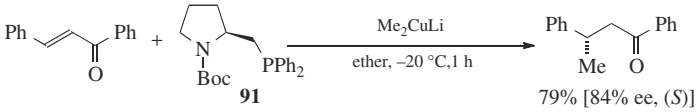
[1143] Henze, W.; Vyater, A.; Krause, N.; Gschwind, R.M. *J. Am. Chem. Soc.* ***2005****, 127,* 17335.
[1144] Murphy, M.D.; Ogle, C.A.; Bertz, S.H. *Chem. Commun.* ***2005***, 854.
[1145] Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* ***1978****, 43,* 3419.
[1146] Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815.
[1147] Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973****, 95,* 7788.
[1148] See Ledlie, D.B.; Miller, G. *J. Org. Chem.* ***1979****, 44,* 1006.
[1149] See Lipshutz, B.H. *Tetrahedron Lett.* ***1983****, 24,* 127.
[1150] See Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* ***1984****, 49*, 3938.
[1151] Zinn, F.K.; Ramos, E.C.; Comasseto, J.V. *Tetahedron Lett.* ***2001****, 42,* 2415.
[1152] Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2005****, 127,* 4697.
[1153] See also, Kireev, A.S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* ***2006****, 71,* 2630.
[1154] Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A.; Taylor, B.J. *J. Am. Chem. Soc.* ***2007****, 129,* 7208. See Hu, H.; Snyder, J.P. *J. Am. Chem. Soc.* ***2007****, 129,* 7210.
[1155] Charonnat, J.A.; Mitchell, A.L.; Keogh, B.P. *Tetrahedron Lett.* ***1990****, 31*, 315.
[1156] House, H.O.; Fischer Jr., W.F. *J. Org. Chem.* ***1969****, 34,* 3615. See also, Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* ***1973***, 3345.
[1157] Domínguez, E.; Carretero, J.C. *Tetrahedron Lett.* ***1993****, 34*, 5803
[1158] House, H.O.; Umen, M.J. *J. Org. Chem.* ***1973****, 38*, 3893.
[1159] Truce, W.E.; Lusch, M.J. *J. Org. Chem.* ***1974****, 39*, 3174; ***1978****, 43,* 2252.
[1160] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 456–457.
[1161] Lee, P.H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* ***1999****, 40,* 7109.

acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents $RCu \bullet BF_3$ (R = primary).[1162] Amine units have been transferred using α-lithio amides, CuCN, and various additives, which gave conjugate addition of an amidomethyl unit [$—CH_2N(Me)Boc$].[1163] Other amino-cuprates are known to give conjugate addition reactions.[1164]



89 **90**

Conjugate addition of the cuprate to the α,β-unsaturated ketone leads to an enolate ion (**89**), as noted above. It is possible for this enolate anion to react with an electrophilic species (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.[1165] For example, if an alkyl halide R^2X is present (R^2 = primary alkyl or allylic), the enolate (**89**) can be alkylated directly to give **90**.[1166] Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation (see also, Reaction **15-22**).



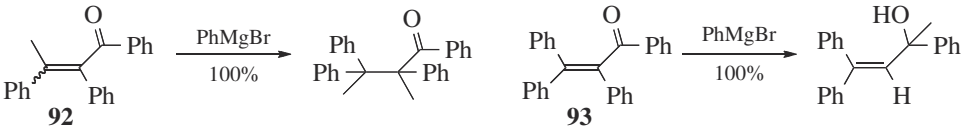
91

79% [84% ee, (*S*)]

As with the *Michael reaction* (**15-24**) the 1,4-addition of organometallic compounds has been performed diastereoselectivity[1167] and enantioselectively.[1168] The influence of solvent and additives on yield and selectivity has been examined.[1169] Addition of chiral ligands to the organocuprate conjugate addition reaction leads to alkylation with good-to-excellent enantioselectivity.[1170] The conjugate addition of dimethyl cuprate in the presence of a chiral ligand (e.g., **91**) is an example.[1171] Chiral bis(oxazoline) copper catalysts have been used for the conjugate addition of indoles to α,β-unsaturated esters.[1172] In the presence of a chiral additive and a Cu catalyst, conjugate addition to trisubstituted cyclohexeneones leads to the formation of stereogenic quaternary centers.[1173] Enantioselectivity was improved by the addition of styrene in the conjugate addition reactions of

[1162] Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. *J. Am. Chem. Soc.* ***1988****, 110,* 4834; ***1989****, 111,* 1351.
[1163] Alexander, C.W.; Nice, L.E. *Tetrahedron* ***2000****, 56*, 2767; Dieter, R.K.; Lu, K.; Velu, S.E. *J. Org. Chem.* ***2000****, 65*, 8715. See Dieter, R.K.; Topping, C.M.; Nice, L.E. *J. Org. Chem.* ***2001****, 66*, 2302.
[1164] Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* ***1992****, 114*, 5427.
[1165] Chapdelaine, M.J.; Hulce, M. *Org. React.* ***1990****, 38,* 225; Taylor, R.J.K. *Synthesis* ***1985***, 364; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1609–1612, 1826.
[1166] Coates, R.M.; Sandefur, L.O. *J. Org. Chem.* ***1974****, 39*, 275; Posner, G.H.; Lentz, C.M. *Tetrahedron Lett.* ***1977***, 3215.
[1167] Page, P.C.B.; Prodger, J.C.; Hursthouse, M.B.; Mazid, M. *J. Chem. Soc. Perkin Trans. 1,* ***1990***, 167; Corey, E.J.; Hannon, F.J. *Tetrahedron Lett.* ***1990****, 31*, 1393.
[1168] See Posner, G.H. *Acc. Chem. Res.* ***1987****, 20,* 72; The articles by Tomioka, K.; Koga, K. in Morrison, J.D. *Assymmetric Synthesis* Vol. 2, Academic Press, NY, ***1983***, pp. 201–224; Posner, G. pp. 225–241.
[1169] Christenson, B.; Ullenius, C.; Håkansson, M.; Jagner, S. *Tetrahedron* ***1992****, 48*, 3623.
[1170] Wu, J.; Mampreian, D.M.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005****, 127,* 4584; Knöpfel, T.F.; Zarotti, P.; Ichikawa, T.; Carreira, E.M. *J. Am. Chem. Soc.* ***2005****, 127,* 9682; Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* ***2006****, 128,* 2774; De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun.* ***2008***, 5384.
[1171] Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* ***1992****, 33*, 7193.
[1172] Jensen, K.B.; Thorhauge, J.; Hazell, R.G.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001****, 40*, 160.
[1173] d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2005****, 44*, 1376.

α-halo enones.[1174] Enantioselectivity is effectively controlled by the choice of ligand and its interaction with the copper compound, where different ligands on the metal may lead to differences in selectivity.[1175] Chiral templates have also been used with *Grignard reagents*, directly[1176] and in the presence of $AlMe_2Cl$.[1177]



Other organometallic compounds add to conjugated systems. *Grignard reagents* add to conjugated substrates (e.g., α,β-unsaturated ketones, cyano-ketones,[1178] esters, and nitriles),[1179] but 1,2-addition may seriously compete:[1180] The extent of 1,4-addition of *Grignard reagents* can be increased by the use of a Cu catalyst [e.g., CuCl and $Cu(OAc)_2$],[1181] forming a magnesium cuprate *in situ*. Formation of the conjugate addition product is often controlled by steric factors. Thus **92** with phenylmagnesium bromide gives 100% 1,4-addition, while **93** gives 100% 1,2-addition. In general, substitution at the carbonyl group increases 1,4-addition, while substitution at the double bond increases 1,2-addition. In most cases, both products are obtained, but α,β-unsaturated *aldehydes* nearly always give exclusive 1,2-addition when treated with *Grignard reagents*. *Grignard reagents* mixed with $CeCl_3$ generates a reactive species that gives primarily 1,4-addition.[1182] It is likely that alkylcopper reagents, formed from RMgX and Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual reactive species in these cases.[1134] Alkylidene malonic ester derivatives [$C{=}C(CO_2R)$] increase the facility of 1,4-addition with the two electron-withdrawing groups.[1183]

A dialkyl copper–magnesium iodide complex ($R_2Cu \cdot MgI$) has been used for conjugate addition to chiral α,β-unsaturated amides.[1184] Catalytic enantioselective conjugate addition has been reported with Grignard reagents.[1185]

Organolithium reagents[1186] generally react with conjugated aldehydes, ketones, and esters by 1,2-addition,[1187] but 1,4-addition was achieved with esters of the form

[1174] Li, K.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2006****, 45*, 7600.
[1175] See Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *Chem. Commun.* ***2009***, 7363.
[1176] Han, Y.; Hruby, V.J. *Tetrahedron Lett.* ***1997****, 38*, 7317.
[1177] Bongini, A.; Cardillo, G.; Mingardi, A.; Tomasini, C. *Tetrahedron Asymmetry* ***1996****, 7*, 1457.
[1178] Kung, L.-R.; Tu, C.-H.; Shia, K.-S.; Liu, H.-J. *Chem. Commun.* ***2003***, 2490.
[1179] Fleming, F.F.; Wang, Q.; Zhang, Z.; Steward, O.W. *J. Org. Chem.* ***2002****, 67*, 5953.
[1180] See Negishi, E. *Organometallics in Organic Synthesis* Vol. 1, Wiley, NY, ***1980***, pp. 127–133.
[1181] Posner, G.H. *Org. React.* ***1972****, 19*, 1; López, F.; Harutyanyan, S.R.; Minnaard, A.J.; Feringa, B.L. *J. Am. Chem. Soc.* ***2004****, 126*, 12784; Martin D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* ***2006****, 128*, 8416.
[1182] Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* ***1994****, 35*, 8651.
[1183] See Kim, Y.M.; Kwon, T.W.; Chung, S.K.; Smith, M.B. *Synth. Commun.* ***1999****, 29*, 343.
[1184] Schneider, C.; Reese, O. *Synthesis* ***2000***, 1689.
[1185] López, F.; Minnaard, A.J.; Feringa, B.L. *Acc. Chem. Res.* ***2007****, 40*, 179; Harutyunyan, S.R.; den Hartog, T.; Geurts, K.; Minnaard, A.J.; Feringa, B.L. *Chem. Rev.* ***2008****, 108*, 2824; Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2007****, 129,* 276; Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* ***2008****, 73,* 4578.
[1186] See Hunt, D.A. *Org. Prep. Proced. Int.* ***1989****, 21*, 705–749.
[1187] Cohen, T.; Abraham, W.D.; Myers, M. *J. Am. Chem. Soc.* ***1987****, 109,* 7923.

C=C—CO_2Ar, where Ar was a bulky group (e.g., 2,6-di-*tert*-butyl-4-methoxyphenyl).[1188] Alkyllithium reagents can be made to give 1,4-addition with α,β-unsaturated ketones[1189] and aldehydes,[1190] if the reactions are conducted in the presence of HMPA.[1191] Among organolithium reagents that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see Reaction **10-71**),[1192] vinyllithium reagents,[1193] and α-lithio allylic amides.[1194] Lithium–halogen exchange (**12-22**) generates an organolithium species that adds intramolecularly to conjugated esters to give cyclic and bicyclic products.[1195] A reagent based on RMgX—3 MeLi gave conjugate addition with α,β-unsaturated amides and carboxylic acid derivatives.[1196] 1,4-Addition of alkyllithium reagents to α,β-unsaturated aldehydes can also be achieved by converting the aldehyde to a benzothiazole derivative (masking the aldehyde function),[1197] from which the aldehyde group can be regenerated. α,β-Unsaturated nitro compounds undergo conjugate addition with aryllithium reagents, and subsequent treatment with acetic acid gives the α-aryl ketone.[1198]

If the organolithium reagent is complexed, 1,4-addition is more successful. The reaction of an aryllithium reagent with $B(OMe)_3$, for example, led to a Rh catalyzed conjugate addition with excellent enantioselectivity when a chiral ligand was employed.[1199] Allylic Te reagents that are treated with lithium diisopropyl amide and then conjugated esters give the 1,4-addition product, which cyclizes to form the corresponding cyclopropane derivative.[1200]

Organozinc compounds add to conjugated systems, especially dialkyl zinc compounds (R_2Zn). Many dialkylzinc compounds can be used, including vinylzinc compounds.[1201] The use of chiral ligands is effective for conjugate addition of dialkylzinc compounds to α,β-unsaturated ketones, esters, and so on,[1202] including conjugated lactones.[1203] The addition of a chiral complex to dialkylzinc compounds leads to enantioselective conjugate addition in conjunction with $Cu(OTf)_2$[1204] CuCN,[1205] or

[1188] Cooke Jr., M.P. *J. Org. Chem.* ***1986****, 51,* 1637.
[1189] Roux, M.C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* ***1981****, 37,* 1927; *Synth. Commun.* ***1981****, 11*, 85.
[1190] El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980****, 21*, 2897.
[1191] Sikorski, W.H.; Reich, H.J. *J. Am. Chem. Soc.* ***2001****, 123*, 6527.
[1192] Lucchetti, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* ***1979***, 2695; El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980****, 21*, 2897. See also, Bürstinghaus, R.; Seebach, D. *Chem. Ber.* ***1977****, 110,* 841.
[1193] See Maezaki, N.; Sawamoto, H.; Yuyama, S.; Yoshigami, R.; Suzuki, T.; Izumi, M.; Ohishi, H.; Tanaka, T. *J. Org. Chem.* ***2004****, 69*, 6335.
[1194] Sparteine is used as a chiral additive, see Curtis, M.D.; Beak, P. *J. Org. Chem.* ***1999****, 64*, 2996.
[1195] Piers, E.; Harrison, C.L.; Zetina-Rocha, C. *Org. Lett.* ***2001****, 3*, 3245.
[1196] Kikuchi, M.; Niikura, S.; Chiba, N.; Terauchi, N.; Asaoka, M. *Chem. Lett.* ***2007****, 36,* 736.
[1197] Corey, E.J.; Boger, D.L. *Tetrahedron Lett.* ***1978***, 9. Also see Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1988****, 29*, 2979.
[1198] Santos, R.P.; Lopes, R.S.C.; Lopes, C.C. *Synthesis* ***2001***, 845.
[1199] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1999****, 40*, 6957.
[1200] Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* ***2003****, 125*, 13030.
[1201] See Ikeda, S.-i.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* ***1999****, 121*, 4712.
[1202] Liang, L.; Au-Yeung, T.T.-L.; Chan, A.S.C. *Org. Lett.* ***2002****, 4*, 3799.
[1203] Reetz, M.T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* ***2002****, 43*, 1189.
[1204] Liang, L.; Yan, M.; Li, Y.-M.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2004****, 15*, 2575, and references cited therein; Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* ***2004****, 69*, 5660, and references cited therein; Duncan, A.P.; Leighton, J.L. *Org. Lett.* ***2004****, 6,* 4117, and references cited therein; Hajra, A.; Yoshikai, N.; Nakamura, E. *Org. Lett.* ***2006****, 8,* 4153; Valleix, F.; Nagai, K.; Soeta, T.; Kuriyama, M.; Yamada, K.-i.; Tomioka, K. *Tetrahedron* ***2005****, 61,* 7420.
[1205] Hird, A.W.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005****, 127*, 14988.

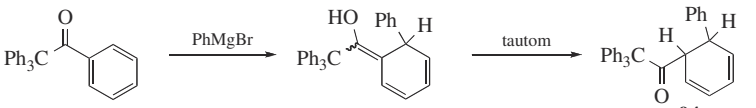
other copper compounds.[1206] Chiral ionic liquids have also been employed.[1207] Diethylzinc adds to conjugated nitro compounds in the presence of a catalytic amount of Cu $(OTf)_2$ to give the conjugate addition product.[1208] 1,6-Addition of dialkylzinc compounds has been reported, in the presence of a Rh catalyst.[1209] Other transition metal compounds can be used in conjunction with dialkylzinc compounds[1210] or with arylzinc halides (ArZnCl).[1211] Reaction of alkyl iodides with Zn/CuI and ultrasound generates an organometallic that adds to conjugated esters.[1212] Diarylzinc compounds (prepared with the aid of ultrasound) in the presence of nickel acetylacetonate, undergo 1,4-addition not only to α,β-unsaturated ketones, but also to α,β-unsaturated aldehydes.[1213] Mixed-alkylzinc compounds also add to conjugated systems.[1214] Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.[1215] Internal alkynes undergo 1,4-addition to conjugated esters using a combination of zinc metal and a Co complex as catalysts.[1216]

Trialkylalanes (R_3Al) add 1,4 to α,β-unsaturated carbonyl compounds in the presence of nickel acetylacetonate[1217] or $Cu(OTf)_2$.[1218] In the presence of aluminum chloride, benzene reacts with conjugated amides to add a phenyl group to C-4.[1219] Alkyl halides react via conjugate addition using BEt_3 or $AlEt_3$.[1220] Other metals are known to catalyzed conjugate addition of alkyl or aryl groups, including Co.[1221] An In/Cu mediated conjugate addition reaction is known using unactivated alkyl iodides.[1222]

Terminal alkynes add to conjugated systems when using a Ru,[1223] Pd,[1224] Ni,[1225] or a Rh catalyst.[1226] Intramolecular addition of terminal alkynes, in the presence of

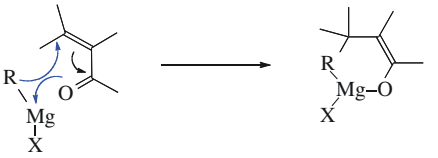
[1206] Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *J. Org. Chem.* ***2005****, 70*, 9009; Ito, K.; Eno, S.; Saito, B.; Katsuki, T. *Tetrahedron Lett.* ***2005****, 46,* 3981. For the use of Pd or Cu catalysts, see Marshall, J.A.; Herold, M.; Eidam, H.S.; Eidam, P. *Org. Lett.* ***2006****, 8,* 5505.
[1207] Malhotra, S.V.; Wang, Y. *Tetrahedron Asymmetry* ***2006****, 17,* 1032.
[1208] Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* ***2004****, 6*, 2689; Mampreian, D.M.; Hoveyda, A.H. *Org. Lett.* ***2004****, 6*, 2829; Duursma, A.; Minnaard, A.J.; Feringa, B.L. *J. Am. Chem. Soc.* ***2003****, 125*, 3700.
[1209] Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem. Int. Ed.* ***2005****, 44,* 4224.
[1210] Hirao, T.; Takada, T.; Sakurai, H. *Org. Lett.* ***2000****, 2*, 3659; Yin, Y.; Li, X.; Lee, D.-S.; Yang, T.-K. *Tetrahedron Asymmetry* ***2000****, 11*, 3329; Shadakshari, U.; Nayak, S.K. *Tetrahedron* ***2001****, 57*, 8185.
[1211] Shitani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* ***2004****, 126*, 6240.
[1212] Sarandeses, L.A.; Mouriño, A.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* ***1992***, 798. See also, Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* ***2004****, 6*, 3349.
[1213] Pétrier, C.; de Souza Barboza, J.C.; Dupuy, C.; Luche, J. *J. Org. Chem.* ***1985****, 50,* 5761.
[1214] Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T.A.; Reddy, C.K. *Angew. Chem. Int. Ed.* ***1997****, 36*, 1496.
[1215] Knochel, P.; Normant, J.F. *J. Organomet. Chem.* ***1986****, 309,* 1.
[1216] Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* ***2002****, 124*, 9696.
[1217] Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1975****, 28*, 817; Ashby, E.C.; Heinsohn, G. *J. Org. Chem.* ***1974****, 39,* 3297. See also, Kunz, H.; Pees, K.J. *J. Chem. Soc. Perkin Trans. 1,* ***1989***, 1168.
[1218] Su, L.; Li, X.; Chan, W.L.; Jia, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2003****, 24*, 1865.
[1219] Koltunov, K.Yu.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* ***2004****, 45*, 3547.
[1220] Liu, J.-Y.,; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* ***2003****, 68*, 4030.
[1221] In the presence of Mn, see Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* ***2006****, 71*, 6130.
[1222] Shen, Z.-L.; Cheong, H.-L.; Loh, T.-P. *Tetrahedron Lett.* ***2009****, 50*, 1051.
[1223] Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T.*J. Am. Chem. Soc.* ***2008, 130,*** 1576.
[1224] Chen, L.; Li, C.-J. *Chem. Commun.* ***2004***, 2362.
[1225] Herath, A.; Thompson, B.B.; Montgomery, J. *J. Am. Chem. Soc.* ***2007****, 129*, 8712; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* ***2008****, 130,* 8132.
[1226] Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J.W. *J. Am. Chem. Soc.* ***2002****, 124*, 12102; Lerum, R.V.; Chisholm, J.D. *Tetrahedron Lett.* ***2004****, 45*, 6591.

phenylboronic acid and a Rh catalyst, leads to cyclic compounds.[1227] Lithium tetraalkylgallium reagents give 1,4-addition.[1228] Trimethyl(phenyl)tin and a Rh catalyst gives conjugate addition of a methyl group[1229] and tetraphenyltin and a Pd catalyst adds a phenyl group.[1230] Triphenylbismuth (Ph_3Bi) and a Rh catalyst give conjugate addition of the phenyl group upon exposure to air.[1231] Similar reactivity is observed with a Pd catalyst in aqueous media.[1232] Allyltin compounds add an allyl group in the presence of a Sc catalyst.[1233] Benzylic bromides add to conjugated nitriles using a 2:1 mixture of $CrCl_3$ and Mn metal.[1234] Aryl halides add in the presence of $NiBr_2$.[1235] Vinyl Zr complexes undergo conjugate addition when using a Rh catalyst.[1236]



94

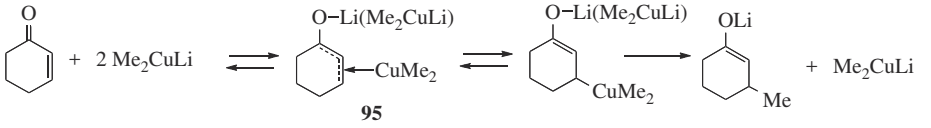
In certain cases, *Grignard reagents* add 1,4 to *aromatic* systems to give **94** after tautomerization (Sec. 2.N.i) of the initial formed enol.[1237] Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds where 1,3,5-trinitrobenzene reacts with excess methylmagnesium halide to give 2,4,6-trinitro-1,3,5-trimethylcyclohexane.[1238]



The mechanisms of most of these reactions are not well known. The 1,4-uncatalyzed *Grignard reaction* has been postulated to proceed by the cyclic mechanism shown, but there is evidence against it.[1239] The R_2CuLi[1240] and copper-catalyzed *Grignard additions* may

[1227] Chen, Y.; Lee, C. *J. Am. Chem. Soc.* ***2006****, 128,* 15598.
[1228] Han, Y.; Huang, Y.-Z.; Fang, L.; Tao, W.-T. *Synth. Commun.* ***1999****, 29*, 867.
[1229] Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* ***2002****, 58*, 91.
[1230] Ohe, T.; Uemura, S. *Tetrahedron Lett.* ***2002****, 43*, 1269.
[1231] Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2001****, 42*, 781.
[1232] Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* ***2004***, 1822.
[1233] Williams, D.R.; Mullins, R.J.; Miller, N.A. *Chem. Commun.* ***2003***, 2220.
[1234] Augé, J.; Gil, R.; Kalsey, S. *Tetrahedron Lett.* ***1999****, 40,* 67.
[1235] Condon, S.; Dupré, D.; Falgayrac, G.; Nédélec, J.-Y. *Eur. J. Org. Chem.* ***2002***, 105.
[1236] Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* ***2004****, 60*, 1293.
[1237] This example is from Schmidlin, J.; Wohl, J. *Ber.* ***1910****, 43,* 1145; Mosher, W.A.; Huber, M.B. *J. Am. Chem. Soc.* ***1953****, 75,* 4604. See Fuson, R.C. *Adv. Organomet. Chem.* ***1964****, 1,* 221.
[1238] See Bartoli, G. *Acc. Chem. Res.* ***1984****, 17*, 109; Bartoli, G.; Dalpozzo, R.; Grossi, L. *J. Chem. Soc. Perkin Trans. 2,* ***1989***, 573. For a study of the mechanism, see Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans. 2,* ***1985***, 773.
[1239] House, H.O.; Thompson, H.W. *J. Org. Chem.* ***1963****, 28,* 360; Klein, J. *Tetrahedron* ***1964****, 20*, 465. See, however, Marets, J.; Rivière, H. *Bull. Soc. Chim. Fr.* ***1970***, 4320.
[1240] Kingsbury, C.L.; Smith, R.A.J. *J. Org. Chem.* ***1997****, 62*, 4629. See, Bertz, S.H.; Miao, G.; Rossiter, B.E.; Snyder, J.P. *J. Am. Chem. Soc.* ***1995****, 117*, 11023; Snyder, J.P. *J. Am. Chem. Soc.* ***1995****, 117*, 11025.

involve a number of mechanisms, since the actual attacking species and substrates are so diverse.[1241] A free radical mechanism of some type (perhaps SET) has been suggested[1242] although the fact that retention of configuration at R has been demonstrated in several cases completely rules out a free $R^{\bullet}$ radical.[1243] For simple α,β-unsaturated ketones (e.g., 2-cyclohexenone and Me_2CuLi), there is evidence[1244] for this mechanism:

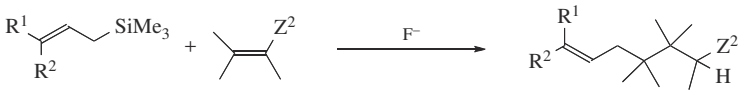


95 is a *d*, π* complex, with bonding between copper, as a base supplying a pair of *d* electrons, and the enone as a Lewis acid using the π* orbital of the allylic system.[1242] The ^{13}C NMR spectrum of an intermediate similar to **95** has been reported.[1245]

For the addition of organocopper reagents to alkynes and conjugated dienes, see Reaction **15-22**.

OS **IV**, 93; **V**, 762; **VI**, 442, 666, 762, 786; **VIII**, 112, 257, 277, 479; **IX**, 328, 350, 640.

15-26 The Sakurai Reaction



Allylic silanes ($R_2C{=}CHCH_2SiMe_3$) can be added to conjugated systems rather than silyl enol ethers in what is known as the *Sakurai reaction*.[1246] For example, an allyl group can be added to α,β-unsaturated carboxylic esters, amides and nitriles, with $CH_2{=}CHCH_2SiMe_3$ and F^- ion (see Reaction **15-47**).[1247] This reagent gave better results than lithium diallylcuprate (Reaction **15-25**). Catalytic *Sakurai reactions* are known.[1248] The Pd catalyzed reaction of conjugated ketones with $PhSi(OEt)_3$ and $SbCl_3$ and Bu_4NF in acetic acid gave the 1,4-addition product.[1249] A similar reaction was reported using $PhSi(OMe)_3$ with a Rh catalyst.[1250] Silver fluoride was used to catalyze the reaction with allyl (trimethoxy)silane.[1251] In a related reaction, Ph_2SiCl_2, NaF, and a Rh catalyst gives conjugate addition of a phenyl group to α,β-unsaturated ketones.[1252] An interesting Rh catalyzed, conjugate addition of a phenyl group was reported using a siloxane polymer

[1241] See Yamamoto, Y.; Yamada, J.; Uyehara, T. *J. Am. Chem. Soc.* ***1987****, 109*, 5820; Ullenius, C.; Christenson, B. *Pure Appl. Chem.* ***1988****, 60,* 57; Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* ***1989****, 45*, 523; Krause, N. *Tetrahedron Lett.* ***1989****, 30,* 5219.

[1242] See Wigal, C.T.; Grunwell, J.R.; Hershberger, J. *J. Org. Chem.* ***1991****, 56,* 3759.

[1243] Whitesides, G.M.; Kendall, P.E. *J. Org. Chem.* ***1972****, 37*, 3718.

[1244] Corey, E.J.; Hannon, F.J.; Boaz, N.W. *Tetrahedron* ***1989****, 45,* 545.

[1245] Bertz, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1989****, 111,* 8276.

[1246] Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* ***VII***, 443; Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* ***1998****, 39*, 3215; Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989****, 37*, 57, see p. 127, 335–370; Schinzer, D. *Synthesis* ***1988***, 263.

[1247] Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* ***1986****, 51,* 1745.

[1248] See Lee, P.H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* ***2001****, 66*, 8646.

[1249] Denmark, S.E.; Amishiro, N. *J. Org. Chem.* ***2003****, 68*, 6997.

[1250] Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2003****, 5*, 97.

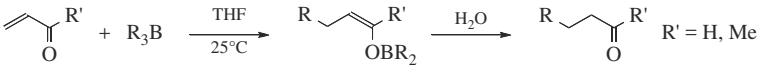
[1251] Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***2005****, 127,* 14556.

[1252] Huang, T.-S.; Li, C.-J. *Chem. Commun.* ***2001***, 2348.

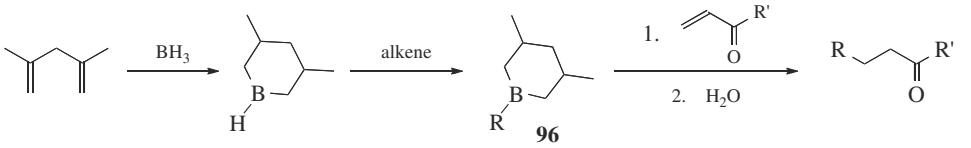
bearing Si—Ph units.[1253] The *Sakurai reaction* has been used in multi-component reactions.[1254]

15-27 Conjugate Addition of Boranes to Activated Double Bonds

Hydro-alkyl-addition (overall transformation)



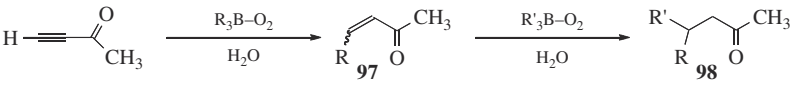
Just as trialkylboranes add to simple alkenes (Reaction **15-16**), they rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain related derivatives in THF to give enol borinates (also see Reaction **10-68**), which can be hydrolyzed to aldehydes or ketones.[1255] If water is present in the reaction medium from the beginning, the reaction can be run in one laboratory step. Since the boranes can be prepared from alkenes (Reaction **15-16**), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group [e.g., such as crotonaldehyde ($CH_3CH{=}CHCHO$) and 3-penten-2-one], fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of O_2 or by initiation with peroxides or UV light.[1256] A disadvantage is that only one of the



three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a β-alkyl borinate (e.g., **96**),[1257] which can be prepared as shown. Borinate (**96**, R = *tert*-butyl) can be made by treatment of **96** (R = OMe) with *t*-BuLi. The use of this reagent permits *tert*-butyl groups to be added. β-1-Alkenyl-9-BBN compounds β-RCH=CR′-9-BBN (prepared by treatment of alkynes with 9-BBN or of RCH=CR′Li with β-methoxy-9-BBN[1258]) add to methyl vinyl ketones to give, after hydrolysis, γ,δ-unsaturated ketones,[1259] although β-R-9-BBN, where R = a saturated group, are not useful here, because the R group of these reagents does not preferentially add to the substrate.[1253] Transition metals catalyze the addition of trialkylboranes to conjugated systems (e.g., the addition of allylboranes in the presence of a Ni catalyst).[1260] The Ni catalyzed addition was enhanced by the addition of methanol.[1261]

[1253] Koike, T.; Du, X.; Mori, A.; Osakada, K. *Synlett* ***2002***, 301.
[1254] Pospíšil, J.; Kumamoto, T.; Markó, I.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3357.
[1255] Köster, R.; Zimmermann, H.; Fenzl, W. *Liebigs Ann. Chem.* ***1976***, 1116. See Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents,* Academic Press, NY, ***1988***, pp. 301–305, 318–323; Brown, H.C. *Boranes in Organic Chemistry* Cornell University Press, Ithica, NY, ***1972***, pp. 413–433.
[1256] Brown, H.C.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1970***, *92,* 712, 714. See also, Miyaura, N.; Kashiwagi, M.; Itoh, M.; Suzuki, A. *Chem. Lett.* ***1974***, 395.
[1257] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1971***, *93,* 3777.
[1258] Brown, H.C.; Bhat, N.G.; Rajagopalan, S. *Organometallics* ***1986***, *5*, 816.
[1259] Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* ***1985***, *107*, 5225. See also, Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* ***1990***, *31*, 247.
[1260] Sieber, J.D.; Liu, S.; Morken, J.P. *J. Am. Chem. Soc.* ***2007***, *129,* 2214.
[1261] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2007***, *9,* 1541.

The corresponding β-1-alkynyl-9-BBN compounds also give the reaction.[1262] Since the product **97** is an α,β-unsaturated ketone, it can be made to react with another BR_3, the same or different, to produce a wide variety of ketones (**98**).



Vinyl boranes add to conjugated ketones in the presence of a Rh catalyst (with high asymmetric induction in the presence of BINAP).[1263] Alkynyl-boranes also add to conjugated ketones, in the presence of BF_3.[1264]

Other boron reagents add to conjugated carbonyl compounds.[1265] Tetraphenylborates add to conjugated alkynes in the presence of a Pd catalyst in a reaction known as hydrophenylation.[1266] Alkynyl boronate esters (Reaction **12-28**) give conjugate addition[1267] in the presence of boron trifluoride etherate,[1268] as do arylboronic acids (Reaction **12-28**) with a Rh,[1269] Pd,[1270] or a Bi catalyst.[1271] Diethylzinc has also been used.[1272] Aryl boronic acids add to the double bond of vinyl sulfones in the presence of a Rh catalyst.[1273] Vinylboronic acids add directly to conjugated ketones.[1274] An Ir catalyzed 1,6-addition of arylboronic acids is known.[1275] Conjugated alkynes undergo conjugate addition with arylboronic acids in the presence of a Cu catalyst.[1276] Organocatalysts have also been used for the conjugate addition of arylboronic acids to conjugated systems.[1277] Potassium vinyltrifluoroborates (see Reactions **10-59**, **13-10**, and **13-13**) give 1,4-addition with a Rh catalyst,[1278] as do

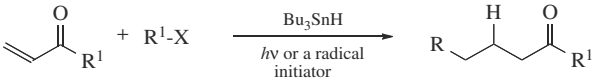
[1262] Sinclair, J.A.; Molander, G.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1977****, 99*, 954. See also, Molander, G.A.; Brown, H.C. *J. Org. Chem.* ***1977****, 42,* 3106.
[1263] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1998****, 39*, 8479.
[1264] Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* ***1992***, 695.
[1265] Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* ***2002****, 43*, 2323.
[1266] Zeng, H.; Hua, R. *J. Org. Chem.* ***2008****, 73,* 558.
[1267] Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* ***2005****, 127*, 3244; Pellegrinet, S.C.; Goodman, J.M. *J. Am. Chem. Soc.* ***2006****, 128,* 3116.
[1268] Chong, J.M.; Shen, L.; Taylor, N.J. *J. Am. Chem. Soc.* ***2000****, 122*, 1822.
[1269] Paquin, J.-F.; Defieber, C.; Stephenson, C.R.J.; Carreira, E.M. *J. Am. Chem. Soc.* ***2005****, 127*, 10850; Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* ***2006****, 128,* 5628; Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* ***2007****, 129,* 2130; Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* ***2008****, 130* 2172; Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* ***2005****, 70,* 2503; Stemmler, R.T.; Bolm, C. *J. Org. Chem.* ***2005****, 70,* 9925; Paquin, J.-F.; Stephenson, C.R.J.; Defieber, C.; Carreira, E.M. *Org. Lett.* ***2005****, 7,* 3821; Martina, S.L.X.; Minnaard, A.J.; Hessen, B.; Feringa, B.L. *Tetrahedron Lett.* ***2005****, 46,* 7159.
[1270] Lu, X.; Lin, S. *J. Org. Chem.* ***2005****, 70,* 9651.
[1271] Sakuma, S.; Miyaura, N. *J. Org. Chem.* ***2001****, 66*, 8944.
[1272] Dong, L.; Xu, Y.-J.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Synthesis* ***2004***, 1057.
[1273] With a chiral ligand, see Mauleón, P.; Carretero, J.C. *Org. Lett.* ***2004****, 6*, 3195.
[1274] Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* ***2007****, 129*, 4908.
[1275] Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* ***2006****, 45,* 5164.
[1276] Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* ***2008***, 2010.
[1277] Sugiura, M.; Tokudomi, M.; Nakajima, M. *Chem. Commun.* ***2010***, 7799.
[1278] Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J.A.F.; de Vries, A.H.M.; de Vires, J.G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* ***2004****, 69*, 8045.

aryltrifluoroborates.[1279] The Rh catalyzed addition of vinyl tetrafluoroborates has been reported.[1280]

In the presence of a Rh catalyst, $LiBPh(OMe)_3$ gave conjugate addition of the phenyl group to α,β-unsaturated esters.[1281] The fact that these reactions are catalyzed by free radical initiators and inhibited by galvinoxyl[1282] (a free radical inhibitor) indicates that free-radical mechanisms are involved.

15-28 Radical Addition to Activated Double Bonds

Hydro-alkyl-addition



In a reaction similar to **15-25**, alkyl groups can be added to alkenes activated by such groups as COR′, CO_2R', CN, and even Ph.[1283] This is a radical addition reaction.[1284] In the method illustrated above, the R group comes from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride (H atom transfer agents). The reaction of tert-butyl bromide, Bu_3SnH and AIBN (Sec. 14.A.i), for example, adds a tert-butyl group to a conjugated ester via 1,4-addition.[1285] An alkene is converted to an alkylborane with catecholborane (Reaction **12-28**) and when treated with a conjugated ketone and O_2, radical conjugate addition leads to the β-substituted ketone.[1286] The Bu_3SnH can also be generated in situ, from R_3SnX and $NaBH_4$. Like Reaction **15-27**, these additions have free radical mechanisms. The reaction has been used for free radical cyclizations of the type discussed in Reaction **15-30**.[1287] Such cyclizations normally give predominant formation of five-membered rings, but large rings (11–20 members) have also been synthesized by this reaction.[1288]

[1279] Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* ***2008****, 130,* 6159; Navarre, L.; Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett* ***2005****, 46,* 4247.

[1280] Lalic, G.; Corey, E.J. *Tetrahedron Lett.* ***2008****, 49,* 4894; Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* ***2009****, 11*, 3486.

[1281] Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron Asymmetry* ***1999****, 10*, 4047.

[1282] Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* ***1970****, 92,* 710. See also, Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1976****, 49*, 2275.

[1283] Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds,* Pergamon, Elmsford, NY, ***1986***, pp. 36–68; Giese, B. *Angew. Chem. Int. Ed.* ***1985****, 24,* 553; Larock, R.C. *Organomercury Compounds in Organic Synthesis, Springer,* NY, ***1985***, pp. 263–273. See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1809–1813.

[1284] Srikanth, G.S.C.; Castle, S.L. *Tetrahedron* ***2005****, 61,* 10377.

[1285] Hayen, A.; Koch, R.; Metzger, J.O. *Angew. Chem. Int. Ed.* ***2000****, 39*, 2758.

[1286] Ollivier, C.; Renaud, P. *Chem. Eur. J.* ***1999****, 5*, 1468.

[1287] See Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* ***1991****, 91,* 1237; Curran, D.P. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990****, 1, 121*; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds,* Pergamon, Elmsford, NY, ***1986***, pp. 151–169. See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 413–418.

[1288] See Porter, N.A.; Chang, V.H. *J. Am. Chem. Soc.* ***1987****, 109*, 4976.

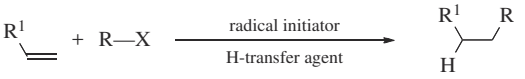
A BEt_3 (see Sec. 14.A.i) initiated reaction of conjugated amides with an alkyl iodide, in the presence of Bu_3SnH and O_2, leads to conjugate addition of the alkyl group.[1289] Enantioselective radical addition has been reported.[1290]

Conjugate addition is possible using photolysis. The photoinduced 1,4-addition of indoles to enones proceeds when irradiated at 350 nm.[1291]

OS **VII**, 105.

15-29 Radical Addition to Unactivated Double Bonds[1292]

Alkyl-hydro-addition



Radical addition to alkenes is usually difficult, except when addition occurs to conjugated carbonyl compounds (Reaction **15-24**). An important exception involves radicals bearing a heteroatom α to the carbon bearing the radical center. Such radicals are much more stable and can add to alkenes, usually with *anti-Markovnikov* orientation, as in the radical induced addition of HBr to alkenes (Reaction **15-2**).[1293]

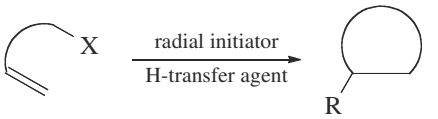
Examples of this type of reaction include the use of alcohol-, ester-,[1294] amino-, and aldehyde-stabilized radicals.[483] The alkyl group of alkyl iodides adds to alkenes with BEt_3/O_2 as the initiator and in the presence of a tetraalkylammonium hypophosphite.[1295] The radical generated from $(EtO)_2POCH_2Br$ adds to alkenes to generate a new phosphonate ester.[1296] α-Bromo esters add to alkenes in the presence of BEt_3/air to give a γ-bromo ester.[1297] α-Bromo amides add the Br and the acyl carbon to an alkene using $Yb(OTf)_3$ with BEt_3/O_2 as the radical initiator.[1298] α-Iodo amides add to alkenes using a water-soluble azobis initiator (see Sec. 14.A.i) to give the iodo ester, which cyclizes under the reaction conditions to give a lactone.[1299] β-Keto dithiocarbonates [RC(=O)—C—SC(=S)OEt] generate the radical in the presence of a peroxide and add to alkenes.[1300] 2-Fluoropyridyl derivatives of allylic alcohols react with xanthates in the presence of lauroyl peroxide to give alkenes.[1301] Malonate derivatives add to alkenes in the presence of a mixture of Mn/Co catalyst, in oxygenated acetic acid.[1302]

[1289] Sibi, M.P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* ***2005****, 127,* 2390; Sibi, M.P.; Patil, K. *Org. Lett.* ***2005****, 7,* 1453; He, L.; Srikanth, G.S.C.; Castle, S.L. *J. Org. Chem.* ***2005****, 70,* 8140. Also see Sibi, M.P.; Zimmerman, J. *J. Am. Chem. Soc.* ***2006****, 128,* 13346.
[1290] Lee, S.; Lim, C.J.; Kim, S.; Subramaniam, R.; Zimmerman, J.; Sibi, M.P. *Org. Lett.* ***2006****, 8,* 4311.
[1291] Moran, J.; Suen, T.; Beauchemin, A.M. *J. Org. Chem.* ***2006***, 71, 676.
[1292] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1278–1282.
[1293] See Curran, D.P. *Synthesis* ***1988***, 489 (see pp. 497–498).
[1294] Deng, L.X.; Kutateladze, A.G. *Tetrahedron Lett.* ***1997****, 38*, 7829.
[1295] Jang, D.O.; Cho, D.H.; Chung, C.-M. *Synlett* ***2001***, 1923.
[1296] Bałczewski, P.; Mikołajczyk, M. *Synthesis* ***1995***, 392.
[1297] Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***2001****, 66*, 7776.
[1298] Mero, C.L.; Porter, N.A. *J. Am. Chem. Soc.* ***1999****, 121*, 5155.
[1299] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1963.
[1300] Ouvry, G.; Zard, S.Z. *Chem. Commun.* ***2003***, 778.
[1301] Charrier, N.; Quiclet-Sire, B.; Zard, S.Z. *J. Am. Chem. Soc.* ***2008****, 130,* 8898.
[1302] Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002****, 67*, 970.

Other radicals can add to alkenes, and the rate constant for the addition of methyl radicals to alkenes has been studied.[1303] The rate of radical additions to alkenes in general has also been studied.[1304] The kinetic and thermodynamic control of a radical addition regiochemistry has also been studied.[1305] Alkynes are generally less reactive than alkenes in radical coupling reactions.[1306] Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.[1307]

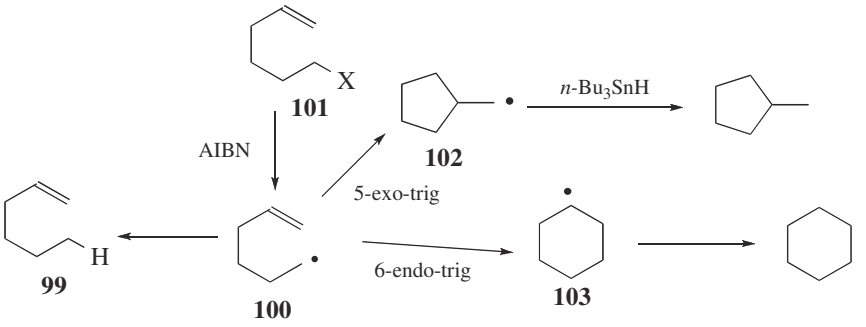
15-30 Radical Cyclization[1308]

Alkyl-hydro-addition



ω-Haloalkenes generate radicals upon treatment with radical initiator reagents (e.g., AIBN) or under photolysis conditions,[1309] and the radical carbon adds to the alkene to form cyclic compounds.[1310] This intramolecular addition of a radical to an alkene is called *radical cyclization*. In a typical example, haloalkene (**101**) reacts with the radical produced by AIBN to give radical **100**. The radical can add to the more substituted carbon to give **102** via a 5-exo-trig reaction (Sec. 6.E).[1311] If the radical adds to the less substituted carbon, **103** is formed via a 6-endo-trig reaction.[1312] In both cases, the product is another radical, which must be converted to an unreactive product. This is generally accomplished by adding a hydrogen-transfer agent[1313] [e.g., tributyltin hydride (Bu_3SnH)], which reacts with **102** to form methylcyclopentane and $Bu_3Sn^{\bullet}$, or with **103** to give cyclohexane. The $Bu_3Sn^{\bullet}$ formed in both cases usually dimerizes to form $Bu_3SnSnBu_3$. Cyclization can compete with hydrogen transfer[1314] from Bu_3SnH to **100** to give **99**, the reduction product. Atom-transfer cyclization is possible with other atoms (e.g., halogen), catalyzed by $InCl_3$[1315]or CuBr.[1316] Tin-free radical cyclizations are known using peroxyacids.[1317]

[1303] Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* ***1996*** *118*, 437.
[1304] Avila, D.V.; Ingold, K.U.; Lusztyk, J.; Dolbier, Jr., W.R.; Pan, H.-Q. *J. Org. Chem.* ***1996,*** *61*, 2027.
[1305] Leach, A.G.; Wang, R.; Wohlhieter, G.E.; Khan, S.I.; Jung, M.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2003,*** *125*, 4271.
[1306] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982,*** *21,* 768.
[1307] Dickstein, J.I.; Miller, G.I. in *The Chemistry of Carbon Carbon Triple Bonds, Vol. 2,* Patai, S. (Ed.), Wiley, NY ***1978***.
[1308] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1283–1295; Rheault, T.R.; Sibi, M.P. *Synthesis* ***2003***, 803.
[1309] See Pandey, G.; Reddy, G.D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 219.
[1310] Chang, S.-Y.; Jiang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* ***1997,*** *62*, 9089. See McCarroll, A.J.; Walton, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3215.
[1311] Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, Z.T. *J. Am. Chem. Soc.* ***2002,*** *124*, 10765. See Guan, X.; Phillips, D.L.; Yang, D. *J. Org. Chem.* ***2006,*** *71,* 1984.
[1312] See Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* ***2002***, 695.
[1313] See Ha, C.; Horner, J.H.; Newcomb, M.; Varick, T.R.; Arnold, B.R.; Lusztyk, J. *J. Org. Chem.* ***1993,*** *58* 1194.
[1314] See Furxhi, E.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***1999,*** *64*, 4064; Tauh, P.; Fallis, A.G. *J. Org. Chem.* ***1999,*** *64*, 6960.
[1315] Cook, G.R.; Hayashi, R. *Org. Lett.* ***2006,*** *8,* 1045.
[1316] Clark, A.J.; Wilson, P. *Tetrahedron Lett.* ***2008,*** *49*, 4848.
[1317] Smith, D.M.; Pulling, M.E.; Norton, J.R. *J. Am. Chem. Soc.* ***2007,*** *129,* 770.



In general, formation of the five-membered ring dominates the cyclization, but if addition to the C=C unit is relatively slow, the reduction product is formed preferentially. Radical rearrangements can also diminish the yield of the desired product.[1318] Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring,[1319] but not always.[1320] Formation of other size rings is possible of course. A 4-exo-trig radical cyclization has been studied,[1321] selectivity in a 7-endo versus 6-exo cyclization,[1322] and also an 8-endo-trig reaction.[1323] In radical cyclization to form large rings, 1,5- and 1,9-hydrogen atom abstractions can pose a problem[1324] Ring expansion during radical cyclization is possible when the terminal intermediate is a cyclobutylcarbinyl radical.[1325]

The mechanism of this reaction has been discussed.[1326] Cyclization via 5-endo-dig transition states require reorientation of the radical orbital needed to reach the in-plane acetylene π orbital in the bond-forming step, with accompanying loss of conjugative stabilization, and an increase in the activation energy. Therefore, many 5-endo cyclizations undergo H abstraction or equilibration with an isomeric radical.[1327]

In cases where hydrogen atom transfer gives primarily reduced products, one solution to promote cyclization generates the radical by photochemical cleavage of $Bu_3Sn—SnBu_3$ and the resulting carbon radical can cyclize (see Reaction **15-46**).[1328] A halogen atom transfer agent (e.g., iodoethane) is used rather than a hydrogen-transfer agent, so the final product is an alkyl iodide.

A mixture of a *Grignard reagent* and $CoCl_2$ has been used to initiate aryl radical cyclizations.[1329] Titanium(III)-mediated radical cyclizations are known,[1330] and SmI_2

[1318] Mueller, A.M.; Chen, P. *J. Org. Chem.* ***1998****, 63*, 4581.
[1319] Bogen, S; Malacria, M. *J. Am. Chem. Soc.* ***1996*** *118*, 3992.; Beckwith, A.L.J.; Ingold, K.U. in Vol. 1 of *Rearrangements in Ground States and Excited States,* de Mayo, P., Ed., Academic Press, NY ***1980***, pp. 162–283. Gómez, A.M.; Company, M.D.; Uriel, C.; Valverde, S.; López, J.C. *Tetrahedron Lett.* ***2002****, 43*, 4997.
[1320] Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* ***1994****, 35*, 3703; Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* ***1993****, 58*, 4293.
[1321] Jung, M.E.; Marquez, R.; Houk, K.N. *Tetrahedron Lett.* ***1999****, 40*, 2661.
[1322] Kamimura, A.; Taguchi, Y. *Tetrahedron Lett.* ***2004****, 45*, 2335.
[1323] Wang, Li.C. *J. Org. Chem.* ***2002****, 67*, 1271.
[1324] Kraus, G.A.; Wu, Y. *J. Am. Chem. Soc.* ***1992*** *114*, 8705.
[1325] Zhang, W.; Dowd, P. *Tetrahedron Lett.* ***1995****, 36*, 8539.
[1326] Bailey, W.F.; Carson, M.W. *Tetrahedron Lett.* ***1999****, 40*, 5433.
[1327] Alabugin, I.V.; Manoharan, M. *J. Am. Chem. Soc.* ***2005****, 127*, 9534
[1328] Afor a polymer-bound Sn catalyst see Hernán, A.G.; Kilburn, J.D. *Tetrahedron Lett.* ***2004****, 45*, 831.
[1329] Clark, A.J.; Davies, D.I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* ***1994***, 41.
[1330] Barrero, A.F.; Oltra, J.E.; Cuerva, J.M.; Rosales, A. *J. Org. Chem.* ***2002****, 67,* 2566.

mediated reactions are possible in the presence of a Ni catalyst.[1331] Organoborane-mediated radical cyclizations are known (see Sec. 14.A.i).[1332] The influence of the halogen atom on radical cyclization has been studied.[1333]

Both phenylthio[1334] and phenylseleno groups[1335] can be used as "leaving groups" for radical cyclization, where S or Se atom transfer leads to formation of the radical. A seleno ester ($R_2N—CH_2C(—O)SeMe$) has also been used with $(Me_3Si)_3SiH$ (tristrimethylsilylane, TTMSS) and AIBN to generate $R_2NCH_2^{\bullet}$.[1336] *O*-Phosphonate esters have also served as the leaving group.[1337] *N*-(2-bromophenylbenzyl)methylamino have been used as leaving groups for formation of a radical.[1338]

Radical cyclization reaction often proceeds with high diastereoselectivity[1339] and high asymmetric induction when chiral precursors are used. Internal alkynes are good substrates for radical cyclization,[1340] but terminal alkynes tend to give mixtures of *exo/endo-dig* products (Sec. 6.E).[1341] Radical cyclization has been used to transfer asymmetry from transient atropisomers to form lactams.[1342]

Radical cyclization is compatible with the presence of other functional groups, and heterocyclic rings may be formed via radical cyclization.[1343] Aryl radicals participate in radical cyclization reactions when the aromatic ring has an alkene or alkyne substituent. *o*-Iodo aryl allyl ethers cyclize to benzofuran derivatives, for example, when treated with AIBN, aq H_3PO_2 and $NaHCO_3$ in ethanol.[1344] Cyclization of vinyl radicals[1345] and allenyl radicals[1346] are also well known. Treatment of $XCH_2CON(R)—C(R^1)=CH_2$ derivatives (X = Cl, Br, I) with Ph_3SnH and AIBN led to formation of a lactam via radical cyclization.[1347] Cyclization of *N*-iodoethyl-5-vinyl-2-pyrrolidinone led to the corresponding bicyclic lactam,[1348] and there are other examples of radical cyclization with molecules containing a lactam unit[1349] or an amide unit.[1350] β-Lactams can be produced by radical

[1331] Molander, G.A.; St. Jean, Jr., D.J. *J. Org. Chem.* ***2002****, 67*, 3861.
[1332] Becattini, B.; Ollivier, C.; Renaud, P. *Synlett* ***2003***, 1485.
[1333] Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* ***2002****, 67*, 5537.
[1334] See Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* ***1999****, 50*, 31.
[1335] See Ericsson, C.; Engman, L. *Org. Lett.* ***2001****, 3*, 3459.
[1336] Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* ***2002****, 67*, 2323.
[1337] Crich, D.; Ranganathan, K.; Huang, X. *Org. Lett.* ***2001****, 3*, 1917.
[1338] Andrukiewicz, R.; Loska, R.; Prisyahnyuk, V.; Stalinski, K. *J. Org. Chem.* ***2003****, 68*, 1552.
[1339] See Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* ***2001****, 3*, 1391; Bailey, W.F.; Longstaff, S.C. *Org. Lett.* ***2001****, 3*, 2217; Stalinski, K.; Curran, D.P. *J. Org. Chem.* ***2002****, 67*, 2982.
[1340] See Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* ***1993****, 34*, 764; Miyabe, H.; Takemoto, Y. *Chemistry: European J.* ***2007****, 13,* 7280.
[1341] Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* ***1986***, 735; Robertson, J.; Lam, H.W.; Abazi, S.; Roseblade, S.; Lush, R.K. *Tetrahedron* ***2000****, 56*, 8959.
[1342] Petit, M.; Lapierre, A.J.B.; Curran, D.P. *J. Am. Chem. Soc.* ***2005****, 127,* 14994.
[1343] Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron* ***2005****, 61,* 10603, *Tetrahedron* ***2007****, 63,* 793.
[1344] Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***2000***, 104.
[1345] Sha, C.-K.; Zhan, Z.-P.; Wang, F.-S. *Org. Lett.* ***2000****, 2*, 2011.
[1346] Wartenberg, F.-H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* ***1993****, 34*, 5251. See Shi, J.; Zhang, M.; Fu, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron* ***2007****, 63,* 12681.
[1347] Gilbert, B.C.; Kalz, W.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1187. See El Bialy, S.A.A.; Ohtani, S.; Sato, T.; Ikeda, M. *Heterocycles* ***2001****, 54*, 1021; Liu, L.; Wang, X.; Li, C. *Org. Lett.* ***2003****, 5*, 361.
[1348] Keusenkothen, P.F.; Smith, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 2485.
[1349] Padwa, A.; Rashatasakhon, P.; Ozdemir, A.D.; Willis, J. *J. Org. Chem* ***2005****, 70,* 519.
[1350] Beckwith, A.L.J.; Joseph, S.P.; Mayadunne, R.T.A. *J. Org. Chem.* ***1993****, 58*, 4198.

cyclization, using $Mn(OAc)_3$.[1351] Radical cyclization occurs with enamines as well.[1352] Radical cyclization occurs with oximes to form the corresponding heterocyclic ring.[1353] Phenylseleno *N*-allylamines led to cyclic amines.[1354] ω-Iodo acrylate esters cyclize to form lactones,[1355] and allylic acetoxy compounds of the type $C{=}C{-}C{-}O_2C{-}CH_2I$ cyclize in a similar manner to give lactones.[1356] Iodolactonization (see Reaction **15-41**) occurs under standard radical cyclization conditions using allylic acetoxy compounds[1357] and $HGaCl_2/BEt_3$ has been used to initiate the radical process.[1358] α-Bromo mixed acetals give α-alkoxy THF derivatives[1359] and α-iodoacetals cyclize to give similar products.[1360] The reaction of an *o*-alkynyl aryl isonitrile with AIBN and 2.2 equiv of Bu_3SnH gave an indole via 5-exo-dig cyclization.[1361] Indole derivatives have also been prepared from *o*-iodoaniline derivatives, using AIBN and TTMSS.[1362] Samarium(II) has been used to initial 5-exo-trig ketyl-alkene coupling, and the mechanism of the reaction has been examined.[1363]

Acyl radicals can be generated and they cyclize in the usual manner.[1364] Molecular orbital calculations have shown that acyl, as well as silyl radicals, simultaneously use SOMO–LUMO (SOMO = singly occupied molecular orbital and LUMO = lowest unoccupied molecular orbital) and LUMO–HOMO interactions in reactions with alkenes.[1365] A polyene-cyclization reaction generated four rings, initiating the sequence by treatment of a phenylseleno ester with Bu_3SnH/AIBN to form the acyl radical, which added to the first alkene unit.[1366] The newly formed carbon radical added to the next alkene, and so on. Acyl radicals generated from Ts(R)NCOSePh derivatives cyclize to form lactams.[1367]

Radical cyclization of iodo aldehydes or ketones, at the carbon of the carbonyl, is effectively an acyl addition reaction (**16-24** and **16-25**). This cyclization is often reversible, and there are many fewer examples of addition to an alkene or alkyne. In one example, a δ-iodo aldehyde was treated with BEt_3/O_2 to initiate formation of the radical, and in the presence of Bu_3SnH cyclization gave a cyclopentanol.[1368] The reaction of an

[1351] D'Annibale, A.; Nanni, D.; Trogolo, C.; Umani, F. *Org. Lett.* ***2000,*** *2*, 401. See Lee, E.; Kim, S.K.; Kim, J.Y.; Lim, J. *Tetrahedron Lett.* ***2000,*** *41*, 5915. For a related reaction with tin hydride, see Curran, D.P.; Guthrie, D.B.; Geib, S.J. *J. Am. Chem. Soc.* ***2008,*** *130*, 8437. For a discussion of mechanism, see Snider, B.B. *Tetrahedron* ***2009,*** *65*, 10738.

[1352] Glover, S.A.; Warkentin, J. *J. Org. Chem.* ***1993,*** *58*, 2115.

[1353] Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* ***2008,*** *81,* 539.

[1354] Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* ***1998,*** *39*, 2429.

[1355] Ryu, I.; Nagahara, K.; Yamazaki, H.; Tsunoi, S.; Sonoda, N. *Synlett* ***1994***, 643.

[1356] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* ***2000,*** *122*, 6496.

[1357] Ollivier, C.; Bark, T.; Renaud, P. *Synthesis* ***2000***, 1598.

[1358] Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* ***2001,*** *3*, 1853.

[1359] Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* ***2000,*** *2*, 1061.

[1360] Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2002,*** *4*, 2257.

[1361] Rainer, J.D.; Kennedy, A.R.; Chase, E. *Tetrahedron Lett.* ***1999,*** *40*, 6325.

[1362] Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J.A.; Hursthouse, M.B.; Hobbs, D. *J. Org. Chem.* ***1999,*** *64*, 7856.

[1363] Sadasivam, D.V.; Antharjanam, P.K.S.; Prasad, E.; Flowers II, R.A. J. *Am. Chem. Soc.* ***2008,*** *130,* 7228.

[1364] See Jiaang, W.-T.; Lin, H.-C.; Tang, K.-H.; Chang, L.-B.; Tsai, Y.-M. *J. Org. Chem.* ***1999,*** *64*, 618.

[1365] Schiesser, C.H.; Matsubara, H.; Ritsner, I.; Wille, U. *Chem. Commun.* ***2006***, 1067.

[1366] Pattenden, G.; Roberts, L.; Blake, A.J. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 863;. Also see, Pattenden, G.; Smithies, A.J.; Tapolczay, D.; Walter, D.S. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 7.

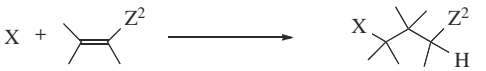
[1367] Rigby, J.H.; Danca, D.M.; Horner, J.H. *Tetrahedron Lett.* ***1998,*** *39*, 8413.

[1368] Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* ***1999,*** *40*, 5511.

aldehyde-alkene with AIBN, 0.5 $PhSiH_3$ and 0.1 Bu_3SnH generated a radical from the alkene, which cyclized at the aldehyde to give cyclopentanol derivatives.[1369] An aldehyde–*O*-methyloxime generated a radical adjacent to nitrogen under standard conditions, which cyclized at the carbonyl to give a cyclic α-hydroxy *N*-methoxyamine.[1370] Alternatively, an α-bromoacetal–*O*-methyl oxime cyclized at the C=NOMe unit under electrolytic conditions in the presence of cobaloxime.[1371] Alkynyl-imines are cyclized to the imino carbon to form alkylidene lactams under radical conditions in the presence of CO.[1372]

The attacking radical in radical cyclization reactions is not limited to a carbon, and a number of heterocycles can be prepared.[1373] Amidyl radicals are known and give cyclization reactions.[1374] Aminyl radical cyclizations have been reported.[1375] *N*-Chloroamine-alkenes give an aminyl radical when treated with $TiCl_3{\cdot}BF_3$, and cyclization gave a pyrrolidine derivative with a pendant chloromethyl group.[1376] *N*-(*S*-substituted) amines give similar results using AIBN/Bu_3SnH.[1377] Oxime-alkenes cyclize to imines when treated with PhSSPh and TEMPO (Sec. 5.C.i).[1378] An oxygen radical can be generated under photochemical conditions, and they add to alkenes in a normal manner.[1379] Note that radical substitution occurs, and reaction of Ph_3SnH/AIBN and an *O*-amidyl compound having a phosphonate ester elsewhere in the molecule gave cyclization to a THF derivative.[1380]

15-31 Conjugate Addition with Heteroatom Nucleophiles



Heteroatom nucleophiles add to conjugated systems to give *Michael-type* products. Conjugated carbonyl compounds react via conjugate addition with amines to give β-amino derivatives (See Reaction **15-31**)[1381] Conjugate addition of nitrogen-containing compounds is often called the *aza-Michael reaction*.[1382] Amines add to conjugated systems in the presence of In,[1383] Pd,[1384] Sm,[1385] Bi,[1386] Cu,[1387]

[1369] Hays, D.S.; Fu, G.C. *Tetrahedron.* ***1999****, 55*, 8815.
[1370] Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* ***1999****, 64*, 2003.
[1371] Inokuchi, T.; I.; Kawafuchi, H. *Synlett* ***2001***, 421.
[1372] Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* ***2006****, 128*, 7712.
[1373] See Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron* ***2004****, 60*, 6239; Bowman, W.R.; Cloonan, M.O.; Krintel, S.L. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2885.
[1374] Clark, A.J.; Peacock, J.L. *Tetrahedron Lett.* ***1998****, 39*, 6029. See Prabhakaran, E.N.; Nugent, B.M.; Williams, A.L.; Nailor, K.E.; Johnston, J.N. *Org. Lett.* ***2002****, 4*, 4197.
[1375] Martinez, II, E.; Newcomb, M. *J. Org. Chem.* ***2006****, 71*, 557.
[1376] Hemmerling, M.; Sjöholm, Å,; Somfai, P. *Tetrahedron Asymmetry* ***1999****, 10*, 4091.
[1377] Guindon, Y.; Guérin, B.; Landry, S.R. *Org. Lett.* ***2001****, 3*, 2293.
[1378] Lin, X.; Stien, D.; Weinreb, S.M. *Org. Lett.* ***1999****, 1*, 637.
[1379] For a review, see Hartung, J. *Eur. J. Org. Chem.* ***2001***, 619.
[1380] Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* ***1999****, 1*, 225.
[1381] See Cossu, S.; DeLucchi, O.; Durr, R. *Synth. Commun.* ***1996****, 26*, 4597.
[1382] Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005****, 127*, 13419. See Munro-Leighton, C.; Blue, E.D.; Gunnoe, T.B. *J. Am. Chem. Soc.* ***2006****, 128,* 1446.
[1383] Loh, T.-P.; Wei, L.-L. *Synlett* ***1998***, 975.
[1384] Takasu, K.; Nishida, N.; Ihara, M. *Synlett* ***2004***, 1844.
[1385] Yadav, J.S.; Reddy, A.R.; Rao, Y.G.; Narsaiah, A.V.; Reddy, B.V.S. *Synthesis* ***2007***, 3447.
[1386] Srivastava, N.; Banik, B.K. *J. Org. Chem.* ***2003****, 68*, 2109.
[1387] Xu, L.-W.; Wei, J.-W.; Xia, C.-G.; Zhou, S.-L.; Hu, X.-X. *Synlett* ***2003***, 2425.

Ce,[1388] La,[1389] or Yb compounds[1390] to give β-amino derivatives. This reaction can be initiated photochemically[1391] or with microwave irradiation.[1392] Aniline derivatives add to conjugated aldehydes in the presence of a catalytic amount of DBU,[1393] and indeed, DBU promotes the *aza-Michael reaction*.[1394] Lithium amides add to conjugated esters to give the β-amino ester.[1395] Amidocuprates add to conjugated systems to give β-nitrogen compounds, and a β-silyl group has an activating effect of the amidocuprate.[1396] A solvent-free conjugate addition of amines occurs on alumina in the presence of a Ce catalyst.[1397] Boric acid has been used as a catalyst of *aza-Michael reactions* in water.[1398] An intramolecular addition of an amine unit to a conjugated ketone in the presence of a Pd catalyst, or photochemically, led to cyclic amines.[1399] Amines add to conjugated thiolactams.[1400]

There are asymmetric versions of the *aza-Michael reaction*,[1401] and high enantioselectivity is possible using an organocatalyst.[1402] Chiral catalysts lead to enantioselective reactions.[1403] Chiral additives (e.g., chiral Cinchona alkaloids[1404] or chiral naphthol derivatives)[1405] have also been used. Chiral imines add in a highly stereoselective manner.[1406] Chiral catalysts have been used for the conjugated addition of carbamates.[1407] Indoles add to nitro alkenes in the presence of an organocatalyst.[1408] Other N-heterocycles add with good enantioselectivity in the presence of an organocatalyst.[1409]

Lactams have been shown to add to conjugated esters in the presence of $Si(OEt)_4$ and CsF.[1410] Phthalimide adds to alkylidene malononitriles via 1,4-addition with a Pd catalyst, and the resulting anion can be alkylated with an added allylic halide.[1411] Alkylidene

[1388] Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* ***2001****, 66*, 9052.
[1389] Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* ***1994***, 827.
[1390] Jenner, G. *Tetrahedron Lett.* ***1995****, 36*, 233.
[1391] Das, S.; Kumar, J.S.D.; Shivaramayya, K.; George, M.V. *J. Chem. Soc. Perkin Trans. 1,* ***1995***, 1797.
[1392] Moghaddam, F.M.; Mohammadi, M.; Hosseinnia, A. *Synth. Commn.* ***2000****, 30*, 643.
[1393] Markó, I.E.; Chesney, A. *Synlett* ***1992***, 275.
[1394] Yeom, C.-E.; Kim, M.J.; Kim, B.M. *Tetrahedron* ***2007****, 63*, 904.
[1395] Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.-i.; Tomioka, K. *J. Am. Chem. Soc.* ***2003****, 125*, 2886.
[1396] Bertz, S.H.; Ogle, C.A.; Rastogi, A. *J. Am. Chem. Soc.* ***2005****, 127*, 1372.
[1397] Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* ***2005****, 70*, 169.
[1398] Chaudhuri, M.K.; Hussain, S.; Kantam, M.L.; Neelima, B. *Tetrahedron Lett.* ***2005****, 46,* 8329.
[1399] Zhang, X.; Jung, Y.S.; Mariano, P.S.; Fox, M.A.; Martin, P.S.; Merkert, J. *Tetrahedron Lett.* ***1993****, 34*, 5239.
[1400] Sosnicki, J.G.; Jagodzinski, T.S.; Liebscher, J. *J. Heterocyclic Chem.* ***1997****, 34*, 643.
[1401] Vicario, J.L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proceed. Int.* ***2005****, 37*, 513; Krishna, P.R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* ***2009****, 65*, 9657.
[1402] Chen, Y.K.; Yoshida, M.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2006****, 128,* 9328; Sibi, M.P.; Itoh, K. *J. Am. Chem. Soc.* ***2007****, 129,* 8064; Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G.-L.; Xu, Y.; Córdova, A. *Tetrahedron Lett.* ***2007****, 48,* 2193; Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* ***2008****, 47,* 7710; Fadini, L.; Togni, A. *Helv. Chim. Acta* ***2007****, 90*, 411.
[1403] Sugihara, H.; Daikai, K.; Jin, X.L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* ***2002****, 43*, 2735.
[1404] Jew, S.-s.; Jeong, B.S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.
[1405] Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003****, 125*, 16178.
[1406] Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* ***1994****, 35*, 9705.
[1407] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J.M. *J. Am. Chem. Soc.* ***2004****, 126*, 9188.
[1408] Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* ***2008****, 130*, 16464.
[1409] Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2007****, 46*, 1983.
[1410] Ahn, K.H.; Lee, S.J. *Tetrahedron Lett.* ***1994****, 35*, 1875.
[1411] Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***2002****, 67*, 5977.

amido-amides, C=C(NHAc)CONHR, react with secondary amines in water to give the β-amino amido amide.[1412] Amines also add in a conjugate manner to alkynyl phosphonate esters, C≡C—$PO(OEt)_2$, using a CuI catalyst.[1413] Hydroxylamines add to conjugated nitro compounds to give 2-nitro hydroxylamines.[1414] *N,O*-Trimethylsilyl hydroxylamines add to conjugated esters, via nitrogen, using a Cu catalyst.[1415] Trimethylsilyl azide with acetic acid reacts with conjugated ketones to give the β-azido ketone.[1416] Sodium azide adds to conjugated ketones in aq acetic acid and 20% PBu_3.[1417] An interesting variation involves a double *Michael addition* of amido amines, amido alcohols or amido thiols to conjugated alkynes, forming pyrrolidine, oxazolidine, or thiazolidine derivatives.[1418]

The nitrogen of carbamates adds to conjugated ketones with a Pt,[1419] Pd,[1420] Cu,[1421] or with a bis(triflamide) organocatalyst.[1422] The amine moiety of a carbamate adds to conjugated ketones with a polymer-supported acid catalyst,[1423] or with $BF_3 \cdot OEt_2$.[1424] The reaction of ammonium formate with 1,4-diphenylbut-2-en-1,4-dione, in PEG-200 and a Pd catalyst under microwave irradiation, gave 2,5-diphenylpyrrole.[1425]

Phosphines react similarly to amines under certain conditions. Conjugate addition of R_2PH and a Ni catalyst give conjugate addition to α,β-unsaturated nitriles.[1426] A Pd catalyzed addition of diarylphosphines proceeds with good enantioselectivity to give chiral phosphines.[1427] Phosphites add to nitroalkenes in the presence of a chiral organocatalyst to give the corresponding nitro phosphite compound.[1428]

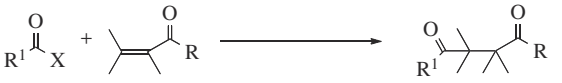
Alcohols add to conjugated ketones with a PMe_3 catalyst to give the β-alkoxy ketone.[1429] This reaction is called an *oxy-Michael reaction*.[1430] Alcohol addition is catalyzed by *N*-heterocyclic carbenes[1431] and other organocatalysts,[1432] often with enantioselectivity.[1433] The conjugate addition of peroxide anions (HOO^- and ROO^-) to α,β-unsaturated carbonyl compounds is discussed in Reaction **15-48**. An intramolecular variation is known that produces dihydropyrones.[1434]

[1412] Naidu, B.N.; Sorenson, M.E.; Connolly, J.P.; Ueda, Y. *J. Org. Chem.* ***2003****, 68*, 10098.
[1413] Panarina, A.E.; Dogadina, A.V.; Zakharov, V.I.; Ionin, B.I. *Tetrahedron Lett.* ***2001****, 42*, 4365.
[1414] O'Neil, I.A.; Cleator, E.; Southern, J.M.; Bickley, J.F.; Tapolczay, D.J. *Tetrahedron Lett.* ***2001****, 42*, 8251.
[1415] Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, R.; Tolomelli, A. *Tetrahedron Asymmetry* ***2001****, 12*, 2395.
[1416] Guerin, D.J.; Horstmann, T.E.; Miller, S.J. *Org. Lett.* ***1999****, 1*, 1107.
[1417] Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Zhou, S.-L. *Synlett* ***2003***, 2246.
[1418] Sriramurthy, V.; Barcan, G.A.; Kwon, O. *J. Am. Chem. Soc.* ***2007****, 129,* 12928.
[1419] Kakumoto, K.; Kobayashi, S.; Sugiura, M. *Org. Lett.* ***2002****, 4*, 1319.
[1420] Gaunt, M.J.; Spencer, J.B. *Org. Lett.* ***2001****, 3*, 25.
[1421] Wabnitz, T.C.; Spencer, J.B. *Tetrahedron Lett.* ***2002****, 43, 3*891.
[1422] Wabnitz, T.C.; Spencer, J.B. *Org. Lett.* ***2003****, 5*, 2141.
[1423] Wabnitz, T.C.; Yu, J.-Q.; Spencer, J.B. *Synlett* ***2003***, 1070.
[1424] Xu, L.-W.; Li, L.; Xia, C.-G.; Zhou, S.-L.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2337.
[1425] Rao, H.S.P.; Jothilingam, S. *Tetrahedron Lett.* ***2004****, 42*, 6595.
[1426] Sadow, A.D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* ***2004****, 126*, 14704.
[1427] Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* ***2010****, 132,* 5562.
[1428] Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* ***2007****, 129,* 14112.
[1429] Stewart, I.C.; Bergman, R.G.; Toste, F.D. *J. Am. Chem. Soc.* ***2003****, 125*, 8696.
[1430] Also called hydroalkoxylation. See Ramachary, D.B.; Mondal, R. *Tetrahedron Lett.* ***2006****, 47*, 7689.
[1431] Phillips, E.M.; Riedrich, M.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2010****, 132,* 13179.
[1432] Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron Lett.* ***2006****, 47*, 3039.
[1433] Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* ***2007****, 63*, 8658.
[1434] Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. J. *Am. Chem. Soc.* ***2005****, 127,* 1481.

Thiophenol and butyllithium (lithium phenylthiolate) adds to conjugated esters.[1435] Similar addition is observed with selenium compounds (RSeLi).[1436] Thiols react with conjugated amides via 1,4-addition with the addition of 10% $Hf(OTf)_4$ or other lanthanide triflates[1437] or to conjugated ketones in ionic solvents.[1438] Alkyl thiols add to conjugated carbonyl compounds with high enantioselectivity using an organocatalyst.[1439] Iron(III)-catalyzed addition of thiols occurs under solvent-free conditions.[1440] Thiols add without a catalyst in water[1441] in PEG,[1442] or in ionic liquids.[1443] Thiol addition is also catalyzed by iodine under solvent-free conditions.[1444] Ceric ammonium nitrate promotes the conjugate addition of thiols.[1445] Thioaryl moieties can be added in the presence of Yb[1446] or a catalytic amount of $(DHQD)_2PYR$ (a dihydroquinidine, see Reaction **15-48**).[1447] Thioalkyl units (e.g., BuS—) add to conjugated ketones using BuS—SnBu and In—I.[1448] Addition of conjugated lactones is possible to produce β-arylthiolated lactones.[1449] Dithiocarbamates are prepared by the reaction of an amine, CS_2, and a conjugated carbonyl compound.[1450] α,β-Unsaturated sulfones undergo conjugate addition of a cyano group using Et_2AlCN.[1451]

15-32 Acylation of Activated Double Bonds and of Triple Bonds

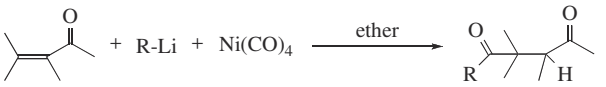
Hydro-acyl-addition



Under some conditions, acid derivatives add directly to activated double bonds. Acetic anhydride, Mg metal, and Me_3SiCl react with conjugated esters to give a γ-keto ester.[1452] Similar reaction with vinyl phosphonate esters leads to a γ-keto phosphonate ester.[1453] Thioesters undergo conjugate addition to α,β-unsaturated ketones in the presence of SmI_2.[1454] Using DBU and a thioimidazolium salt, acyl silanes, $Ar(C{=}O)SiMe_3$, add in a

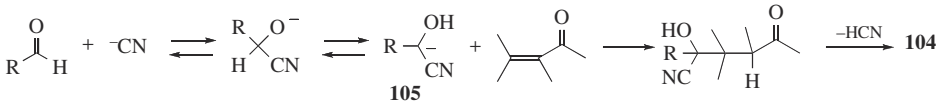
[1435] Kamimura, A.; Kawahara, F.; Omata, Y.; Murakami, N.; Morita, R.; Otake, H.; Mitsudera, H.; Shirai, M.; Kakehi, A. *Tetrahedron Lett.* ***2001****, 42*, 8497.
[1436] Zeni, G.; Stracke, M.P.; Nogueira, C.W.; Braga, A.L.; Menezes, P.H.; Stefani, H.A. *Org. Lett.* ***2004****, 6*, 1135.
[1437] Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* ***2001***, 983.
[1438] Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *J. Org. Chem.* ***2003****, 68*, 7098.
[1439] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005****, 127*, 15710; Kumar, A.; Akanksha *Tetrahedron* ***2007****, 63,* 11086.
[1440] Chu, C.-M.; Huang, W.-J.; Lu, C.; Wu, P.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* ***2006****, 47*, 7375.
[1441] Khatik, G.L.; Kumar, R.; Chakraborti, A.K. *Org. Lett.* ***2006****, 8,* 2433.
[1442] Kamal, A.; Reddy, D.R.; Rajendar *Tetrahedron Lett.* ***2005****, 46*, 7951.
[1443] Mečiarová, M.; Toma, Š.; Kotrusz, P. *Org. Biomol. Chem.* ***2006****, 4,* 1420.
[1444] Chu, C.-M.; Gao, S.; Sastry, M.N.V.; Yao, C.-F. *Tetrahedron Lett.* ***2005****, 46*, 4971; Gao, S.; Tzeng, T.; Sastry, M.N.V.; Chu, C.-M.; Liu, J.-T.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* ***2006****, 47,* 1889.
[1445] Chu, C.-M.; Gao, S.; Sastry, M.N.V.; Kuo, C.-W.; Lu, C.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* ***2007****, 63,* 1863.
[1446] Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett.* ***1994****, 35*, 7789.
[1447] McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* ***2002***, *41*, 338.
[1448] Ranu, B.C.; Mandal, T. *Synlett* ***2004***, 1239.
[1449] Nishimura, K.; Tomioka, K. *J. Org. Chem.* ***2002****, 67*, 431.
[1450] Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M.R. *J. Org. Chem.* ***2006****, 71*, 3634.
[1451] Ruano, J.L.G.; García, M.C.; Laso, N.M.; Castro, A.M.M.; Ramos, J.H.R. *Angew. Chem. Int. Ed.* ***2001****, 40*, 2507.
[1452] Ohno, T.; Sakai, M.; Ishino, Y.; Shibata, T.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* ***2001****, 3*, 3439.
[1453] Kyoda, M.; Yokoyama, T.; Maekawa, H.; Ohno, T.; Nishiguchi, I. *Synlett* ***2001***, 1535.
[1454] Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* ***2003****, 125*, 4030.

similar manner.[1455] Under microwave irradiation, aldehydes add to conjugated ketones using DBU/Al_2O_3 and a thiazolium salt.[1456] The conjugate addition of acyl zirconium complexes in the presence of $BF_3{\cdot}OEt_2$ is catalyzed by palladium acetate.[1457]



104

An acyl group can be introduced into the 4 position of an α,β-unsaturated ketone by treatment with an organolithium compound and nickel carbonyl[1458] to give a 1,4-diketone (**104**). The R group may be aryl or primary alkyl. The reaction can also be applied to alkynes, which need not be activated, in which case 2 molar equivalents add and the product is also a 1,4-diketone (e.g., $R'C{\equiv}CH \rightarrow RCOCHR'CH_2COR$).[1459] In a different procedure, α,β-unsaturated ketones and aldehydes are acylated by treatment at −110°C with $R_2(CN)CuLi_2$ and CO. This method is successful for R = primary, secondary, and tertiary alkyl.[1460] For secondary and tertiary groups, R(CN)CuLi, which does not waste an R group, can be used instead.[1461]



105

The reaction of an aldehyde and cyanide ion (See Reaction **16-52**) in a polar aprotic solvent (e.g., DMF or DMSO) leads to a cyanohydrin, which generates a diketone via loss of HCN.[1462] This method has been applied to α,β-unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ-keto esters, and γ-keto nitriles, respectively (see also, Reaction **16-55**). The initial product of this reaction is ion **105**, which is a synthon for the unavailable $R^-C{=}O$ anion (see Reaction **10-68**). It is a masked $R^-C{=}O$ anion that upon reaction with the conjugated carbonyl gives **104** after loss of HCN from the cyanohydrin addition product. Other masked carbanions that have been used in this reaction are the $RC^-(CN)NR$ ion,[1463] the EtSCRSOEt ion,[1464] the $CH_2{=}C^-OEt$ ion,[1465] $CH_2{=}C(OEt)Cu_2Li$,[1466] $CH_2{=}CMe(SiMe_3)$,[1466] and the $RC^-(OCHMeOEt)CN$ ion.[1467] In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes

[1455] Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004****, 126*, 2314.
[1456] Yadav, J.S.; Anuradha, K.; Reddy, B.V.S.; Eeshwaraiah, B. *Tetrahedron Lett.* ***2003****, 44*, 8959.
[1457] Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* ***2002****, 58*, 7559.
[1458] Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969****, 91*, 4926.
[1459] Sawa, Y.; Hashimoto, I.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* ***1968****, 33*, 2159.
[1460] Seyferth, D.; Hui, R.C. *J. Am. Chem. Soc.* ***1985****, 107*, 4551. See also, Lipshutz, B.H.; Elworthy, T.R. *Tetrahedron Lett.* ***1990****, 31,* 477.
[1461] Seyferth, D.; Hui, R.C. *Tetrahedron Lett.* ***1986****, 27*, 1473.
[1462] See Stetter, H.; Kuhlmann, H. *Org. React.* ***1991****, 40,* 407–496; Stetter, H.; Kuhlmann, H.; Haese, W. *Org. Synth., 65,* 26.
[1463] Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem. Int. Ed.* ***1990****, 29,* 179.
[1464] Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3271, 3275.
[1465] Beockman Jr., R.K.; Bruza, K.J.; Baldwin, J.E.; Lever, Jr., O.W. *J. Chem. Soc., Chem. Commun.* ***1975***, 519.
[1466] Boeckman Jr., R.K ; Bruza, K.J. *J. Org. Chem.* ***1979****, 44,* 4781.
[1467] Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* ***1974****, 96,* 5272.

(Reaction **10-71**) do not give 1,4-addition to these substrates (except in the presence of HMPA, see Reaction **15-25**), but add 1,2 to the C=O group instead (Reaction **16-38**).

Interestingly, acylation occurs at the α-position of an enone when and α,β-unsaturated ketone is treated with an acid chloride and Et_2Zn in the presence of a Rh catalyst.[1468]

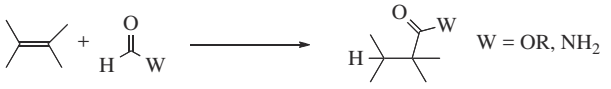
In another procedure, acyl radicals derived from phenyl selenoesters (ArCOSePh) (by treatment with Bu_3SnH) add to α,β-unsaturated esters and nitriles to give γ-keto esters and γ-keto nitriles, respectively.[1469]

OS **VI**, 866; **VIII**, 620.

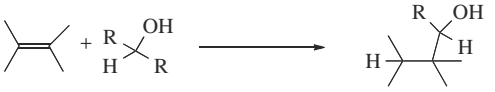
15-33 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, and so on

Hydro-acyl-addition, and so on

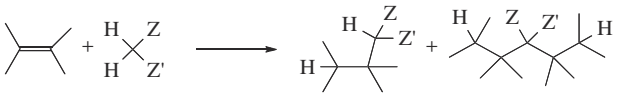
Formates, primary and secondary alcohols, amines, ethers, alkyl halides, compounds of the type $Z—CH_2—Z'$, and a few other compounds add to double bonds in the presence of free radical initiators.[1470] This is formally the addition of RH to a double bond, but the "R" is not just any carbon, but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as in Sec. 15.A.ii). Formates and formamides[1471] add similarly:



Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):



The ZCH_2Z' compounds react at the carbon bearing the active hydrogen[1472]:



Similar additions have been successfully carried out with carboxylic acids, anhydrides,[1473] acyl halides, carboxylic esters, nitriles, and other types of compounds.[1474]

Similar reactions have been carried out on acetylene.[1475] In an interesting variation, thiocarbonates add to alkynes in the presence of a Pd catalyst to give a β-phenylthio α,β-unsaturated ester.[1476] Aldehydes add to alkynes in the presence of a Rh catalyst to give

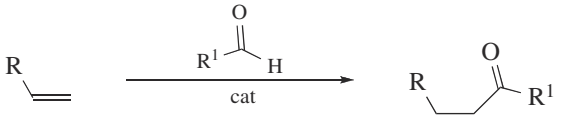
[1468] Sato, K.; Yamazoe, S.; Yamamoto, R.; Ohata, S.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Org. Lett.* ***2008****, 10,* 2405.
[1469] Boger, D.L.; Mathvink, R.J. *J. Org. Chem.* ***1989****, 54*, 1777.
[1470] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 69–77; Vogel, H. *Synthesis* ***1970***, 99; Dang, H.-S.; Roberts, B.P. *Chem. Commun.* ***1996***, 2201.
[1471] Elad, D. *Fortschr. Chem. Forsch.* ***1967****, 7,* 528, see pp. 530–543.
[1472] See Hájek, M.; Málek, J. *Coll. Czech. Chem. Commun.* ***1979****, 44*, 3695.
[1473] de Klein, W.J. *Recl. Trav. Chim. Pays-Bas* ***1975****, 94,* 48.
[1474] Cadogan, J.I.G. *Pure Appl. Chem.* ***1967****, 15*, 153, pp. 153–158. See also, Giese, B.; Zwick, W. *Chem. Ber.* ***1982****, 115,* 2526; Giese, B.; Erfort, U. *Chem. Ber.* ***1983****, 116*, 1240.
[1475] See DiPietro, J.; Roberts, W.J. *Angew. Chem. Int. Ed.* ***1966****, 5,* 415.
[1476] Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* ***2001****, 123*, 2899.

conjugated ketones.[1477] In a cyclic version of the addition of aldehydes, 4-pentenal was converted to cyclopentanone with a Rh complex catalyst.[1478] An intramolecular acyl addition to an alkyne was reported using silyl ketones, acetic acid, and a Rh catalyst.[1479] Formamides add to alkynes in the presence of a Pd catalyst to form conjugated amides.[1480]

OS **IV**, 430; **V**, 93; **VI**, 587, 615.

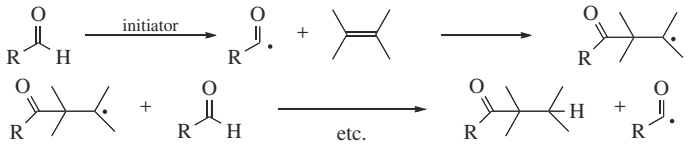
15-34 Addition of Aldehydes

Alkyl-carbonyl-addition



In the presence of metal catalysts (e.g., Rh[1481] or Yb[1482]), aldehydes can add directly to alkenes to form ketones. Additives play an important role in such reactions.[1483] The reaction of ω-alkenyl aldehydes with a Rh catalyst leads to cyclic ketones,[1484] with high enantioselectivity if chiral ligands are employed. A carbene organocatalyst was used for an enantioselective intramolecular reaction.[1485] β,γ-Unsaturated ketones are prepared by the Rh catalyzed addition of aldehydes to dienes.[1486] The addition of aldehydes to activated double bonds, mediated by a catalytic amount of thiazolium salt in the presence of a weak base, is called the *Stetter reaction*,[1487] An internal addition of an alkynyl aldehyde, catalyzed by a Rh complex, led to a cyclopentenone derivative.[1488] These reactions are not successful when the alkene contains electron-withdrawing groups (e.g., halo or carbonyl groups). A free radical initiator is required,[1489] usually peroxides or UV light. The mechanism is illustrated for aldehydes, but is similar for the other compounds:

[1477] Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997****, 62*, 4564.
[1478] Fairlie, D.P.; Bosnich, B. *Organometallics* ***1988****, 7,* 936, 946. Also see, Barnhart, R.W.; Wang, X.; Noheda, P.; Bergens, S.H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* ***1994****, 116*, 1821.
[1479] Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* ***2001***, 1210.
[1480] Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2010****, 132*, 2094.
[1481] Willis, M.C.; Randell-Sly, H.E.; Woodward, R.L.; McNally, S.J.; Currie, G.S. *J. Org. Chem* ***2006****, 71,* 5291; Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* ***2007****, 72,* 2543. For a discussion of the mechanism, see Roy, A.H.; Lenges, C.P.; Brookhart, M. *J. Am. Chem. Soc.* ***2007****, 129*, 2082.
[1482] Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* ***2003***, 552.
[1483] See Jo, E.-A.; Jun, C.-H. *Tetrahedron Lett.* ***2009****, 50*, 3338.
[1484] Barnhart, R.W.; McMorran, D.A.; Bosnich, B. *Chem. Commun.* ***1997***, 589.
[1485] de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* ***2005****, 127,* 6284; Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* ***2006****, 128,* 2552; Kundu, K.; McCullagh, J.V.; Morehead, Jr., A.T. *J. Am. Chem. Soc.* ***2005****, 127,* 16042; Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* ***2008***, 3989.
[1486] Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* ***2008****, 130,* 14094. For a related reaction, see Shibahara, F.; Bower, J.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2008****, 130,* 14120.
[1487] Stetter, H.; Kuhlmann, H. *Org. React.* ***1991****, 40*, 407; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004****, 126,* 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. See also, Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004****, 126*, 2314.
[1488] Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2002****, 124*, 10296.
[1489] See Lee, E.; Tae, J.S.; Chong, Y.H.; Park, Y.C.; Yun, M.; Kim, S. *Tetrahedron Lett.* ***1994****, 35*, 129 for an example.

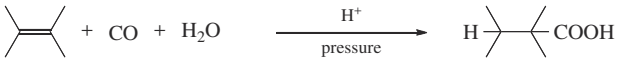


In the presence of BF_3 and a Ag salt, aldehydes add to alkynes to give the corresponding conjugated ketone.[1490] Polymers are often side products. Photochemical addition of aldehyde to conjugated C=C units can be efficient when a triplet sensitizer (Sec. 7.A.vi, category 5, e.g., benzophenone) is used.[1491]

A variation that is more of an acyl addition (Reaction **16-25**) involves the reaction of an allylic alcohol with benzaldehyde. With a Ru catalyst and in an ionic liquid, the C=C unit reacts with the aldehyde, with concomitant oxidation of the allylic alcohol unit, to give a β-hydroxy ketone, $PhCHO + C{=}C{-}CH(OH)R \rightarrow PhCH(OH){-}CH(Me)COR$.[1492] In another variation, formate esters add to alkenes using a Ru catalyst to give an alkyl ester via a formylation process.[1493]

15-35 Hydrocarboxylation

Hydro-carboxy-addition



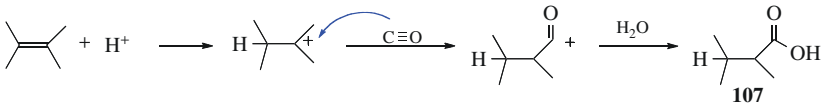
The acid-catalyzed hydrocarboxylation of alkenes (the *Koch reaction*) can be performed in a number of ways.[1494] In one method, the alkene is treated with CO and water at 100–350°C and 500–1000-atm pressure with a mineral acid catalyst. However, the reaction can also be performed under milder conditions. If the alkene is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0–50°C and 1–100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.[1495] The formic acid procedure is called the *Koch–Haaf reaction* (the Koch–Haaf reaction can also be applied to alcohols, see Reaction **10-77**). Nearly all alkenes can be hydrocarboxylated by one of these procedures. However, conjugated dienes are polymerized under these conditions. Hydrocarboxylation can also be accomplished under mild conditions (160°C and 50 atm) by the use of nickel carbonyl as catalyst. Acid catalysts are used along with the nickel carbonyl, but basic catalysts can also be employed.[1496] The $Ni(CO)_4$ catalyzed oxidative carbonylation with

[1490] Rhee, J.U.; Krische, M.J. *Org. Lett.* ***2005****, 7*, 2493.
[1491] Kraus, G.A.; Liu, P. *Tetrahedron Lett.* ***1994****, 35*, 7723.
[1492] Yang, X.-F.; Wang, M.; Varma, R.S.; Li, C.-J. *Org. Lett.* ***2003****, 5,* 657.
[1493] Na, Y.; Ko, S.; Hwang, L.K.; Chang, S. *Tetrahedron Lett.* ***2003****, 44,* 4475.
[1494] See Lapidus, A.L.; Pirozhkov, S.D. *Russ. Chem. Rev.* ***1989****, 58*, 117; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 335–359, 335–348; in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, the articles by Mullen, A. pp. 243–308; and Bahrmann, H. pp. 372–413; Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer: Berlin, ***1970***, pp. 78–174.
[1495] Haaf, W. *Chem. Ber.* ***1966****, 99,* 1149; Christol, H.; Solladié, G. *Bull. Soc. Chim. Fr.* ***1966***, 1307.
[1496] Sternberg, H.W.; Markby, R.; Wender, P. *J. Am. Chem. Soc.* ***1960****, 82*, 3638.

CO and H_2O as a nucleophile is often called *Reppe carbonylation*.[1497] The toxic nature of nickel tetracarbonyl has led to development of other catalysts.[1498] Indeed, variations in the reaction procedure include the use of Pd,[1499] Pt,[1500] and Rh[1501] catalysts. This reaction converts alkenes, alkynes, and dienes and is tolerant of a wide variety of functional groups. When the additive is alcohol or acid, saturated or unsaturated acids, esters, or anhydrides are produced (see Reaction **15-36**). The transition metal catalyzed carbonylation has been done enantioselectively, with moderate-to-high optical yields, by the use of an optically active palladium-complex catalyst.[1502] Alkenes also react with $Fe(CO)_5$ and CO to give carboxylic acids.[1503] Electrochemical carboxylation procedures have been developed, including the conversion of alkenes to 1,4-butanedicarboxylic acids.[1504] A reductive carboxylation of alkenes with CO and cesium carbonate has been reported.[1505]

When applied to triple bonds, hydrocarboxylation gives α,β-unsaturated acids under very mild conditions. Triple bonds give unsaturated acids and saturated dicarboxylic acids when treated with CO_2 and an electrically reduced Ni complex catalyst.[1506] Alkynes also react with $NaHFe(CO)_4$, followed by $CuCl_2 \cdot 2\,H_2O$, to give alkenyl acid derivatives.[1507] A related reaction with CO and Pd catalysts in the presence of $SnCl_2$ leads to conjugated acid derivatives.[1508] Terminal alkynes react with CO_2 and $Ni(cod)_2$ (cod = 1,5-cyclooctadiene), and subsequent treatment with DBU gives the α,β-unsaturated carboxylic acid.[1509]

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism[1510] involves initial attack on a proton, followed by attack by CO on the resulting carbocation to give an acyl cation, and subsequent reaction with water gives the product **107**. *Markovnikov's rule* is followed, and carbon skeleton rearrangements and double-bond isomerizations (prior to attack by CO) are frequent.



107

[1497] Tsuji, J. *Palladium Reagents and Catalysts* Wiley, NY, **1999**; Hohn, A. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, ***1996***, p. 137; Beller, M.; Tafesh, A.M. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, ***1996***, p. 187; Drent, E.; Jager, W.W.; Keijsper, J.J.; Niele, F.G.M. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, ***1996***, p. 1119.; Bertoux, F.; Monflier, E.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* ***1999***, *143,* 11; Beller, M.; Cornils, B.; Frohning, C.D.; Kohlpaintner, C.W. *J. Mol. Catal. A: Chem.* ***1995***, *104, 17*; Milstein, D. *Acc. Chem. Res.* ***1988***, *21*, 428; Tsuji, J. *Acc. Chem. Res.* ***1969***, *2,* 144; Bird, C.W. *Chem. Rev.* ***1962***, *62,* 283.

[1498] For a review, see Kiss, G. *Chem. Rev.* ***2001***, *101,* 3435.

[1499] See Heck, R.F. *Palladium Reagents in Organic Synthesis* Academic Press, NY, ***1985***, pp. 381–395; Mukhopadhyay, K.; Sarkar, B.R.; Chaudhari, R.V. *J. Am. Chem. Soc.* ***2002***, *124*, 9692; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2008***, *130*, 15254.

[1500] Xu, Q.; Fujiwara, M.; Tanaka, M.; Souma, Y. *J. Org. Chem.* ***2000***, *65*, 8105.

[1501] Xu, Q.; Nakatani, H.; Souma, Y. *J. Org. Chem.* ***2000***, *65,* 1540.

[1502] Alper, H.; Hamel, N. *J. Am. Chem. Soc.* ***1990***, *112*, 2803.

[1503] Brunet, J.-J.; Neibecker, D.; Srivastava, R.S. *Tetrahedron Lett.* ***1993***, *34*, 2759.

[1504] Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. *Synlett* ***2001***, 418.

[1505] Williams, C.M.; Johnson, J.B.; Rovis, T. *J. Am. Chem. Soc.* ***2008***, *130,* 14936.

[1506] Duñach, E.; Dérien, S.; Périchon, J. *J. Organomet. Chem.* ***1989***, *364*, C33.

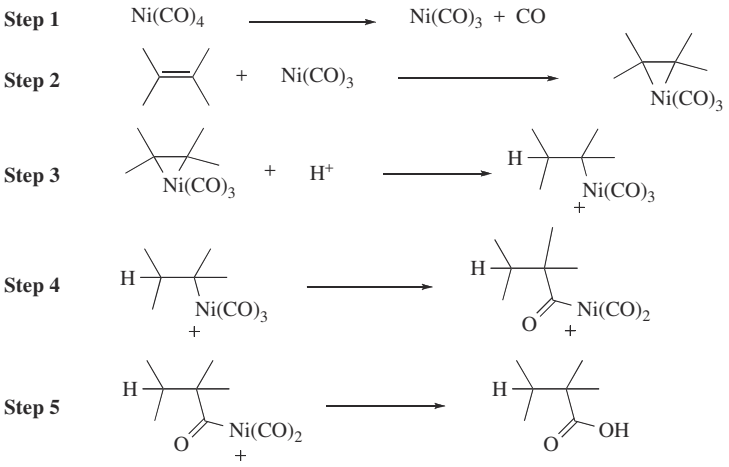
[1507] Periasamy, M.; Radhakrishnan, U.; Rameshkumar, C.; Brunet, J.-J. *Tetrahedron Lett.* ***1997***, *38*, 1623.

[1508] Takeuchi, R.; Sugiura, M. *J. Chem. Soc. Perkin Trans. 1,* ***1993***, 1031.

[1509] Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 3975. See also, Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* ***2001***, *3*, 3345.

[1510] See Hogeveen, H. *Adv. Phys. Org. Chem.* ***1973***, *10*, 29.

For the transition metal catalyzed reactions, the nickel carbonyl reaction has been well studied and the addition is syn for both alkenes and alkynes.[1511] The following is the accepted mechanism:[1511]

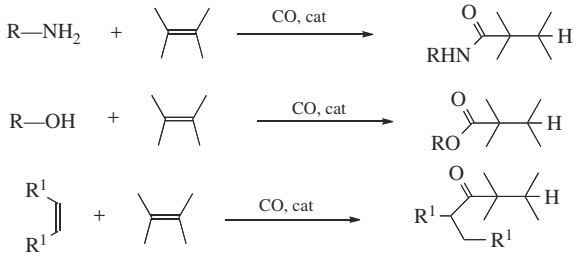


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

An indirect method for hydrocarboxylation involves the reaction of an alkene with a borate [$(RO)_2BH$] and a Rh catalyst. Subsequent reaction with $LiCHCl_2$, and then $NaClO_2$, gives the *Markovnikov* carboxylic acid ($RC{=}C \rightarrow RC(CO_2H)CH_3$.[1512] When a chiral ligand is used, the reaction proceeds with good enantioselectivity.

15-36 Carbonylation, Alkoxycarbonylation, and Aminocarbonylation of Double and Triple Bonds

Alkyl, Alkoxy, or Amino-carbonyl-addition



In the presence of certain metal catalysts, alkenes and alkynes can be carbonylated or converted to give an amide or an ester.[1513] There are several variations. The reaction of an alkyl iodide and a conjugated ester with CO, $(Me_3Si)_3SiH$, and AIBN in supercritical CO_2 (Sec. 9.D.ii) gave a γ-keto ester.[1514] Terminal alkynes react with

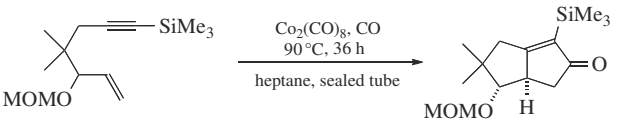
[1511] Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* ***1963***, 410.
[1512] Chen, A.; Ren, L.; Crudden, C.M.; *J. Org. Chem.* ***1999***, *64*, 9704.
[1513] See Fallis, A.G.; Forgione, P. *Tetrahedron* ***2001***, *57*, 5899.
[1514] Kishimoto, Y.; Ikariya, T. *J. Org. Chem.* ***2000***, *65*, 7656.

CO and methanol in the presence of $CuCl_2$ and $PdCl_2$ to give a β-chloro-α,β-unsaturated methyl ester.[1515] Conjugated dienes react with thiophenol, CO and $Pd(OAc)_2$ to give the β,γ-unsaturated thioester.[1516] Allene reacts with CO, CH_3OH, and a Ru catalyst to give methacrylic acid.[1517] Alkynes react with thiophenol and CO with a Pd[1518] or Pt[1519] catalyst to give a conjugated thioester. Terminal alkynes react with CO and CH_3OH, using a combination of a palladium(II) halide and a copper(II) halide, to give a conjugated diester, $MeO_2C—C{=}C—CO_2Me$.[1520] A similar reaction with alkenes using a combination of a Pd and a Mo catalyst led to a saturated diester ($MeO_2C—C—C—CO_2Me$).[1521] Alkenes were converted to the dimethyl ester of 1,4-butanedioic acid derivatives with CO/O_2 and a combination of $PdCl_2$ and CuCl catalysts.[1522] Note that alkenes primarily are converted to the *anti-Markovnikov* ester upon treatment with arylmethyl formate esters ($ArCH_2OCHO$) and a Ru catalyst.[1523] Terminal alkynes react with tosyl azide, water, and a catalytic amount of CuI to give an *N*-tosyl amide.[1524]

A bicyclic ketone was generated when 1,2-diphenylethyne was heated with carbon monoxide, methanol and a dirhodium catalyst.[1525] 2-Iodostyrene reacted at 100 °C with CO and a Pd catalyst to give the bicyclic ketone 1-indanone.[1526] Another variation reacted a conjugated allene–alkene with 5 atm of CO and a Rh catalyst to give a bicyclic ketone.[1527] An intermolecular version of this reaction is known using a Co catalyst, giving a cyclopentenone[1528] in a reaction related to the *Pauson–Khand reaction* (see below). The reaction of a conjugated diene having a distal alkene unit and CO with a Rh catalyst led to a bicyclic conjugated ketone.[1529] When a *Stille coupling* (Reaction **12-15**) is done in a CO atmosphere, conjugated ketones of the type C=C—CO—C=C are formed,[1530] suitable for a *Nazarov cyclization* (Reaction **15-20**). Alkynes were converted to cyclobutenones using $Fe_3(CO)_{12}$ to form an initial complex, followed by reaction with copper(II) chloride.[1531] An interesting variation treated cyclohexene with 5 molar equivalents of Oxone and a $RuCl_3$ catalyst to give 2-hydroxycyclohexanone.[1532]

[1515] Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* ***1999****, 64,* 5984. See also, Clarke, M.L. *Tetrahedron Lett.* ***2004****, 45*, 4043.
[1516] Xiao, W.-J.; Alper, H. *J. Org. Chem.* ***2001****, 66*, 6229.
[1517] Zhou, D.-Y.; Yoneda, E.; Onitsuka, K.; Takahashi, S. *Chem. Commun.* ***2002***, 2868.
[1518] Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* ***1999****, 64*, 2080.
[1519] Kawakami, J.-i.; Mihara, M.; Kamiya, I.; Takeba, M.; Ogawa, A.; Sonoda, N. *Tetrahedron* ***2003****, 59,* 3521.
[1520] Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001****, 31*, 3131; El Ali, B.; Tijani, J.; El-Ghanam, A.; Fettouhi, M. *Tetrahedron Lett.* ***2001****, 42*, 1567.
[1521] Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002****, 67*, 5005.
[1522] Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, J.; Liang, B.; Chen, J.; Yang, Z. *Eur. J. Org. Chem.* ***2003***, 4346.
[1523] Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* ***2002****, 124*, 750.
[1524] Cho, S.H.; Yoo, E.J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* ***2005****, 127*, 16046.
[1525] Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***1999****, 40*, 7811.
[1526] Gagnier, S.V.; Larock, R.C. *J. Am. Chem. Soc.* ***2003****, 125*, 4804.
[1527] Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* ***1999****, 121,* 4130.
[1528] Jeong, N.; Hwang, S.H. *Angew. Chem. Int. Ed.* ***2000****, 39*, 636.
[1529] Lee, S.I.; Park, J.H.; Chung, Y.K.; Lee, S.-G. *J. Am. Chem. Soc.* ***2004****, 126,* 2714.
[1530] Mazzola, Jr., R.D.; Giese, S.; Benson, C.L.; West, F.G. *J. Org. Chem.* ***2004****, 69*, 220.
[1531] Rameshkumar, C.; Periasamy, M. *Tetrahedron Lett.* ***2000****, 41*, 2719.
[1532] Plietker, B. *J. Org. Chem.* ***2004****, 69*, 8287.

The reaction of dienes, diynes, or enynes with transition metals[1533] (usually Co)[1534] forms organometallic coordination complexes. Rhodium,[1535] Ti,[1536] Mo,[1537] and W[1538] complexes have been used for this reaction. In the presence of CO, the metal complexes derived primarily from enynes (alkene–alkynes) generate cyclopentenone derivatives in what is known as the *Pauson–Khand reaction*.[1539] This reaction involves (1) formation of a hexacarbonyldicobalt–alkyne complex and (2) decomposition of the complex in the presence of an alkene.[1540] A typical example is the preparation of **108**.[1541] Cyclopentenones can be prepared by an intermolecular reaction of a vinyl silane and an alkyne using CO and a Ru catalyst.[1542] Carbonylation of an alkene–diene using a Rh catalyst leads to cyclization to an α-vinyl cyclopentanone.[1543] An yne–diene can also be used for the *Pauson–Khand reaction*.[1544]



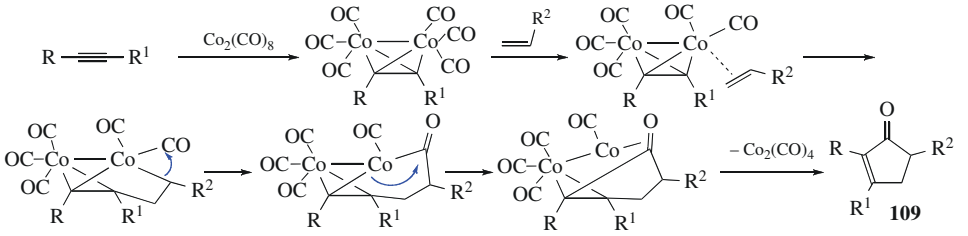
108

The reaction can be promoted photochemically[1545] and the rate is enhanced by the presence of primary amines.[1546] Coordinating ligands also accelerate the reaction,[1547] polymer-supported promoters have been developed[1548] and there are many possible variations in reaction conditions.[1549] The *Pauson–Khand reaction* has been done under heterogeneous reaction conditions,[1550] with Co nanoparticles,[1551] and in water.[1552] A

[1533] See Krafft, M.E.; Hirosawa, C.; Bonaga, L.V.R. *Tetrahedron Lett.* ***1999****, 40*, 9177.
[1534] See Krafft, M.E.; Boñaga, L.V.R.; Hirosawa, C. *J. Org. Chem.* ***2001****, 66*, 3004.
[1535] Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* ***1998***, 249. An entrapped-Rh catalyst has been used: Park, K.H.; Son, S.U.; Chung, Y.K. *Tetrahedron Lett.* ***2003****, 44*, 2827.
[1536] Hicks, F.A.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997****, 118*, 9450; Hicks, F.A.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999****, 121*, 5881.
[1537] Adrio, J.; Carretero, J.C. *J. Am. Chem. Soc.* ***2007****, 129,* 778; Adrio, J.; Rivero, M.R.; Carretero, J.C. *Org. Lett.* ***2005****, 7,* 431.
[1538] Hoye, T.R.; Suriano, J.A. *J. Am. Chem. Soc.* ***1993****, 115*, 1154.
[1539] Khand, I.U.; Pauson, P.L.; Habib, M.J. *J. Chem. Res. (S)* ***1978***, 348; Khand, I.U; Pauson, P.L. *J. Chem. Soc. Perkin Trans. 1,* ***1976***, 30. Gibson, S.E.; Stevenazzi, A. *Angew. Chem. Int. Ed.* ***2003****, 42*, 1800; Gibson, S.E.; Mainolfi, N. *Angew. Chem. Int. Ed.* ***2005****, 44*, 3022; Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* ***2010***, 789.
[1540] See de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.* ***2004****, 69*, 1075. See also, Rivero, M.R.; Adrio, J.; Carretero, J.C. *Eur. J. Org. Chem.* ***2002***, 2881.
[1541] Magnus, P.; Principe, L.M. *Tetrahedron Lett.* ***1985****, 26,* 4851.
[1542] Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2004****, 126*, 11058.
[1543] Wender, P.A.; Croatt, M.P.; Deschamps, N.M. *J. Am. Chem. Soc.* ***2004****, 126*, 5948.
[1544] Wender, P.A; Deschamps, N.M.; Gamber, G.G. *Angew. Chem. Int. Ed.* ***2003****, 42*, 1853.
[1545] Pagenkopf, B.L.; Livinghouse, T. *J. Am. Chem. Soc.* ***1996****, 118*, 2285.
[1546] Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem. Int. Ed.* ***1997****, 36*, 2801.
[1547] Krafft, M.E.; Scott, I.L.; Romero, R.H. *Tetrahedron Lett.* ***1992****, 33*, 3829.
[1548] Kerr, W.J.; Lindsay, D.M.; McLaughlin, M.; Pauson, P.L. *Chem. Commun.* ***2000***, 1467; Brown, D.S.; Campbell, E.; Kerr, W.J.; Lindsay, D.M.; Morrison, A.J.; Pike, K.G.; Watson, S.P. *Synlett* ***2000***, 1573.
[1549] Krafft, M.E.; Boñaga, L.V.R.; Wright, J.A.; Hirosawa, C. *J. Org. Chem.* ***2002****, 67*, 1233; Blanco- Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* ***2002****, 43*, 5763. The reaction has been done in aqueous media: Krafft, M.E.; Wright, J.A.; Boñaga, L.V.R. *Tetrahedron Lett.* ***2003****, 44*, 3417.
[1550] Kim, S.-W.; Son, S.U.; Lee, S.I.; Hyeon, T.; Chung, Y.K. *J. Am. Chem. Soc.* ***2000****, 122*, 1550.
[1551] Kim, S.-W.; Son, S.U.; Lee, S.S.; Hyeon, T.; Chung, Y.K. *Chem. Commun.* ***2001***, 2212; Son, S.U.; Lee, S.I.; Chung, Y.K.; Kim, S.-W.; Hyeon, T. *Org. Lett.* ***2002****, 4*, 277.
[1552] Krafft, M.E.; Wright, J.A.; Llorente, V.R.; Boñaga, L.V.R. *Can. J. Chem.* ***2005****, 83,* 1006.

dendritic Co catalyst has been used.[1553] Ultrasound promoted[1554] and microwave promoted[1555] reactions have been developed. Polycyclic compounds (tricyclic and higher) are prepared in a relatively straightforward manner using this reaction.[1556] Asymmetric *Pauson–Khand reactions* are known.[1557]

The *Pauson–Khand reaction* is compatible with other groups or heteroatoms elsewhere in the molecule. These include ethers and aryl halides,[1558] esters,[1559] amides,[1560] alcohols,[1561] diols,[1562] and an indole unit.[1563] A silicon-tethered *Pauson–Khand reaction* is known.[1564] Allenes are reaction partners in the *Pauson–Khand reaction*.[1565] This type of reaction can be extended to form six-membered rings using a Ru catalyst.[1566] A double-*Pauson–Khand process* was reported.[1567] In some cases, an aldehyde can serve as the source of the carbonyl for carbonylation.[1568]



The accepted mechanism was proposed by Magnus and Principe,[1569] shown for the formation of **109**,[1570] and supported by Krafft's work.[1571] It has been shown that CO is lost from the *Pauson–Khand* complex prior to alkene coordination and insertion.[1572] Calculations

[1553] Dahan, A.; Portnoy, M. *Chem. Commun.* ***2002***, 2700.
[1554] Ford, J.G.; Kerr, W.J.; Kirk, G.G.; Lindsay, D.M.; Middlemiss, D. *Synlett* ***2000***, 1415.
[1555] Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett.* ***2002****, 43*, 7859.
[1556] Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* ***2001****, 57,* 2729; Son, S.U.; Yoon, Y.A.; Choi, D.S.; Park, J.K.; Kim, B.M.; Chung, Y.K. *Org. Lett.* ***2001****, 3*, 1065.
[1557] Verdaguer, X.; Moyano, A.; Pericás, M.A.; Riera, A.; Maestro, M.A.; Mahía, J. *J. Am. Chem. Soc.* ***2000****, 122*, 10242l; Konya, D.; Robert, F.; Gimbert, Y.; Greene, A.E. *Tetrahedron Lett.* ***2004****, 45*, 6975.
[1558] Pérez-Serrano, L.; Banco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* ***2000****, 65*, 3513. For a review, see Suh. W.H.; Choi, M.; Lee, S.I.; Chung, Y.K. *Synthesis* ***2003***, 2169.
[1559] Krafft, M.E.; Boñaga, L.V.R. *Angew. Chem. Int. Ed.* ***2000****, 39,* 3676, and references cited therein; Jeong, N.; Sung, B.S.; Choi, Y.K. *J. Am. Chem. Soc.* ***2000****, 122*, 6771; Sturla, S.J.; Buchwald, S.L. *J. Org. Chem.* ***2002****, 67*, 3398.
[1560] Comely, A.C.; Gibson, S.E.; Stevenazzi, A.; Hales, N.J. *Tetrahedron Lett.* ***2001****, 42*, 1183.
[1561] Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* ***2001****, 42*, 3315.
[1562] Mukai, C.; Kim, J.S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* ***1999****, 64*, 6822.
[1563] Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* ***2004****, 69*, 5413.
[1564] Brummond, K.M.; Sill, P.C.; Rickards, B.; Geib, S.J. *Tetrahedron Lett.* ***2002****, 43*, 3735; Reichwein, J.F.; Iacono, S.T.; Patel, U.C.; Pagenkopf, B.L. *Tetrahedron Lett.* ***2002****, 43*, 3739.
[1565] Brummond, K.M.; Chen, H.; Fisher, K.D.; Kerekes, A.D.; Rickards, B.; Sill, P.C.; Geib, A.D. *Org. Lett.* ***2002****, 4*, 1931. See Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K. *Synlett* ***2003***, 573.
[1566] Trost, B.M.; Brown, R.E.; Toste, F.D. *J. Am. Chem. Soc.* ***2000****, 122*, 5877.
[1567] Rausch, B.J.; Gleiter, R. *Tetrahedron Lett.* ***2001****, 42*, 1651.
[1568] See Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* ***2002****, 67*, 7446; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Tetrahedron Lett.* ***2004****, 45*, 9163.
[1569] Magnus, P.; Principe, L.M. *Tetrahedron Lett.* ***1985****, 26,* 4851.
[1570] For a review, see Brummond, K.M.; Kent, J.L. *Tetrahedron* ***2000****, 56*, 3263.
[1571] Krafft, M.E. *Tetrahedron Lett.* ***1988****, 29*, 999.
[1572] Gimbert, Y.; Lesage, D.; Milet, A.; Fournier, F.; Greene, A.E.; Tabet, J.-C. *Org. Lett.* ***2003****, 5,* 4073. See Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A.E. *J. Am. Chem. Soc.* ***2001****, 123,* 5396.

concluded that the LUMO of the coordinated alkene plays a crucial role in alkene reactivity by determining the degree of back-donation in the complex.[1573]

Other carbonylation methods are available. Carbonylation occurs with conjugated ketones to give 1.4-diketones, using phenylboronic acid (see Reaction **13-12**), CO and a Rh catalyst.[1574] A noncarbonylation route treated a conjugated diene with an excess of *tert*-butyllithium, and quenching with CO_2 led to a cyclopentadienone.[1575] When quenched with CO rather than CO_2, a nonconjugated cyclopentenone was formed.[1576] Note that a carbonylation reaction with CO, a diyne, and an Ir[1577] or a Co catalyst[1578] provided similar molecules.

With any method, if the alkene contains a functional group (e.g., OH, NH_2, or $CONH_2$), the corresponding lactone (Reaction **16-63**),[1579] lactam (Reaction **16-74**), or cyclic imide may be the product.[1580] Titanium,[1581] Pd,[1582] Ru,[1583] and Rh[1584] catalysts have been used to generate lactones. Allenic alcohols are converted to butenolides with 10 atm of CO and a Ru catalyst.[1585] Larger ring conjugated lactones can also be formed by this route using the appropriate allenic alcohol.[1586] Propargylic alcohols lead to β-lactones[1587] or to butenolides with CO/H_2O and a Rh catalyst.[1588] Allenic tosyl-amides are converted to *N*-tosyl α,β-unsaturated pyrrolidinones using 20 atm of CO and a Ru catalyst.[1589] Conjugated imines are converted to similar products with CO, ethylene, and a Ru catalyst.[1590] Propargyl alcohols generate lactones when treated with a chromium pentacarbonyl carbene complex.[1591] Amines add to allenes, in the presence of CO and a Pd catalyst, to form conjugated amides.[1592]

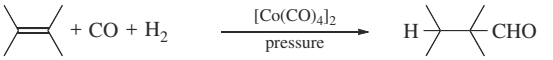
The reaction of a secondary amine, CO, a terminal alkyne, and *t*-$BuMe_2SiH$ with a Rh catalyst led to a conjugated amide bearing the silyl group of the C=C unit.[1593] Reaction of a molecule containing an amine and an alkene unit was carboxylated with CO in the presence of a Pd catalyst to give a lactam.[1594] A similar reaction with a molecule containing an amine and an alkyne also generated a lactam, in the presence of CO and

[1573] de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.,* ***2004*** *69*, 1075.
[1574] Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun.* ***2004*** 1520.
[1575] Xi, Z.; Song, Q. *J. Org. Chem.* ***2000****, 65*, 9157.
[1576] Song, Q.; Chen, J.; Jin, X.; Xi, Z. *J. Am. Chem. Soc.* ***2001****, 123*, 10419; Song, Q.; Li, Z.; Chen, J.; Wang, C.; Xi, Z. *Org. Lett.* ***2002****, 4,* 4627.
[1577] Shibata, T.; Yamashita, K.; Katayama, E.; Takagi, K. *Tetrahedron* ***2002****, 58,* 8661.
[1578] Sugihara, T.; Wakabayashi, A.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2001***, 2456.
[1579] Dong, C.; Alper, H. *J. Org. Chem.* ***2004****, 69*, 5011.
[1580] See Ohshiro, Y.; Hirao, T. *Heterocycles* ***1984****, 22*, 859; Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 147–174. See Krafft, M.E.; Wilson, L.J.; Onan, K.D. *Tetrahedron Lett.* ***1989****, 30,* 539.
[1581] Kablaoui, N.M.; Hicks, F.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997****, 119*, 4424.
[1582] El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* ***1996****, 118*, 4264. Also see, Brunner, M.; Alper, H. *J. Org. Chem.* ***1997****, 62*, 7565.
[1583] Kondo, T.; Kodoi, K.; Mitsudo, T.-a.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* ***1994***, 755.
[1584] Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Takahashi, S. *Tetrahedron Lett.* ***1998****, 39*, 5061.
[1585] Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* ***2000****, 2*, 441.
[1586] Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2001****, 42*, 5459.
[1587] Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* ***2003****, 5*, 4429.
[1588] Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2001****, 42*, 1301.
[1589] Kang, S.-K.; Kim, K.-J.; Yu, C.-M.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* ***2001****, 3,* 2851.
[1590] Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* ***2002****, 67*, 7014.
[1591] Good, G.M.; Kemp, M.I.; Kerr, W.J. *Tetahedron Lett.* ***2000****, 41,* 9323.
[1592] Grigg, R.; Monteith, M.; Sridharan, V.; Terrier, C. *Tetrahedron* ***1998****, 54*, 3885.
[1593] Matsuda, I.; Takeuchi, K.; Itoh, K. *Tetrahedron Lett.* ***1999****, 40*, 2553.
[1594] Okuro, K.; Kai, H.; Alper, H. *Tetrahedron Asymmetry* ***1997****, 8*, 2307.

a Rh catalyst.[1595] An intramolecular carbonylation reaction of a conjugated imine, with CO, ethylene and a Ru catalyst, led to a highly substituted β,γ-unsaturated lactam.[1596]

15-37 Hydroformylation

Hydro-formyl-addition



Alkenes can be hydroformylated[1597] by treatment with CO and hydrogen over a catalyst, usually a Co carbonyl (see below for a description of the mechanism) or a Rh complex,[1598] but other transition metal compounds have also been used. Cobalt catalysts are less active than the Rh type, and catalysts of other metals are generally less active.[1599] Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal alkenes > straight-chain internal alkenes > branched-chain alkenes. With terminal alkenes, for example, the aldehyde unit is formed on both the primary and secondary carbon, but proper choice of catalyst and additive leads to selectivity for the secondary[1600] or primary product.[1601] Alkylidenecyclopropane derivatives undergo hydroformylation to give aldehydes with a quaternary center.[1602]

Good yields for hydroformylation have been reported using Rh catalysts in the presence of certain other additives.[1603] Among the side reactions are the *aldol Reaction* (**16-34**), acetal formation, the *Tischenko Reaction* (**19-82**), and polymerization. In one case using a Rh catalyst, 2-octene gave nonanal, presumably via a η^3-allyl complex (Sec. 3.C).[1604] Conjugated dienes give dialdehydes when Rh catalysts are used[1605] but saturated monoaldehydes (the second double bond is reduced) with cobalt carbonyls. Both 1,4- and 1,5-dienes may give cyclic ketones.[1606]

Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.[1607] However, in the presence of a Rh catalyst, the triple bond of a conjugated

[1595] Shiba, T.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2004****, 45,* 3211.
[1596] Berger, D.; Imhof, W. *Tetrahedron* ***2000****, 56*, 2015.
[1597] See Kalck, P.; Peres, Y.; Jenck, J. *Adv. Organomet. Chem.* ***1991****, 32*, 121; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 361–389; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 621–632; Pino, P. *J. Organomet. Chem.* ***1980****, 200,* 223; Falbe, J. *Carbon Monoxide in Organic Synthesis* Springer, NY, ***1980***, pp. 3–77. See Ohshiro, Y.; Hirao, T. *Heterocycles* ***1984****, 22,* 859.
[1598] See Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1990****, 112*, 3674; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond,* Vol. 4, Wiley, NY, ***1987***, pp. 733–818, pp. 778–784.
[1599] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry,* University Science Books, Mill Valley, CA ***1987***, p. 630.
[1600] Chan, A.S.C.; Pai, C.-C.; Yang, T.-K.; Chen, S.M. *J. Chem. Soc., Chem. Commun.* ***1995***, 2031; Doyle, M.P.; Shanklin, M.S.; Zlokazov, M.V. *Synlett* ***1994***, 615.
[1601] Breit, B.; Seiche, W. *J. Am. Chem. Soc.* ***2003****, 125*, 6608.
[1602] Simaan, S.; Marek, I. *J. Am. Chem. Soc.* ***2010****, 132*, 4066.
[1603] Johnson, J.R.; Cuny, G.D.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1995****, 34*, 1760.
[1604] van der Veen, L.A.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *Angew. Chem. Int. Ed.* ***1999****, 38,* 336.
[1605] Fell, B.; Rupilius, W. *Tetrahedron Lett.* ***1969***, 2721.
[1606] See Mullen, A. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 414–439. See also, Eilbracht, P.; Hüttmann, G.; Deussen, R. *Chem. Ber.* ***1990****, 123,* 1063, and other papers in this series.
[1607] See Botteghi, C.; Salomon, C. *Tetrahedron Lett.* ***1974***, 4285. For an indirect method, see Campi, E.; Fitzmaurice, N.J.; Jackson, W.R.; Perlmutter, P.; Smallridge, A.J. *Synthesis* ***1987***, 1032.

enyne is formylated.[1608] The Rh catalyzed reaction can be regioselective.[1609] Many functional groups (e.g., OH, CHO, CO_2R,[1610] CN), can be present in the molecule, although halogens usually interfere. Stereoselective syn addition has been reported,[1611] and also stereoselective anti addition.[1612]

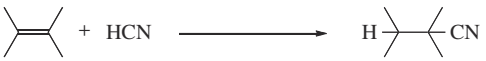
Asymmetric hydroformylation of alkenes has been accomplished with a chiral catalyst,[1613] and in the presence of chiral additives.[1614] The choice of ligand is important in such reactions.[1615] Cyclization to prolinal derivatives has been reported with allylic amines.[1616]

When dicobalt octacarbonyl $[Co(CO)_4]_2$ is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt $[HCo(CO)_3]$.[1617] Carbonylation $[RCo(CO)_3 + CO \rightarrow RCo(CO)_4]$ takes place followed by a rearrangement and a reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in Reaction **15-35**. The reducing agent in the reduction step is tetracarbonylhydrocobalt $[HCo(CO)_4]$,[1618] or, under some conditions, H_2.[1619] When $HCo(CO)_4$ was the agent used to hydroformylate styrene, the observation of CIDNP (Sec. 5.C.i) indicated that the mechanism is different, and involves free radicals.[1620] Key intermediates have been detected in the Co catalyzed hydroformylation reaction.[1621] Alcohols can be obtained by allowing the reduction to continue after all the CO is used up. It has been shown[1622] that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that $HCo(CO)_3$ is the reducing agent.

OS **VI**, 338.

15-38 Addition of HCN

Hydro-cyano-addition



Ordinary alkenes do not react with HCN, but polyhalo alkenes and alkenes of the form C=C—Z add HCN to give nitriles.[1623] The reaction is therefore a nucleophilic addition

[1608] van den Hoven, B.G.; Alper, H. *J. Org. Chem.* ***1999****, 64*, 3964.
[1609] Kuil, M.; Soltner, T.; van Leeuwen, P.W.N.M.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2006****, 128,* 11344.
[1610] See Hu, Y.; Chen, W.; Osuna, A.M.B.; Stuart, A.M.; Hope, E.G.; Xiao, J. *Chem. Commun.* ***2001***, 725.
[1611] See Haelg, P.; Consiglio, G.; Pino, P. *Helv. Chim. Acta* ***1981****, 64*, 1865.
[1612] Krauss, I.J.; Wang, C.C-Y.; Leighton, J.L. *J. Am. Chem. Soc.* ***2001****, 123*, 11514.
[1613] Ojima, I.; Hirai, K. in Morrison, J.D. *Organic Synthesis Vol. 5,* Wiley, NY, ***1985***, pp. 103–145, pp. 125–139; Breit, B.; Seiche, W. *Synthesis* ***2001***, 1; Clark, T.P.; Landis, C.R.; Freed, S.L.; Klosin, J.; Abboud, K.A. *J. Am. Chem. Soc.* ***2005****, 127,* 5040; Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* ***2006****, 128,* 7198; Watkins, A.L.; Hashiguchi, B. G.; Landis, C.R. *Org. Lett.* ***2008****, 10,* 4553.
[1614] Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 395. See Gladiali, S.; Bayón, J.C.; Claver, C. *Tetrahedron Asymmetry* ***1995****, 6*, 1453.
[1615] Klosin, J.; Landis, C.R. *Acc. Chem. Res.* ***2007****, 40*, 1251.
[1616] Anastasiou, D.; Campi, E.M.; Chaouk, H.; Jackson, W.R.; McCubbin, Q.J. *Tetrahedron Lett.* ***1992****, 33*, 2211
[1617] Mirbach, M.F. *J. Organomet. Chem.* ***1984****, 265,* 205. For the mechanism see Orchin, M. *Acc. Chem. Res.* ***1981****, 14*, 259; Versluis, L.; Ziegler, T.; Baerends, E.J.; Ravenek, W. *J. Am. Chem. Soc.* ***1989****, 111*, 2018.
[1618] Ungváry, F.; Markó, L. *Organometallics* ***1982****, 1,* 1120.
[1619] See Kovács, I.; Ungváry, F.; Markó, L. *Organometallics* ***1986****, 5,* 209.
[1620] Bockman, T.M.; Garst, J.F.; King, R.B.; Markó, L.; Ungváry, F. *J. Organomet. Chem.* ***1985****, 279*, 165.
[1621] Godard, C.; Duckett, S.B.; Polas, S.; Tooze, R.; Whitwood, A.C. *J. Am. Chem. Soc.* ***2005****, 127,* 4994.
[1622] Aldridge, C.L.; Jonassen, H.B. *J. Am. Chem. Soc.* ***1963****, 85,* 886.
[1623] See Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Nagata, W.; Yoshioka, M. *Org. React.* ***1977****, 25,* 255; Brown, E.S. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 655–672.

and is base catalyzed. Hydrogen cyanide can be added to ordinary alkenes in the presence of dicobalt octacarbonyl[1624] or certain other transition metal compounds.[1625] When Z is COR or, more especially, CHO, 1,2-addition (Reaction **16-53**) is an important competing reaction and may be the only reaction. An acid-catalyzed hydrocyanation is also known.[1626] Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH_4Cl, and HCl or by Ni or Pd compounds.[1627] The HCN can be generated *in situ* from acetone cyanohydrin (see Reaction **16-52**), avoiding the use of the poisonous HCN.[1628] Alkenes react with HCN via this procedure to give a nitrile in the presence of a Ni complex.[1629]

One or 2 molar equivalents of HCN can be added to a triple bond, since the initial product is a *Michael-type* substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides (e.g., Et_2AlCN), or mixtures of HCN and trialkylalanes (R_3Al) are especially good reagents for conjugate addition of HCN[1630] to α,β-unsaturated ketones and α,β-unsaturated acyl halides. An indirect method for the addition of HCN to ordinary alkenes uses an isocyanide (RNC) and *Schwartz's reagent* (see Reaction **15-17**); this method gives anti-Markovnikov addition.[1631] *tert*-Butyl isocyanide and $TiCl_4$ have been used to add HCN to C=C—Z alkenes.[1632] Pretreatment with NaI/Me_3SiCl followed by CuCN converts alkynes to vinyl nitriles.[1633]

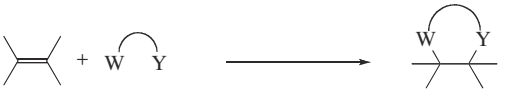
When an alkene is treated with Me_3SiCN and $AgClO_4$, followed by aq $NaHCO_3$, the product is the isonitrile (RNC) formed with *Markovnikov* selectivity.[1634] Enantioselective cyanation using TMSCN and HCN, and a Gd catalyst, leads to β-cyano amides.[1635]

OS **I**, 451; **II**, 498; **III**, 615; **IV**, 392, 393, 804; **V**, 239, 572; **VI**, 14.

For addition of ArH, see Reaction **11-12** (Friedel–Crafts alkylation).

15.C.iii. Reactions in Which Hydrogen Adds to Neither Side

Some of these reactions are *cycloadditions* (Reactions **15-50**, **15-62**, **15-54**, and **15-57–15-66**). In such cases, addition to the multiple bond closes a ring:

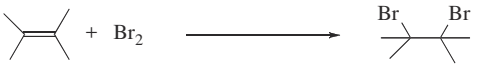


[1624] Arthur, Jr., P.; England, D.C.; Pratt, B.C.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954****, 76*, 5364.
[1625] See Brown, E.S. in Wender, P.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 658–667; Tolman, C.A.; McKinney, R.J.; Seidel, W.C.; Druliner, J.D.; Stevens, W.R. *Adv. Catal.* ***1985****, 33,* 1. For studies of the mechanism see McKinney, R.J.; Roe, D.C. *J. Am. Chem. Soc.* ***1986****, 108*, 5167; Funabiki, T.; Tatsami, K.; Yoshida, S. *J. Organomet. Chem.* ***1990****, 384*, 199. See also, Bini, L.; Müller, C.; Vogt, D. *Chem. Commun.* ***2010***, 8325.
[1626] Yanagisawa, A.; Nezu, T.; Mohri, S.-i. *Org. Lett.* ***2009****, 11*, 5286.
[1627] Jackson, W.R.; Lovel, C.G. *Aust. J. Chem.* ***1983****, 36*, 1975.
[1628] Jackson, W.R.; Perlmutter, P. *Chem. Br.* ***1986***, 338.
[1629] Yan, M.; Xu, Q.-Y.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2000****, 11*, 845.
[1630] See Nagata, W.; Yoshioka, M. *Org. React.* ***1977****, 25*, 255.
[1631] Buchwald, S.L.; LeMaire, S.J. *Tetrahedron Lett.* ***1987****, 28,* 295.
[1632] Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* ***1982****, 104,* 6449.
[1633] Luo, F.-T.; Ko, S.-L.; Chao, D.-Y. *Tetrahedron Lett.* ***1997****, 38*, 8061.
[1634] Kitano, Y.; Chiba, K.; Tada, M. *Synlett* ***1999***, 288.
[1635] Mita, T.; Kazuki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005****, 127,* 514.

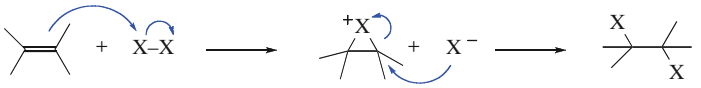
A. Halogen on One or Both Sides

15-39 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)

Dihalo-addition



Most double bonds are easily halogenated[1636] with bromine, chlorine, or inter-halogen compounds.[1637] Substitution can compete with addition in some cases.[1638] Iodination has also been accomplished, but the reaction is slower.[1639] Under free radical conditions, iodination proceeds more easily.[1640] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the alkene.



110

The mechanism is usually electrophilic (see Sec. 15.A.i), involving formation of an halonium ion (Reaction **110**),[1641] followed by nucleophilic ring opening to give the *vic*-dihalide. Nucleophilic attack occurs with selectivity for the less substituted carbon. When free radical initiators (or UV light) are present, addition can occur by a free radical mechanism.[1642] Once $Br^{\bullet}$ or $Cl^{\bullet}$ radicals are formed, however, substitution may compete (Reactions **14-1** and **14-3**). This is especially important when the alkene has allylic or benzylic hydrogen atoms. Under free radical conditions (UV light) bromine or chlorine adds to a benzene substituent to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see Sec. 4.K.ii).[1643]

Under ordinary conditions fluorine itself is too reactive to give simple addition, and mixtures are obtained.[1644] However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (−78 °C), usually by diluting the F_2 gas with Ar or N_2.[1645] Addition of fluorine has also been accomplished with other reagents (e.g., *p*-Tol-IF_2/$Et_3N{\cdot}5$ HF),[1646] and a mixture of PbO_2 and SF_4.[1647] The Au catalyzed reaction of Et_3N—HF with alkynes gives vinyl fluorides.[1648]

[1636] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 629–632.
[1637] de la Mare, P.B.D. *Electrophilic Halogenation* Cambridge University Press, Cambridge, ***1976***; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 422–431.
[1638] McMillen, D.W.; Grutzner, J.B. *J. Org. Chem.* ***1994****, 59*, 4516.
[1639] Zanger, M.; Rabinowitz, J.L. *J. Org. Chem.* ***1975****, 40*, 248.
[1640] Ayres, R.L.; Michejda, C.J.; Rack, E.P. *J. Am. Chem. Soc.* ***1971****, 93,* 1389.
[1641] See Lenoir, D.; Chiappe, C. *Chem. Eur. J.* ***2003****, 9*, 1037. For a theoretical study of these intermediates, see Okazaki, T.; Laali, K.K. *J. Org. Chem.* ***2005****, 70,* 9139. Also see Zabalov, M.V.; Karlov, S.S.; Lemenovskii, D.A.; Zaitseva, G.S. *J. Org. Chem.* ***2005****, 70,* 9175.
[1642] See Dessau, R.M. *J. Am. Chem. Soc.* ***1979****, 101*, 1344.
[1643] See Cais, M. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 993.
[1644] See Fuller, G.; Stacey, F.W.; Tatlow, J.C.; Thomas, C.R. *Tetrahedron* ***1962****, 18,* 123.
[1645] Rozen, S.; Brand, M. *J. Org. Chem.* ***1986****, 51,* 3607.
[1646] Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* ***1998***, 495.
[1647] Bissell, E.R.; Fields, D.B. *J. Org. Chem.* ***1964****, 29,* 1591.
[1648] Akana, J.A.; Bhattacharyya, K.X.; Müller, P.; Sadighi, J.P. *J. Am. Chem. Soc.* ***2007****, 129,* 7736.

The reaction with bromine is very rapid and is easily carried out at room temperature,[1649] although the reaction is reversible under some conditions.[1650] In the case of bromine, an alkene•Br_2 complex has been detected in at least one case.[1651] Bromine is often used as a qualitative or quantitative test for unsaturation[1652] because the vast majority of double bonds can be successfully brominated. Even when functions (aldehyde, ketone, amine, etc.) are present in the molecule, they do not interfere, since the reaction with double bonds is faster. Bromination has been carried out in an ionic liquid.[1653]

Several reagents other than chlorine gas add Cl_2 to double bonds, among them $Me_3SiCl^-MnO_2$,[1654] $BnNEt_3MnO_4/Me_3SiCl$,[1655] and $KMnO_4$–oxalyl chloride.[1656] A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide ($C_5H_5NH^+ Br_3^-$).[1657] Potassium bromide with ceric ammonium nitrate, in water/dichloromethane, gives the dibromide.[1658] A combination of KBr and Selectfluor also give the dibromide.[1659] A combination of $CuBr_2$ in aq THF and a chiral ligand led to the dibromide with good enantioselectivity.[1660] Either Br_2 or Cl_2 can also be added using $CuBr_2$ or $CuCl_2$ in the presence of acetonitrile, methanol, or triphenylphosphine.[1661] Alkenes are brominated using KBr and diacetoxyiodobenzene.[1662] Note that theoretical and experimental studies have shown that in nonpolar solvents the bromination of acetylene via a covalent tribromide adduct is strongly favored over the textbook mechanism via a bridged bromonium ion.

Mixed halogenations have also been achieved, and the order of activity for some of the reagents is $BrCl > ICl$[1663] $> Br_2 > IBr > I_2$.[1664] Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,[1665] as has tetrabutylammonium dichlorobromate (Bu_4NBrCl_2).[1666] Iodochlorination has been achieved with $KICl_2$,[1667] $CuCl_2$, and either I_2, HI, or CdI_2; iodofluorination[1668] with mixtures of AgF and I_2;[1669] and mixtures of *N*-bromo amides in anhydrous HF give bromofluorination.[1670] Bromo-, iodo-, and

[1649] See Bellucci, G.; Chiappe, C. *J. Org. Chem.* ***1993****, 58*, 7120.
[1650] Zheng, C.Y.; Slebocka-Tilk, H.; Nagorski, R.W.; Alvarado, L.; Brown, R.S. *J. Org. Chem.* ***1993****, 58*, 2122.
[1651] Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* ***1995****, 117*, 12001.
[1652] See Kuchar, E.J. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 273–280.
[1653] Chiappe, C.; Capraro, D.; Conte, V.; Picraccini, D. *Org. Lett.* ***2001****, 3*, 1061.
[1654] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1989****, 108,* 360.
[1655] Markó, I.E.; Richardson, P.R.; Bailey, M.; Maguire, A.R.; Coughlan, N. *Tetrahedron Lett.* ***1997****, 38*, 2339.
[1656] Markó, I.E.; Richardson, P.F. *Tetrahedron Lett.* ***1991****, 32,* 1831.
[1657] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, ***1967***, pp. 967–970. For a discussion of the mechanism, see Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* ***1986****, 51,* 4224.
[1658] Nair, V.; Panicker, S.B.; Augstine, A.; George, T.G.; Thomas, S.; Vairamani, M. *Tetrahedron* ***2001****, 57*, 7417.
[1659] Ye, C.; Shreeve, J.M. *J. Org. Chem.* ***2004****, 69*, 8561.
[1660] El-Quisairi, A.K.; Qaseer, H.A.; Katsigras, G.; Lorenzi, P.; Tribedi, U.; Tracz, S.; Hartman, A.; Miller, J.A.; Henry, P.M. *Org. Lett.* ***2003****, 5*, 439.
[1661] Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1,* ***1977***, 676.
[1662] Das, B.; Srinivas, Y.; Sudhakar, C.; Damodar, K.; Narender, R. *Synth. Commun.* ***2009****, 39,* 220.
[1663] See McCleland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164.
[1664] White, E.P.; Robertson, P.W. *J. Chem. Soc.* ***1939***, 1509.
[1665] Buckles, R.E.; Forrester, J.L.; Burham, R.L.; McGee, T.W. *J. Org. Chem.* ***1960****, 25,* 24.
[1666] Negoro, T.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* ***1986****, 59*, 3519.
[1667] Zefirov, N.S.; Sereda, G.A.; Sosounk, S.E.; Zyk, N.V.; Likhomanova, T.I. *Synthesis* ***1995***, 1359.
[1668] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974****, 21*, 125, see pp. 137–157; Boguslavskaya. L.S. *Russ. Chem. Rev.* ***1984****, 53*, 1178.
[1669] Evans, R.D.; Schauble, J.H. *Synthesis* ***1987***, 551; Kuroboshi, M.; Hiyama, T. *Synlett* ***1991***, 185.
[1670] Pattison, F.L.M.; Peters, D.A.V.; Dean, F.H. *Can. J. Chem.* ***1965****, 43,* 1689. For other methods, see Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1881.

chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2, I_2, or an *N*-halo amide in polyhydrogen fluoride–pyridine;[1671] while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodo(I) tetrafluoroborate [$I(Py)_2BF_4$] and Br^-, Cl^-, or F^-, respectively.[1672] This reaction, which is also successful for triple bonds,[1673] can be extended to addition of I and other nucleophiles (e.g., NCO, OH, OAc, and NO_2).[1673]

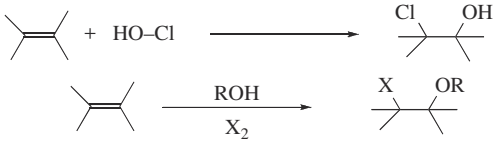
Conjugated systems give both 1,2- and 1,4-addition.[1644] Triple bonds add bromine, although generally more slowly than double bonds (see Sec. 15.B.i). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Addition of 2 molar equivalents of bromine to triple bonds gives tetrabromo products. There is evidence that the addition of the first molar equivalent of bromine to a triple bond may take place by a nucleophilic mechanism.[1674] Molecular diiodine on Al_2O_3 adds to triple bonds to give good yields of 1,2-diiodoalkenes.[1675] Interestingly, 1,1-diiodo alkenes are prepared from an alkynyltin compound, via initial treatment with $Cp_2Zr(H)Cl$, and then 2.15 equiv of iodine.[1676] A mixture of $NaBO_3$ and NaBr adds two bromine atoms across a triple bond.[1677] With allenes it is easy to stop the reaction after only 1 equiv has added, to give X—C—CX=C.[1678] Addition of halogen to ketenes gives α-halo acyl halides, but the yields are not good.

OS **I**, 205, 521; **II**, 171, 177, 270, 408; **III**, 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV**, 130, 195, 748, 851, 969; **V**, 136, 370, 403, 467; **VI**, 210, 422, 675, 862, 954; **IX**, 117; **76**, 159.

15-40 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)

Hydroxy-chloro-addition, and so on.[1679]

Alkoxy-chloro-addition, and so on



Hypohalous acids (HOCl, HOBr, and HOI) react with alkenes[1680] to produce halohydrins.[1681] Both HOBr and HOCl can be generated *in situ* by the reaction between water and Br_2 or Cl_2, respectively. The compound HOI, generated from I_2 and H_2O, also adds to

[1671] Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979****, 44*, 3872. See Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* ***1989****, 54,* 4294; Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* ***1990****, 31*, 3167.

[1672] Barluenga, J.; González, J.M.; Campos, P.J.; Asensio, G. *Angew. Chem. Int. Ed.* ***1985****, 24*, 319.

[1673] Barluenga, J.; Rodríguez, M.A.; González, J.M.; Campos, P.J.; Asensio, G. *Tetrahedron Lett.* ***1986****, 27*, 3303.

[1674] Sinn, H.; Hopperdietzel, S.; Sauermann, D. *Monatsh. Chem.* ***1965****, 96,* 1036.

[1675] Hondrogiannis, G.; Lee, L.C.; Kabalka, G.W.; Pagni, R.M. *Tetrahedron Lett.* ***1989****, 30*, 2069.

[1676] Dabdoub, M.J.; Dabdoub, V.B.; Baroni, A.C.M. *J. Am. Chem. Soc.* ***2001****, 123,* 9694.

[1677] Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998****, 28*, 3807; Kabalka, G.W.; Yang, K.; Reddy, N.K.; Narayana, A. *Synth. Commun.* ***1998****, 28*, 925.

[1678] See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Acaademic Press, NY, ***1982***, pp. 466–483.

[1679] Addends are listed in order of priority in the Cahn–Ingold–Prelog system (Sec. 4.E.i).

[1680] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 638–642.

[1681] See Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1972****, 41*, 740.

double bonds, if the reaction is carried out in tetramethylene sulfone–$CHCl_3$[1682] or if an oxidizing agent (e.g., HIO_3) is present.[1683] Iodine and cerium sulfate in aq acetonitrile generates iodohydrins,[1684] as do iodine and ammonium acetate in acetic acid,[1685] or $NaIO_4$ with sodium bisulfite.[1686]

The HOBr can also be conveniently added by the use of a reagent consisting of an *N*-bromo amide (e.g., NBS or *N*-bromoacetamide) and a small amount of water in a solvent (e.g., DMSO or dioxane).[1687] *N*-Iodosuccinimide in aq dimethoxyethane leads to the iodohydrin.[1688] An especially powerful reagent for HOCl addition is *tert*-butyl hydroperoxide (or di-*tert*-butyl peroxide) along with $TiCl_4$.[1689] Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T ($TsNCl^-\ Na^+$)[1690] in acetone–water.[1691] The compound HOI can be added by treatment of alkenes with periodic acid and $NaHSO_3$.[1692] There are Se catalyzed iodohydrin forming reactions.[1693] The reaction of an alkene with polymeric $(SnO)_n$, and then HCl with $Me_3SiOOSiMe_3$, leads to the chlorohydrin.[1694] Hypervalent iodine compounds react with an alkene and iodine in aqueous media to give the iodohydrin.[1695] Halohydrins are produced in ionic liquids.[1696] *N*-Bromo and *N*-iodosaccharin have been used to prepare the corresponding halohydrins.[1697]

The compound HOF has also been added, but this reagent is difficult to prepare in a pure state and *explosions have occurred*.[1698]

The mechanism of HOX addition is electrophilic, with initial attack by the alkene on the positive halogen end of the HOX dipole. Following *Markovnikov's rule*, the positive halogen goes to the side of the double bond that has more hydrogen atoms (forming a more stable carbocation). This carbocation (or bromonium or iodonium ion in the absence of an aqueous solvent) reacts with ^-OH or H_2O to give the product. If the substrate is treated with Br_2 or Cl_2 (or another source of positive halogen, e.g., NBS) in an alcohol or a carboxylic acid solvent, it is possible to obtain, directly C—C—C—OR or X—C—C—OCOR, respectively (see also, Reaction **15-48**).[1699] Even the weak nucleophile $CF_3SO_2O^-$ can participate in the second step. The addition of Cl_2 or Br_2 to alkenes in the presence of this ion resulted in the formation of some β-haloalkyl triflates.[1700] There is evidence that the mechanism with Cl_2 and H_2O is

[1682] Cambie, R.C.; Noall, W.I.; Potter, G.J.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1,* ***1977***, 266.
[1683] See Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* ***1983****, 39*, 1765.
[1684] Horiuchi, C.A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T.T. *J. Chem. Res. (S)* ***1997***, 60.
[1685] Myint, Y.Y.; Pasha, M.A. *Synth. Commun.* ***2004***, *34*, 4477.
[1686] Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* ***1994****, 59*, 5550.
[1687] SeeDalton, D.R.; Dutta, V.P. *J. Chem. Soc. B* ***1971***, 85; Sisti, A.J. *J. Org. Chem.* ***1970****, 35,* 2670.
[1688] Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetahedron Lett.* ***2000****, 41*, 193.
[1689] Klunder, J.M.; Caron M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.* ***1985****, 50*, 912.
[1690] See Bremner, D.H. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 9–59; Campbell, M.M.; Johnson, G. *Chem. Rev.* ***1978****, 78,* 65.
[1691] Damin, B.; Garapon, J.; Sillion, B. *Synthesis* ***1981***, 362.
[1692] Ohta, M.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* ***1990***, 733.
[1693] Carrera, I.; Brovetto, M.C.; Seoane, G.A. *Tetrahedron Lett.* ***2006****, 47,* 7849.
[1694] Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000****, 122*, 1245.
[1695] DeCorso, A.R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* ***2001****, 42*, 7245.
[1696] Yadav, J.S.; Reddy, B.V.S.; Baishya, G.; Harshavardhan, S.J.; Chary, Ch.J.; Gupta, M.K. *Tetrahedron Lett.* ***2005****, 46*, 3569.
[1697] Urankar, D.; Rutar, I.; Modec, B.; Dolenc, D. *Eur. J. Org. Chem.* ***2005***, 2349.
[1698] Migliorese, K.G.; Appelman, E.H.; Tsangaris, M.N. *J. Org. Chem.* ***1979****, 44,* 1711.
[1699] Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 642–643.
[1700] Zefirov, N.S.; Koz'min, A.S. *Acc. Chem. Res.* ***1985****, 18,* 154; *Sov. Sci. Rev. Sect. B* ***1985****, 7,* 297.

different from that with HOCl.[1701] Both HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds (—CX_2—CO—).

Alcohols and halogens react with alkenes to form halo ethers. When a homoallylic alcohol is treated with bromine, cyclization occurs to give a 3-bromotetrahydrofuran derivative.[1702] *tert*-Butyl hypochlorite (Me_3COCl), hypobromite, and hypoiodite[1703] add to double bonds to give halogenated *tert*-butyl ethers (X—C—C—$OCMe_3$). This is a convenient method for the preparation of tertiary ethers. Iodine and ethanol convert some alkenes to iodo-ethers.[1704] Iodine, alcohol, and a $Ce(OTf)_2$ catalyst also generates the iodo-ether.[1705] When Me_3COCl or Me_3COBr is added to alkenes in the presence of excess ROH, the ether X—C—C—OR is produced.[1706] Vinylic ethers give β-halo acetals.[1707] Chlorine acetate [solutions of which are prepared by treating Cl_2 with $Hg(OAc)_2$ in an appropriate solvent] adds to alkenes to give acetoxy chlorides.[1708] Acetoxy fluorides have been obtained by treatment of alkenes with CH_3COOF.[1709]

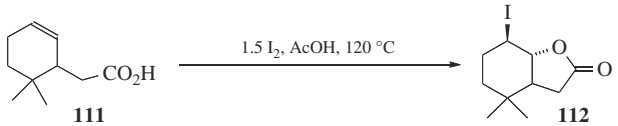
For a method of iodoacetyl addition, see Reaction **15-48**.

OS **I**, 158; **IV**, 130, 157; **VI**, 184, 361, 560; **VII**, 164; **VIII**, 5, 9.

15-41 Halolactonization and Halolactamization

Halo-alkoxylation

Halo esters can be formed by addition of halogen atoms and ester groups to an alkene. Alkene carboxylic acids give a tandem reaction of formation of a halonium ion followed by intramolecular displacement of the carboxylic group to give a halo lactone. This tandem addition of X and OCOR is called *halolactonization*.[1710]



111 **112**

The most common version of this reaction is known as *iodolactonization*,[1711] and a typical example is the conversion of **111** to **112**.[1712] Bromo lactones and, to a lesser extent, chloro lactones have also been prepared. In general, addition of the halogen to an alkenyl acid, as shown, leads to the halo-lactone. Other reagents include $I^+(collidine)_2PF_6^-$,[1713] KI/sodium

[1701] Buss, E.; Rockstuhl, A.; Schnurpfeil, D. *J. Prakt. Chem.* ***1982****, 324*, 197.

[1702] Chirskaya, M.V.; Vasil'ev, A.A.; Sergovskaya, N.L.; Shovshinev, S.V.; Sviridov, S.I. *Tetrahedron Lett.* ***2004****, 45*, 8811.

[1703] Glover, S.A.; Goosen, A. *Tetrahedron Lett.* ***1980****, 21,* 2005.

[1704] Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***1998***, 1584. See Horiuchi, C.A.; Hosokawa, H.; Kanamori, M.; Muramatsu, Y.; Ochiai, K.; Takahashi, E. *Chem. Lett.* ***1995***, 13.

[1705] Iranpoor, N.; Shekarriz, M. *Tetahedron* ***2000****, 56*, 5209.

[1706] Bresson, A.; Dauphin, G.; Geneste, J.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* ***1970***, 2432; ***1971***, 1080.

[1707] Weissermel, K.; Lederer, M. *Chem. Ber.* ***1963****, 96*, 77.

[1708] Wilson, M.A.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 2,* ***1976***, 141. See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 643–644.

[1709] Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* ***1985****, 50*, 4753.

[1710] See Cardillo, G.; Orena, M. *Tetrahedron* ***1990****, 46*, 3321; Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* ***1979****, 8*, 171. For a list of reagents that accomplish this, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1870–1876. Also see Bartlett, P.A. in Morrison, J.D. *Organic Synthesis* Vol. 3, Wiley, NY, ***1984***, pp. 411–454, 416–425.

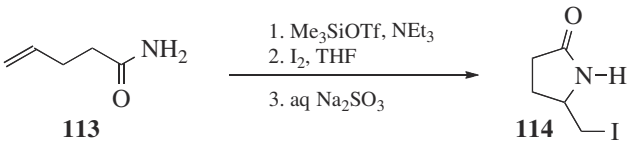
[1711] Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* ***1971****, 93*, 1491.

[1712] Yaguchi, Y.; Akiba, M.; Harada, M.; Kato, T. *Heterocycles* ***1996****, 43*, 601.

[1713] Homsi, F.; Rousseau, G. *J. Org. Chem.* ***1998****, 63*, 5255.

persulfate.[1714] The Tl[1715] and Y[1716] reagents, along with the halogen, have also been used. An enantioselective 5-endo-halolactonization procedure has been reported using systems, such as iodobis(collidine) hexafluorophosphate or $AgSbF_6$, followed by iodine.[1717] When done in the presence of a chiral Ti reagent, I_2, and CuO, lactones are formed with good enantioselectivity.[1718] Iodine monochloride (ICl) has been used, with formation of a quaternary center at the oxygen-bearing carbon of the lactone.[1719] Organocatalysts have also been used to mediate asymmetric halolactonization reactions.[1720] Enantioselective iodolactonization occurs with pentenoic acid derivatives in the presence of a chiral Co(salen) complex.[1721]

In the case of γ,δ-unsaturated acids, five-membered rings (γ-lactones) are predominantly formed (as shown above; note that *Markovnikov's rule* is followed), but six-membered and even four-membered lactones have also been made by this procedure. There is a *gem-dimethyl effect* that favors formation of 7–11 membered ring lactones by this procedure.[1722]



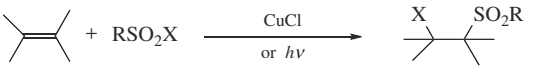
113 **114**

Formation of halo-lactams (Reaction **15-43**) by a procedure similar to halolactonization is difficult, but the problems have been overcome. Formation of a triflate from **113** followed by treatment with iodine leads to the iodolactam (**114**).[1723] A related cyclization of *N*-sulfonyl-amino alkenes and NBS gave the bromo-lactam,[1724] and a dichloro-*N,N*-bis (allylamide) was converted to a dichloro-lactam with $FeCl_2$.[1725] Note that lactone formation is possible from unsaturated amides

OS IX, 516

15-42 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

Alkylsulfonyl-chloro-addition, and so on[1726]



[1714] Royer, A.C.; Mebane, R.C.; Swafford, A.M. *Synlett* ***1993***, 899.
[1715] See Cambie, R.C.; Rutledge, P.S.; Somerville, R.F.; Woodgate, P.D. *Synthesis* ***1988***, 1009, and references cited therein.
[1716] Genovese, S.; Epifano, F.; Pelucchini, C.; Procopio, A.; Curini, M. *Tetrahedron Lett.* ***2010***, *51*, 5992.
[1717] Garnier, J.M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* ***2007***, 3281.
[1718] Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* ***1995***, *36*, 1479.
[1719] Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* ***2002***, *4*, 297.
[1720] Whitehead, D.C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* ***2010***, *132*, 3298; Zhou, L.; Tan, C.K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* ***2010***, *132*, 15474; Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem. Int. Ed.* ***2010***, *49*, 9174.
[1721] Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* ***2009***, 2291.
[1722] Simonot, B.; Rousseau, G. *Tetrahedron Lett.* ***1993***, *34*, 4527.
[1723] Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.* ***1985***, *26*, 1803.
[1724] Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* ***1984***, *25*, 1063.
[1725] Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* ***1984***, *14*, 1027.
[1726] When a general group (e.g., halo) is used, its priority is that of the lowest member of its group (see Ref. 1680). Thus the general name for this transformation is halo-alkylsulfonyl addition because "halo" has the same priority as "fluoro", its lowest member.

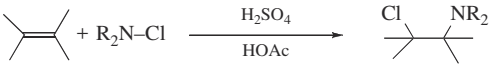
Sulfonyl halides add to double bonds to give β-halo sulfones, in the presence of free radical initiators or UV light. A particularly good catalyst is cuprous chloride.[1727] In the presence of TsCl, AIBN and a Ru catalyst, β-chloro sulfones are generated from alkenes.[1728] A combination of the anion $ArSO_2Na$, NaI, and ceric ammonium nitrate converts alkenes to vinyl sulfones.[1729] Triple bonds behave similarly, to give β-halo-α,β-unsaturated sulfones.[1730] In a similar reaction, sulfenyl chlorides, (RSCl) give β-halo thioethers.[1731] The latter may be free radical or electrophilic additions, depending on conditions. The addition of MeS and Cl has also been accomplished by treating the alkene with Me_3SiCl and Me_2SO.[1732] The use of Me_3SiBr and Me_2SO does not give this result; dibromides (Reaction **15-39**) are formed instead.

β-Iodothiocyanates can be prepared from alkenes by treatment with I_2 and isothiocyanatotributylstannane (Bu_3SnNCS).[1733] Bromothiocyanation can be accomplished with Br_2 and thallium(I) thiocyanate.[1734] Lead(II) thiocyanate reacts with terminal alkynes in the presence of $PhICl_2$ to give the bis(thiocyanato) alkene [ArC(SCN)—CHSCN].[1735] Such compounds were also prepared from alkenes using KSCN and $FeCl_3$[1736]or iodine thiocyanate.[1737] β-Halo disulfides, formed by addition of arenethiosulfenyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.[1738]

OS **VIII**, 212. See also, OS **VII**, 251.

15-43 Addition of Halogen and a Nitrogen Group (Addition of Halogen, Nitrogen)

Dialkylamino-chloro-addition



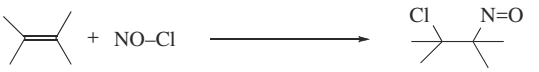
The groups R_2N and Cl can be added directly to alkenes, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-*N*-chloroamines and acids.[1739] *N*-Halo amides (RCONHX) add RCONH and X to double bonds under the influence of UV light or chromous chloride.[1740] *N*-Bromoamides add to alkenes in the presence of a transition metal

[1727] Sinnreich, J.; Asscher, M. *J. Chem. Soc. Perkin Trans. 1,* ***1972***, 1543.
[1728] Quebatte, L.; Thommes, K.; Severin, K. *J. Am. Chem. Soc.* ***2006****, 128,* 7440.
[1729] Nair, V.; Augustine, A.; George, T.G.; Nair, L.G. *Tetrahedron Lett.* ***2001****, 42,* 6763.
[1730] Amiel, Y. *J. Org. Chem.* ***1974****, 39*, 3867; Okuyama, T.; Izawa, K.; Fueno, T. *J. Org. Chem.* ***1974****, 39,* 351.
[1731] See Rasteikiene, L.; Greiciute, D.; Lin'kova, M.G.; Knunyants, I.L. *Russ. Chem. Rev.* ***1977****, 46,* 548; Kühle, E. *Synthesis* ***1971***, 563.
[1732] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1987***, 238. See also, Liu, H.; Nyangulu, J.M. *Tetrahedron Lett.* ***1988****, 29*, 5467.
[1733] Woodgate, P.D.; Janssen, S.J.; Rutledge, P.S.; Woodgate, S.D.; Cambie, R.C. *Synthesis* ***1984***, 1017, and references cited therein. See also, Watanabe, N.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1983****, 56*, 2458.
[1734] Cambie, R.C.; Larsen, D.S.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1,* ***1981***, 58.
[1735] Prakash, O.; Sharma, V.; Batra, H.; Moriarty, R.M. *Tetrahedron Lett.* ***2001****, 42*, 553.
[1736] Yadav, J.S.; Reddy, B.V.S.; Gupta, M.K. *Synthesis* ***2004***, 1983.
[1737] For a discsssion of substituent effects, see Brammer, C.N.; Nelson, D.J.; Li, R. *Tetrahedron Lett.* ***2007****, 48,* 3237.
[1738] Fujisawa, T.; Kobori, T. *Chem. Lett.* ***1972***, 935; Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* ***1988****, 29,* 4177.
[1739] See Mirskova, A.N.; Drozdova, T.I.; Levkovskaya, G.G.; Voronkov, M.G. *Russ. Chem. Rev.* ***1989****, 58*, 250; Neale, R.S. *Synthesis* ***1971***, 1.
[1740] Tuaillon, J.; Couture, Y.; Lessard, J. *Can. J. Chem.* ***1987****, 65,* 2194, and other papers in this series. For a review, see Labeish, N.N.; Petrov, A.A. *Russ. Chem. Rev.* ***1989****, 58*, 1048.

catalyst (e.g., $SnCl_4$) to give the corresponding β-bromo amide.[1741] The reaction of $TsNCl_2$ and a $ZnCl_2$ catalyst gave the chloro tosylamine.[1742] Aminochlorination of alkenes occurs in a CO_2 promoted reaction with Chloramine-T ($TolSO_2N^-$—Cl).[1743] These are free radical additions, with initial attack by the $R_2NH^{\bullet+}$ radical ion.[1744] Amines add to allenes in the presence of a Pd catalyst.[1745] A mixture of *N*-(2-nosyl)NCl_2 and sodium *N*-(2-nosyl)NH^- with a CuOTf catalyst reacted with conjugated esters to give the *vicinal* (*E*)-3-chloro-2-amino ester.[1746] A variation of this latter reaction was done in an ionic liquid.[1747]

15-44 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)

Nitroso-chloro-addition



There are three possible products when NOCl is added to alkenes, a β-halo nitroso compound, an oxime, or a β-halo nitro compound.[1748] The initial product is always the β-halo nitroso compound,[1749] but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime, H—C—N=O → C=N—OH. With some alkenes, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.[1750] Many functional groups may be present without interference (e.g., CO_2H, CO_2R, CN, OR). The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, although syn addition has been reported in some cases.[1751] *Markovnikov's rule* is followed, the positive NO going to the carbon that has more hydrogen atoms.

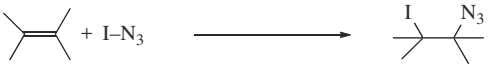
Nitryl chloride (NO_2Cl) also adds to alkenes, to give β-halo nitro compounds, but this is a free radical process. The NO_2 goes to the less-substituted carbon.[1752] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro alkenes.[1753] The compound FNO_2 can be added to alkenes[1754] by treatment with HF in HNO_3[1755] or by addition of the alkene to a solution of nitronium tetrafluoroborate ($NO_2^+ BF_4^-$; see Reaction **11-2**) in 70% polyhydrogen fluoride–pyridine solution[1756] (see also, Reaction **15-37**).

OS **IV**, 711; **V**, 266, 863.

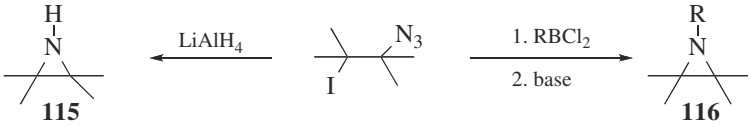
[1741] Yeung, Y.-Y.; Gao, X.; Corey, E.J. *J. Am. Chem. Soc.* ***2006****, 128,* 9644.
[1742] Wei, H.-X.; Ki, S.H.; Li, G. *Tetrahedron* ***2001****, 57*, 3869.
[1743] Minakata, S.; Yoneda, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2006****, 8,* 967.
[1744] See Chow, Y.L.; Danen, W.C.; Nelson, S.F.; Rosenblatt, D.H. *Chem. Rev.* ***1978****, 78,* 243.
[1745] Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* ***1995****, 36*, 3857.
[1746] Li, G.; Wei, H.-X.; Kim, S.H. *Tetrahedron* ***2001****, 57*, 8407.
[1747] Xu, X.; Kotti, S.R.S.S.; Liu, J.; Cannon, J.F.; Headley, A.D.; Li, G. *Org. Lett.* ***2004****, 6*, 4881.
[1748] See Kadzyauskas, P.P.; Zefirov, N.S. *Russ. Chem. Rev.* ***1968****, 37*, 543.
[1749] See Gowenlock, B.G.; Richter-Addo, G.B. *Chem. Rev.* ***2004****, 104*, 3315.
[1750] Shvekhgeimer, G.A.; Smirnyagin, V.A.; Sadykov, R.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1968****, 37*, 351.
[1751] See Meinwald, J.; Meinwald, Y.C.; Baker, III, T.N. *J. Am. Chem. Soc.* ***1964****, 86*, 4074.
[1752] Shechter, H. *Rec. Chem. Prog.,* ***1964****, 25*, 55–76.
[1753] Schlubach, H.H.; Braun, A. *Liebigs Ann. Chem.* ***1959****, 627,* 28.
[1754] Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974****, 21,* 125–406, see pp. 236–243.
[1755] Knunyants, I.L.; German, L.S.; Rozhkov, I.N. *Bull Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1794.
[1756] Olah, G.A.; Nojima, M. *Synthesis* ***1973***, 785.

15-45 Addition of XN_3 (Addition of Halogen, Nitrogen)

Azido-iodo-addition



The addition of iodine azide to double bonds gives β-iodo azides.[1757] The reagent can be prepared *in situ* from KI—NaN_3 in the presence of Oxone–wet alumina.[1758] The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion intermediate.[1759] The reaction has been performed on many double-bond compounds, including allenes[1760] and α,β-unsaturated ketones. Similar reactions can be performed with BrN_3[1761] and ClN_3. 1,4-Addition has been found with acyclic conjugated dienes.[1762] In the case of BrN_3, both electrophilic and free radical mechanisms are important,[1763] while with ClN_3 the additions are chiefly free radical.[1764] Iodine monoazide (IN_3) also adds to triple bonds to give β-iodo-α,β-unsaturated azides.[1765]

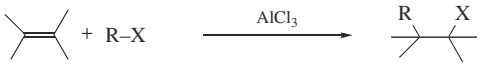


β-Iodo azides can be reduced to aziridines (**115**) with $LiAlH_4$[1766] or converted to *N*-alkyl- or *N*-arylaziridines (**116**) by treatment with an alkyl- or aryldichloroborane followed by a base.[1767] In both cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (Reaction **10-31**) follows. With Chloramine T ($TsNCl^- Na^+$) and 10% of pyridinium bromide perbromide, however, the reaction with alkenes give an *N*-tosyl aziridine directly.[1768]

OS **VI**, 893.

15-46 Addition of Alkyl Halides (Addition of Halogen, Carbon)

Alkyl-halo-addition[1135]



[1757] Dehnicke, K. *Angew. Chem. Int. Ed.* ***1979****, 18,* 507; Hassner, A. *Acc. Chem. Res.* ***1971****, 4*, 9; Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 136–147. See Nair, V.; George, T.G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L.G. *Synlett* ***2000***, 1597.

[1758] Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.* ***2002****, 43*, 1201.

[1759] See, however, Cambie, R.C.; Hayward, R.C.; Rutledge, P.S.; Smith-Palmer, T.; Swedlund, B.E.; Woodgate, P. D. *J. Chem. Soc. Perkin Trans. 1,* ***1979***, 180.

[1760] Hassner, A.; Keogh, J. *J. Org. Chem.* ***1986****, 51*, 2767.

[1761] Olah, G.A.; Wang, Q.; Li, X.; Prakash, G.K.S. *Synlett* ***1990***, 487.

[1762] Hassner, A.; Keogh, J. *Tetrahedron Lett.* ***1975***, 1575.

[1763] Hassner, A.; Teeter, J.S. *J. Org. Chem.* ***1971****, 36*, 2176.

[1764] See Cambie, R.C.; Jurlina, J.L.; Rutledge, P.S.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1,* ***1982***, 327. Also see Hassner, A. *Intra-Sci. Chem. Rep.,* ***1970****, 4*, 109.

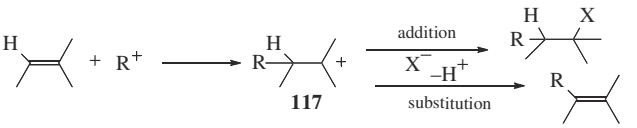
[1765] Hassner, A.; Isbister, R.J.; Friederang, A. *Tetrahedron Lett.* ***1969***, 2939.

[1766] Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.* ***1969****, 91,* 5046.

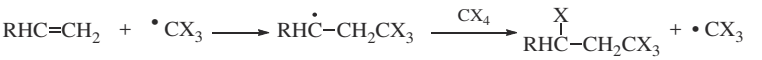
[1767] Levy, A.B.; Brown, H.C. *J. Am. Chem. Soc.* ***1973****, 95,* 4067.

[1768] Ali, S.I.; Nikalje, M.D.; Sudalai, A. *Org. Lett.* ***1999****, 1*, 705.

Alkyl halides can be added to alkenes in the presence of a *Friedel–Crafts catalyst,* most often $AlCl_3$.[1769] The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with Reaction **11-11**). The reactive species is the carbocation formed from the alkyl halide and the catalyst (see Reaction **11-11**).[1770] The reaction with an alkene follows *Markovnikov's rule*, and generates the more stable carbocation from the alkene after reaction with the carbocation. Methyl and ethyl halides, which cannot rearrange to a more stable secondary or tertiary carbocation, give no reaction at all. Substitution is a side reaction, arising from loss of hydrogen from the carbocation (**117**). Conjugated dienes give 1,4-addition.[1771] Triple bonds also undergo the reaction, to give vinylic halides.[1772]



Simple polyhalo alkanes (e.g., CCl_4, $BrCCl_3$, ICF_3 and related molecules) add to alkenes in good yield.[1773] These are free radical additions and require initiation, for example,[1774] by peroxides, metal halides (e.g., $FeCl_2$, CuCl),[1775] Ru catalysts,[1776] or UV light. The initial reaction generates the more stable radical intermediate, as in most free radical reactions with alkenes:



Polyhalo alkanes add to halogenated alkenes in the presence of $AlCl_3$ by an electrophilic mechanism. This has been called the *Prins reaction* (not to be confused with the other *Prins Reaction*, **16-54**).[1777]

α-Iodolactones add to alkenes in the presence of BEt_3/O_2 to give the addition product.[1778] Other α-iodoesters add under similar conditions to give the lactone.[1779] Iodoesters also add to alkenes in the presence of BEt_3 to give iodo-esters that have not cyclized.[1780]

A variant of the free radical addition method has been used for ring closure (see Reaction **15-30**).

For another method of adding R and I to a triple bond, see Reaction **15-23**.

OS **II**, 312; **IV**, 727; **V**, 1076; **VI**, 21; **VII**, 290.

[1769] Schmerling, L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1133–1174; Mayr, H.; Schade, C.; Rubow, M.; Schneider, R. *Angew. Chem. Int. Ed.* ***1987****, 26*, 1029.
[1770] See Pock, R.; Mayr, H.; Rubow, M.; Wilhelm, E. *J. Am. Chem. Soc.* ***1986****, 108*, 7767.
[1771] Kolyaskina, Z.N.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962****, 32,* 1067.
[1772] See Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc. Perkin Trans. 1,* ***1973***, 2491; ***1974***, 353.
[1773] See Freidlina, R.Kh.; Velichko, F.K. *Synthesis* ***1977***, 145; Freidlina, R.Kh.; Chukovskaya, E.C. *Synthesis* ***1974***, 477.
[1774] For other initiators, see Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* ***1985****, 41*, 393; Phelps, J.C.; Bergbreiter, D.E.; Lee, G.M.; Villani, R.; Weinreb, S.M. *Tetrahedron Lett.* ***1989****, 30,* 3915.
[1775] See Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* ***1985****, 41*, 4057. Also see Mitani, M.; Nakayama, M.; Koyama, K. *Tetrahedron Lett.* ***1980****, 21*, 4457.
[1776] Simal, F.; Wlodarczak, L.; Demonceau, A.; Noels, A.F. *Eur. J. Org. Chem.* ***2001***, 2689.
[1777] For a review with respect to fluoroalkenes, see Paleta, O. *Fluorine Chem. Rev.* ***1977****, 8,* 39.
[1778] Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* ***1998***, 1351.
[1779] Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1998****, 63*, 8604.
[1780] Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* ***1994****, 35*, 2763.

15-47 Addition of Acyl Halides (Addition of Halogen, Carbon)

Acyl-halo-addition



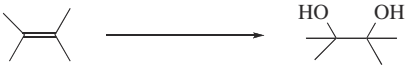
Acyl halides add to many alkenes using *Friedel–Crafts* catalysts, although polymerization is a problem. The reaction has been applied to straight-chain, branched, and cyclic alkenes, but to very few containing functional groups, other than halogen.[1781] The mechanism is similar to that of Reaction **15-46**, and, as in that case, substitution competes (Reaction **12-16**). Increasing temperature favors substitution,[1782] but good yields of addition products can be achieved if the temperature is kept under 0°C. The reaction usually fails with conjugated dienes, since polymerization predominates.[1783] Iodo acetates have been formed from alkenes using iodine and $Pb(OAc)_2$ in acetic acid.[1784] Rhodium-catalyzed variations are known.[1785] The reaction can be performed on triple-bond compounds, producing compounds of the form RCO—C=C—Cl.[1786] A *formyl* group and a halogen can be added to triple bonds by treatment with *N,N*-disubstituted formamides and $POCl_3$ (*Vilsmeier conditions*, Reaction **11-18**).[1787] Chloroformates add to allenes in the presence of a Rh catalyst to give a β-chloro, β,γ-unsaturated ester.[1788]

OS **IV**, 186; **VI**, 883; **VIII**, 254.

B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

15-48 Dihydroxylation and Dialkoxylation (Addition of Oxygen, Oxygen)

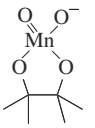
Dihydroxy-addition, Dialkoxy-addition



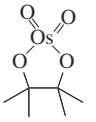
There are many reagents that add two OH groups to a double bond (dihydroxylation).[1789] The most common are OsO_4,[1790] first used by Criegee in 1936,[1791] and alkaline $KMnO_4$.[1792] Both give syn addition from the less-hindered side of the double bond. Less

[1781] See Groves, J.K. *Chem. Soc. Rev.* ***1972****, 1,* 73; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.
[1782] Jones, N.; Taylor, H.T.; Rudd, E. *J. Chem. Soc.* ***1961***, 1342.
[1783] See Melikyan, G.G.; Babayan, E.V.; Atanesyan, K.A.; Badanyan, Sh.O. *J. Org. Chem. USSR* ***1984****, 20,* 1884.
[1784] Bedekar, A.V.; Nair, K.B.; Soman, R. *Synth. Commun.* ***1994****, 24*, 2299.
[1785] Hua, R.; Onozawa, S.-y.; Tanaka, M. *Chemistry: European J.* ***2005****, 11*, 3621.
[1786] See Brownstein, S.; Morrison, A.; Tan, L.K. *J. Org. Chem.* ***1985****, 50*, 2796.
[1787] Yen, V.Q. *Ann. Chim. (Paris)* ***1962****, [13] 7*, 785.
[1788] Hua, R.; Tanaka, M. *Tetrahedron Lett.* ***2004****, 45*, 2367.
[1789] See Hudlicky, M. *Oxidations in Organic Chemistry* American Chemical Society, Washington, ***1990***, pp. 67–73; Haines, A.H. *Methods for the Oxidation of Organic Compounds* Academic Press, NY, ***1985***, pp. 73–98, 278–294; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds* Academic Press, NY, ***1981***, pp. 162–171, 294–296. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 996–1003.
[1790] See Schröder, M. *Chem. Rev.* ***1980****, 80,* 187. Also see, Norrby, P.-O.; Gable, K.P. *J. Chem. Soc. Perkin Trans. 2,* ***1996***, 171; Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1992****, 33*, 5113.
[1791] Criegee, R. *Liebigs Ann. Chem.* ***1936****, 522*, 75.
[1792] See Fatiadi, A.J. *Synthesis* ***1987***, 85; Nelson, D.J.; Henley, R.L. *Tetrahedron Lett.* ***1995****, 36*, 6375.

substituted double bonds are oxidized more rapidly than more substituted alkenes.[1793] Permanganate adds to alkenes to form an intermediate manganate ester (Reaction **118**), which is decomposed under alkaline conditions. Transition state structures and the energetics of the permanganate oxidation of alkenes has been studied using molecular mechanics.[1794] Bases catalyze the decomposition of **118** by coordinating with the ester. Note that there are alternative Mn complexes that may be used for cis-dihydroxylation of alkenes.[1795] Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic osmate ester (e.g., **119**) as an intermediate,[1796] which may be isolated in some cases, but is usually decomposed in solution with sodium sulfite (Na_2SO_3) in ethanol or other reagents.[1797]



118



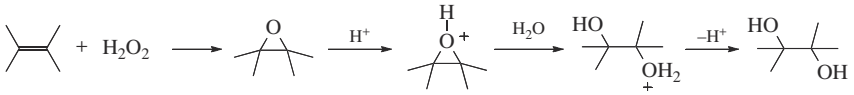
119

The chief drawbacks to the use of OsO_4 are the facts that it is expensive and toxic, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO),[1798] *tert*-butyl hydroperoxide in alkaline solution,[1799] H_2O_2,[1800] peroxyacid,[1801] $K_3Fe(CN)_6$,[1802] and non-heme iron catalysts.[1803] Polymer-bound OsO_4,[1804] and encapsulated OsO_4 have been shown to give the diol in the presence of NMO,[1805] as well as OsO_4^{2-} on an ion exchange resin.[1806] Dihydroxylation has also been reported in ionic liquids.[1807] Other metals have been used to catalyze dihydroxylation, including Fe[1808] or Ru catalyzed[1809] reactions with H_2O_2. A catalytic amount of K_2OsO_4 with a Cinchona alkaloid on a ordered inorganic support, in the presence of $K_3Fe(CN)_6$, gives the *cis*-diol.[1810]

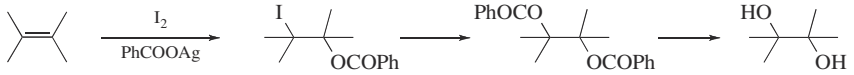
[1793] Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* ***1993****, 58*, 3785.
[1794] Wiberg, K.B.; Wang, Y.-g.; Sklenak, S.; Deutsch, C.; Trucks, G. *J. Am. Chem. Soc.* ***2006****, 128*, 11537.
[1795] de Boer, J.W.; Brinksma, J.; Browne, W.R.; Meetsma, A.; Alsters, P.L.; Hage, R.; Feringa, B.L. *J. Am. Chem. Soc.* ***2005****, 127,* 7990.
[1796] See Jørgensen, K.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1986****, 108*, 1867.
[1797] See Ogino, T.; Hasegawa, K.; Hoshino, E. *J. Org. Chem.* ***1990****, 55,* 2653. See, however, Freeman, F.; Kappos, J.C. *J. Org. Chem.* ***1989****, 54,* 2730, and other papers in this series.
[1798] Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* ***1988***, 1721. See also, Ray, R.; Matteson, D.S. *Tetrahedron Lett.* ***1980***, 449.
[1799] Akashi, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1978****, 43,* 2063.
[1800] See Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2003****, 42*, 5623.
[1801] Bergstad, K.; Piet, J.J.N.; Bäckvall, J.-E. *J. Org. Chem.* ***1999****, 64*, 2545.
[1802] Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* ***1995***, 319; Soderquist, J.A.; Rane, A.M.; López, C.J. *Tetrahedron Lett.* ***1993****, 34*, 1893. See Corey, E.J.; Noe, M.C.; Grogan, M.J. *Tetrahedron Lett.* ***1994****, 35*, 6427; Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* ***1992****, 33*, 5081 for oxidation using an asymmetric ligand.
[1803] Chen, K.; Costas, M.; Kim, J.; Tipton, A.K.; Que, Jr., L. *J. Am. Chem. Soc.* ***2002****, 124*, 3026.
[1804] Ley, S.V.; Ramarao, C.; Lee, A.-L.; Ostergaard, N.; Smith, S.C.; Shirley, I.M. *Org. Lett.* ***2003****, 5*, 185.
[1805] Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* ***1998****, 63*, 6094.
[1806] Choudary, B.M.; Chowdari, N.S.; Jyothi, K.; Kantam, M.L. *J. Am. Chem. Soc.* ***2002****, 124*, 5341.
[1807] Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* ***2004***, 1494; Branco, L.C.; Serbanovic, A.; da Ponte, M.N.; Afonso, C.A.M. *Chem. Commun.* ***2005***, 107.
[1808] Oldenburg, P.D.; Shteinman, A.A.; Que, Jr., L. *J. Am. Chem. Soc.* ***2005****, 127, 15*672.
[1809] Yip, W.-P.; Ho, C.-M.; Zhu, N.; Lau, T.-C.; Che, C.-M. *Chemistry: Asian J.* ***2008****, 3*, 70.
[1810] Motorina, I.; Crudden, C.M. *Org. Lett.* ***2001****, 3*, 2325.

The end product of the reaction is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product[1811] (see Reaction **19-7** and **19-10**). In acidic and neutral solution, it always does so; hence glycols must be prepared with alkaline[1812] permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis[1813] or increased stirring.[1814] The use of ultrasound with permanganate has resulted in good yields of the diol.[1815] This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.[1816]

Anti-hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (Reaction **15-50**) occurs first, followed by an S_N2 reaction, which results in overall anti addition:



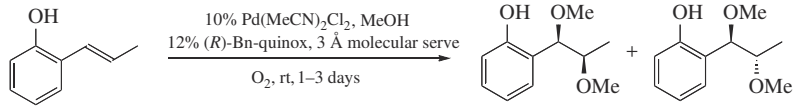
The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.[1817] Overall anti addition can also be achieved by the method of Prévost (the *Prévost reaction*). In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate, as shown. These can be isolated, and this represents a method of addition of IOCOPh. However, under normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction via the neighboring-group mechanism (Sec. 10.C), so the groups are still anti:



Hydrolysis of the ester does not change the configuration. The *Woodward modification* of the Prévost reaction is similar, but results in overall syn hydroxylation.[1818] In this procedure, the alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process,[1819] so the monoacetate is syn and

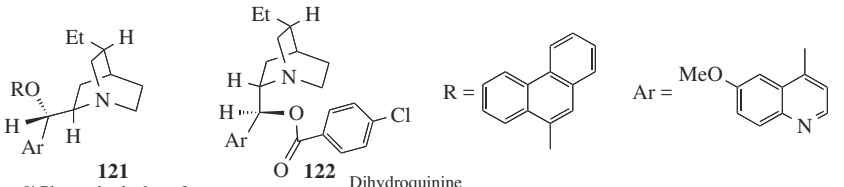
[1811] See Wolfe, S.; Ingold, C.F.; Lemieux, R.U. *J. Am. Chem. Soc.* ***1981****, 103,* 938; Wolfe, S.; Ingold, C.F. *J. Am. Chem. Soc.* ***1981****, 103*, 940. Also see, Lohray, B.B.; Bhushan, V.; Kumar, R.K. *J. Org. Chem.* ***1994****, 59*, 1375.
[1812] See Taylor, J.E.; Green, R. *Can. J. Chem.* ***1985****, 63*, 2777.
[1813] See Ogino, T.; Mochizuki, K. *Chem. Lett.* ***1979***, 443.
[1814] Taylor, J.E.; Williams, D.; Edwards, K.; Otonnaa, D.; Samanich, D. *Can. J. Chem.* ***1984****, 62*, 11; Taylor, J.E. *Can. J. Chem.* ***1984****, 62,* 2641.
[1815] Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1998****, 39*, 7463.
[1816] Donohoe, T.J.; Blades, K.; Moore, P.R.; Waring, M.J.; Winter, J.J.G.; Helliwell, M.; Newcombe, N.J.; Stemp, G. *J. Org. Chem.* ***2002****, 67*, 7946.
[1817] Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* ***1989****, 19*, 1939.
[1818] See Brimble, M.A.; Nairn, M.R. *J. Org. Chem.* ***1996****, 61*, 4801.
[1819] For another possible mechanism: Woodward, R.B.; Brutcher, Jr., F.V. *J. Am. Chem. Soc.* ***1958****, 80*, 209.

hydrolysis gives the diol as the product, with overall syn addition. Although the *Woodward* method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the *more hindered side* of the alkene.[1820] Both the *Prévost* and the *Woodward* methods[1821] have been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.[1822] Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and $SO_3 \cdot DMF$.[1823] Diacetates have been prepared from alkenes using a Cu catalyzed reaction with $PhI(OAc)_2$ as the oxidizing agent.[1824] A similar Pd/Cu catalyzed reaction is known using O_2 as the oxidant.[1825]



120 (5 : 1) (63%)

Dialkoxylation reactions are possible. The reaction of an aryl alkene with CH_3OH, O_2, and a Pd catalyst leads to the dimethoxy compound (see Reaction **120**), with moderate enantioselectivity if a chiral ligand is used.[1826] Dihydroxylation to alkenes of the form $RCH{=}CH_2$ has been made enantioselective, and addition to $RCH{=}CHR'$ both diastereoselective[1827] and enantioselective,[1828] using chiral additives or chiral catalysts[1829] (e.g., **121** or **122**, derivatives of the naturally occurring quinine and quinuclidine),[1830] along with OsO_4, in what is called

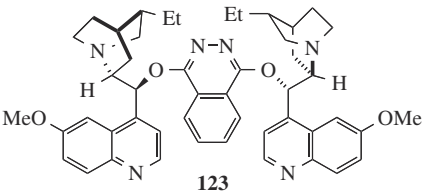


121
9'-Phenanthryl ether of dihydroquinidine

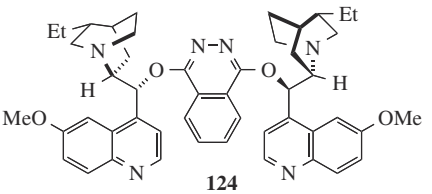
122 Dihydroquinine *p*-chlorobenzoate

[1820] Also see Corey, E.J.; Das, J. *Tetrahedron Lett.* ***1982****, 23,* 4217.
[1821] See Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1988***, 1209; Campi, E.M.; Deacon, G.B.; Edwards, G.L.; Fitzroy, M.D.; Giunta, N.; Jackson, W.R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* ***1989***, 407.
[1822] Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc. Perkin Trans. 1,* ***1974***, 1858, 1864; Cambie, R.C.; Rutledge, P.S. *Org. Synth.* ***VI***, 348.
[1823] Robinson, R.I.; Woodward, S. *Tetrahedron Lett.* ***2003****, 44*, 1655.
[1824] Seayad, J.; Seayad, A.M.; Chai, C.L.L. *Org. Lett.* ***2010****, 12,* 1412.
[1825] Schultz, M.J.; Sigman, M.S. *J. Am. Chem. Soc.* ***2006****, 128*, 1460.
[1826] Zhang, Y.; Sigman, M.S. *J. Am. Chem. Soc.* ***2007****, 129*, 3076.
[1827] For diastereoselective, but not enantioselective, addition of OsO_4, see Vedejs, E.; McClure, C.K. *J. Am. Chem. Soc.* ***1986****, 108,* 1094; Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* ***1990****, 55,* 1698.
[1828] Lohray, B.B. *Tetrahedron Asymmetry* ***1992****, 3*, 1317; Zaitsev, A.B.; Adolfsson, H. *Synthesis* ***2006***, 1725.
[1829] McNamara, C.A.; King, F.; Bradley, M. *Tetrahedron Lett.* ***2004****, 45*, 8527; Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S. *Tetrahedron Asymmetry* ***2004****, 15*, 743.
[1830] Wai, J.S.M.; Marko, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989****, 111*, 1123; Sharpless, K.B.; Amberg, W.; Beller, M.; Chens, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* ***1991****, 56*, 4585.

Sharpless asymmetric dihydroxylation.[1831] Other chiral ligands[1832] have also been used, as well as polymer[1833] and silica-bound[1834] *Cinchona* alkaloids. These amines bind to the OsO_4 *in situ* as chiral ligands, causing it to add asymmetrically.[1835] This has been done both with the stoichiometric and with the catalytic method.[1836] The catalytic method has been extended to conjugated ketones[1837] and to conjugated dienes, which give tetrahydroxy products diastereoselectively.[1838] Asymmetric dihydroxylation has also been reported with chiral alkenes.[1839] Ligands **121** and **122** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.[1840] Although **121** and **122** are not enantiomers, they give enantioselective addition to a given alkene in the opposite sense; for example, styrene predominantly gave the (*R*) diol with **121**, and the (*S*) diol with **122**.[1841] Note that ionic liquids have been used in asymmetric dihydroxylation.[1842]



123



124

Two phthalazine derivatives,[1843] $(DHQD)_2PHAL$ (**123**) and $(DHQ)_2PHAL$ (**124**) are used in conjunction with an Os reagent to improve the efficiency and ease of use, and are commercial available as AD-mix-β (using **123**) and AD-mix-α (using **124**). Catalyst **123** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **124** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidation using AD-mix α or β- uses **124** or **123**, respectively, mixed with potassium osmate $[K_2OsO_2(OH)_6]$, powdered $K_3Fe(CN)_6$, and powdered K_2CO_3 in an aqueous solvent mixture.[1843] One study

[1831] Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* ***1994****, 94*, 2483. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 294–301.

[1832] Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992****, 114*, 7568; Xu, D.; Crispino, G.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992****, 114*, 7570; Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron Asymmetry* ***1996****, 7*, 2971; Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992****, 57*, 2768.

[1833] Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* ***1998***, 21. For a review, see Karjalainen, J.K.; Hormi, O.E.O.; Sherrington, D.C. *Tetrahedron Asymmetry* ***1998****, 9*, 1563.

[1834] Song, C.E.; Yang, J.W.; Ha, H.-J. *Tetrahedron Asymmetry* ***1997****, 8*, 841.

[1835] See Corey, E.J.; Noe, M.C. *J. Am. Chem. Soc.* ***1996****, 118*, 319; Norrby, P.-O.; Kolb, H.C.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1994****, 116*, 8470; Wu, Y.-D.; Wang, Y.; Houk, K.N. *J. Org. Chem.* ***1992****, 57*, 1362. Also see Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.-L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.-O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1997****, 119*, 1840.

[1836] See Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* ***1987****, 28,* 3139; Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 665.

[1837] Walsh, P.J.; Sharpless, K.B. *Synlett* ***1993***, 605.

[1838] Park, C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1991****, 32*, 1003.

[1839] Oishi, T.; Iida, K.; Hirama, M. *Tetrahedron Lett.* ***1993****, 34*, 3573.

[1840] See Jacobsen, E.N.; Marko, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989****, 111*, 737.

[1841] Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988****, 110,* 1968.

[1842] See Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004****, 69*, 4381.

[1843] Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992****, 57*, 2768.

showed that osymylation does not always occur preferentially on the most electron-rich double bond. There are examples of the less-rich double bond reacting preferentially, and such preferences may be amplified using AD type reagents, which adds significant steric hindrance to the overall system.[1844]

These additives have been used in conjunction with microencapsulated OsO_4,[1845] and polymer bound **123** has been used.[1846] An asymmetric dihydroxylation was reported catalyzed by ionic polymer-supported OsO_4.[1847] A catalytic amount of flavin has been used.[1848] Both **123**[1849] and **124**[1850] have been used to generate diols with high enantioselectivity. Oxidation of a terminal alkene with AD-mix and then oxidation with TEMPO/NaOCl/$NaOCl_2$ leads to α-hydroxyl carboxylic acids with high enantioselectivity.[1851]

Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO_4, already containing chiral ligands,[1852] and by the use of OsO_4 on alkenes that have a chiral group elsewhere in the molecule.[1853] A Rh catalyzed diboration of alkenes in the presence of a chiral ligand, leads to the corresponding diol with good enantioselectivity after oxidation.[1854]

Alkenes can also be oxidized with metallic acetates [e.g., lead tetraacetate[1855] or thallium(III) acetate][1856] to give bis(acetates) of glycols.[1857] Oxidizing agents (e.g., benzoquinone, MnO_2, or O_2), along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4-addition).[1858]

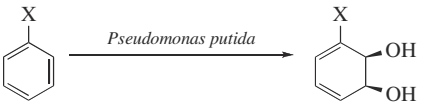
1,2-Diols are also generated from terminal alkynes by two sequential reactions with a Pt catalyst and then a Pd catalyst, both with $HSiCl_3$, and a final oxidation with H_2O_2—KF.[1859] The dihydroxylation of a vinyl ether, derived from an alkyne, leads to α-hydroxy aldehydes.[1860] Dihydroxylation of alkenes has been reported using a lipase and hydrogen peroxide, under microwave irradiation.[1861] A Pd catalyzed diacetoxylation is also known.[1862]

[1844] For a review, see Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* ***2008****, 64,* 2495.
[1845] Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* ***2001****, 3*, 2649.
[1846] Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* ***2001****, 42*, 5925.
[1847] Lee, B.S.; Mahajan, S.; Janda, K.D. *Tetrahedron Lett.* ***2005****, 46*, 4491.
[1848] Jonsson, S.Y.; Adolfsson, H.; Bäckvall, J.-E. *Org. Lett.* ***2001****, 3*, 3463.
[1849] Krief, A.; Colaux-Castillo, C. *Tetrahedron Lett.* ***1999****, 40*, 4189.
[1850] Junttila, M.H.; Hormi, O.E.O. *J. Org. Chem.* ***2004****, 69*, 4816.
[1851] Aladro, F.J.; Guerra, I.M.; Moreno-Dorado, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2000****, 41*, 3209.
[1852] Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* ***1983***, 769.
[1853] Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.* ***1984****, 106*, 2458; Johnson, C.R.; Barbachyn, M.R. *J. Am. Chem. Soc.* ***1984****, 106,* 2459.
[1854] Trudeau, S.; Morgan, J.B.; Shrestha, M.; Morken, J.P. *J. Org. Chem.* ***2005****, 70*, 9538.
[1855] For a review, see Moriarty, R.M. *Sel Org. Transform.* ***1972****, 2*, 183–237.
[1856] See Uemura, S.; Miyoshi, H.; Tabata, A.; Okano, M. *Tetrahedron* ***1981****, 37,* 291; Uemura, S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wley, NY, ***1987***, pp. 473–538, 497–513; Uemura, S. in Pizey, J. S. *Synthetic Reagents,* Vol. 5, Wiley, NY, ***1983***, pp. 165–187.
[1857] For another method see Fristad, W.E.; Peterson, J.R. *Tetrahedron* ***1984****, 40,* 1469.
[1858] See Bäckvall, J.E.; Awasthi, A.K.; Renko, Z.D. *J. Am. Chem. Soc.* ***1987****, 109,* 4750 and references cited therein; Bäckvall, J.E. *Bull. Soc. Chim. Fr.* ***1987***, 665; *New. J. Chem.* ***1990****, 14,* 447. For another method, see Uemura, S.; Fukuzawa, S.; Patil, S.R.; Okano, M. *J. Chem. Soc. Perkin Trans. 1,* ***1985***, 499.
[1859] Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J.W.; Hayashi, T. *J. Am. Chem. Soc.* ***2004****, 124*, 1584.
[1860] DeBergh, J.R.; Spivey, K.M.; Ready, J.M. *J. Am. Chem. Soc.* ***2008****, 130,* 7828.
[1861] Sarma, K.; Borthakur, N.; Goswami, A. *Tetrahedron Lett.* ***2007****, 48*, 6776.
[1862] Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* ***2009****, 131,* 3846.

1,2-Dithiols can be prepared from alkenes by largely indirect methods.[1863]
OS **II**, 307; **III**, 217; **IV**, 317; **V**, 647; **VI**, 196, 342, 348; **IX**, 251, 383.

15-49 Dihydroxylation of Aromatic Rings

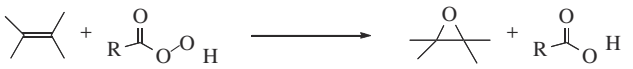
Dihydroxy-addition



One π bond of an aromatic ring can be converted to a cyclohexadiene 1,2-diol by reaction with enzymes associated with *P. putida*.[1864] A variety of substituted aromatic compounds can be oxidized, including bromobenzene, chlorobenzene,[1865] and toluene.[1866] In these latter cases, introduction of the hydroxyl groups generates a chiral molecule that can be used as a template for asymmetric syntheses.[1867]
OS **X**, 217.

15-50 Epoxidation (Addition of Oxygen, Oxygen)

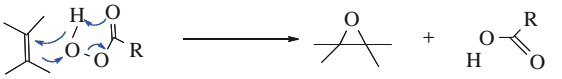
epi-Oxy-addition



Alkenes are converted to epoxides (oxiranes) by reaction with many peroxyacids.[1868] The reaction, called the *Prilezhaev reaction*, has wide utility.[1869] The most common is probably *m*-chloroperoxybenzoic acid, but peroxyacetic and peroxybenzoic are available, and trifluoroperoxyacetic acid[1870] and 3,5-dinitroperoxybenzoic acid[1871] are particularly reactive. The limiting factor concerning choice of the peroxyacid is usually whether or not it is commercially available because an in-lab preparation is potentially rather dangerous. Magnesium monoperoxyphthalate (MMPP)[1872] is commercially available, and has been shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.

[1863] Elgemeie, G.H.; Sayed, S.H. *Synthesis* ***2001***, 1747.
[1864] Gibson, D.T.; Koch, J.R.; Kallio, R.E. *Biochemistry* ***1968****, 7,* 2653; Brown, S.M. in Hudlicky, T. *Organic Synthesis: Theory and Practice* JAI Press, Greenwich, CT., ***1993***, Vol. 2, p. 113; Carless, H.A.J. *Tetrahedron Asymmetry* ***1992****, 3*, 795.
[1865] Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* ***1968****, 7*, 3795; Hudlicky, T.; Price, J.D. *Synlett*. ***1990***, 159.
[1866] Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemsitry,* ***1970****, 9,* 1626.
[1867] Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* ***1999****, 32*, 35; Ley, S.V.; Redgrave, A.J. *Synlett* ***1990***, 393. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 303–306.
[1868] For a list of reagents, including peroxyacids and others, used for epoxidation, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 915–927.
[1869] See Hudlicky, M. *Oxidations in Organic Chemistry* American Chemical Society, Washington, ***1990***, pp. 60–64; Haines, A.H. *Methods for the Oxidation of Organic Compunds*, Academic Press, NY, ***1985***, pp. 98–117, 295–303; Dryuk, V.G. *Russ. Chem. Rev.* ***1985****, 54,* 986; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry* pt. C, Academic Press, NY, ***1978***, pp. 211–252; Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2; Marcel Dekker, NY, ***1971***; pp. 113–140.
[1870] Emmons, W.D.; Pagano, A.S. *J. Am. Chem. Soc.* ***1955****, 77,* 89.
[1871] Rastetter, W.H.; Richard, T.J.; Lewis, M.D. *J. Org. Chem.* ***1978****, 43*, 3163.
[1872] Foti, C.J.; Fields, J.D.; Kropp, P.J. *Org. Lett.* ***1999****, 1*, 903.

Alkyl, aryl, hydroxyl, ester, and other groups may be present, but not amino groups since they are oxidized by the reagent. The presence of electron-donating groups increases the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly.[1873]



125

The one-step mechanism involving a transition state (e.g., **125**)[1874] was proposed by Bartlett.[1875] Evidence for this concerted mechanism is as follows[1876]: (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.[1877] (3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.[1878] (4) The addition is stereospecific (i.e., a *trans*-alkene gives a *trans*-epoxide and a *cis*-alkene gives a *cis*-epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.[1879] However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly and exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxyacid.[1880]

In general, peroxides (HOOH[1881] and ROOH) are poor reagents for epoxidation of simple alkenes since OH and OR are poor leaving groups in the concerted mechanism shown above.[1882] Transition metal catalysts[1883] have been used with alkyl hydroperoxides,[1884]

[1873] Stack, T.D.P. *Org. Lett.* ***2003****, 5*, 2469; Murphy, A.; Pace, A.; Stack, T.D.P. *Org. Lett.* ***2004****, 6*, 3119.

[1874] See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Wiley, NY, ***1985***, pp. 247–308; Bach, R.D.; Canepa, C.; Winter, J.E.; Blanchette, P.E. *J. Org. Chem.* ***1997****, 62,* 5191; Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2002****, 67*, 8519.

[1875] Bartlett, P.D. *Rec. Chem. Prog.,* ***1957****, 18,* 111. For other proposed mechanisms see Kwart, H.; Hoffman, D.M. *J. Org. Chem.* ***1966****, 31,* 419; Hanzlik, R.P.; Shearer, G.O. *J. Am. Chem. Soc.* ***1975****, 97*, 5231.

[1876] Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2004****, 69*, 7479. See also, Vedejs, E.; Dent III, W.H.; Kendall, J.T.; Oliver, P.A. *J. Am. Chem. Soc.* ***1996****, 118*, 3556.

[1877] See Gisdakis, P.; Rösch, N. *Eur. J. Org. Chem.* ***2001***, 719.

[1878] Schneider, H.; Becker, N.; Philippi, K. *Chem. Ber.* ***1981****, 114,* 1562; Batog, A.E.; Savenko, T.V.; Batrak, T.A.; Kucher, R.V. *J. Org. Chem. USSR* ***1981****, 17*, 1860.

[1879] See Freccero, M.; Gandolfi, R.; Sarzi-Amade, M.; Rastelli, A. *J. Org. Chem.* ***2000****, 65*, 8948.

[1880] See Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* ***1997****, 119*, 10147.

[1881] Arends, I.W.C.E. *Angew. Chem. Int. Ed.* ***2006****, 45*, 6250.

[1882] See Deubel, D.V.; Frenking, G.; Gisdakis, P.; Herrmann, W.A.; Rösch, N.; Sundermeyer, J. *Acc. Chem. Res.* ***2004****, 37*, 645.

[1883] **La**: Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2002****, 124*, 14544. **Mn**: Lane, B.S.; Vogt, M.; De Rose, V.T.; Burgess, K. *J. Am. Chem. Soc.* ***2002****, 124*, 11946. **Ti**: Lattanzi, A.; Iannece, P.; Screttri, A. *Tetrahedron Lett.* ***2002****, 43*, 5629. **Pd**: Yu, J.-Q.; Corey, E.J. *Org. Lett.* ***2002****, 4*, 2727. **Ru**: Adam, W.; Alsters, P.L.; Neumann, R.; Saha-Möller, C.; Sloboda-Rozner, D.; Zhang, R. *Synlett* ***2002***, 2011. **V**: Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* ***1979****, 12,* 63; Torres, G.; Torres, W.; Prieto, J.A. *Tetrahedron* ***2004****, 60*, 10245.

[1884] See Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, p 124.

however. Epoxidation occurs with Fe,[1885] and with Ti[1886] or V catalysts.[1887] In the presence of some other reagents,[1888] peroxides give good yields of the epoxide. These coreagents include DCC,[1889] magnesium aluminates,[1890] metalloporphyrins,[1891] hydrotalcite[1892] with microwave irradiation,[1893] and arsines in fluorous solvents.[1894] The catalyst $MeReO_3$[1895] has been used for epoxidation using sodium percarbonate and pyrazole,[1896] or hydrogen peroxide,[1897] or urea–H_2O_2.[1898]

Epoxidation has been done in ionic liquids using 10% H_2O_2 with $MnSO_4$[1899] or an Fe catalyst.[1900] Hypervalent iodine compounds [e.g., $PhI(OAc)_2$], in conjunction with a Ru catalyst in aqueous media, converts alkenes to epoxides.[1901] This reagent has been used in an ionic liquid with a Mn catalyst.[1902] Sodium chlorite ($NaClO_2$) in water gives epoxidation from alkenes.[1903] Microwave assisted epoxidations are known using H_2O_2.[1904] Epoxidation of vinyl ethers has been studied.[1905]

Several homogeneous and heterogeneous asymmetric epoxidation protocols have been developed.[1906] Enzymatic epoxidation[1907] and epoxidation with catalytic antibodies[1908] have been reported. Organocatalysts (e.g., chiral iminium salts) have been used.[1909] Asymmetric *Weitz–Scheffer epoxidation*[1910] (epoxidation of electron-deficient alkenes

[1885] Anilkumar, G.; Bitterlich, B.; Gelalcha, F.G.; Tse, M.K.; Beller, M. *Chem. Commun.* ***2007***, 289; Bitterlich, B.; Schröder, K.; Tse, M.K.; Beller, M. *Eur. J. Org. Chem.* ***2008***, 4867.

[1886] Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2007****, 46*, 4559; Malkov, A.V.; Bourhani, Z.; Kočovský, P. *Org. Biomol. Chem.* ***2005****, 3,* 3194; Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* ***2008****, 80*, 1071.

[1887] Zeng, W.; Ballard, T.E.; Melander, C. *Tetrahedron Lett.* ***2006****, 47*, 5923. See Malkov, A.V.; Czemerys, L.; Malyshev, D.A. *J. Org. Chem.* ***2009****, 74*, 3350.

[1888] See Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989****, 22,* 205.

[1889] Majetich, G.; Hicks, R.; Sun, G.-r.; McGill, P. *J. Org. Chem.* ***1998****, 63*, 2564; Murray, R.W.; Iyanar, K. *J. Org. Chem.* ***1998****, 63*, 1730.

[1890] Yamaguchi, K.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* ***1999****, 64,* 2966.

[1891] Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* ***2004****, 6*, 1597.

[1892] For an example without microwave irradiation, see Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Synth. Commun.* ***2003****, 33,* 2017.

[1893] Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Tetrahedron Lett.* ***2002****, 43*, 2909.

[1894] Van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Tetrahedron Lett.* ***1999****, 40*, 5239.

[1895] Yamazaki, S. *Tetrahedron* ***2008****, 64*, 9253; Yamazaki, S. *Org. Biomol. Chem.* ***2007****, 5*, 2109–2113; Saladino, R.; Neri, V.; Pelliccia, A.R.; Caminiti, R.; Sadun, C. *J. Org. Chem.* ***2002****, 67*, 1323.

[1896] Vaino, A.R. *J. Org. Chem.* ***2000****, 65*, 4210.

[1897] See Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2002****, 43*, 1001.

[1898] Owens, G.S.; Abu-Omar, M.M. *Chem. Commun.* ***2000***, 1165.

[1899] Tong, K.-H.; Wong, K.-Y.; Chan, T.H. *Org. Lett.* ***2003****, 5*, 3423.

[1900] Srinivas, K.A.; Kumar, A.; Chauhan, S.M.S. *Chem. Commun.* ***2002***, 2456.

[1901] Tse, M.K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett.* ***2003****, 44*, 7479.

[1902] Li, Z.; Xia, C.-G. *Tetrahedron Lett.* ***2003****, 44*, 2069.

[1903] Geng, X.-L.; Wang, Z.; Li, X.-Q.; Zhang, C. *J. Org. Chem.* ***2005****, 70,* 9610.

[1904] Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Bednarz, S. *Synth. Commun.* ***2005****, 35,* 2973.

[1905] Orendt, A.M.; Roberts, S.W.; Rainier, J.D. *J. Org. Chem.* ***2006****, 71*, 5565.

[1906] Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* ***2005****, 105,* 1603.

[1907] Kubo, T.; Peters, M.W.; Meinhold, P.; Arnold, F.H. *Chemistry: European J.* ***2006****, 12,* 1216. For a method of electrochemical regenration of monooxygenase, see Hollmann, F.; Hofstetter, K.; Habicher, T.; Hauer, B.; Schmid, A. *J. Am. Chem. Soc.* ***2005****, 127,* 6540.

[1908] Chen, Y.; Reymond, J.-L. *Synthesis* ***2001***, 934.

[1909] Bulman Page, P.C.; Buckley, B.R.; Rassias, G.A.; Blacker, A.J. *Eur. J. Org. Chem.* ***2006***, 803.

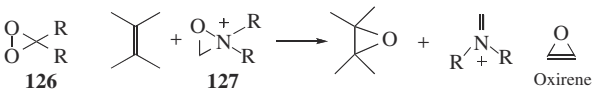
[1910] Weitz, E.; Scheffer, A. *Chem. Ber.* ***1921****, 54*, 2327. See Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem. Int. Ed.* ***1996****, 35,* 1725.

using H_2O_2 in a strong alkaline solution) is common. Cinchona-derived phase-transfer catalysts, initially used by Wynberg, are now common.[1911] Enantioselectivities can be significantly improved by changes of the catalyst structure, as well as the type of oxidant.[1912] A Yb—BINOL complex, with *t*-BuOOH led to epoxidation of conjugated ketones with high asymmetric induction,[1913] as did a mixture of NaOCl and a *Cinchona* alkaloid.[1914] Treatment with aq NaOCl[1915] or with an alkyl hydroperoxide[1916] and a chiral phase-transfer agent leads to chiral nonracemic epoxy-ketones. Epoxides can also be prepared by treating alkenes with oxygen or with an alkyl peroxide[1917] catalyzed by a complex of a transition metal (e.g., V, Mo, Ti, La,[1918] Y,[1919] or Co).[1920] The use of chiral additive leads to enantioselective epoxidation,[1921] and organocatalysts have been used as well.[1922] Chiral hydroperoxides have been used for enantioselective epoxidation.[1923]

Other epoxidation methods are available. Dioxiranes,[1924] (e.g., dimethyl dioxirane, **126**),[1925] either isolated or generated *in situ*,[1926] are important epoxidation reagents. With dimethyloxirane, C—H insertion reactions can occur preferentially.[1927] The reaction with alkenes is rapid, mild, safe, and a variety of methods have been developed using an oxidant as a coreagent. Substituent effects in such reactions have been studied[1928] and also substrate variations.[1929] The most commonly used coreagent is probably potassium peroxomonosulfate ($KHSO_5$). Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is a common source of $KHSO_5$. Oxone reacts with ketones[1930] and sodium bicarbonate to convert an alkene to

[1911] Helder, R.; Hummelen, J.C.; Laane, R.W.P.M.; Wiering, J.S.; Wynberg, H. *Tetrahedron Lett.* ***1976****, 17*, 1831; Wynberg, H.; Marsman, B. *J. Org. Chem.* ***1980****, 45*, 158; Pluim, H.; Wynberg, H. *J. Org. Chem.* ***1980****, 45,* 2498.
[1912] Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999****, 55,* 6375; Corey, E.J.; Zhang, F.-Y. *Org. Lett.* ***1999****, 1,* 1287; Lygo, B.; Wainwright, P.G. *Tetrahedron* ***1999****, 55,* 6289. See Adam, W.; Rao, P.B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Moller, C.R. *J. Org. Chem.* ***2002****, 67,* 259.
[1913] Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* ***1998****, 63*, 8090.
[1914] Lygo, B.; Wainwright, P.G. *Tetrahedron Lett.* ***1998****, 39*, 1599.
[1915] Lygo, B.; To, D.C.M. *Tetrahedron Lett.* ***2001****, 42*, 1343.
[1916] Adam, W.; Rao, P.B.; Degen, H.-G.; Saha-Möller, C.R. *Tetrahedron Asymmetry* ***2001****, 12*, 121.
[1917] For example, see Ledon, H.J.; Durbut, P.; Varescon, F. *J. Am. Chem. Soc.* ***1981****, 103*, 3601; Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* ***1986****, 108*, 3711; Laszlo, P.; Levart, M.; Singh, G.P. *Tetrahedron Lett.* ***1991****, 32,* 3167.
[1918] Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem.Soc.* ***2001****, 123*, 9474.
[1919] Kakei, H.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005****, 127,* 8962.
[1920] See Jørgensen, K.A. *Chem. Rev.* ***1989****, 89,* 431.
[1921] Wang, X.; Reisinger, C.M.; List, B. *J. Am. Chem. Soc.* ***2008****, 130*, 6070; Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* ***2008****, 130,* 8134.
[1922] Lu, J.; Xu, Y.-H.; Liu, F.; Loh, T.-P. *Tetrahedron Lett.* ***2008****, 49*, 6007.
[1923] Kośnik, W.; Bocian, W.; Kozerski, L.; Tvaroška, I.; Chmielewski, M. *Chemistry: European J.* ***2008****, 14*, 6087.
[1924] Murray, R.W. *Chem. Rev.* ***1989****, 89,* 1187; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989****, 22*, 205; Curci, R.; Dinoi, A.; Rubino, M.E *Pure Appl. Chem.* ***1995****, 67,* 811; Clennan, E.L. *Trends in Organic Chemistry* ***1995****, 5*, 231; Denmark, S.E.; Wu, Z. *Synlett* ***1999***, 847; Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.* ***2008****, 130,* 1197.
[1925] Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998****, 63*, 6425. See Angelis, Y.; Zhang, X.; Organopoulos, M. *Tetrahedron Lett.* ***1996****, 37*, 5991 for a discussion of the mechanism of this oxidation.
[1926] See Denmark, S.E.; Wu, Z. *J. Org. Chem.* ***1998****, 63,* 2810 and references cited therein; Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* ***1998****, 63,* 9888 and references cited therein; Masuyama, A.; Yamaguchi, T.; Abe, M.; Nojima, M. *Tetrahedron Lett.* ***2005****, 46,* 213.
[1927] Adam, W.; Prechtl, F.; Richter, M.J.; Smerz, A.K. *Tetrahedron Lett.* ***1993****, 34*, 8427.
[1928] Düfert,, A.; Werz, D.B. *J. Org. Chem.* ***2008****, 73,* 5514.
[1929] Nieto, N.; Munslow, I.J.; Fernández-Pérez, H.; Vidal-Ferran, A. *Synlett* ***2008***, 2856.
[1930] Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* ***2003****, 68*, 3232.

an epoxide. Oxone converts alkenes to epoxides in the presence of certain additives (e.g., *N,N*-dialkylalloxans).[1931] Oxone, with hydrogen peroxide or a similar oxidant, can be used with chiral ketones[1932] or aldehydes to convert alkenes to chiral, nonracemic epoxides.[1933] This reaction probably converts alkenes to epoxides with good enantioselectivity by *in situ* generation of dioxirane.[1934] Chiral dioxiranes have reportedly given nonracemic epoxides.[1935] This transformation with chiral carbohydrates is sometimes called *Shi epoxidation*.[1936] Epoxidation does not occur in good yields with these reagents in most other solvents, and it is suggested that the active agent that generates dioxirane is peroxyimidic acid [MeC(=NH)OOH].[1937] Note that benzaldehyde with Chloramine-M[1938] will convert alkenes to epoxides.[1939]



Oxone oxidizes iminium salts to an oxaziridinium intermediate (**127**), which can transfer oxygen to an alkene to form an epoxide and regenerate the iminium salt.[1940] This variation has been applied to asymmetric[1941] epoxidations using chiral iminium salt precursors.[1942] Other asymmetric epoxidation reactions of alkenes use chiral ketones and iminium salts with an organocatalyst.[1943] Direct epoxidation of alkenes has been done using oxaziridinium salts.[1944]

[1931] Carnell, A.J.; Johnstone, R.A.W.; Parsy, C.C.; Sanderson, W.R. *Tetrahedron Lett.* ***1999****, 40*, 8029.

[1932] Shi, Y. *Acc. Chem. Res.* ***2004****, 37*, 488; Yang, D. *Acc. Chem. Res.* ***2004****, 37*, 497; Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O.A.; Wang, B.; Shi, Y. *J. Org. Chem.* ***2006****, 71,* 1715; Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* ***2005****, 61,* 6409; Armstrong, A.; Tsuchiya, T. *Tetrahedron* ***2006****, 62,* 257; Boutureira, O.; McGouran, J.F.; Stafford, R.L.; Emmerson, D.P.G.; Davis, B. *Org. Biomol. Chem.* ***2009****, 7*, 4285; Armstrong, A.; Bettati, M.; White, A.J.P. *Tetrahedron* ***2010****, 66,* 6309.

[1933] See Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* ***2002****, 67*, 2435; Denmark, S.E.; Matsuhashi, H. *J. Org. Chem.* ***2002****, 67*, 3479; Arsmtrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B.R.; Wailes, J.S. *J. Org. Chem.* ***2002****, 67*, 8610; Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* ***2002****, 124*, 8792; Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* ***2003****, 44*, 7403; Chan, W.-K.; Yu, W.-y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* ***2003****, 68*, 6576.

[1934] Shu, L.; Shi, Y. *Tetrahedron Lett.* ***1999****, 40*, 8721. DFT modeling of the ee is discussed in Schneebeli, S.T.; Hall, M.L.; Breslow, R.; Friesner, R. *J. Am. Chem. Soc.* ***2009****, 131,* 3965.

[1935] Burke, C.P.; Shi, Y. *Angew. Chem. Int. Ed.* ***2006****, 45*, 4475.

[1936] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* ***1997****, 119*, 11224; Frohn, M.; Shi, Y. *Synthesis* ***2000***, 1979; Shi, Y. *Acc. Chem. Res.* ***2004****, 37*, 488; Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. USA.* ***2004****, 101*, 5794.

[1937] Arias, L.A.; Adkins, S.; Nagel, C.J.; Bach, R.D. *J. Org. Chem.* ***1983****, 48,* 888.

[1938] See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996****, 35,* 2810.

[1939] Yang, D.; Zhang, C.; wang, X.-C. *J. Am. Chem. Soc.* ***2000****, 122*, 4039.

[1940] See Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2002****, 43*, 803; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2004****, 45*, 747.

[1941] See Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* ***2000****, 122*, 2948.

[1942] See Jacobson, E. N. in Ojima, I. *Catalytic Asymmetric Synthesis* VCH, NY, ***1993***, pp. 159–203; Page, P.C.B.; Barros, D.; Buckley, B.R.; Ardakani, A.; Marples, B.A. *J. Org. Chem.* ***2004****, 69*, 3595; Page, P.C.B.; Buckley, B.R.; Blacker, A.J. *Org. Lett.* ***2004****, 6*, 1543.

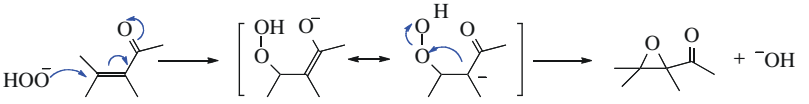
[1943] Wong, O.A.; Shi, Y. *Chem. Rev.* ***2008****, 108,* 3958; Page, P.C.B.; Buckley, B.R.; Farah, M.M.; Blacker, A.J. *Eur. J. Org. Chem.* ***2009***, 3413.

[1944] Biscoe, M.R.; Breslow, R. *J. Am. Chem. Soc.* ***2005****, 127,* 10812.

Although cis–trans isomerization of epoxides is not formally associated with this section, it is a potential issue in the conversion of an alkene to an epoxide. There are several catalysts for this process.[1945]

It would be useful if triple bonds could be similarly epoxidized to give oxirenes (see oxirene, above), but they are not stable compounds.[1946] Two oxirenes have been trapped in solid argon matrices at very low temperatures, but they decayed upon warming to 35 K.[1947] Oxirenes probably form in the reaction,[1948] but react further before they can be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (Sec. 2.B and 2.K.ii).

Conjugated dienes can be epoxidized (1,2-addition), although the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peroxyacids.[1949] The epoxidation of α,β-unsaturated ketones with H_2O_2 under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921.[1950] This fundamental reaction has been extended to α,β-unsaturated ketones (including quinones), aldehydes, and sulfones.[1951] This is a nucleophilic addition by a *Michael-type* mechanism, involving attack by HO_2^-[1952]: This reaction is another example of 1,4-addition of a heteroatom-containing species, as discussed in Reaction **15-31**.



α,β-Unsaturated compounds can be epoxidized alkyl hydroperoxides and a base,[1953] or with H_2O_2 and a base[1954]or heteropoly acids.[1955] The reaction has been done with LiOH and polymer-bound quaternary ammonium salts.[1956]

Another important asymmetric epoxidation of a conjugated system is the reaction of alkenes with polyleucine,[1957] DBU, and urea–H_2O_2, giving an epoxy–carbonyl compound with good enantioselectivity.[1958] The hydroperoxide anion epoxidation of conjugated

[1945] Lo, C.-Y.; Pal, S.; Odedra, A.; Liu, R.-S. *Tetrahedron Lett.* ***2003****, 44*, 3143.
[1946] See Lewars, E.G. *Chem. Rev.* ***1983****, 83*, 519.
[1947] Torres, M.; Bourdelande, J.L.; Clement, A.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983****, 105,* 1698. See also, Laganis, E.D.; Janik, D.S.; Curphey, T.J.; Lemal, D.M. *J. Am. Chem. Soc.* ***1983****, 105,* 7457.
[1948] Ibne-Rasa, K.M.; Pater, R.H.; Ciabattoni, J.; Edwards, J.O. *J. Am. Chem. Soc.* ***1973****, 95*, 7894; Ogata, Y.; Sawaki, Y.; Inoue, H. *J. Org. Chem.* ***1973****, 38,* 1044.
[1949] Exceptions are known. See Hart, H.; Verma, M.; Wang, I. *J. Org. Chem.* ***1973****, 38*, 3418. For diiron-catalysis, see Marchi-Delapierre, C.; Jorge-Robin, A.; Thibon, A.; Ménage, S. *Chem. Commun.* ***2007***, 1166.
[1950] Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* ***1921****, 54,* 2327.
[1951] See Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* ***1970***, 935.
[1952] Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* ***1983****, 105*, 2784. See Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, pt. 1, Wiley, NY, ***1964***, pp. 512–517.
[1953] Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* ***2002****, 58*, 1623; Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron Asymmetry* ***2001****, 12*, 1113; Honma, T.; Nakajo, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* ***2002****, 43*, 6229.
[1954] See Marigo, M.; Franzén, J.; Poulsen, T.B.; Zhuang, W.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005****, 127,* 6964.
[1955] Oguchi, T.; Sakata, Y.; Takeuchi, N.; Kaneda, K.; Ishii, Y.; Ogawa, M. *Chem. Lett.* ***1989***, 2053.
[1956] Anand, R.V.; Singh, V.K. *Synlett* ***2000***, 807.
[1957] For a mechanistic discussion of polypeptide catalyzed epoxidation, see Mathew, S.P.; Gunathilagan, S.; Roberts, S.M.; Blackmond, D.G. *Org. Lett.* ***2005****, 7,* 4847.
[1958] Allen, J.V.; Drauz, K.-H.; Flood, R.W.; Roberts, S.M.; Skidmore, J. *Tetrahedron Lett.* ***1999****, 40*, 5417; Geller, T.; Roberts, S.M. *J. Chem. Soc., Perkin Trans. 1,* ***1999***, 1397; Bentley, P.A.; Bickley, J.F.; Roberts, S.M.; Steiner, A. *Tetrahedron Lett.* ***2001****, 42*, 3741.

carbonyl compounds with a polyamino acid (e.g., poly-L-alanine or poly-L-leucine is known as the *Juliá–Colonna epoxidation*.[1959] Epoxidation of conjugated ketones to give nonracemic epoxy-ketones was done with aq NaOCl and a Cinchona alkaloid derivative as catalyst.[1960] A triphasic phase-transfer catalysis protocol has also been developed.[1961] β-Peptides have been used as catalysts in this reaction.[1962]

When a carbonyl group is elsewhere in the molecule, but not conjugated with the double bond, the *Baeyer–Villiger Reaction* (**18-19**) may compete. Allenes[1963] are converted by peroxyacids to allene oxides[1964] or spiro dioxides, both of which species can in certain cases be isolated,[1965] but more often are unstable under the reaction conditions and react further to give other products.[1966]

Allylic alcohols can be converted to epoxy-alcohols with *tert*-butylhydroperoxide on molecular sieves,[1967] or with peroxyacids.[1968] The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high enantioselectivity. This important modification is known as the *Sharpless asymmetric epoxidation*,[1969] where allylic alcohols are converted to optically active epoxides with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetraisopropoxide, and optically active diethyl tartrate.[1970] The $Ti(OCHMe_2)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol%) if molecular sieves are present.[1971] Polymer-supported catalysts have also been reported.[1972] The use of a tartrate–PEG reagent (PEG_{350} or PEG_{750}) allows generation of both enantiomers.[1973] Both (+) and (−) diethyl tartrate are readily available, so either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di, tri-, and tetrasubstituted,[1974] and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound[1975] formed from the titanium

[1959] Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron, **1984**, 40*, 5207. For reviews, see Lin, P. *Tetrahedron: Asymmetry **1998**, 9*, 1457; Ebrahim, S.; Wills, M. *Tetrahedron; Asymmetry **1997**, 8*, 3163.
[1960] Lygo, B.; Wainwright, P.G. *Tetrahedron **1999**, 55*, 6289.
[1961] Geller, T.; Krüger, C.M.; Militzer, H.-C. *Tetrahedron Lett. **2004**, 45*, 5069.
[1962] Coffey, P.E.; Drauz, K.-H.; Roberts, S.M.; Skidmore, J.; Smith, J.A. *Chem. Commun. **2001***, 2330.
[1963] See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes* Vol. 2, Academic Press, NY, ***1982***, pp. 417–510, 483–491.
[1964] For a review of allene oxides, see Chan, T.H.; Ong, B.S. *Tetrahedron **1980**, 36,* 2269.
[1965] Crandall, J.K.; Batal, D.J. *J. Org. Chem. **1988**, 53*, 1338.
[1966] See Crandall, J.K.; Rambo, E. *J. Org. Chem. **1990**, 55*, 5929.
[1967] Antonioletti, R.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett. **1992**, 33*, 3205.
[1968] Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem. **1992**, 57*, 1198.
[1969] See Pfenninger, A. *Synthesis **1986***, 89; Rossiter, B.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 193–246. For histories of its discovery, see Sharpless, K.B. *Chem. Br. **1986***, 38. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 284–290.
[1970] Sharpless, K.B.; Woodard, S.S.; Finn, M.G. *Pure Appl. Chem. **1983**, 55,* 1823 and references cited therein.
[1971] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc. **1987**, 109*, 5765. See Massa, A.; D'Ambrosi, A.; Proto, A.; Screttri, A. *Tetrahedron Lett. **2001**, 42*, 1995. For another improvement, see Wang, Z.; Zhou, W. *Tetrahedron **1987**, 43,* 2935.
[1972] Canali, L.; Karjalainen, J.K.; Sherrington, D.C.; Hormi, O. *Chem. Commun. **1997***, 123.
[1973] Reed, N.N.; Dickerson, T.J.; Boldt, G.E.; Janda, K.D. *J. Org. Chem. **2005**, 70*, 1728.
[1974] See the table in Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 249–250. See also, Schweiter, M.J.; Sharpless, K.B. *Tetrahedron Lett. **1985**, 26,* 2543.
[1975] See Williams, I.D.; Pedersen, S.F.; Sharpless, K.B.; Lippard, S.J. *J. Am. Chem. Soc. **1984**, 106*, 6430.

alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.[1976]

Ordinary alkenes (without an allylic OH group) do not give optically active alcohols by the Sharpless protocol because binding to the catalyst is necessary for enantioselectivity. Homoallylic alcohols have been converted to the epoxide, however, using a V catalyst in the presence of a chiral bis(hydroxyamide).[1977] Simple alkenes can be epoxidized enantioselectively with sodium hypochlorite (NaOCl, commercial bleach) and an optically active manganese complex catalyst.[1978] Apart from the commonly used NaOCl, urea–H_2O_2 has been used.[1979]

The use of a manganese–salen complex[1980] with various oxidizing agents, in what is called the *Jacobsen–Katsuki reaction*.[1981] Simple alkenes can be epoxidized with high enantioselectivity.[1982] In addition to Mn, Cr–salen,[1983] Ti–salen,[1984] and Ru–salen complexes[1985] have been used for epoxidation.[1986] Note that salen ligands are based on salen. The mechanism of this reaction has been examined.[1987] Radical intermediates have been suggested for this reaction,[1988] A polymer-bound Mn(III)–salen complex, in conjunction with NaOCl, has been used for asymmetric epoxidation,[1989] and manganese porphyrin complexes have also been used.[1990] Cobalt complexes give similar results.[1991] A related epoxidation reaction used an iron complex with molecular oxygen and isopropanal.[1992] Nonracemic epoxides can be prepared from racemic epoxides with (salen) cobalt(II) catalysts following a modified procedure for kinetic resolution.[1993]

[1976] See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, p. 247. Also see Corey, E.J. *J. Org. Chem.* ***1990****, 55,* 1693; Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991****, 113*, 106; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991****, 113,* 113; Takano, S.; Iwebuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* ***1991****, 113*, 2786; Cui, M.; Adam, W.; Shen, J.H.; Luo, X.M.; Tan, X.J.; Chen, K.X.; Ji, R.Y.; Jiang, H.L. *J. Org. Chem.* ***2002****, 67*, 1427.

[1977] Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* ***2007****, 129*, 286.

[1978] Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* ***1991****, 113,* 7063. See also, Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* ***1991****, 32,* 1055; Halterman, R.L.; Jan, S. *J. Org. Chem.* ***1991****, 56*, 5253.

[1979] Kureshy, R.I.; Khan, N.H.; Abdi, S.H.R.; Patel, S.T.; Jasra, R.V. *Tetrahedron Asymmetry* ***2001****, 12*, 433.

[1980] Wu, M.; Wang, B.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* ***2009****, 11*, 3622. See Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C.R.; Herderich, M. *J. Am. Chem. Soc.* ***2000****, 122,* 9685.

[1981] Brandes, B.D.; Jacobsen, E.N. *Tetrahedron Lett.* ***1995****, 36,* 5123; Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* ***2000***, 1557; Tangestaninejad, S.; Habibi, M.H.; Mirkhani, V.; Moghadam, M. *Synth. Commun.* ***2002****, 32*, 3331. See Fristrup, P.; Dideriksen, B.B.; Tanner, D.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2005****, 127,* 13672. For a discussion on the origin of enantioselectivity, see Kürti, L.; Blewett, M.M.; Corey, E.J. *Org. Lett.* ***2009****, 11*, 4592.

[1982] See Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***2000****, 41*, 7053.

[1983] Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001****, 3,* 663; O'Mahony, C.P.; McGarrigle, E.M.; Renehan, M.F.; Ryan, K.M.; Kerrigan, N.J.; Bousquet, C.; Gilheany, D.G. *Org. Lett.* ***2001****, 3*, 3435. See the references cited therein.

[1984] Matsumoto, K.; Oguma, T.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2009****, 48,* 7432.

[1985] Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* ***2001****, 7*, 3776.

[1986] McGarrigle, E.M.; Gilheany, D.G. *Chem. Rev.* ***2005****, 105*, 1563.

[1987] See Linker, T. *Angew. Chem,. Int. Ed.* ***1997****, 36*, 2060; Adam, W.; Roschmann, K.J.; Saha-Möller, C.R. *Eur. J. Org. Chem.* ***2000***, 3519. Also see Cavallo, L.; Jacobsen, H. *J. Org. Chem.* ***2003****, 68*, 6202.

[1988] Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed.* ***2000****, 39,* 589.

[1989] Song, C.E.; Roh, E.J.; Yu, B.M.; Chi, D.Y.; Kim, S.C.; Lee, K.J. *Chem. Commun.* ***2000***, 615; Ahn, K.-H.; Park, S.W.; Choi, S.; Kim, H.-J.; Moon, C.J. *Tetrahedron Lett.* ***2001****, 42*, 2485.

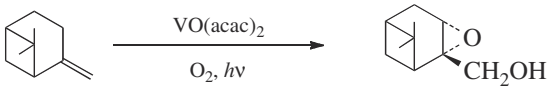
[1990] Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* ***1992****, 114*, 1313.

[1991] Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* ***1992***, 2077.

[1992] Saalfrank, R.W.; Reihs, S.; Hug, M. *Tetrahedron Lett,* ***1993****, 34*, 6033.

[1993] Savle, P.S.; Lamoreaux, M.J.; Berry, J.F.; Gandour, R.D. *Tetrahedron Asymmetry* ***1998****, 9*, 1843.

In a different type of reaction, alkenes are photooxygenated (with singlet O_2, see Reaction **14-7**) in the presence of a Ti, V, or Mo complex to give epoxy alcohols (e.g., **128**), formally derived from allylic hydroxylation followed by epoxidation.[1994] In other cases, modification of the procedure gives simple epoxidation.[1995] Alkenes react with aldehydes and oxygen, with Pd-on-silica[1996] or a Ru catalyst,[1997] to give the epoxide.



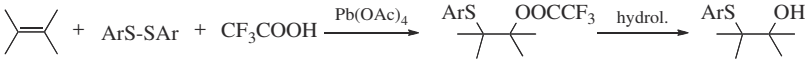
128
(67%)

Thiiranes can be prepared directly from alkenes using specialized reagents.[1998] Thiourea with a tin catalyst gives the thiirane, for example.[1999] Interestingly, internal alkynes were converted to 1,2-dichorothiiranes by reaction with S_2Cl_2 (sulfur monochloride).[2000] Note that epoxides are converted to thiiranes with ammonium thiocyanate and a cerium complex.[2001] A trans-thiiration reaction occurs with a Mo catalyst, in which an alkene reacts with styrene thiirane to give the new thiirane.[2002]

OS **I**, 494; **IV**, 552, 860; **V**, 191, 414, 467, 1007; **VI**, 39, 320, 679, 862; **VII**, 121, 126, 461; **VIII**, 546; **IX**, 288; **X**, 29; **80**, 9.

15-51 Hydroxysulfenylation (Addition of Oxygen, Sulfur)

Hydroxy-arylthio-addition (overall transformation)



Both hydroxy and an arylthio group are added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.[2003] Manganese and copper acetates have been used instead of $Pb(OAc)_4$.[2004] Addition of the groups OH and RSO has been achieved by treatment of alkenes with O_2 and a thiol (RSH).[2005] Addition to RS groups to give *vic*-dithiols was observed by treatment of the alkene

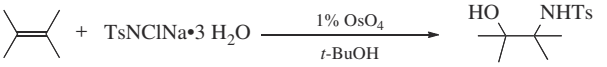
[1994] Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* ***1989****, 111*, 203.
[1995] See Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2000***, 163.
[1996] Ragagnin, G.; Knochel, P. *Synlett* ***2004***, 951.
[1997] Srikanth, A.; Nagendrappa, G.; Chandrasekaran, S. *Tetrahedron* ***2003****, 59*, 7761; Qi, J.Y.; Qiu, L.Q.; Lam, K.H.; Yip, C.W.; Zhou, Z.Y.; Chan, A.S.C. *Chem. Commun.* ***2003***, 1058.
[1998] Adam, W.; Bargon, R.M. *Eur. J. Org. Chem.* ***2001***, 1959; See Sugihara, Y.; Onda, K.; Sato, M.; Suzu, T. *Tetrahedron Lett.* ***2010****, 51*, 4110.
[1999] Tangestaninejad, S.; Mirkhani, V. *Synth. Commun.* ***1999****, 29*, 2079.
[2000] Nakayama, J.; Takahashi, K.; Watanabe, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* ***2000***, 41, 8349.
[2001] Iranpoor, N.; Tamami, B.; Shekarriz, M. *Synth. Commun.* ***1999****, 29*, 3313.
[2002] Adam, W.; Bargon, R.M.; Schenk, W.A. *J. Am. Chem. Soc.* ***2003****, 125*, 3871.
[2003] Trost, B.M.; Ochiai, M.; McDougal, P.G. *J. Am. Chem. Soc.* ***1978****, 100*, 7103; See Zefirov, N.S.; Zyk, N.V.; Kutateladze, A.G.; Kolbasenko, S.I.; Lapin, Yu.A. *J. Org. Chem. USSR* ***1986****, 22*, 190.
[2004] Bewick, A.; Mellor, J.M.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1,* ***1985***, 1039; Bewick, A.; Mellor, J.M.; Milano, D.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1,* ***1985***, 1045; Samii, Z.K.M.A.E.; Ashmawy, M.I.A.; Mellor, J.M. *Tetrahedron Lett.* ***1986****, 27*, 5289.
[2005] Chung, M.; D'Souza, V.T.; Szmant, H.H. *J. Org. Chem.* ***1987****, 52,* 1741, and other papers in this series.

with a disulfide (RSSR) and BF_3–etherate.[2006] This reaction has been carried out intramolecularly.[2007] In a similar manner, the reaction of alkenes with ceric ammonium nitrate and diphenyl diselenide in methanol leads to vicinally substituted phenylselenyl methyl ethers.[2008] Dimethyl diselenide adds to alkenes to form vicinal bis(methylselenyl) compounds, in the presence of tin tetrachloride.[2009]

Halo-ethers can be formed by the reaction of alkenyl alcohols with various reagents. Hept-6-en-1-ol reacts with $(collidine)_2I^+PF_6^-$, for example, to form 2-iodomethyl-1-oxacycloheptane.[2010]

15-52 Oxyamination (Addition of Oxygen, Nitrogen)

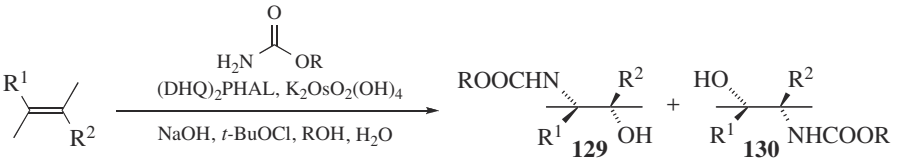
Tosylamino-hydroxy-addition



N-Tosylated β-hydroxy alkylamines, which can be easily hydrolyzed to β-hydroxyamines[2011], can be prepared[2012] by treatment of alkenes with the trihydrate of Chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt)[1690] and a catalytic amount of OsO_4.[2013] In some cases, yields can be improved by the use of phase-transfer catalysis.[2014] The reaction has been carried out enantioselectively.[2015] Alkenes can be converted to amido alcohols enantioselectivity by modification of this basic scheme. The *Sharpless asymmetric aminohydroxylation* employs a catalyst consisting of *Cinchona* alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.[2016] The Cu catalyzed reaction of an alkene with a *N*-sulfone oxaziridine leads to an oxazolidine.[2017] *N*-Chlorosulfonyl isocyanate has been used to prepare 1,2-amino alcohols.[2018] The Cu catalyzed hydroxyamination of alkenes was reported using Boc-hydroxylamine.[2019]

The reaction of a carbamate with $(DHQ)_2PHAL$ (**124**) and the osmium compound, with NaOH and *tert*-butyl hypochlorite, leads to a diastereomeric mixture of amido alcohols **129** and **130**, each formed with high enantioselectivity.[2020] An enantioselective aminohydroxylation of acrylamides has been reported.[2021]

[2006] Inoue, H.; Murata, S. *Heterocycles* ***1997****, 45*, 847.
[2007] Tuladhar, S.M.; Fallis, A.G. *Tetrahedron Lett.* ***1987****, 28*, 523. See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 905–908.
[2008] Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* ***1994****, 35*, 6525. See Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* ***1992****, 57*, 111.
[2009] Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* ***1992****, 33*, 4629.
[2010] Brunel, Y.; Rousseau, G. *Synlett* ***1995***, 323.
[2011] See Bäckvall, J.E.; Oshima, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1979****, 44,* 1953.
[2012] Sharpless, K.B.; Chong, A.O.; Oshima, K. *J. Org. Chem.* ***1976****, 41,* 177. See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996****, 35*, 2810.
[2013] See Fokin, V.V.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***2001****, 40*, 3455.
[2014] Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1978****, 43,* 2544.
[2015] Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985****, 94*, 759.
[2016] For a review, see Bodkin, J.A.; McLeod, M.D. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2733.
[2017] Michaelis, D.J.; Shaffer, C.J.; Yoon, T.P. *J. Am. Chem. Soc.* ***2007****, 129,* 1866.
[2018] Kim, J.D.; Kim, I.S.; Hua, J.C.; Zee, O.P.; Jung, Y.H. *Tetrahedron Lett.* ***2005****, 46,* 1079.
[2019] Kalita, B.; Nicholas, K.M. *Tetrahedron Lett.* ***2005****, 46*, 1451.
[2020] Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem., Int. Ed.* ***1996****, 35,* 451.
[2021] Streuff, J.; Osterath, B.; Nieger, M.; Muñiz, K. *Tetrahedron Asymmetry* ***2005****, 16,* 3492.



In general, the nitrogen adds to the less sterically hindered carbon of the alkene to give the major product. *N*-Bromoamides, in the presence of a catalytic amount of $(DHQ)_2PHAL$ and LiOH converts conjugated esters to β-amido-α-hydroxy esters with good enantioselectivity.[2022] Another oxyamination reaction involves treatment of a Pd complex of the alkene with a secondary or primary amine, followed by lead tetraacetate or another oxidant.[2023]

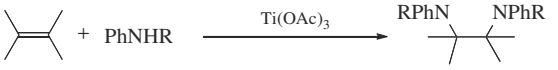
The organolanthanide-catalyzed alkene hydroamination has been reported.[2024] With this approach, amino alkenes (not enamines) can be cyclized to form cyclic amines,[2025] and amino alkynes lead to cyclic imine.[2026] The use of synthesized C-1[2027] and C-2 symmetric[2028] chiral organolanthanide complexes give the amino alcohol with good enantioselectivity.

β-Amino alcohols can be prepared by treatment of an alkene with a reagent prepared from HgO and HBF_4 along with aniline to give an aminomercurial compound (PhHN—C—C—$HgBF_4$, aminomercuration; see Reaction **15-7**), which is hydrolyzed to PhHN—C—C—OH.[2029] The use of an alcohol instead of water gives the corresponding amino ether. β-Azido alcohols are prepared by the reaction of an alkene with $Me_3SiOOSiMe_3$, Me_3SiN_3, and 20% $(Cl_2SnO)_n$, followed by treatment with aqueous acetic acid.[2030]

OS **VII**, 223, 375.

15-53 Diamination (Addition of Nitrogen, Nitrogen)

Di(alkylarylamino)-addition



Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.[2031] The reaction is not successful for primary aliphatic amines. In another procedure, alkenes can be diaminated by treatment

[2022] Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* ***2000****, 2*, 2221.
[2023] Bäckvall, J.E.; Björkman, E.E. *Acta Chem. Scand. Ser. B* ***1984****, 38*, 91; Bäckvall, J.E.; Bystrom, S.E. *J. Org. Chem.* ***1982****, 47,* 1126.
[2024] Ryu, J.-S.; Li, G.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2003****, 125,* 12584. For a review, see Hong, S.; Marks, T.J. *Acc. Chem. Res.* ***2004****, 37,* 673.
[2025] Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am Chem. Soc.* ***1992****, 114,* 275.
[2026] Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1998****, 120*, 1757.
[2027] Douglass, M.R.; Ogasawara, M.; Hong, S.; Metz, M.V.; Marks, T.J. *Organometallics* ***2002****, 21,* 283; Giardello, M.A.; Conticello, V.P.; Brard, L.; Gagné, M.R.; Marks, T.J. *J. Am. Chem. Soc.* ***1994****, 116,* 10241; Giardello, M.A.; Conticello, V.P.; Brard, L.; Sabat, M.; Rheingold, A.L.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* ***1994****, 116,* 10212.
[2028] Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003****, 125,* 14768.
[2029] Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1981***, 376.
[2030] Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* ***2000****, 41,* 2415.
[2031] Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* ***1974***, 504.

with the Os compounds R_3NOsO (R = *t*-Bu) and R_2NOsO_2,[2032] analogous to the Os compound mentioned at Reaction **15-52**.[2033] The Pd promoted method of Reaction **15-52** has also been extended to diamination.[2034] Alkenes can also be diaminated[2035] indirectly by treatment of the aminomercurial compound mentioned in Reaction **15-52** with a primary or secondary aromatic amine.[2036] The reaction of an alkene with *N*-arylsulfonyl dichloroamines ($ArSO_2NCl_2$) followed by reaction with aq Na_2SO_3, gives the *anti-vic*-diacetamde.[2037] The Pd catalyzed addition of saccharin and $H(NTs)_2$ with an alkene, in the presence of a hypervalent iodine oxidant leads to a precursor that can be converted to a 1,2-diamine.[2038]

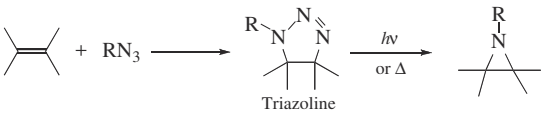
Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid, $C{=}C + NaN_3 + PhIO \rightarrow N_3{-}C{-}C{-}N_3$.[2039]

Dienes react with ureas in the presence of a Pd catalyst, to give an oxazolidinone.[2040] A Pd catalyzed reaction of dienes with di-*tert*-butyldiaziridinone also leads to an oxazolidinone.[2041]

Alkynes react with the bis(tosylate) of ethylenediamine, in the presence of a CuI catalyst, to give a dihydropiperazine.[2042]

15-54 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

***epi*-Arylimino-addition**, and so on



Triazoline

Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.[2043] The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO_2, as well as other groups. The reaction can take place by at least two pathways.

In one pathway, a 1,3-dipolar addition (Reaction **15-58**) takes place to give a triazoline, which can be isolated, followed thermal by extrusion of nitrogen (Reaction **17-34**). Evidence for the nitrene pathway is most compelling for R = acyl groups. In the other, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to

[2032] Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977****, 99*, 3420. See also, Sharpless, K.B.; Singer, S.P. *J. Org. Chem.* ***1976****, 41*, 2504.

[2033] For a X-ray structure of the osmium intermediate, see Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur.J.* ***2003****, 9*, 5581.

[2034] Bäckvall, J. *Tetrahedron Lett.* ***1978***, 163.

[2035] See Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis* ***1990***, 505.

[2036] Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1979***, 962.

[2037] Li, G.; Kim, S.H.; Wei, H.-X. *Tetrahedron Lett.* ***2000****, 41*, 8699.

[2038] Iglesias, Á.; Pérez, E.G.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2010****, 49,* 8109.

[2039] Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* ***1986****, 27,* 2809. See Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* ***1985****, 50,* 3647.

[2040] Bar, G.L.J.; Lloyd-Jones, G.C.; Booker-Milburn, K.I. *J. Am. Chem. Soc.* ***2005****, 127*, 7308.

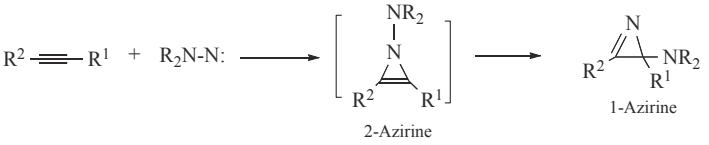
[2041] Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* ***2007****, 129*, 762; Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* ***2007****, 129,* 7496; Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* ***2007****, 129,* 11688.

[2042] Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* ***2008****, 130*, 1820.

[2043] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines* Academic Press, NY, ***1969***, pp. 68–79; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***. See Singh, G.S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* ***2007****, 107*, 2080.

that of carbene addition (Reaction **15-64**). Sulfonyloxy amines (e.g., $ArSO_2ONHCO_2Et$) form an aziridine when treated with CaO in the presence of a conjugated carbonyl compound.[2044] In the presence of Cu,[2045] Co,[2046] or Rh complexes,[2047] ethyl diazoacetate adds to imines to give aziridines. Diazirenes (Sec. 5.D.ii) with *n*-butyllithium converted conjugated amides to the α,β-aziridino amide.[2048] Calcium oxide has also been used to generate the nitrene,[2049] including nitrene precursors that have an attached chiral ester.[2050] Other specialized reagents have also been used.[2051] As discussed in Section 5.E, singlet nitrenes add stereospecifically while triplet nitrenes do not. Aminonitrenes (R_2NN:) have been shown to add to alkenes[2052] to give N-substituted aziridines and to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.[2053] *N*-Aminophthalimide generates a nitrene in the presence of a Pd catalyst, giving an *N*-phthalimido aziridine upon reaction with electron-deficient alkenes.[2054] Alkyl azides add to conjugated alkenes in the presence of an acid.[2055] Intramolecular aziridination reactions are known (e.g., the Pd catalyzed addition of *N*-tosyloxycarbamates to alkenes to form the bicyclic oxaziridinone).[2056] Tosylamines react with alkenes in the presence of a Rh catalyst[2057] or with iodine/$PhI(OAc)_2$.[2058] Trichloroethylsulfamate esters react with $PhI(OAc)_2$ and a Rh catalyst to give the corresponding *N*-sulfonyl aziridine.[2059]

Like oxirenes (see Reaction **15-50**), 2-azirines are unstable. 1-Azirines can be reduced to give chiral aziridines.[2060]



[2044] Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Synthesis* ***2001***, 1975. For an enantioselective version, see Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *J. Org. Chem.* ***2002****, 67*, 4972.
[2045] Sanders, C.J.; Gillespie, K.M.; Scott, P. *Tetrahedron Asymmetry* ***2001****, 12,* 1055; Ma, J.-A.; Wang, L.-X.; Zhang, W.; Zhou, W.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2001****, 12*, 2801.
[2046] Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* ***2001***, 406.
[2047] Mohan, J.M.; Uphade, T.S.S.; Choudhary, V.R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* ***1997***, 1429; Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* ***1995****, 78*, 2048.
[2048] Ishihara, H.; Ito, Y.N.; Katsuki, T. *Chem. Lett.* ***2001***, 984.
[2049] Carducci, M.; Fioravanti, S.; Loreta, M.A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***1996****, 37*, 3777.
[2050] Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***2003****, 44*, 3031.
[2051] Aires-de-Sousa, J.; Labo, A.M.; Prabhakar, S. *Tetrahedron Lett.* ***1996****, 37*, 3183.
[2052] Siu, T.; Yudin, A.K. *J. Am. Chem. Soc.* ***2002****, 124*, 530.
[2053] Anderson, D.J.; Gilchrist, T.L.; Rees, C.W. *Chem. Commun.* ***1969***, 147.
[2054] Siu, T.; Picard, C.J.; Yudin, A.K. *J. Org. Chem.* ***2005****, 70*, 932.
[2055] Mahoney, J.M.; Smith, C.R.; Johnston, J.N. *J. Am. Chem. Soc.* ***2005****, 127,* 1354.
[2056] Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* ***2005****, 127*, 14198.
[2057] Catino, A.J.; Nichols, J.M.; Forslund, R.E.; Doyle, M.P. *Org. Lett.* ***2005****, 7*, 2787.
[2058] Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* ***2008****, 49,* 4925.
[2059] Espino, C.G.; Wehn, P.M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* ***2001****, 123*, 6935; Wehn, P.M.; Lee, J.; Du Bois, J. *Org. Lett.* ***2003****, 5*, 4823; Espino, C.G.; Fiori, K.W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* ***2004****, 126*, 15378; Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* ***2002****, 124*, 13672; Keaney, G.F.; Wood, J.L. *Tetrahedron Lett.* ***2005****, 46,* 4031; Guthikonda, K.; Wehn, P.M.; Caliando, B.J.; Du Bois, J. *Tetrahedron* ***2006****, 62,* 11331.
[2060] Roth, P.; Andersson, P.G.; Somfai, P. *Chem. Commun.* ***2002***, 1752.

An alternative preparation of aziridines reacts an alkene with iodine and Chloramine-T, generating the corresponding *N*-tosyl aziridine.[2061] Chloramine T and NBS also give the *N*-tosyl aziridine,[2062] and Bromamine-T ($TsNBr^-Na^+$) or TsNIK and have also been used in a similar manner,[2063,2064] Diazoalkanes react with imines to give aziridines.[2065] Another useful reagent is NsN=IPh, which reacts with alkenes in the presence of Rh compounds[2066] or Cu complexes[2067] to give *N*-Ns aziridines. Other sulfonamide reagents can be used,[2068] including PhI=NTs.[2069] Enantioselective aziridination is possible using this reaction with chiral ligands.[2070] This reagent has been used in ionic liquids with a Cu catalyst.[2071] Palladium catalyzes such reactions[2072] and we can also use methyl trioxorhenium ($MeReO_3$).[2073] Manganese(salen) catalysts have also been used with this reagent.[2074] A nitrido Mn(salen) complex was used with ditosyl anhydride, converting a conjugated diene to an allylic *N*-tosylaziridine.[2075] Arylsulfonamides react with alkenes via the nitrene using an Au[2076] or a Cu catalyst.[2077]

Organocatalysts have been used for the enantioselective aziridination of the C=C unit in conjugated aldehydes.[2078]

Nitrenes can add to aromatic rings to give ring-expansion products analogous to those mentioned in Reaction **15-62**.[2079]

OS **VI**, 56.

[2061] Wu, H.; Xu, L.-W.; Xia, C.-G.; Ge, J.; Yang, L. *Synth. Commun.* ***2005****, 35*, 1413; Karabal, P.U.; Chouthaiwale, P.V.; Shaikh, T.M.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* ***2010****, 51*, 6460. Also see Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* ***2004***, 2479.

[2062] Thakur, V.V.; Sudalai, A. *Tetrahedron Lett.* ***2003****, 44*, 989.

[2063] Vyas, R.; Chanda, B.M.; Bedekar, A.V. *Tetrahedron Lett.* ***1998****, 39*, 4715; Hayer, M.F.; Hossain, M.M. *J. Org. Chem.* ***1998****, 63*, 6839. See Antunes, A.M.M.; Bonifácio, V.D.B.; Nascimento, S.C.C.; Lobo, A.M.; Branco, P.S.; Prabhakar, S. *Tetrahedron* ***2007****, 63,* 7009.

[2064] Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2003****, 44*, 575.

[2065] Casarrubios, L.; Pérez, J.A.; Brookhart, M.; Templeton, J.L. *J. Org. Chem.* ***1996****, 61*, 8358.

[2066] Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* ***1996****, 52*, 1543. Also see, Södergren, M.J.; Alonso, D.A.; Bedekar, A.V.; Andersson, P.G. *Tetrahedron Lett.* ***1997****, 38*, 6897.

[2067] Knight, J.G.; Muldowney, M.P. *Synlett* ***1995***, 949. See also, Mohr, F.; Binfield, S.A.; Fettinger, J.C.; Vedernikov, A.N. *J. Org. Chem.* ***2005****, 70,* 4833.

[2068] See GuthiKonda, K.; Du Bois, J. *J. Am. Chem. Soc.* ***2002****, 124*, 13672. See also, Dichenna, P.H.; Robert-Peillard, F.; Dauban, P.; Dodd, R.H. *Org. Lett.* ***2004****, 6*, 4503; Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* ***2004****, 45*, 3965.

[2069] Vedernikov, A.N.; Caulton, K.G. *Org. Lett.* ***2003****, 5,* 2591; Cui, Y.; He, C. *J. Am. Chem. Soc.* ***2003****, 125*, 16202. See Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* ***2002****, 67*, 2101.

[2070] See Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Cott, P. *J. Org. Chem.* ***2002****, 67*, 3450.

[2071] Kantam, M.L.; Neeraja, V.; Kavita, B.; Haritha, Y. *Synlett* ***2004***, 525.

[2072] Antunes, A.M.M.; Marto, S.J.L.; Branco, P.S.; Prabhakar, S.; Lobo, A.M. *Chem. Commun.* ***2001***, 405.

[2073] Jean, H.-J.; Nguyen, S.B.T. *Chem. Commun.* ***2001***, 235.

[2074] Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* ***1996****, 37*, 9245.

[2075] Nishimura, M.; Minakata, S.; Thonchant, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* ***2000****, 41*, 7089.

[2076] Li, Z.; Ding, X.; He, C. *J. Org. Chem.* ***2006****, 71*, 5876.

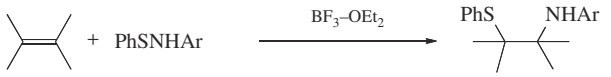
[2077] Jain, S.L.; Sharma, V.B.; Sain, B. *Synth. Commun.* ***2005****, 35*, 9.

[2078] Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed.* ***2007****, 46,* 778.

[2079] See Lwowski, W.; Johnson, R.L. *Tetrahedron Lett.* ***1967***, 891.

15-55 Aminosulfenylation (Addition of Nitrogen, Sulfur)

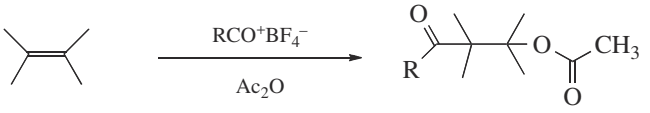
Arylamino-arylthio-addition



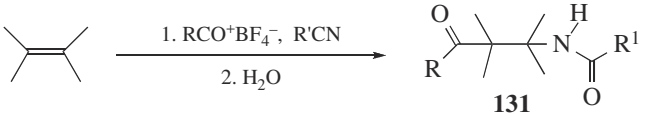
An amino and an arylthio group can be added to a double bond by treatment with a sulfenanilide (PhSNHAr) in the presence of BF_3–etherate.[2080] The addition is anti, and the mechanism probably involves a thiiranium ion.[2081] In another aminosulfenylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate ($MeSSMe_2$ BF_4^-) and ammonia or an amine,[2082] the latter acting as a nucleophile. This reaction was extended to other nucleophiles:[2083] N_3^-,[2084] NO_2^-, CN^-, ^-OH, and ^-OAc to give MeS—C—C—A, where A = N_3, NO_2, CN, OH, and OAc, respectively. An RS (R = alkyl or aryl) and an NHCOMe group have been added in an electrochemical procedure.[2085]

15-56 Acylacyloxylation and Acylamidation (Addition of Oxygen, Carbon, or Nitrogen, Carbon)

Acyl-acyloxy-addition



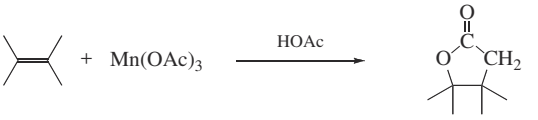
An acyl and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.[2086] As expected, the addition follows Markovnikov's rule, with the electrophile Ac^+ going to the carbon with more hydrogen atoms. In an analogous reaction, an acyl and an amido group can be added to give **131**, if a nitrile is used in place of the anhydride. Similarly, halo-acetoxylation is known.[2087] This reaction has also been carried out on triple bonds, to give the unsaturated analogues of **131** (syn addition).[2088]



131

[2080] Benati, L.; Montavecchi, P.C.; Spagnolo, P. *Tetrahedron Lett.* ***1984****, 25*, 2039. See also, Brownbridge, P. *Tetrahedron Lett*. ***1984***, *25*, 3759.
[2081] See Ref. 21.
[2082] Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982****, 104,* 3225; Caserio, M.C.; Kim., J.K. *J. Am. Chem. Soc.* ***1982****, 104,* 3231.
[2083] Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.* ***1982****, 104*, 3228; Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982****, 104,* 3225. For an extension that allows A to be C≡CR, see Trost, B.M.; Martin, S.J. *J. Am. Chem. Soc.* ***1984****, 106*, 4263.
[2084] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Chem. Commun.* ***1997***, 1133.
[2085] Bewick, A.; Coe, D.E.; Mellor, J.M.; Owton, M.W. *J. Chem. Soc. Perkin Trans. 1,* ***1985***, 1033.
[2086] Shastin, A.V.; Balenkova, E.S. *J. Org. Chem. USSR* ***1984****, 20,* 870.
[2087] Hashem, Md.A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* ***1998***, 195.
[2088] Gridnev, I.D.; Balenkova, E.S. *J. Org. Chem. USSR* ***1988****, 24,* 1447.

15-57 The Conversion of Alkenes or Alkynes to Lactones (Addition of Oxygen, Carbon)



This reaction is clearly related to forming esters and lactones by reaction of carboxylic acids with alkenes (Reaction **15-6**), but the Mn reagent leads to differences. Alkenes react with manganese(III) acetate to give γ-lactones.[2089] The mechanism is probably free radical, involving addition of $^{\bullet}CH_2COOH$ to the double bond. Ultrasound improves the efficiency of the reaction.[2090] In a related reaction, cyclohexene reacted with $MeO_2CCH_2CO_2K$ and $Mn(OAc)_3$ to give an α-carbomethoxy bicyclic lactone.[2091] The use of dimethyl malonate and ultrasound in this reaction gave the same type of product.[2092] Lactone formation has also been accomplished by treatment of alkenes with α-bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,[2093] and with alkylidene $Cr(CO)_5$ complexes.[2094] Alkenes can also be converted to γ-lactones by indirect routes.[2095] Chromium carbene complexes add to alkenes to give β-lactones using ultrasound.[2096]

Cyclic dienes react with β-keto esters, in the presence of a Ga[2097] catalyst and water, to give an α-acyl bicyclic lactone.

Alkenyl acids cyclize to the corresponding lactone upon treatment with sodium hypochlorite and a Lewis acid.[2098] Alkynyl acids cyclize upon treatment with PIFA [phenyliodine(III)-bis(trifluoroacetate)] to give ω-acyl lactones.[2099] A variation of this reaction also employs a diselenide.[2100] Treatment of alkynyl acids with a Au catalyst[2101] leads to an alkylidene lactone.

An intramolecular variation of this reaction is known, involving amides, which generate a lactam.[2102]

OS **VII**, 400.

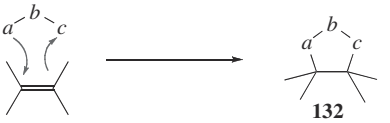
Note that the related halolacctonization reaction, including iodolactonization, is discussed in Reaction **15-41**.

For addition of aldehydes and ketones, see the *Prins reaction* (**16-54**), and Reactions **16-95** and **16-96**.

[2089] Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* ***1991****, 47*, 831. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1985****, 26*, 4291.
[2090] D'Annibale, A.; Trogolo, C. *Tetrahdron Lett.* ***1994****, 35*, 2083.
[2091] Lamarque, L.; Méou, A.; Brun, P. *Tetrahedron* ***1998****, 54*, 6497.
[2092] Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* ***1993****, 49*, 10705.
[2093] Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* ***1987****, 60*, 1049. See also, Kraus, G.A.; Landgrebe, K. *Tetrahedron Lett.* ***1984****, 25*, 3939.
[2094] Wang, S.L.B.; Su, J.; Wulff, W.D. *J. Am. Chem. Soc.* ***1992****, 114*, 10665.
[2095] See Bäuml, E.; Tscheschlok, K.; Pock, R.; Mayr, H. *Tetrahedron Lett.* ***1988****, 29,* 6925.
[2096] Caldwell, J.J.; Harrity, J.P.A.; Heron, N.M.; Kerr, W.J.; McKendry, S.; Middlemiss, D. *Tetrahedron Lett.* ***1999****, 40*, 3481; Caldwell, J.J.; Kerr, W.J.; McKendry, S. *Tetrahedron Lett.* ***1999****, 40*, 3485.
[2097] Nguyen, R.V.; Li, C.-J. *J. Am. Chem. Soc.* ***2005****, 127,* 17184.
[2098] López-López, J.A.; Guerra, F.M.; Moreno-Dorado, F.J.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2007****, 48,* 1749.
[2099] Tellitu, I.; Serna, S.; Herrero, M.T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* ***2007****, 72,* 1526;
[2100] Browne, D.M.; Niyomura, O.; Wirth, T. *Org. Lett.* ***2007****, 9,* 3169.
[2101] Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* ***2006****, 47,* 6273.
[2102] Davies, D.T.; Kapur, N.; Parsons, A.F. *Tetrahedron Lett.* ***1998****, 39*, 4397.

15.C.iv. Cycloaddition Reactions

15-58 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



132

There are a large group of reactions ([3 + 2]-cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds. This reaction is quite useful in the synthesis of alkaloids,[2103] including asymmetric syntheses.[2104] These dipolar compounds have a sequence of three atoms *a*—*b*—*c*, of which a has a sextet of electrons in the outer shell and *c* has an octet with at least one unshared pair (see Table 15.3).[2105] The reaction can then be formulated as shown to generate **132**. Note that the initial reaction of potassium permanganate (Reaction **15-48**) occurs by [3 + 2]-cycloaddition to give a manganate ester (**119**).[2106] [3 + 2]-Cycloaddition occurs with other metal oxides.[2107] Hydrazones have also been reported to give [3 + 2]-cycloadditions.[2108]

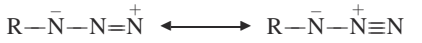
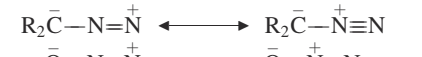
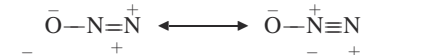
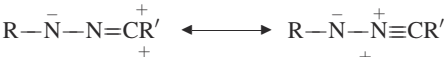
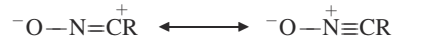
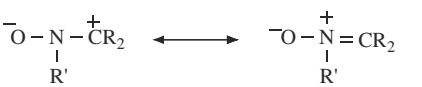
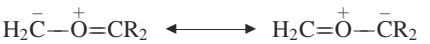
1,3-Dipoles of the type shown in Table 15.3 have an atom with six electrons in the outer shell, which is usually unstable. Such compounds will delocalize the change to alleviate this electronic arrangement (they are resonance stabilized). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom:

$$^{-}\mathrm{a} - \mathrm{b}{=}\mathrm{c}^{\pm} \longleftrightarrow {}^{-}\mathrm{a} - \mathrm{b}{\equiv}\mathrm{c}^{\pm}$$

[2103] See Broggini, G.; Zecchi, G. *Synthesis* ***1999***, 905.
[2104] Karlsson, S.; Högberg, H.-E. *Org. Prep. Proceed. Int.* ***2001****, 33*, 103.
[2105] See Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, ***1990***; Huisgen, R. *Helv. Chim. Acta* ***1967****, 50,* 2421; *Angew. Chem. Int. Ed.* ***1963****, 2,* 565, 633; Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis* VCH, NY, ***1988***; Scriven, E.F.V. *Azides and Nitrenes* Academic Press, NY, ***1984***; Stanovnik, B. *Tetrahedron* ***1991****, 47,* 2925 (diazoalkanes); Kanemasa, S.; Tsuge, O. *Heterocycles* ***1990****, 30,* 719 (nitrile oxides); Paton, R.M. *Chem. Soc. Rev.* ***1989****, 18,* 33 (nitrile sulfides); Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* ***1988****, 27,* 981; Coldham, I.; Hufton, R. *Chem. Rev.* ***2005****, 105,* 2765 (azomethine ylids); Vedejs, E. *Adv. Cycloaddit.* ***1988****, 1,* 33 (azomethine ylids); DeShong, P.; Lander, Jr., S.W.; Leginus, J.M.; Dicken, C.M. *Adv. Cycloaddit.* ***1988****, 1,* 87 (nitrones); Balasubramanian, N. *Org. Prep. Proced. Int.* ***1985****, 17,* 23 (nitrones); Confalone, P.N.; Huie, E.M. *Org. React.* ***1988****, 36,* 1 (nitrones); Padwa, A. in Horspool, W.M. *Synthetic Organic Photochemistry, Plenum, NY,* ***1984***, pp. 313–374 (nitrile ylids); Bianchi, G.; Gandolfi, R.; Grünanger, P. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 752–784 (nitrile oxides); Stuckwisch, C.G. *Synthesis* ***1973***, 469 (azomethine ylids, azomethine imines). For reviews of intramolecular 1,3-dipolar additions see Padwa, A. in Padwa, A. treatise cited above, Vol. 2, pp. 277–406; Padwa, A.; Schoffstall, A.M. *Adv. Cycloaddit.* ***1990****, 2,* 1; Tsuge, O.; Hatta, T.; Hisano, T. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups,* Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 345–475; Padwa, A. *Angew. Chem. Int. Ed.* ***1976****, 15,* 123. For a review of azomethine ylids, see Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* ***1989****, 45,* 231. For reviews of 1,3-dipolar cycloreversions, see Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed.* ***1979****, 18,* 721. For the use of this reaction to synthesize natural products, see papers in Tetrahedron **1985**, 41, 3447.
[2106] Houk, K.N.; Strassner, T. *J. Org. Chem.* ***1999****, 64*, 800.
[2107] See Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* ***2001****, 123*, 697.
[2108] Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* ***2003****, 44*, 3351.

TABLE 15.3 Some Common 1,3-Dipolar Compounds

Compound	Reaction
	Type 1
Azide	
Diazoalkane[a]	
Nitrous oxide	
Nitile imine[b]	
Nitrile ylid[c]	
Nitrile oxide[d]	
	Type 2
Azomethine imine[e]	
Azoxy compound	
Azomethine ylid[f]	
Nitrone	
Carbonyl oxide[g]	
Ozone	
Carbonyl ylid[h]	

[a]See Ref. 2109.

[b]See Ref. 2110.

[c]See Ref. 2111.

[d]See Ref. 2112.

[e]See Ref. 2113.

[f]See Ref. 2114.

[g]See Ref. 2115.

[h]See Ref. 2116.

[2109] See Baskaran, S.; Vasu, J.; Prasad, R.; Kodukulla, K.; Trivedi, G.K. *Tetrahedron* ***1996,*** *52*, 4515.

[2110] Sibi, M.P.; Stanley, L.M.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2005,*** *127*, 8276.

[2111] Raposo, C.; Wilcox, C.S. *Tetrahedron Lett.* ***1999,*** *40*, 1285.

[2112] See Nishiwaki, N.; Uehara, T.; Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* ***1998,*** *39*, 4851; Jung, M.E.; Vu, B.T. *Tetrahedron Lett.* ***1996,*** *37*, 451. See Muri, D.; Bode, J.W.; Carreira, E.M. *Org. Lett.* ***2000,*** *2*, 539; Gissot, A.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* ***2000,*** *41*, 1191. For a discussion of transition structures, see Luft, J.A.R.; Meleson, K.; Houk, K.N. *Org. Lett.* ***2007,*** *9,* 555.

[2113] For a reaction using a chiral Si Lewis acid, see Shirakawa, S.; Lombardi, P.J.; Leighton, J.L. *J. Am. Chem. Soc.* ***2005,*** *127*, 9974.

[2114] See Cabrera, S.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2005,*** *127,* 16394; Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* ***2008,*** *130,* 17250; Nájera, C.; Sansano, J.M. *Angew. Chem. Int. Ed.* ***2005,*** *44,* 6272.

[2115] See Iesce, M.R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M.L. *J. Chem. Soc. Perkin Trans. 1,* ***1994***, 3295; MuCullough, K.J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1,* ***1994***, 643.

[2116] Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2005,*** *127,* 2709; Diev, V.V.; Kostikov, R.R.; Gleiter, R.; Molchanov, A.P. *J. Org. Chem.* ***2006,*** *71,* 4066.

If the discussion is limited to the first row of the periodic table, b can only be nitrogen, c can be carbon or nitrogen, and a can be carbon, oxygen, or nitrogen; hence there are six types. Among these are azides (a = b = c = N) and diazoalkanes.

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond:

$$^{-}a - b^{\pm} c— \longleftrightarrow {}^{-}a - b^{+}{=}c—$$

Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N—N—C is only another form of C—N—N. Examples are shown in Table 15.3.

Of the 18 systems, some of which are unstable and must be generated *in situ*,[2117] the reaction has been accomplished for at least 15, but not in all cases with a carbon–carbon double bond (the reaction also can be carried out with other double bonds[2118]). Not all alkenes undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the *Diels–Alder Reaction* (**15-60**).

The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process,[2119] as illustrated above,[2120] largely controlled by Frontier Molecular Orbital considerations.[2121] Reactivity has been shown to correlate with the energy required to distort 1,3-dipole and dipolarophiles to the transition state.[2122] In-plane aromaticity has been invoked for these dipolar cycloadditions.[2123] As expected for this type of mechanism, the rates do not vary much with changes in solvent,[2124] although rate acceleration has been observed in ionic liquids.[2125] Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide.[2126] There are no simple rules covering orientation in 1,3-dipolar additions. The regioselectivity has been explained by MO treatments,[2127] where overlap of the largest orbital coefficients of the atoms forming the new bonds leads to the major regioisomer. When the 1,3-dipolar compound is a thiocarbonyl ylid ($R_2C{=}S^{+}{-}CH_2^{-}$) the addition has been shown to be nonstereospecific with certain

[2117] For a review of some aspects of this, see Grigg, R. *Chem. Soc. Rev.* ***1987****, 16*, 89.

[2118] See Bianchi, G.; De Micheli, C.; Gandolfi, R. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, ***1977***, pp. 369–532. Also see Dunn, A.D.; Rudorf, W. *Carbon Disulfide in Organic Chemistry*, Wiley, NY, ***1989***, pp. 97–119.

[2119] Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000****, 65*, 6112. For a theoretical study of transition states, see Lu, X.; Xu, X.; Wang, N.; Zhang, Q. *J. Org. Chem.* ***2002****, 67*, 515; DiValentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000****, 65*, 6112. For a discussion of loss of concertedness in reactions of azomethine ylids, see Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F.P. *J. Am. Chem. Soc.* ***2000****, 122*, 6078. See Ess, D.H.; Houk, K.N. *J. Am. Chem. Soc.* ***2007****, 129,* 10646.

[2120] For Huisgen, R. *Adv. Cycloaddit.* ***1988****, 1,* 1; Al-Sader, B.H.; Kadri, M. *Tetrahedron Lett.* ***1985****, 26,* 4661; Houk, K.N.; Firestone, R.A.; Munchausen, L.L.; Mueller, P.H.; Arison, B.H.; Garcia, L.A. *J. Am. Chem. Soc.* ***1985****, 107*, 7227; Majchrzak, M.W.; Warkentin, J. *J. Phys. Org. Chem.* ***1990****, 3*, 339.

[2121] Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1977****, 99*, 385 and references cited therein.

[2122] Engels, B.; Christl, M. *Angew. Chem. Int. Ed.* ***2009****, 48*, 7968.

[2123] Cossío, F.P.; Marao, I.; Jiao, H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999****, 121*, 6737.

[2124] For a review of the role of solvents in this reaction, see Kadaba, P.K. *Synthesis* ***1973***, 71.

[2125] Dubreuil, J.F.; Bazureau, J.P. *Tetrahedron Lett.* ***2000****, 41*, 7351.

[2126] Lee, C.K.Y; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.* ***2004***, 2622.

[2127] See Houk, K.N.; Yamaguchi, K. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* Vol. 2, Wiley, NY, ***1984***, pp. 407–450. See also, Burdisso, M.; Gandolfi, R.; Quartieri, S.; Rastelli, A. *Tetrahedron* ***1987***, *43,* 159.

substrates, but stereospecific with others, indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism *c* in Reaction **15-63**, category 4) has been trapped in one such case.[2128] In a theoretical study of the 1,3-dipolar cycloadditions (diazomethane and ethene; fulminic acid [H—C≡N—O] and ethyne),[2129] calculations based on valence bond descriptions suggest that many concerted 1,3-dipolar cycloaddition reactions follow an electronic heterolytic mechanism where the movement of well-identifiable orbital pairs is retained along the entire reaction path from reactants to product.[2130]

An antibody-catalyzed [3 + 2]-cycloaddition has been reported.[2131] Metal-assisted dipolar additions are also known.[2132] In a different metal-mediated reaction, alkenyl *Fischer carbene complexes* react with alkynes, in the presence of a Ni catalyst, to give cyclopentenones.[2133] Fischer carbene complexes take the form $R_2C{=}M(CO)_x$,[2134] and the metals include those of low oxidation state, and Fe, Mo, Cr, or W. Ligands include π-electron acceptors and π-donor substituents on methylene groups (e.g., alkoxy and amino groups).

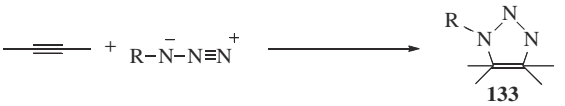
Many of the cycloadducts formed from the dipoles in Table 15.3 are unstable, which lead to other products. The reaction of alkyl azides with alkenes generates triazolines (Reaction **15-54**), which extrude nitrogen (N≡N) upon heating or photolysis to give an aziridine.[2135] With a transition metal catalyst, alkyl azides add to alkynes to give triazoles.[2136] Retro [3 + 2]-cycloaddition reactions are also known.[2137] Cycloaddition of azides to allenes leads to pyrrolidines.[2138]

[3 + 2]-Cycloaddition reactions occur intramolecularly to generate bicyclic and polycyclic compounds.[2139] The intramolecular cycloaddition of azomethine imines give bicyclic pyrazolidines, for example.[2140] When diazoalkanes (including diazo acetates, e.g., ethyl diazoacetate, N_2CHCO_2Et) react with an alkene and a Cr catalyst the initially formed product is a five-membered ring, a pyrazoline.[2141] Pyrazolines are generally unstable and extrusion of nitrogen leads to a cyclopropane.[2142] Rhodium-catalyzed cycloaddition using chiral ligands leads to formation of cyclopropanes with good enantioselectivity.[2143]

[2128] Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* ***1989****, 30,* 5373; Huisgen, R.; Mloston, G. *Tetrahedron Lett.* ***1989****, 30,* 7041.
[2129] Karadakov, P.B.; Cooper, D.L.; Gerratt, J. *Theor. Chem. Acc.* ***1998****, 100*, 222.
[2130] Blavins, J.J.; Karadakov, P.B.; Cooper, D.L. *J. Org. Chem.* ***2001****, 66,* 4285.
[2131] Toker, J.D.; Wentworth, Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. *J. Am. Chem. Soc.* ***2000****, 122*, 3244.
[2132] Kanemasa, S. *Synlett* ***2002***, 1371.
[2133] Barluenga, J.; Barrio, P.; Riesgo, L.; López, L.A.; Tomás, M. *J. Am. Chem. Soc.* ***2007****, 129,* 14422.
[2134] See Fischer, H. *Chem. Ber.* ***1980****, 113*, 193.
[2135] For a discussion of reactivity and regioselectivity with strained alkenes and alkynes, see Schoenebeck, F.; Ess, D.H.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* ***2009****, 131,* 8121.
[2136] Zhang, L.; Chen, X.; Xue, P.; Sun, H.H.Y.; Williams, I.D.; Sharpless, K.B.; Fokin, V.V.; Jia, G. *J. Am. Chem. Soc.* ***2005****, 127,* 15998; Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* ***2008****, 130,* 15304.
[2137] da Silva, G.; Bozzelli, J.W. *J. Org. Chem.* ***2008****, 73,* 1343.
[2138] Feldman, K.S.; Iyer, M.R. *J. Am. Chem. Soc.* ***2005****, 127*, 4590.
[2139] See Padwa, A. *Angew. Chem. Int. Ed.* ***1976,*** *15*, 123; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977****, 16*, 10 (see pp. 18–22).
[2140] Dolle, R.E.; Barden, M.C.; Brennan, P.E.; Ahmed, G.; Tran, V.; Ho, D.M. *Tetrahedron Lett.* ***1999****, 40*, 2907.
[2141] For an enantioselective reaction, see Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* ***2006****, 128*, 2174.
[2142] Jan, D.; Simal, F.; Demonceau, A.; Noels, A.F.; Rufanov, K.A.; Ustynyuk, N.A.; Gourevitch, D.N. *Tetrahedron Lett.* ***1999****, 40*, 5695.
[2143] For a discussion of the mechansim and origin of enantioselectivity, see Nowlan, III, D.T.; Singleton, D.A. *J. Am. Chem. Soc.* ***2005****, 127,* 6190. Also see Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* ***2008****, 130,* 7178.

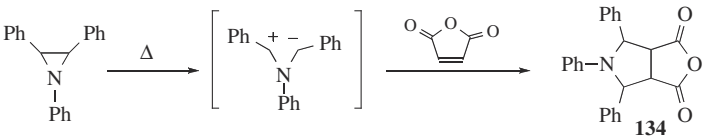
There are many cases where the [3 + 2]-cycloaddition leads to cycloadducts with high enantioselectivity.[2144] Cycloaddition of diazo esters with a Co catalyst having a chiral ligand leads to cyclopropane derivatives with good enantioselectivity.[2145] Cycloaddition of nitrones and pyrazolinones with a Cu catalyst and a chiral ligand leads to pyrrolidine derivatives with good enantioselectivity.[2146] In the presence of a Ni catalyst and a chiral ligand, nitrones react with activated cyclopropanes to give a tetrahydro-1,2-oxazine, with high enantioselectivity.[2147] Nitrones react with conjugated carbonyl compounds, with a transition metal catalyst (e.g., a Ti complex) to give an 1,2-oxazoline.[2148]

Conjugated dienes generally give exclusive 1,2-addition, although 1,4-addition (a 3 + 4 cycloaddition) has been reported.[2149] Carbon–carbon triple bonds can also undergo 1,3-dipolar addition.[2150] For example, azides react to give triazoles, (**133**).



133

The 1,3-dipolar reagent can in some cases be generated by the *in situ* opening of a suitable three-membered ring system. For example, aziridines open to give a zwitterion (e.g., **134**), which can add to activated double bonds to give pyrrolidines.[2151]



134

Aziridines also add to C≡C triple bonds, as well as to other unsaturated linkages, including C=O, C=N, and C≡N.[2152] In some of these reactions, it is a C—N bond of the aziridine that opens rather than the C—C bond.

For other [3 + 2]-cycloadditions, see Reaction **15-59**.

OS **V**, 957, 1124; **VI**, 592, 670; **VIII**, 231. Also see, OS **IV**, 380.

[2144] Stanley, L.M.; Sibi, M.P. *Chem. Rev.* ***2008****, 108,* 2887. See Bădoiu, A.; Brinkmann,Y.; Viton, F.; Kündig, E.P. *Pure Appl. Chem.* ***2008****, 80*, 1013.

[2145] Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2000****, 41*, 3647.

[2146] Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2004****, 126*, 718.

[2147] Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2005****, 127*, 5764.

[2148] Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* ***2005****, 127*, 11926.

[2149] Baran, J.; Mayr, H. *J. Am. Chem. Soc.* ***1987****, 109*, 6519.

[2150] See Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y.V. *Bull. Soc. Chim. Fr.* ***1973***, 2555; 2871; Fuks, R.; Viehe, H. G. in Viehe, H.G. *Acetylenes* Marcel Dekker, NY, ***1969***, p. 460–477.

[2151] Lown, J.W. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry,* vol 1. Wley, NY, ***1984***, pp. 683–732.

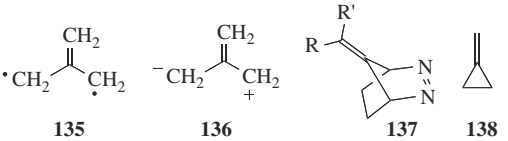
[2152] See Lown, J.W. *Rec. Chem. Prog.* ***1971****, 32,* 51; Gladysheva, F.N.; Sineokov, A.P.; Etlis, V.S. *Russ. Chem. Rev.* ***1970****, 39,* 118.

C. Carbon on Both Sides

Reactions 15-58–15-64 are cycloaddition reactions.[2153]

15-59 All-Carbon [3 + 2]-Cycloadditions[2154]

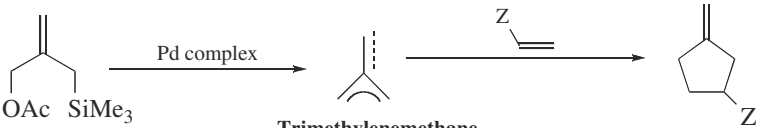
Several methods have been reported for the formation of cyclopentanes by [3 + 2]-cycloadditions.[2155] Heating conjugated ketones with trialkylphosphines generates an intermediate that adds to conjugated alkynes.[2156] One type involves reagents that produce intermediates **135** or **136**.[2157] A synthetically useful example[2158] uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**139**), which is commercially available, and a Pd or other transition metal catalyst to generate **135** or **136**, which adds to double bonds to give cyclopentanes



135 **136** **137** **138**

with an exocyclic double bond. The reaction occurs with **139** to generate trimethylenemethane *in situ*, which reacts with alkenes to give methylenecyclopentane derivatives.[2159] A similar reaction occurs with imines to give methylene pyrrolidines.[2160] The Pd catalyzed reaction with CO_2 leads to butenolides.[2161]

Note that **136** also reacts with *N*-tosyl aziridines, with 20% *n*-butyllithium and 10% of $Pd(OAc)_2$, to give a vinylidene piperidine derivative.[2162] Similar or identical intermediates generated from bicyclic azo compounds **137** (see Reaction **17-34**) or methylenecyclopropane (**138**)[2163] also add to activated double bonds. With suitable substrates the addition can be enantioselective.[2164]



139 **Trimethylenemethane**

[2153] For a system of classification of cycloaddition reactions, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1968,*** *7*, 321. See Posner, G.H. *Chem. Rev.* ***1986,*** *86*, 831. See also, the series *Advances in Cycloaddition*.

[2154] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1101–1116.

[2155] See Trost, B.M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* ***1989,*** *111*, 7487.

[2156] Wang, J.-C.; Ng, S.-S.; Krische, M.J. *J. Am. Chem. Soc.* ***2003,*** *125*, 3682.

[2157] See Trost, B.M. *Pure Appl. Chem.* ***1988,*** *60,* 1615; *Angew. Chem. Int. Ed.* ***1986,*** *25,* 1.

[2158] See Trost, B.M.; Lynch, J.; Renaut, P.; Steinman, D.H. *J. Am. Chem. Soc.* ***1986,*** *108,* 284.

[2159] Trost, B.M.; MacPherson, D.T. *J. Am. Chem. Soc.* ***1987,*** *109*, 3483; Trost, B.M. *Angew. Chem. Int. Ed.* ***1986,*** *25,* 1; Trost, B.M.; Stambuli, J.P.; Silverman, S.M.; Schwörer, U. *J. Am. Chem. Soc.* ***2006,*** *128,* 13328; Trost, B.M.; Cramer, N.; Silverman, S.M. *J. Am. Chem. Soc.* ***2007,*** *129,* 12396.

[2160] Trost, B.M.; Silverman, S.M.; Stambuli, J.P. *J. Am. Chem. Soc.* ***2007,*** *129*, 12398.

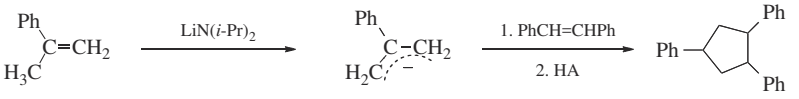
[2161] Greco, G.E.; Gleason, B.L.; Lowery, T.A.; Kier, M.J.; Hollander, L.B.; Gibbs, S.A.; Worthy, A.D. *Org. Lett.* ***2007,*** *9,* 3817.

[2162] Hedley, S. J.; Moran, W. J.; Price, D.A.; Harrity, J.P.A. *J. Org. Chem.* ***2003,*** *68*, 4286.

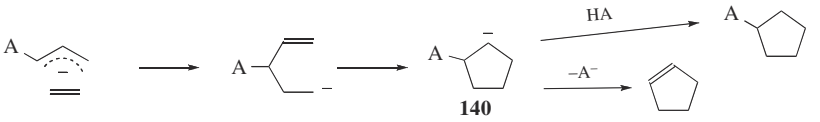
[2163] See Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* ***1989,*** *111,* 7285.

[2164] See Chaigne, F.; Gotteland, J.; Malacria, M. *Tetrahedron Lett.* ***1989,*** *30,* 1803.

In a different type of procedure, [3 + 2]-cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.[2165] For example, α-methylstyrene adds to stilbene on treatment with the strong base LDA.[2166]



The mechanism can be outlined as:



140

In the case above, **140** is protonated in the last step by the acid HA, but if the acid is omitted and a suitable nucleofuge is present, it may leave, resulting in a cyclopentene.[2167] In these cases, the reagent is an allylic anion, but similar [3 + 2]-cycloadditions involving allylic cations have also been reported.[2168]

OS **VIII**,173, 347.

15-60 The Diels–Alder Reaction

(4 + 2) *cyclo*- Ethylene-1/4/addition or **(4 + 2) *cyclo*-[Bu *t*-2-ene-1,4-diyl]-1/2/addition**, and so on



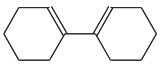
In the prototype *Diels–Alder reaction*, the double bond of an alkene adds 1,4- to a conjugated diene (a [4 + 2]-cycloaddition),[2169] so the product is always a cyclohexene. The cycloaddition is not limited to alkenes or to dienes (see Reaction **15-61**), but the substrate that reacts with the diene is called a *dienophile*. The reaction is of very broad scope[2170] and reactivity of dienes and dienophiles can be predicted based on analysis of *the* HOMOs[2171] and LUMOs of these species (FMO theory).[2172] Ethylene and simple alkenes make poor dienophiles, unless high temperatures and/or pressures are used. Most dienophiles are of the form —C=C—Z or Z—C=C—Z′, where Z and Z′ are

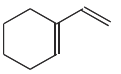
[2165] Kauffmann, T. *Top. Curr. Chem.* ***1980****, 92,* 109, pp. 111–116; *Angew. Chem. Int. Ed.* ***1974****, 13*, 627.
[2166] Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* ***1972****, 11,* 292.
[2167] See Beak, P.; Burg, D.A. *J. Org. Chem.* ***1989****, 54,* 1647.
[2168] See Noyori, R.; Hayakawa, Y. *Tetrahedron* ***1985****, 41*, 5879.
[2169] Wasserman, A. *Diels–Alder Reactions* Elsevier, NY, ***1965***; Roush, W.R. *Adv. Cycloaddit.* ***1990****, 2,* 91; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis,* Pergamon, Elmsford, NY, ***1990***; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980****, 80,* 63; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977****, 16,* 10; Sauer, J. *Angew. Chem. Int. Ed.* ***1966****, 5,* 211; ***1967****, 6,* 16; Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions,* Springer, NY, ***1984***; Deslongchamps, P. *Aldrichimica Acta* ***1991****, 24*, 43; Craig, D. *Chem. Soc. Rev.* ***1987****, 16,* 187. For a long list of references to various aspects of the Diels–Alder reaction, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 523–544.
[2170] See Konovalov, A.I. *Russ. Chem. Rev.* ***1983****, 52*, 1064.
[2171] See Nelson, D.J.; Li, R.; Brammer, C. *J. Org. Chem.* ***2001****, 66*, 2422.
[2172] Spino, C.; Rezaei, H.; Dory, Y.L. *J. Org. Chem.* ***2004****, 69*, 757. For tables of HOMOs and LUMOs for dienes and dienophiles, see Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 999–1032, especially pp. 1003–1004 and 1008–1009.

electron-withdrawing groups[2173] (e.g., CHO, COR,[2174] CO_2H, CO_2R, COCl, COAr, CN,[2175] NO_2,[2176] Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2CO_2H, halogen, $PO(OEt)_2$,[2177] or C=C). In the last case, the dienophile is itself a diene.[2178]

The low reactivity of simple alkenes can be overcome by incorporating an electron-withdrawing group to facilitate the cycloaddition, as indicated above. Electron-withdrawing groups may be incorporated to facilitate the *Diels–Alder reaction* and then removed after cycloaddition. An example is phenyl vinyl sulfone ($PhSO_2CH=CH_2$),[2179] and the $PhSO_2$ group can be easily removed with Na—Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide ($PhSOCH=CH_2$) can be used as a synthon for acetylene.[2180] In this case, PhSOH is lost from the sulfoxide product (Reaction **17-12**).


141


142


143

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it.[2181] For the dienophile, it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. The s-cis (cisoid) conformation is required for the cycloaddition,[2182] and acyclic dienes are conformationally mobile so the s-cis conformation will be available.[2183] Cyclic dienes, in which the s-cis conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the s-cis conformation by rotation.[2184] Dienes can be open-chain, inner-ring (e.g., **141**), outer-ring[2185] (e.g., **142**), across rings (e.g., **143**), or inner–outer (e.g., **145**), except that they may not be frozen into a s-trans (transoid) conformation (see category 3). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.[2186]

[2173] See Domingo, L.R. *Eur. J. Org. Chem.* ***2004***, 4788.
[2174] Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* ***1990****, 22,* 131.
[2175] See Butskus, P.F. *Russ. Chem. Rev.* ***1962****, 31*, 283; Also see Ciganek, E.; Linn, W.J.; Webster, O.W. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 449–453.
[2176] See Novikov, S.S.; Shuekhgeimer, G.A.; Dudinskaya, A.A. *Russ. Chem. Rev.* ***1960****, 29,* 79.
[2177] McClure, C.K.; Herzog, K.J.; Bruch, M.D. *Tetrahedron Lett.* ***1996****, 37*, 2153.
[2178] Johnstone, R.A.W.; Quan, P.M. *J. Chem. Soc.* ***1963***, 935.
[2179] Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.* ***1983****, 48*, 4976; Kinney, W.A.; Crouse, G.D.; Paquette, L.A. *J. Org. Chem.* ***1983****, 48,* 4986.
[2180] De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* ***1984****, 49,* 596; Hermeling, D.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1984****, 23*, 233; De Lucchi, O.; Pasquato, L. *Tetrahedron* ***1988****, 44,* 6755.
[2181] See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* ***2002****, 58*, 4417.
[2182] For ground state conformations, see Bur, S.K.; Lynch, S.M.; Padwa, A. *Org. Lett.* ***2002****, 4*, 473.
[2183] For a discussion of conformational thermodynamic and kinetic parameters of methyl 1,3-butadienes, see Squillacote, M.E.; Liang, F. *J. Org. Chem.* ***2005****, 70,* 6564.
[2184] Sauer, J.; Lang, D.; Mielert, A. *Angew. Chem. Int. Ed.* ***1962****, 1,* 268; Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962****, 1,* 269. See, however, Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* ***1979****, 112*, 862.
[2185] See Charlton, J.L.; Alauddin, M.M. *Tetrahedron* ***1987****, 43,* 2873; Oppolzer, W. *Synthesis* ***1978***, 793.
[2186] For a monograph on dienes, with tables showing > 800 types, see Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction,* Wiley, NY, ***1990***. See Danishefsky, S. *Chemtracts: Org. Chem.* ***1989****, 2*, 273; Petrzilka, M.; Grayson, J.I. *Synthesis* ***1981***, 753; Smith, M.B. *Org. Prep. Proced. Int.* ***1990****, 22,* 315; Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* ***2003****, 68*, 9809; Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* ***2002****, 122*, 5950.

While *Diels–Alder reactions* generally require no catalyst, Lewis acids are effective catalysts,[2187] particularly those in which Z in the dienophile is a C=O or C=N group.[2188] Chemoselectivity is related to the choice of Lewis acid or Brønsted–Lowry acid catalyst.[2189] A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of endo addition,[2190] and, in the case of enantioselective reactions, the extent of enantioselectivity. Copper catalysts have been used.[2191] Brønsted acids have also been used to accelerate the rate of the *Diels–Alder reaction*.[2192] *Diels–Alder reactions* have been done in ionic liquids (see Sec. 9.D.iii).[2193] Lanthanum triflate [$La(OTf)_3$] has been reported as a reusable catalyst[2194] and Me_3SiNTf_2 has been used as a green Lewis acid catalyst.[2195] Cationic *Diels–Alder* catalysts have been developed (e.g., oxazaborolidine catalysts).[2196] Some *Diels–Alder reactions* can also be catalyzed by the addition of a stable cation radical,[2197] for example, tris(4-bromophenyl)aminium hexachloroantimonate ($Ar_3N^{\bullet+}$ $SbCl_6^-$).[2198] Zirconocene-catalyzed cationic *Diels–Alder reactions* are known.[2199] Certain antibodies have been developed that catalyze *Diels–Alder reactions*.[2200] Photochemically induced *Diels–Alder reactions* are also known.[2201]

A number of other methods have been reported for the acceleration of *Diels–Alder reactions*,[2202] including the use of microwave irradiation,[2203] ultrasound,[2204] absorption of the reactants on chromatographic absorbents,[2205] via encapsulation techniques,[2206] and the

[2187] Avalos, M.; Babiano, R.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palacios, J.C.; Silva, M.A. *J. Org. Chem.* ***2000****, 65*, 6613; Kiselev, V.D.; Konovalov, A.I. *Russ. Chem. Rev.* ***1989****, 58*, 230; Zheng, M.; Zhang, M.-H.; Shao, J.-G.; Zhong, Q. *Org. Prep. Proceed. Int.* ***1996****, 28*, 117; Yamabe, S.; Minato, T. *J. Org. Chem.* ***2000****, 65*, 1830; Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* ***2000****, 41*, 9561.

[2188] For a discussion of the effect of Lewis acids, see Celebi-Olcum, N.; Ess, D.H.; Aviyente, V.; Houk, K.N. *J. Org. Chem.* ***2008****, 73, 7472*.

[2189] Nakashima, D.; Yamamoto, H. *Org. Lett.* ***2005****, 7*, 1251; Shen, J.; Tan. C.-H. *Org. Biomol. Chem.* ***2008***, *6*, 3229.

[2190] See Alston, P.V.; Ottenbrite, R.M. *J. Org. Chem.* ***1975****, 40,* 1111.

[2191] Reymond, S.; Cossy, J. *Chem. Rev.* ***2008****, 108*, 5359.

[2192] Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc,* ***1996****, 118*, 3049.

[2193] For a study of the influence of Lewis acids in ionic liquids, see Silvero, G.; Arévalo, M.J.; Bravo, J.L.; Ávalos, M.; Jiménez, J.L.; López, I. *Tetrahedron* ***2005****, 61,* 7105. See López, I.; Silvero, G.; Arévalo, M.J.; Babiano, R.; Palacios, J.C.; Bravo, J.L. *Tetrahedron* ***2007****, 63,* 2901.

[2194] Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* ***1992****, 33*, 6815.

[2195] Mathieu, B.; Ghosez, L. *Tetrahedron* ***2002****, 58*, 8219.

[2196] See Sprott, K.T.; Corey, E.J. *Org. Lett.* ***2003****, 5,* 2465; Corey, E.J.; Shibata, T.; Lee, T.W. *J. Am. Chem. Soc.* ***2002****, 124*, 3808; Ryu, D.H.; Lee, T.W.; Corey, E.J. *J. Am. Chem. Soc.* ***2002****, 124,* 9992.

[2197] Gao, D.; Bauld, N.L. *J. Org. Chem.* ***2000****, 65*, 6276. See Saettel, N.J.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* ***2001***, 1429.

[2198] For a review, see Bauld, N.L. *Tetrahedron* ***1989****, 45*, 5307.

[2199] Wipf, P.; Xu, W. *Tetrahedron* ***1995****, 51*, 4551.

[2200] Zhang, X.; Deng, Q.; Yoo, S.H.; Houk, K.N. *J. Org. Chem.* ***2002****, 67*, 9043.

[2201] Pandey, B.; Dalvi, P.V. *Angew. Chem. Int. Ed.* ***1993****, 32*, 1612.

[2202] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1037–1049.

[2203] Jankowski, C.K.; LeClair, G.; Bélanger, J.M.R.; Paré, J.R.J.; Van Calsteren, M.-R. *Can. J. Chem.* ***2001****, 79*, 1906. For a review, see de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* ***2000***, 3659; Kaval, N.; Dehaen, W.; Kappe, C.O.; van der Eycken, E. *Org. Biomol. Chem.* ***2004****, 2*, 154.

[2204] Raj. C.P.; Dhas, N.A.; Cherkinski, M.; Gedanken, A.; Braverman, S. *Tetrahedron Lett.* ***1998****, 39*, 5413.

[2205] Veselovsky, V.V.; Gybin, A.S.; Lozanova, A.V.; Moiseenkov, A.M.; Smit, W.A.; Caple, R. *Tetrahedron Lett.* ***1988****, 29,* 175.

[2206] Kang, J.; Hilmersson, G.; Sartamaría, J.; Rebek Jr., J. *J. Am. Chem. Soc.* ***1998****, 120*, 3650; Diego-Castro, M.J.; Hailes, H.C. *Tetrahedron Lett.* ***1998****, 39*, 2211.

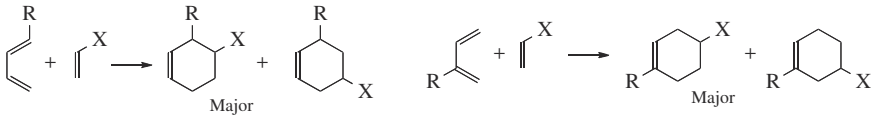
use of an ultracentrifuge[2207] (one of several ways to achieve reaction at high pressures).[2208] Solid-state *Diels–Alder reactions* are known.[2209] One of the most common methods is to use water as a solvent or a cosolvent (a hydrophobic effect).[2210] Catalysts have been developed for aq *Diels–Alder reactions*[2211] that are suitable for ionic *Diels–Alder reactions*.[2212] There are cases of hydrogen-bonding acceleration.[2213] The influence of the hydrophobicity of reactants on the reaction has been examined,[2214] as has micellular effects.[2215] Another alternative reaction medium is the use of 5M $LiClO_4$ in Et_2O as solvent.[2216] An alternative to lithium perchlorate in ether is lithium triflate in acetonitrile.[2217] The addition of HPO_4^- to an aq ethanol solution has also been shown to give a small rate enhancement.[2218] This appears to be the only case where an anion is responsible for a rate enhancement. The *retro-Diels–Alder reaction* has also been done in water.[2219]

Note that *Diels–Alder reactions* have been done with supercritical carbon monoxide[2220] and with supercritical water[2221] as solvents. *Diels–Alder reactions* on solid supports also have been reported,[2222] and zeolites have been used in conjunction with catalytic agents.[2223] Alumina has been used to promote *Diels–Alder reactions*.[2224] *Diels–Alder reactions* can be done in ionic liquids,[2225] including asymmetric *Diels–Alder reactions*.[2226] Note that the rate of *Diels–Alder reactions* is faster in water than in ionic liquids.[2227]

When an unsymmetrical diene adds to an unsymmetrical dienophile, regioisomeric products (not counting stereoisomers) are possible. Rearrangements have been encountered in some cases.[2228] In simple cases, 1-substituted dienes give cyclohexenes with a 1,2-

[2207] Dolata, D.P.; Bergman, R. *Tetrahedron Lett.* ***1987****, 28*, 707.
[2208] For reviews, see Isaacs, N.S.; George, A.V. *Chem. Br.* ***1987***, 47–54; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978****, 78*, 407. See also, Firestone, R.A.; Smith, G.M. *Chem. Ber.* ***1989****, 122,* 1089.
[2209] Kim, J.H.; Hubig, S.M.; Lindeman, S.V.; Kochi, J.K. *J. Am. Chem. Soc.* ***2001****, 123*, 87.
[2210] Breslow, R. *Acc. Chem. Res.* ***1991****, 24,* 159; Breslow, R.; Rizzo, C.J. *J. Am. Chem. Soc.* ***1991****, 113*, 4340; Engberts, J.B.F.N. *Pure Appl. Chem.* ***1995****, 67*, 823; Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* ***1993****, 93*, 741; Otto, S.; Blokzijl, W.; Otto, S.; Egberts, J.B.F.N. *Pure. Appl. Chem.* ***2000****, 72*, 1365; Deshpande, S.S.; Kumar, A. *Tetrahedron* ***2005****, 61*, 8025; Hayashi, Y.; Takeda, M.; Shoji, M.; Morita, M. *Chem. Lett.* ***2007****, 36*, 68.
[2211] See Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* ***2001***, 439; Otto, S.; Engberts, J.B.F. N. *Tetrahedron Lett.* ***1995****, 36*, 2645
[2212] Chavan, S.P.; Sharma, P.; Krishna, G.R.; Thakkar, M. *Tetrahedron Lett.* ***2003****, 44*, 3001.
[2213] Pearson, R.J.; Kassianidis, E.; Philip, D. *Tetrahedron Lett.* ***2004****, 45*, 4777.
[2214] Meijer, A.; Otto, S.; Engberts, J.B.F.N. *J. Org. Chem.* ***1998****, 63*, 8989.
[2215] Jaeger, D.A.; Wang, J. *Tetrahedron Lett.* ***1992****, 33*, 6415.
[2216] Grieco, P.A.; Handy, S.T.; Beck, J.P. *Tetrahedron Lett.* ***1994****, 35*, 2663. See Handy, S.T.; Grieco, P.A.; Mineur, C.; Ghosez, L. *Synlett* ***1995***, 565.
[2217] Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* ***2000***, 877.
[2218] Pai, C.K.; Smith, M.B. *J. Org. Chem.* ***1995****, 60,* 3731.
[2219] Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1997****, 62*, 2039.
[2220] Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. *Chem. Commun.* ***1999***, 1459. For an asymmetric cycloaddition, see Fukuzawa, S.-i.; Metoki, K.; Esumi, S.-i. *Tetrahedron* ***2003****, 59*, 10445.
[2221] Harano, Y.; Sato, H.; Hirata, F. *J. Am. Chem. Soc.* ***2000****, 122*, 2289.
[2222] Yli-Kauhaluoma, J. *Tetrahedron* ***2001****, 57*, 7053.
[2223] Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. *Acta Chem. Scand.* ***1993****, 47*, 581.
[2224] Pagni, R.M.; Kabalka, G.W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* ***1993****, 49*, 6743.
[2225] Bini, R.; Chiappe, C.; Mestre, V.L.; Pomelli, C.S.; Welton, T. *Org. Biomol. Chem.* ***2008****, 6*, 2522. For reactions in low-melting sugar–urea-salt mixtures, see Imperato, G.; Eibler, E.; Niedermaier, J.; König, B. *Chem. Commun.* ***2005***, 1170.
[2226] Meracz, I.; Oh, T. *Tetrahedron Lett.* ***2003****, 44*, 6465.
[2227] Tiwari, S.; Kumar, A. *Angew. Chem. Int. Ed.* ***2006****, 45*, 4824.
[2228] Murali, R.; Scheeren, H.W. *Tetrahedron Lett.* ***1999****, 40*, 3029.

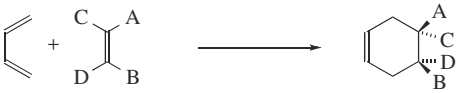
and a 1,3- substitution pattern. 2-Substituted dienes lead to 1,4- and 1,3-disubstituted products.



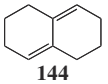
Although mixtures are often obtained, one usually predominates (the one shown lowed major above), but selectivity depends on the nature of the substituents on both diene and alkene. This regioselectivity, in which the "ortho" or "para" product is favored over the "meta", has been explained by molecular orbital considerations.[2229] When $X = NO_2$, regioselectivity to give the "ortho" or "para" product was very high at room temperature. This method, combined with subsequent removal of the NO_2 (see Reaction **19-67**), has been used to perform regioselective *Diels–Alder reactions*.[2230] Competing reactions are polymerization of the diene or dienophile, or both, and [1,2]-cycloaddition (**15-63**).

The stereochemistry of the *Diels–Alder reaction* can be considered from several aspects:[2231]

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.[2232] This means that groups that are cis in the alkene will be cis in the cyclohexene ring (A—B and C—D) and groups that are trans in the alkene will be trans in the cyclohexene ring (A—D and C—B).



2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans*,*trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives. This selectivity is predicted by disrotatory motion of the substituent in the transition state[2233] of the reaction (see **18-27**).
3. The diene must be in the s-cis conformation. If it is frozen into the s-trans conformation, as in **144**, the reaction does not take place. The diene either must be frozen into the s-cis conformation or must be able to achieve it during the reaction.



144

[2229] Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. *J. Org. Chem.* ***1983****, 48,* 5051; Kahn, S.D.; Pau, C.F.; Overman, L.E.; Hehre, W.J. *J. Am. Chem. Soc.* ***1986****, 108*, 7381.

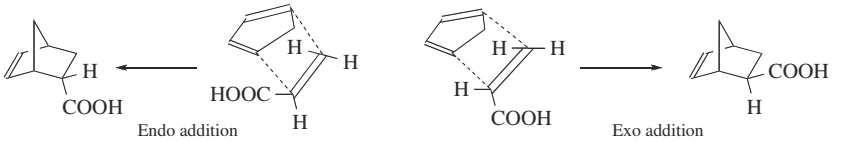
[2230] Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc. Perkin Trans. 1,* ***1987***, 1929. For another method of controlling regioselectivity, see Kraus, G.A.; Liras, S. *Tetrahedron Lett.* ***1989****, 30,* 1907.

[2231] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1023–1032, 1066–1075; Bakalova, S.M.; Santos, A.G. *J. Org. Chem.* ***2004****, 69*, 8475.

[2232] For an exception, see Meier, H.; Eckes, H.; Niedermann, H.; Kolshorn, H. *Angew. Chem. Int. Ed.* ***1987****, 26*, 1046.

[2233] Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* ***2002****, 67*, 6823.

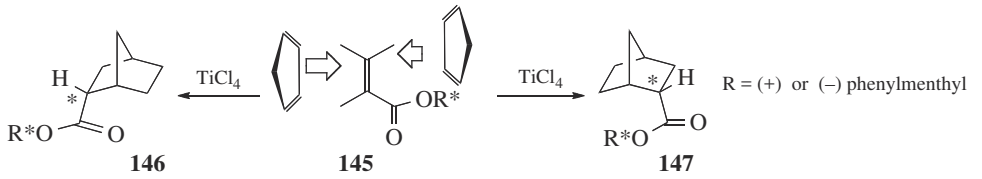
4. There are two possible ways in which addition can occur to a cyclic diene, if the dienophile is not symmetrical: say a monosubstituted alkene. The substituent on the dienophile (usually an electron-withdrawing substituent) may approach under the ring (*endo addition*), or away from the ring (*exo addition*):



Most of the time, the addition is predominantly endo; that is, the more bulky side of the alkene is under the ring, and this is probably true for open-chain dienes also.[2234] However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.[2235] An imidazolidone catalyst was used to give a 1:1.3 mixture favoring the exo isomer in a reaction of conjugated aldehydes and cyclopentadiene.[2236] Secondary orbital interactions.[2237] have been invoked, but this approach has been called into question.[2238] There has been a direct evaluation of such interactions, however.[2239] It has been argued that facial selectivity is not due to torsional angle decompression.[2240] The endo/exo ratio can be influenced by the nature of the solvent.[2241]

5. As seen previously, the *Diels–Alder reaction* can be both stereoselective and regioselective.[2242] In some cases, the *Diels–Alder reaction* can be made enantioselective,[2243] as described above. Solvent effects are important in such reactions.[2244] The role of reactant polarity on the course of the reaction has been examined.[2245] Most enantioselective *Diels–Alder reactions* have used a chiral dienophile (e.g., **145**) and an achiral diene,[2246] along with a Lewis acid catalyst (see below). In such cases, addition of the diene to the two

[2234] See Baldwin, J.E.; Reddy, V.P. *J. Org. Chem.* ***1989****, 54,* 5264. For a theoretical study for endo selectivity, see Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***1999****, 64*, 6697.
[2235] See Mülle, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J. *Chimia* ***1987****, 41*, 244.
[2236] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2000****, 122*, 4243.
[2237] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965****, 87*, 4388, 4389.
[2238] García, J.I.; Mayoral, J.A.; Salvatella, L. *Acc. Chem. Res.* ***2000****, 33*, 658; García, J.-I.; Mayoral, J.A.; Salvatella, L. *Eur. J. Org. Chem.* ***2005***, 85.
[2239] Arrieta, A.; Cossío, F.P.; Lecea, B. *J. Org. Chem.* ***2001****, 66*, 6178.
[2240] Hickey, E.R.; Paquette, L.A. *Tetrahedron Lett.* ***1994****, 35*, 2309, 2313.
[2241] Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* ***2003****, 44,* 93.
[2242] Domingo, L.R.; Picher, M.T.; Andrés, J.; Safont, V.S. *J. Org. Chem.* ***1997****, 62,* 1775. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 1023–1032, 1066–1075; Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* ***2008****, 130,* 8952.
[2243] See Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* ***1994****, 116*, 12089; Taschner, M.J. *Org. Synth: Theory Appl.* ***1989****, 1*, 1; Helmchen, G.; Karge, R.; Weetman, J. *Mod. Synth. Methods* ***1986****, 4,* 261; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1984****, 23,* 876. See also Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* ***1990****, 112*, 1136.
[2244] Ruiz-López, M.F.; Assfeld, X.; García, J.I.; Mayoral, J.A.; Salvatella, L. *J. Am. Chem. Soc.* ***1993****, 115*, 8780.
[2245] Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* ***1996****, 118*, 12562.
[2246] For the use of chiral dienes, see Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990****, 112,* 6743; ***1991****, 113*, 7630; Rieger, R.; Breitmaier, E. *Synthesis* ***1990***, 697.



146 **145** **147**

faces[2247] of **145** takes place at different rates, and **146** and **147** are formed in different amounts.[2248] An achiral compound can be converted to a chiral compound by a chemical reaction with a compound that is enantiopure. After the reaction, the resulting diastereomers can be separated, providing enantiopure compounds, each with a bond between the molecule of interest and chiral compound (a chiral auxiliary). Common chiral auxiliaries include chiral carboxylic acids, alcohols, or sultams. In the case illustrated, hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric *Diels–Alder reactions* have also been carried out with achiral dienes and dienophiles, but with an optically active catalyst.[2249] Many chiral catalysts have been developed.[2250] In many cases, asymmetric Lewis acids form a chiral complex with the dienophile.[2251] Chiral organocatalysts are increasingly important.[2252]

Triple bond compounds (—C≡C—Z or Z—C≡C—Z′) may be dienophiles,[2253] generating nonconjugated cyclohexadienes (**148**). This reaction can be catalyzed by transition metal compounds.[2254] Aromatic rings can be generated by cycloaddition of aryl alkynes.[2255] Allenes react as dienophiles, but without activating groups are

[2247] See Xidos, J.D.; Poirier, R.A.; Pye, C.C.; Burnell, D.J. *J. Org. Chem.* ***1998****, 63*, 105.

[2248] Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. *J. Chem. Soc. Perkin Trans. 1,* ***1990***, 426; Cativiela, C.; López, P.; Mayoral, J.A. *Tetrahedron: Asymmetry* ***1990****, 1,* 61.

[2249] Narasaka, K. *Synthesis* ***1991***, 1; Corey, E.J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* ***1991****, 113,* 728; Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* ***1991****, 64*, 387; Hawkins, J.M.; Loren, S. *J. Am. Chem. Soc.* ***1991****, 113,* 7794; Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. *J. Am. Chem. Soc.* ***1999****, 121*, 7582.

[2250] See Corey, E.J. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1651; Doyle, M.P.; Phillips, I.M.; Hu, W. *J. Am. Chem. Soc.* ***2001****, 123*, 5366; Owens, T.D.; Hollander, F.J.; Oliver A.G.; Ellman, J.A. *J. Am. Chem. Soc.* ***2001****, 123,* 1539; Faller, J.W.; Grimmond, B.J.; D'Alliessi, D.G. *J. Am. Chem. Soc.* ***2001****, 123*, 2525; Bolm, C.; Simic, O. *J. Am. Chem. Soc.* ***2001****, 123*, 3830; Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* ***2003****, 44,* 3671.

[2251] Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem Soc.* ***1994****, 116*, 1657. See Sibi, M.P.; Venkatraman, L.; Liu, M.; Jaspersé, C.P. *J. Am. Chem. Soc.* ***2001****, 123*, 8444.

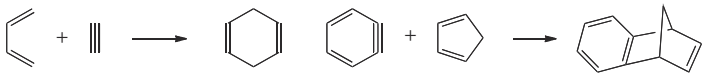
[2252] Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* ***2005****, 127,* 10504; Liu, D.; Canales, E.; Corey, E.J. *J. Am. Chem. Soc.* ***2007****, 129,* 1498; Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B.M.; Deng, L. *J. Am. Chem. Soc.* ***2007****, 129,* 6364; Payette, J.N.; Yamamoto, H. *J. Am. Chem. Soc.* ***2007****, 129,* 9536; Singh, R.P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* ***2008****, 130,* 2422; Futatsugi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***2005****, 44,* 1484; Paddon-Row, M.N.; Kwan, L.C.H.; Willis, A.C.; Sherburn, M.S. *Angew. Chem. Int. Ed.* ***2008****, 47,* 7013.

[2253] See Bastide, J.; Henri-Rousseau, O. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 447–522, Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 477–508.

[2254] See Paik, S.-J.; Son, S.U.; Chung, Y.K. *Org. Lett.* ***1999****, 1*, 2045.

[2255] This type of Diels–Alder reaction has been called the Dehydro-Diels–Alder. See Wessig, P.; Gunnar Müller, G. *Chem. Rev.* ***2008****, 108,* 2051; Dunetz, J.R.; Danheiser, R.L. *J. Am. Chem. Soc.* ***2005****, 127,* 5776; Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S.J.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* ***2007****, 129,* 645.

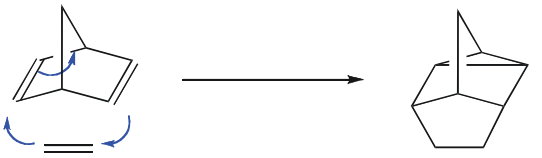
very poor dienophiles.[2256] Ketenes, however, do not undergo *Diels–Alder reactions*.[2257]



148 **149**

Many interesting compounds can be prepared by the *Diels–Alder reaction*,[2258] some of which would be hard to make in any other way. Some aromatic compounds can behave as dienes,[2259] but benzene is very unreactive toward dienophiles,[2260] and very few dienophiles (one of them is benzyne) have been reported to give *Diels–Alder* adducts with it.[2261] Benzynes (e.g., **149**), although not isolable, act as dienophiles and can be trapped with dienes.[2262] The interesting compound triptycene can be prepared by a *Diels–Alder reaction* between benzyne and anthracene.[2263] Naphthalene and phenanthrene are poor reaction partners, although naphthalene has given *Diels–Alder addition* at high pressures.[2264] Anthracene and other compounds with at least three linear benzene rings give *Diels–Alder reactions* readily.

For both all-carbon and hetero systems, the "diene" can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, for example,[2265]

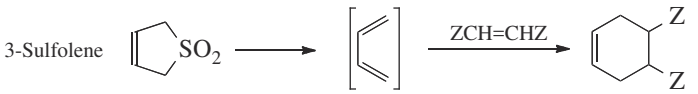


This last reaction is known as the *homo-Diels–Alder reaction*. A similar reaction has been reported with alkynes, using a mixture of a Co complex, ZnI_2, and tetrabutylammonium borohydride.[2266]

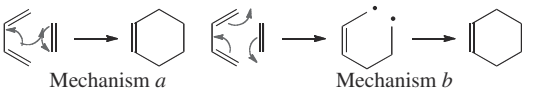
[2256] See Hopf, H. in Landor, S.R. *The Chemistry of Allenes,* Vol. 2, Academic Press, NY, ***1982***, pp. 563–577. See Nendel, M.; Tolbert, L.M.; Herring, L.E.; Islam, Md.N.; Houk, K.N. *J. Org. Chem.* ***1999****, 64*, 976.
[2257] Ketenes react with conjugated dienes to give 1,2-addition (see Reaction **15-49**).
[2258] See Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1669.
[2259] For a review, see Wagner-Jauregg, T. *Synthesis* ***1980***, 165, 769. See also, Balaban, A.T.; Biermann, D.; Schmidt, W. *Nouv. J. Chim.* ***1985****, 9*, 443.
[2260] However, see Chordia, M.D.; Smith, P.L.; Meiere, S.H.; Sabat, M.; Harman, W.D. *J. Am. Chem. Soc.* ***2001****, 123*, 10756.
[2261] Friedman, L. *J. Am. Chem. Soc.* ***1967****, 89*, 3071; Liu, R.S.H.; Krespan, C.G. *J. Org. Chem.* ***1969****, 34*, 1271.
[2262] See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*; Academic Press, NY, ***1967***, pp. 200–239; Bryce, M. R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981****, 28*, 183–229. Also see Liu, W.; You, F.; Mocella, C.J.; Harman, W. D. *J. Am. Chem. Soc.* ***2006****, 128*, 1426.
[2263] Wittig, G.; Niethammer, K. *Chem. Ber.* ***1960****, 93,* 944; Wittig, G.; Härle, H.; Knauss, E.; Niethammer, K. *Chem. Ber.* ***1960****, 93,* 951.
[2264] Plieninger, H.; Wild, D.; Westphal, J. *Tetrahedron* ***1969****, 25*, 5561.
[2265] See Paquette, L.A.; Kesselmayer, M.A.; Künzer, H. *J. Org. Chem.* ***1988****, 53,* 5183.
[2266] Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* ***2000****, 41*, 6757.

Intramolecular versions of the *Diels–Alder reaction* are well known,[2267] and this is a powerful method for the synthesis of mono- and polycyclic compounds.[2268] There are many examples and variations, including Lewis acid catalysis.[2269] The origin of cis/trans stereoselectivity has been examined using density functional theory.[2270]

Internal *Diels–Alder reactions* can be viewed as linking the diene and alkene by a tether, usually of carbon atoms. Dienophile twisting and substituent effects influence the rate of cycloaddition.[2271] If the tether is replaced by functional groups that allow the selectivity inherent to the intramolecular cycloaddition, but can be cleaved afterward, a powerful modification is available. Indeed, such tethered cycloaddition reactions are increasingly common. After cycloaddition, the tether can be cleaved to give a functionalized cyclohexene derivative. Such tethered reactions allow enhancement of stereoselectivity[2272] and sometimes reactivity, relative to an untethered reaction, giving an indirect method for enhancing those parameters. Tethers or linkages include C—O—SiR_2—C[2273] or a C—O—SiR_2—O—C,[2274] or hydroxamides.[2275] The nature of the tether plays a role in cis/trans selectivity for the intramolecular reaction.[2276] Transient tethers can be used, as in the reaction of a diene having an allylic alcohol unit in a reaction with allyl alcohol, with $AlMe_3$ to give the cycloadduct with good selectivity.[2277]

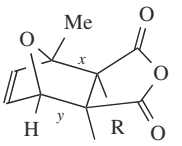


The *Diels–Alder reaction* is usually reversible, although the retro reaction typically occurs at significantly higher temperatures than the forward reaction. However, the reaction is reversible[2278] and this fact has been used. A convenient substitute for butadiene in the *Diels–Alder reaction* is the compound 3-sulfolene, since the latter is a solid, which is easy to handle while the former is a gas.[2279] Butadiene is generated *in situ* by a reverse *Diels–Alder reaction* (see **17-20**).



[2267] For a review of natural product syntheses using Diels–Alder reactions, see Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* ***2005****, 105,* 4779.
[2268] Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977****, 16*, 1; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980****, 80*, 63 (see p. 67); Fallis, A.G. *Can. J. Chem.* ***1984****, 62*, 183; Smith, M.B. *Org. Prep. Proceed. Int.* ***1990****, 22,* 315.
[2269] Au catalyst: Nieto-Oberhuber, C.; López, S.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2005****, 127*, 6178.
[2270] Paddon-Row, M.N.; Moran, D.; Jones, G.A.; Sherburn, M.S. *J. Org. Chem.* ***2005****, 70,* 10841.
[2271] Khuong, K.S.; Beaudry, C.M.; Trauner, D.; Houk, K.N. *J. Am. Chem. Soc.* ***2005****, 127*, 3688.
[2272] See Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* ***2001****, 66*, 1938.
[2273] Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* ***1992****, 114*, 7578.
[2274] Craig, D.; Reader, J.C. *Tetrahedron Lett.* ***1992****, 33*, 6165.
[2275] Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S.; Kobayashi, H. *J. Am. Chem. Soc.* ***2001****, 123*, 4607.
[2276] Paddon-Row, M.N.; Longshaw, A.I.; Willis, A.C.; Sherburn, M.S. *Chemistry: Asian J.* ***2009****, 4,* 126.
[2277] Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* ***2000****, 2*, 1283.
[2278] See Ichihara, A. *Synthesis* ***1987***, 207; Lasne, M.; Ripoll, J.L. *Synthesis* ***1985***, 121; Kwart, H.; King, K. *Chem. Rev.* ***1968****, 68,* 415.
[2279] Sample, Jr., T.E.; Hatch, L.F. *Org. Synth.* ***VI***, 454. For a review, see Chou, T.; Tso, H. *Org. Prep. Proced. Int.* ***1989****, 21*, 257.

There are, broadly speaking, three possible mechanisms that have been considered for the uncatalyzed *Diels–Alder reaction*.[2280] In mechanism *a*, there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In mechanism *b*, one end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened.[2281] A diradical formed in this manner must be a singlet; that is, the two unpaired electrons must have opposite spins, by an argument similar to that outlined in Section 5.C.i. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. Electrophilicity–nucleophilicity indices have been analyzed to understand the mechanism of polar *Diels–Alder reactions*.[2282] There have been many mechanistic investigations of the *Diels–Alder reaction*. The bulk of the evidence suggests that most *Diels–Alder reactions* take place by the one-step cyclic mechanism *a*,[2283] although it is possible that a diradical[2284] or even a diion[2285] mechanism may be taking place in some cases. Radical cation *Diels–Alder reactions* have been considered.[2286] The main evidence in support of mechanism *a* is as follows: (1) the reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of *Diels–Alder reactions* depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (3) It was shown that, in the decomposition of **150**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[2287] If bond *x* were



150

I: R = H, R' = D

II: R = D, R' = H

to break before bond *y*, there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a *Diels–Alder reaction*, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*.

[2280] See Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* ***1980****, 19,* 779; Houk, K.N. *Top. Curr. Chem.* ***1979****, 79*, 1; Babichev, S.S.; Kovtunenko, V.A.; Voitenko, Z.V.; Tyltin, A.K. *Russ. Chem. Rev.* ***1988****, 57*, 397. For a discussion of synchronous versus nonsynchronous mechanisms see Beno, B.R.; Houk, K.N.; Singleton, D.A. *J. Am. Chem. Soc.* ***1996****, 118*, 9984; Singleton, D.A.; Schulmeier, B.E.; Hang, C.; Thomas, A.A.; Leung, S.-W.; Merrigan, S.R. *Tetrahedron* ***2001****, 57*, 5149. Also see, Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1993****, 115*, 7478.

[2281] See Orlova, G.; Goddard, J.D. *J. Org. Chem.* ***2001****, 66*, 4026.

[2282] Domingo, L.R.; Sáez, J.A. *Org. Biomol. Chem.* ***2009****, 7*, 3576. See also, Soto-Delgado, J.; Domingo, L.R.; Contreras, R. *Org. Biomol. Chem.* ***2010****, 8,* 3678.

[2283] For a contrary view, see Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1986****, 108*, 5771. For arguments against this view, see Houk, K.N.; Lin, Y.; Brown, F.K. *J. Am. Chem. Soc.* ***1986****, 108*, 554; Gajewski, J. J.; Peterson, K.B.; Kagel, J.R.; Huang, Y.C.J. *J. Am. Chem. Soc.* ***1989****, 111,* 9078.

[2284] See Van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinet.* ***1987****, 19*, 363; ***1989****, 21*, 967.

[2285] See Gassman, P.G.; Gorman, D.B. *J. Am. Chem. Soc.* ***1990****, 112*, 8624.

[2286] Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* ***1999****, 121*, 6730.

[2287] Seltzer, S. *J. Am. Chem. Soc.* ***1965****, 87,* 1534; Gajewski, J.J. *Isot. Org. Chem.* ***1987****, 7,* 115–176.

Subsequently, a similar experiment was carried out on the forward reaction[2288] and the result was the same. There is other evidence for mechanism *a*.[2289] However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous.[2290] In the transition state of a synchronous reaction both new σ bonds would be formed to the same extent, but a *Diels–Alder reaction* with nonsymmetrical components might very well be nonsynchronous;[2291] that is, it could have a transition state in which one bond has been formed to a greater degree than the other.[2291,2292] A biradical mechanism has been proposed for some *Diels–Alder reactions*.[2293]

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (see above) indicate that the diene behaves as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, although the latter is normally the most reactive dienophile known. This diene is said to be the electrophile in its *Diels–Alder reactions*.[2294] Reactions of this type are said to proceed with *inverse electron demand*.[2295] It is known that alkynylboronates participate in inverse electron demand cyclization.[2296]

The *Diels–Alder reaction* generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of alkenes to cyclobutanes (Reaction **15-63**) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann[2297] showed that these contrasting results can be explained by the *principle of conservation of orbital symmetry*, which predicts that certain reactions are allowed and others are forbidden. The orbital-symmetry rules (also called the *Woodward–Hoffmann rules*)[2298] apply *only to concerted reactions* (e.g., mechanism *a*) and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. In a separate work, Fukui used MO arguments to

[2288] Van Sickle, D.E.; Rodin, J.O. *J. Am. Chem. Soc.* ***1964****, 86,* 3091.

[2289] See Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* ***1980****, 113,* 1663; Tolbert, L.M.; Ali, M.B. *J. Am. Chem. Soc.* ***1981****, 103,* 2104.

[2290] For an example of a study of a reaction that is concerted but asynchronous, see Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. *J. Org. Chem.* ***2000****, 65*, 8251

[2291] Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1989****, 111*, 9172; Lehd, M.; Jensen, F. *J. Org. Chem.* ***1990****, 55,* 1034.

[2292] See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Org. Chem.* ***2003****, 68*, 3884.

[2293] de Echagüen, C.O.; Ortuño, R.M. *Tetrahedron Lett.* ***1995****, 36*, 749. See Li, Y.; Padias, A.B.; Hall, Jr., H.K. *J. Org. Chem.* ***1993****, 58*, 7049 for a discussion of diradicals in concerted Diels–Alder reactions.

[2294] Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962****, 1,* 269.

[2295] Boger, D.L.; Patel, M. *Prog. Heterocycl. Chem.* ***1989****, 1*, 30. Also see, Pugnaud, S.; Masure, D.; Hallé, J.-C.; Chaquin, P. *J. Org. Chem,.* ***1997****, 62*, 8687; Wan, Z.-K.; Snyder, J.K. *Tetrahedron Lett.* ***1998****, 39*, 2487.

[2296] For a mechanistic study, see Gomez-Bengoa, E.; Helm, M.D.; Plant, A.; Harrity, J.P.A. *J. Am. Chem. Soc.* ***2007****, 129,* 2691.

[2297] Fleming, I. *Pericyclic Reactions* Oxford University Press, Oxford, ***1999***, pp. 31–56; Gilchrist, T.L.; Storr, R. C. *Organic Reactions and Orbital Symmetry* 2nd ed., Cambridge University Press, Cambridge, ***1979***; Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, ***1976***; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry,* Academic Press, NY, ***1970*** [the text of this book also appears in *Angew. Chem. Int. Ed.* ***1969****, 8*, 781]; Simonetta, M. *Top. Curr. Chem.* ***1973****, 42*, 1; Houk, K.N. *Surv. Prog. Chem.* ***1973****, 6,* 113; Gill, G.B. *Q. Rev. Chem. Soc.* ***1968****, 22*, 338; Miller, S.I. *Adv. Phys. Org. Chem.* ***1968****, 6*, 185; Miller, S.I. *Bull. Soc. Chim. Fr.* ***1966***, 4031.

[2298] Chattaraj, P.K.; Fuentealba, P.; Gómez, B.; Contreras, R. *J. Am. Chem. Soc.* ***2000****, 122*, 348.

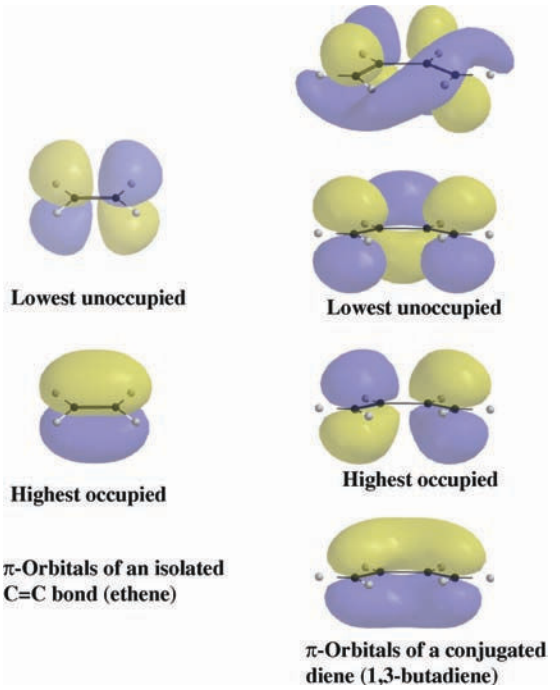


FIG. 15.2. Schematic drawings of the π orbitals of an isolated C=C bond and a conjugated diene

explain these reactions. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others.[2299] Of these three, two will be discussed: the FMO and the Möbius–Hückel method. The third, called the correlation-diagram method,[2300] is less convenient to apply than the other two.

The Frontier-Orbital Method[2301]

As applied to cycloaddition reactions, the rule is that *reactions are allowed only when all overlaps between the HOMO of one reactant and the LUMO of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*.[2302] Recall that monoalkenes have two π molecular orbitals (Sec. 1.D) and that conjugated dienes have four (Sec. 2.C), as shown in Fig. 15.2. A concerted cyclization of two monoalkenes (a [2 + 2] reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Fig. 15.3). On the other

[2299] See Epiotis, N.D. *Theory of Organic Reactions*, Springer, NY, ***1978***; Ponec, R. *Collect. Czech. Chem. Commun.* ***1984****, 49*, 455; ***1985****, 50*, 1121; Hua-ming, Z.; De-xiang, W. *Tetrahedron* ***1986****, 42*, 515; Bernardi, F.; Olivucci, M.; Robb, M.A. *Res. Chem. Intermed.* ***1989****, 12,* 217; *Acc. Chem. Res.* ***1990****, 23,* 405.

[2300] See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry,* Academic Press, NY, ***1970***; *Angew. Chem. Int. Ed.* ***1969****, 8,* 781; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry,* 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–366; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 378–389; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 263–276.

[2301] Fukui, K.; Fujimoto, H. Bull. Chem. Soc. Jpn. **1967**, 40, 2018; **1969**, 42, 3399; Fukui, K. Acc. Chem. Res. **1971**, 4, 57; Houk, K.N. Acc. Chem. Res. **1975**, 8, 361. See Chu, S. Tetrahedron **1978**, 34, 645; Fleming, I. Pericyclic Reactions, Oxford University Press, Oxford, **1999**; Fukui, K. Angew. Chem. Int. Ed. **1982**, 21, 801.

[2302] For a discussion of molecules with small HOMO–LUMO gaps, see Perepichka, D.F.; Bryce, M.R. *Angew. Chem. Int. Ed.* **2005**, 44, 5370.

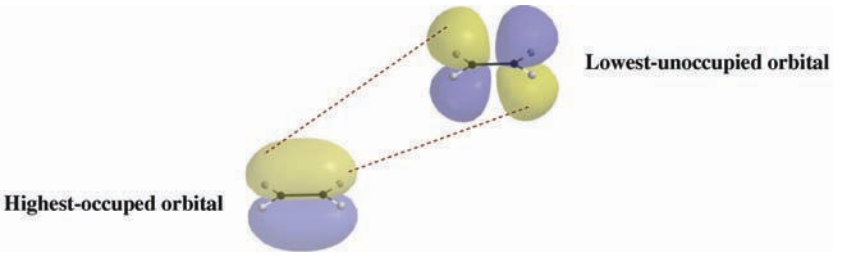


FIG. 15.3. Overlap of orbitals in a thermal [2 + 2]-cycloaddition

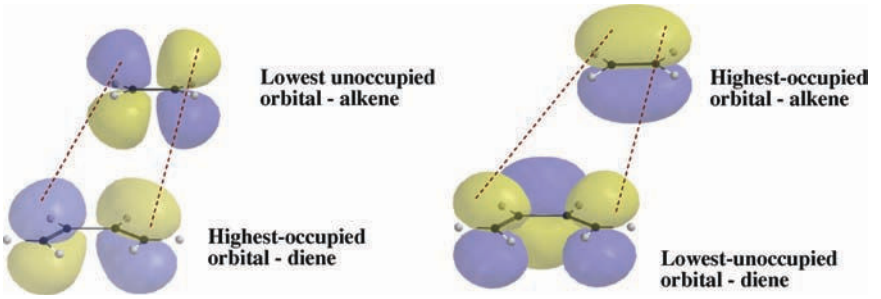


FIG. 15.4. Two ways for orbitals to overlap in a thermal [4 + 2]-cycloaddition

hand, the *Diels–Alder reaction* (a [4 + 2] reaction) is allowed, when considered from either direction (Fig. 15.4).

These considerations are reversed when the ring closures are photochemically induced, since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the [2 + 2] reaction is now allowed (Fig. 15.5) and the [4 + 2]-reaction is disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, *Diels–Alder* adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

The Möbius–Hückel Method[2303]

In this method, the orbital symmetry rules are related to the *Hückel aromaticity* rule discussed in Chapter 2.[2304] *Hückel's rule*, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle, we are not concerned with ground states, but with transition states. In the present method, do not examine the molecular orbitals themselves, but rather the *p* orbitals before they overlap to form the molecular orbitals. Such a set of *p* orbitals is called a *basis set* (Fig. 15.6). In investigating the possibility of a concerted reaction, the basis sets are put into the position they would occupy in the transition state. Figure 15.7 shows this for both the [2 + 2] and the [4 + 2] ring closures, looking for *sign inversions*. In Fig. 15.7, there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or*

[2303] Zimmerman, H.E. in Marchand, A.P.; Lehr , R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971***, *4,* 272; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia,* ***1971***, *25,* 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58,* 371.
[2304] See Morao, I.; Cossío, F.P. *J. Org. Chem.* ***1999***, *64*, 1868.

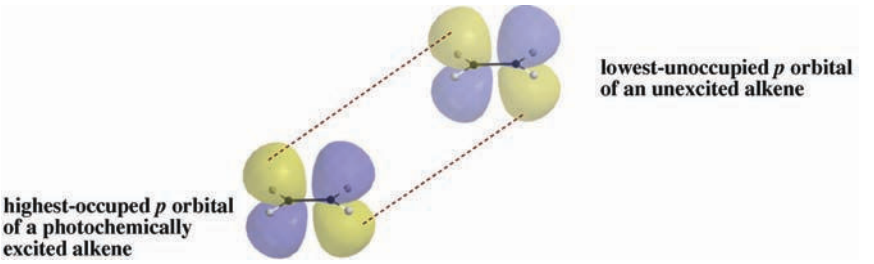


FIG. 15.5. Overlap of orbitals in a photochemical [2 + 2]-cycloaddition

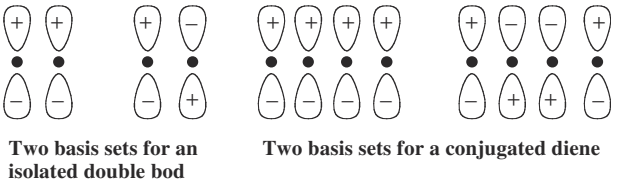


FIG. 15.6. Some basis sets

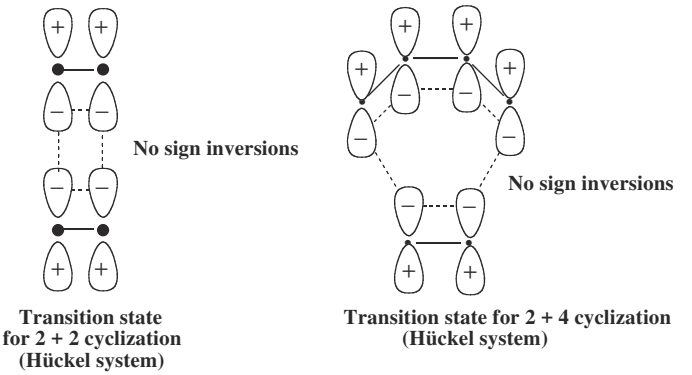


FIG. 15.7. Transition states illustrating Hückel–Möbius rules for cycloaddition reactions

an even number of sign inversions are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with *an odd number* of sign inversions are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Fig. 15.8).[2305] Möbius systems do not enter into either of these reactions, but an example of such a system is shown in Reaction **18.-28, B**. Double-twist *Möbius* aromaticity has been invoked in the *Diels–Alder* transition state for the reaction of a 5,6-di-*tert*-butyl substituted decapentaene.[2306]

The rule may then be stated: *A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is 4n + 2. A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is 4n*. For photochemical reactions, these rules are reversed. Since both the [4 + 2]- and [2 + 2]-cycloadditions are *Hückel* systems, the *Möbius–Hückel method* predicts that the [4 + 2]-reaction, with

[2305] See Hennigar, K.H.R.; Langler, R.F. *Austr. J. Chem.* ***2010****, 63,* 490.
[2306] Rzepa, H.S. *Chem. Commun.* ***2005***, 5220.

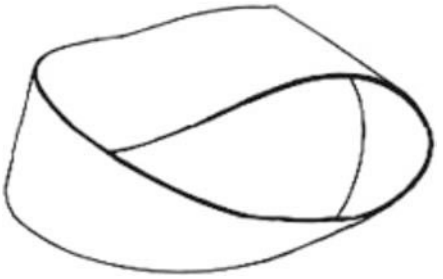


FIG. 15.8. A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together

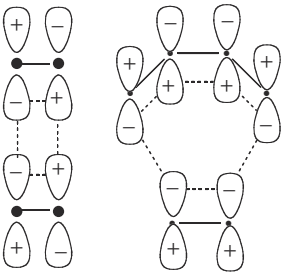


FIG. 15.9. Transition states of $\{2+2]$ - and $[4+2]$-cyclizations involving other basis sets

6 electrons, is thermally allowed, but the $[2+2]$-reaction is not. One the other hand, the $[2+2]$ -reaction is allowed photochemically, while the $[4+2]$-reaction is forbidden.

Note that both the $[2+2]$ and $[4+2]$ transition states are *Hückel* systems no matter what basis sets were chosen. For example, Fig. 15.9 shows other basis sets we might have chosen. In every case there will be zero or an even number of sign inversions.

Thus, the FMO and *Hückel–Möbius* methods (and the correlation-diagram method as well) lead to the same conclusions: Thermal $[4+2]$-cycloadditions and photochemical $[2+2]$-cycloadditions (and the reverse ring openings) are allowed, while photochemical $[4+2]$- and thermal $[2+2]$-ring closings (and openings) are forbidden.

Application of the same procedures to other ring closures shows that $[4+4]$- and $[2+6]$-ring closures and openings require photochemical induction while the $[4+6]$- and $[2+8]$-reactions can take place only thermally (see Reaction **15-53**). In general, cycloaddition reactions allowed thermally are those with $4n+2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms, which is where two σ bonds are formed (or broken) at about the same time.[2307] The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal *Diels–Alder reaction* (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given *Diels–Alder reaction* proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal $[2+2]$-cycloadditions in

[2307] See Lehr, R.E.; Marchand, A.P. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 1, Academic Press, NY, ***1977***, pp. 1–51.

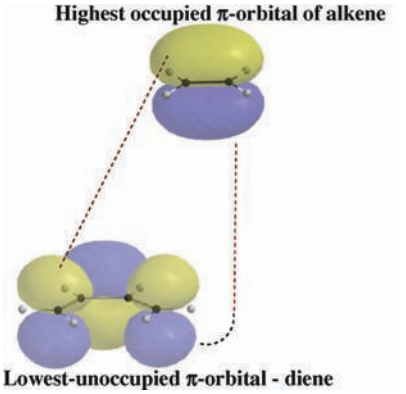


FIG. 15.10. Overlap of orbitals in an antarafacial thermal [4 + 2]-cycloaddition

which the molecules assume a face-to-face geometry cannot[2308] take place by a cyclic mechanism because their activation energies would be too high (however, see below). In Reaction **15-62** it will be seen that such reactions largely occur by two-step mechanisms. Similarly, [4 + 2]-photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism (mechanism *b*).[2309]

In all of the above discussions, it has been assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript *s* is used to designate this geometry, and a normal *Diels–Alder reaction* would be called a $[_{\pi}2_s + {}_{\pi}4_s]$-cycloaddition (the subscript π indicates that π electrons are involved in the cycloaddition). However, there is another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system, that is, they point in opposite directions. This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[_{\pi}2_s + {}_{\pi}4_s]$-cycloaddition (*a* stands for antarafacial). The FMO method shows that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a $[_{\pi}2_s + {}_{\pi}4_a]$ reaction to proceed, overlap between the highest-occupied π orbital of the alkene and the lowest-unoccupied π orbital of the diene would have to occur as shown in Fig. 15.10 , with a + lobe overlapping a −lobe. Since like signs are no



[2308] See Baldwin, J.E.; Andrist, A.H.; Pinschmidt, Jr., R.K. *Acc. Chem. Res.* ***1972****, 5*, 402; Berson, J.A. *Acc. Chem. Res.* ***1972****, 5*, 406; Baldwin, J.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 273–302.

[2309] See Sieber, W.; Heimgartner, H.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1972****, 55*, 3005; Bartlett, P.D.; Helgeson, R.; Wersel, O.A. *Pure Appl. Chem.* ***1968****, 16*, 187; Seeley, D.A. *J. Am. Chem. Soc.* ***1972****, 94*, 4378; Kaupp, G. *Angew. Chem. Int. Ed.* ***1972****, 11,* 313, 718.

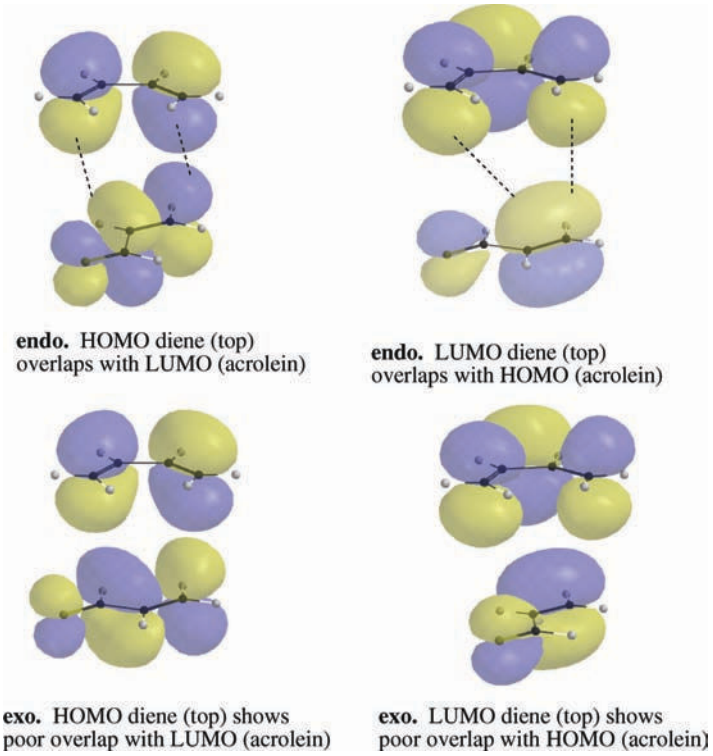


FIG. 15.11. Overlap of orbitals in [4 + 2]-cycloaddition of 1,3-butadiene with acrolein

longer overlapping, the thermal reaction is now forbidden. Similarly, thermal [$[_\pi 4_s + {}_\pi 2_a]$ and $[_\pi 2_s + {}_\pi 4_a]$-cyclizations are forbidden, while thermal [$\pi 4a + \pi 2a$]- and $[_\pi 2_s + {}_\pi 2_a]$-cyclizations are allowed. These considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a [4 + 2]-cyclization,[2310] but larger ring closures could take place by such a pathway, and [2 + 2] -thermal cyclizations, where the $[[_\pi 2_s + {}_\pi 2_s]$-pathway is forbidden, can also do so in certain cases (see Reaction **15-63**). Whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

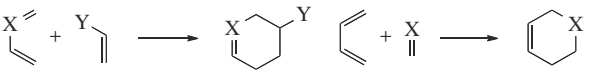
Symmetry considerations have also been advanced to explain predominant endo addition.[2311] In the case of [4 + 2]-addition of butadiene to acrolein, the approach can be exo or endo. It can be seen (Fig. 15.11) that whether the HOMO of the diene overlaps with the LUMO of acrolein or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals[2312] of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization since the sign of the orbitals do not match. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that [4 + 6]-cycloaddition is predicted by similar considerations to

[2310] A possible photochemical [2 + 4] cycloaddition has been reported: Hart, H.; Miyashi, T.; Buchanan, D.N.; Sasson, S. *J. Am. Chem. Soc.* ***1974****, 96*, 4857.
[2311] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965****, 87,* 4388.
[2312] See Ginsburg, D. *Tetrahedron* ***1983****, 39*, 2095; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* ***1983****, 16*, 328. See Singleton, D.A. *J. Am. Chem. Soc.* ***1992****, 114*, 6563.

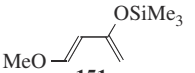
proceed with predominant exo orientation, and that is what is found.[2313] However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional π orbitals, and a number of alternative explanations have been offered.[2314]

OS **II**, 102; **III**, 310, 807; **IV**, 238, 738, 890, 964; **V**, 414, 424, 604, 985, 1037; **VI**, 82, 196, 422, 427, 445, 454; **VII**, 4, 312, 485; **VIII**, 31, 38, 298, 353, 444, 597; **IX**, 186, 722; **75**, 201; **81**, 171. For a reverse Diels–Alder reaction, see OS **VII**, 339.

15-61 Heteroatom Diels–Alder Reactions



Alkenes, alkynes, and dienes are not the only units that can participate in *Diels–Alder reactions*. Other double- and triple-bond compounds can be dienophiles and they give rise to heterocyclic compounds.[2315] Among these are N≡C—, —N=C—,[2316] iminium salts,[2317] —N=N—, O=N—,[2318] and —C=O compounds,[2319] and even molecular oxygen (Reaction **15-62**). Several catalysts can be used, depending on the nature of the heteroatoms incorporated into the alkene or diene.[2320] Intramolecular cycloaddition with a diene–imine substrate leads to pyrrolidines.[2321]



151

Aldehydes react with suitably functionalized dienes (e.g., **151**), known as *Danishefsky's diene*,[2322] and the reaction usually requires a Lewis acid catalyst (e.g., lanthanide compounds).[2323] The *Diels–Alder reaction* of aldehydes with dienes can be catalyzed by many transition metal compounds, including Co[2324] and In[2325] catalysts. Aldehydes react using a chiral Ti[2326] or a Zr[2327] catalyst to give the dihydropyran with good

[2313] See Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* ***1995****, 117*, 5375.
[2314] See Fox, M.A.; Cardona, R.; Kiwiet, N.J. *J. Org. Chem.* ***1987****, 52,* 1469.
[2315] See McCarrick, M.A.; Wu, Y.-D.; Houk, K.N. *J. Org. Chem.* ***1993****, 58*, 3330.
[2316] Anniyappan, M.; Muralidharan, D.; Perumal, P.T. *Tetrahedron Lett.* ***2003****, 44*, 3653. For a review see Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* ***2001****, 57*, 6099.
[2317] Domingo, L.R. *J. Org. Chem.* ***2001****, 66*, 3211; Chou, S.-S.P.; Hung, C.-C. *Synth. Commun.* ***2001****, 31*, 1097.
[2318] Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* ***1992****, 33*, 3583.
[2319] Boger, D.L.; Weinreb, S.M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press, NY, ***1987***; Weinreb, S.M.; Scola, P.M. *Chem. Rev.* ***1989****, 89*, 1525; Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* ***1987****, 42,* 245; Boger, D.L. *Tetrahedron* ***1983****, 39,* 2869; Weinreb, S.M.; Staib, R.R. *Tetrahedron* ***1982****, 38*, 3087; Desimoni, G.; Tacconi, G. *Chem. Rev.* ***1975****, 75*, 651; Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989****, 89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986****, 19*, 250; Boger, D.L. *Chem. Rev.* ***1986****, 86*, 781.
[2320] See Molander, G.A.; Rzasa, R.M. *J. Org. Chem.* ***2000****, 65*, 1215.
[2321] Amos, D.T.; Renslo, A.R.; Danhesier, R.L. *J. Am. Chem. Soc.* ***2003****, 125*, 4970.
[2322] See Danishefsky, S.; Schuda, P.F.; Kitahara, T. Etheredge, S.J. *J. Am. Chem. Soc.* ***1977****, 99*, 6066. Also see Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* ***2008****, 130,* 12588.
[2323] See Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* ***2006****, 71*, 2862.
[2324] Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1333.
[2325] Ali, T.; Chauhan, K.K.; Frost, C.G. *Tetrahedron Lett.* ***1999****, 40,* 5621.
[2326] Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* ***2002****, 67*, 2175.
[2327] Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003****, 125*, 3793.

enantioselectivity. Copper(I) catalysts have been used as well.[2328] Note that the reaction of *Danishefsky's diene* with an imine,[2329] formed *in situ* by reaction of an aryl aldehyde and an aniline derivative, proceeds without a Lewis acid.[2330] Ketones also react with suitably functionalized dienes.[2331] Indium trichloride ($InCl_3$) is a good catalyst for imino-*Diels–Alder reactions*.[2332] Hetero-*Diels–Alder reactions* involving carbonyls have been done in water.[2333] Ultrasound has been used to promote the *Diels–Alder reactions* of 1-azadienes.[2334] Polymer-supported dienes have been used.[2335]

Hetero-*Diels–Alder reactions* that proceed with good-to-excellent asymmetric induction are well known.[2336] Asymmetric *Diels–Alder reactions* of carbonyl compounds are well known.[2337] Chiral 1-aza-dienes have been developed as substrates, for example.[2338] Azadienes also react with chiral dienophiles.[2339] Chiral catalysts have been developed.[2340]

Dienes related to **151** are known, and their reactivity has been examined. Amino-substituted dienes undergo what is known as hydrogen-bonding catalyzed reactions.[2341] Imines react with other substrates (e.g., allenes), to give tetrahydropyridine derivatives, with good enantioselectivity in the presence of a chiral ligand.[2342] Azo compounds (—N=N—) react as dienophiles in the presence of an Ag catalyst.[2343] Iminium ions undergo *Diels–Alder cycloaddition*.[2344]

Azadienes undergo *Diels–Alder reactions* to form pyridine, dihydro- and tetrahydropyridine derivatives.[2345] *Aza-Diels–Alder reactions* have been done in ionic liquids.[2346] Similarly, acyl iminium salts (C=N(R)—C=O) react with alkenes via cycloaddition.[2347] *N*-Vinyl lactim ethers undergo *Diels–Alder reactions* with a limited set of dienophiles.[2348] Brønsted acids can catalyze inverse electron demand aza-*Diels–Alder reactions*.[2349]

Thioketones react with dienes to give *Diels–Alder cycloadducts*.[2350] The carbonyl group of lactams has also been shown to be a dienophile.[2351] Certain heterocyclic aromatic

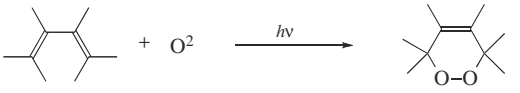
[2328] Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* ***2008****, 10*, 5151.
[2329] In an ionic liquid, see Pégot, B.; Vo-Thanh, G. *Synlett* ***2005***, 1409/
[2330] Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* ***2002****, 4*, 3309.
[2331] See Jørgensen, K.A. *Eur. J. Org. Chem.* ***2004***, 2093.
[2332] Babu, G.; Perumal, P.T. *Tetrahedron* ***1998****, 54*, 1627.
[2333] Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* ***1994****, 50*, 10265.
[2334] Villacampa, M.; Pérez, J.M.; Avendaño, C.; Menéndez, J.C. *Tetrahedron* ***1994****, 50*, 10047.
[2335] Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* ***2003****, 44*, 3645.
[2336] Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***1998****, 120*, 8599.
[2337] Pellissier, H. *Tetrahedron* ***2009****, 65*, 2839.
[2338] Beaudegnies, R.; Ghosez, L. *Tetrahedron Asymmetry* ***1994****, 5*, 557.
[2339] Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* ***2005****, 127,* 12234.
[2340] See He, M.; Struble, J.R.; Bode, J.W. *J. Am. Chem. Soc.* ***2006****, 128,* 8418.
[2341] Jensen, K.H.; Sigman, M.S. *Angew. Chem. Int. Ed.* ***2008****, 47,* 4748.
[2342] Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* ***2005****, 127*, 12234.
[2343] Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***2006****, 128,* 16482.
[2344] See Sarkar, N.; Banerjee, A.; Nelson, S.G. *J. Am. Chem. Soc.* ***2008****, 130,* 9222.
[2345] Jayakumar, S.; Ishar, M.P.S.; Mahajan, M.P. *Tetrahedron* ***2002****, 58*, 379.
[2346] Yadav, J.S.; Reddy, B.V.S.; Reddy, J.S.S.; Rao, R.S. *Tetrahedron* ***2003****, 59*, 1599.
[2347] Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-i. *Org. Lett.* ***2003****, 5*, 945.
[2348] Sheu, J.; Smith, M.B.; Matsumoto, K. *Synth. Commun,* ***1993****, 23*, 253.
[2349] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* ***2006****, 128*, 13070; Esquivias, J.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2007****, 129,* 1480.
[2350] Schatz, J.; Sauer, J. *Tetrahedron Lett.* ***1994****, 35*, 4767.
[2351] Degnan, A.P.; Kim, C.S.; Stout, C.W.; Kalivretenos, A.G. *J. Org. Chem.* ***1995****, 60*, 7724.

rings (among them furans)[2352] can also behave as dienes in the Diels–Alder reaction. Some hetero dienes that give the reaction are —C=C—C=O, O=C—C=O, and N=C—C=N.[2352] Nitroso compounds of the type *t*-BuO_2C-N=O react with dienes to give the corresponding 2-azadihydropyran.[2353] Conjugated aldehydes react with vinyl ethers, with a chiral Cr catalyst, in an inverse electron demand cycloaddition that give a dihydropyran with good enantioselectivity.[2354] Vinyl sulfilimines have been used in chiral *Diels–Alder reactions*.[2355]

OS **IV**, 311; **V**, 60, 96; **80**, 133. See also, OS **VII**, 326.

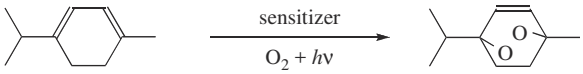
15-62 Photooxidation of Dienes (Addition of Oxygen, Oxygen)

[4 + 2] *OC*,*OC-cyclo*-Peroxy-1/4/addition



152

Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides (**152**).[2356] The reaction has mostly[2357] been applied to cyclic dienes.[2358] Cycloaddition of furan has been reported using singlet oxygen.[2359] The scope extends to certain aromatic compounds (e.g., phenanthrene).[2360] Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that gives the reaction in the presence of a photosensitizer (see Sec. 7.A.vi, category 5; e.g., eosin, a red xanthene dye). Among these is α-terpinene, which is converted to ascaridole:



[2352] Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989****, 89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986****, 19*, 250; Boger, D.L. *Chem. Rev.* ***1986****, 86*, 781. See Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2002****, 41*, 4079.

[2353] Bach, P.; Bols, M. *Tetrahedron Lett.* ***1999****, 40*, 3461.

[2354] Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2002****, 41*, 3059.

[2355] Ruano, J.L.G.; Clemente, F.R.; Gutiérrez, L.G.; Gordillo, R.; Castro, A.M.M.; Ramos, J.H.R. *J. Org. Chem.* ***2002****, 67*, 2926.

[2356] See Clennan, E.L. Tetrahedron **1991**, 47, 1343; Adv. Oxygenated Processes **1988**, 1, 85; Wasserman, H.H.; Ives, J.L. Tetrahedron **1981**, 37, 1825; Denny, R.W.; Nickon, A. Org. React. **1973**, 20, 133; Schönberg, A. Preparative Organic Photochemistry, Springer, NY, **1968**, pp. 382–397; Gollnick, K.; Schenck, G.O. in Hamer, J. 1,4-Cycloaddition Reactions, Academic Press, NY, **1967**, pp. 255–344.

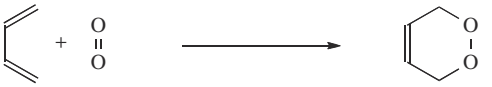
[2357] Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* ***1985****, 41*, 2147.

[2358] See Saito, I.; Nittala, S.S. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 311–374; Balci, M. *Chem. Rev.* ***1981****, 81*, 91; Adam, W.; Bloodworth, A.J. *Top. Curr. Chem.* ***1981****, 97*, 121.

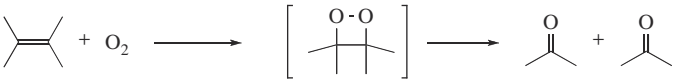
[2359] Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron* ***2001****, 57*, 6003.

[2360] See in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, the articles by Wasserman, H.H.; Lipshutz, B.H. pp. 429–509; Saito, I.; Matsuura, T. pp. 511–574; Rigaudy, J. *Pure Appl. Chem.* ***1968****, 16*, 169.

As in Reaction **14-7**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,[2361,2362] so the reaction is actually a *Diels–Alder reaction* (see Reaction **15-60**) with singlet oxygen as dienophile:[2363]



Like Reaction **15-60**, this reaction is reversible.

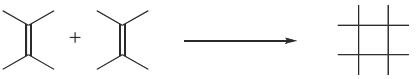


153

As previously discussed, the reaction of singlet oxygen with double-bond compounds gives hydroperoxides (Reaction **14-7**), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate[2364] (Reaction **153**), which usually cleaves to aldehydes or ketones,[2365] but has been isolated.[2366] Both the six-membered cyclic peroxides[2367] and the four-membered **205**[2368] have been formed from oxygenation reactions that do not involve singlet oxygen. If cyclic peroxides (e.g., **205**) are desired, better reagents[2369] are triphenyl phosphite ozonide [$(PhO)_3PO_3$] and triethylsilyl hydrotrioxide [$(Et_3SiOOOH)$], but yields are not high.[2370]

15-63 [2 + 2]-Cycloadditions

[2 + 2]*cyclo*-Ethylene-1/2/addition



[2361] Frimer, A.A. *Singlet O_2*, 4 Vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***. See Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10,* 205; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43,* 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311.

[2362] Turro, N.J.; Ramamurthy, V. in de Mayo, P. *Rearrangements in Ground and Excited States,* Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114; Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.

[2363] Monroe, B.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7253. See also, Hathaway, S.J.; Paquette, L.A. *Tetrahedron Lett.* ***1985***, *41,* 2037; O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* ***1988***, *110*, 7167.

[2364] Adam, W.; Cilento, G. *Angew. Chem. Int. Ed.* ***1983***, *22*, 529; Schaap, A.; Zaklika, K.A. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen* Academic Press, NY, ***1979***, pp. 173–242; Bartlett, P.D. *Chem. Soc. Rev.* ***1976***, *5*, 149. For discussions of the mechanisms see Frimer, A.A. *Chem. Rev.* ***1979***, *79,* 359; Clennan, E.L.; Nagraba, K. *J. Am. Chem. Soc.* ***1988***, *110*, 4312.

[2365] Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395, pp. 422–424; Foote, C.S. *Pure Appl. Chem.* ***1971***, *27*, 635.

[2366] Adam, W. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 829–920; Bartlett, P.D.; Landis, M.E. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 243–286; Adam, W. *Adv. Heterocycl. Chem.* ***1977***, *21,* 437. See also, Adam, W.; Encarnación, L.A.A. *Chem. Ber.* ***1982***, *115*, 2592; Adam, W.; Baader, W.J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 166.

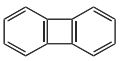
[2367] See Nelson, S.F.; Teasley, M.F.; Kapp, D.L. *J. Am. Chem. Soc.* ***1986***, *108,* 5503.

[2368] See Nelson, S.F. *Acc. Chem. Res.* ***1987***, *20,* 269.

[2369] See Curci, R.; Lopez, L.; Troisi, L.; Rashid, S.M.K.; Schaap, A.P. *Tetrahedron Lett.* ***1987***, *28*, 5319.

[2370] Posner, G.H.; Weitzberg, M.; Nelson, W.M.; Murr, B.L.; Seliger, H.H. *J. Am. Chem. Soc.* ***1987***, *109,* 278.

Two alkene molecules react under thermal conditions to give cyclobutane derivatives in what is known as a *[2 + 2]-cycloaddition*. The cycloaddition occurs when the alkenes are the same or different, but the reaction is not general for all alkenes.[2371] Certain transition metal complexes can catalyze the cycloaddition.[2372] Benzynes undergo cycloaddition to give biphenylene derivatives (**154**),[2373] activated alkenes (e.g., styrene, acrylonitrile, butadiene), and certain methylenecyclopropanes.[2374] Alkenes react with alkynes[2375] or with activated alkynes, with a Ru catalyst, to give cyclobutenes.[2376] Dimerization of allenes leads to bis(alkylidene) cyclobutanes.[2377] Substituted ketenes can dimerize to give cyclobutenone derivatives, although ketene itself dimerizes in a different manner, to give an unsaturated β-lactone (Reaction **16-95**).[2378]



Biphenylene

154

Intramolecular [2 + 2]-cycloadditions are common in which a diene is converted to a bicyclic compound with a four-membered ring fused to another ring. Transition metal catalyzed reactions have been reported, including the use of Fe complexes.[2379] Heating *N*-vinyl imines, where the vinyl moiety is a silyl enol, gives β-lactams.[2380] Apart from photochemical initiation of such reactions (see below), intramolecular cycloaddition of two conjugated ketone units, in the presence of $PhMeSiH_2$ and catalyzed by Co compounds, leads to the bicyclic compound with two ketone substituents.[2381] In a variation of this reaction, a diyne was treated with $Ti(OiPr)_4$/2 *i*PrMgCl to generate a bicyclic cyclobutene with two vinylidene units.[2382]

Ketenes react with many alkenes to give cyclobutanone derivatives[2383] and intermolecular cycloadditions are well known.[2384] A typical reaction of dimethylketene and ethene gives 2,2-dimethylcyclobutanone, as shown.[2385] Ketenes react with imines via

[2371] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, ***1990***; Reinhoudt, D.N. *Adv. Heterocycl. Chem.* ***1977****, 21*, 253; Roberts, J.D.; Sharts, C.M. *Org. React.* ***1962****, 12*, 1; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry,* 2nd ed., Cambridge University Press, Cambridge, ***1979***, pp. 173–212; Dilling, W.L. *Chem. Rev.* ***1983****, 83*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 546–647, 1341–1344.

[2372] See Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* ***2004****, 69*, 517.

[2373] See Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* ***2002****, 43*, 5789.

[2374] Dolbier, Jr., W.R.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* ***1972****, 28,* 3185.

[2375] López-Carrillo, V.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2010****, 132,* 9292.

[2376] Jordan, R.W.; Tam, W. *Org. Lett.* ***2000****, 2*, 3031.

[2377] Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000****, 122*, 10776.

[2378] Dehmlow, E.V.; Pickardt, J.; Slopianka, M.; Fastabend, U.; Drechsler, K.; Soufi, J. *Liebigs Ann. Chem.* ***1987***, 377.

[2379] Bouwkamp, M.W.; Bowman, A.C.; Lobkovsky, E.; Chirik, P.J. *J. Am. Chem. Soc.* ***2006****, 128,* 13340.

[2380] Bandin, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* ***2000****, 2*, 1077.

[2381] Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001****, 123*, 6716.

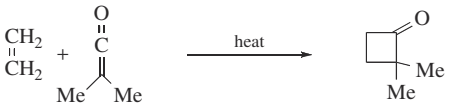
[2382] Delas, C.; Urabe, H.; Sato, F. *Tetrahedron Lett.* ***2001****, 42*, 4147.

[2383] See de Faria, A.R.; Matos, C.R.; Correia, C.R.D. *Tetrahedron Lett.* ***1993****, 34*, 27.

[2384] Martin, P.; Greuter, H.; Bellus, D. *Helv. Chim. Acta.,* ***1984****, 64*, 64.

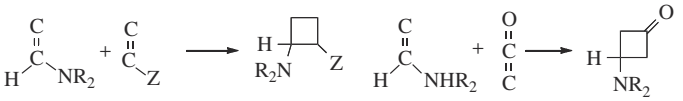
[2385] Sustmann, R.; Ansmann, A.; Vahrenholt, F. *J. Am. Chem. Soc.* ***1972****, 94*, 8099; Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. *Natural Product Synthesis Through Pericyclic Reactions*, American Chemical Society Washington, DC, ***1983***, pp. 119–254, p. 39.

[2 + 2]-cycloaddition to produce β-lactams.[2386] Cycloaddition of an imine with a conjugated ester in the presence of Et_3MeSiH and an Ir catalyst also gives a β-lactam.[2387] See Reaction **19-66** for a discussion of reactions that give β-lactams.



Different alkenes combine as follows:

1. $F_2C{=}CX_2$ (X = F or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many alkenes. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal *Diels–Alder reactions*.[2388]
2. Allenes[2389] and ketenes[2390] react with activated alkenes and alkynes. Ketenes give 1,2-addition, even with conjugated dienes.[2391] Ketenes also add to unactivated alkenes if sufficiently long reaction times are used.[2392] Allenes and ketenes also add to each other.[2393]
3. Enamines[2394] form four-membered rings with *Michael-type* alkenes[2395] and ketenes.[2396] In both cases, only enamines from aldehydes give stable four-membered rings:



Generating the ketene *in situ* from an acyl halide and a tertiary amine is a convenient way to carry out the reaction of enamines with ketenes.

[2386] Brown, M.J. *Heterocycles* ***1989****, 29,* 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976****, 5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327; Sandhu, J.S.; Sain, B. *Heterocycles* ***1987****, 26,* 777.; Wack, H.; France, S.; Hafez, A.M.; Drury, III, W.J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* ***2004****, 69*, 4531.

[2387] Townes, J.A.; Evans, M.A.; Queffelec, J.; Taylor, S.J.; Morken, J.P. *Org. Lett.* ***2002****, 4,* 2537.

[2388] De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985****, 41*, 4183.

[2389] Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wley, NY, ***1984***, pp. 286–317; Hopf, H. in Landor, S.R. *The Chemistry of Allenes,* Vol. 2, Academic Press, NY, ***1982***, pp. 525–562; Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions* Vol. 2, Academic Press, NY, ***1977***, pp. 79–140; Luzung, M.R.; Mauleón, P.; Toste, F.D. *J. Am. Chem. Soc.* ***2007****, 129,* 12402.

[2390] Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reaction,* Vol. 2, Academic Press, NY, ***1977***; Brady, W.T. *Synthesis* ***1971***, 415; Snider, B.B. *Chem. Rev.* ***1988****, 88,* 793. See Ussing, B.R.; Hang, C.; Singleton, D.A. *J. Am. Chem. Soc.* ***2006****, 128,* 7594.

[2391] See Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4491; *Chem. Ber.* ***1969****, 102,* 3475; Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* ***1971****, 93*, 4326. For a review of ketene equivalents, see Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *Synthesis* ***1977***, 289.

[2392] Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979****, 44*, 107.

[2393] Gras, J.; Bertrand, M. *Nouv. J. Chim.* ***1981****, 5,* 521.

[2394] Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, pp. 347–440.

[2395] Brannock, K.C.; Bell, A.; Goodlett, V.W.; Thweatt, J.G. *J. Org. Chem.* ***1964****, 29,* 813.

[2396] Hasek, R.H.; Gott, P.G.; Martin, J.C. *J. Org. Chem.* ***1966****, 31*, 1931.

4. Alkenes with electron-withdrawing groups may form cyclobutanes with alkenes containing electron-donating groups.[2397] The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with alkenes of the form C=C—A, where A may be OR,[2398] SR (enol and thioenol ethers),[2399] cyclopropyl,[2400] or certain aryl groups.[2401]

Enantioselective [2 + 2]-cycloaddition reactions are known. Chiral organocatalysts lead to chiral cyclobutane derivatives.[2402]

Solvents are not necessary for [2 + 2]-cycloadditions. They can be carried out at 100–225 °C under pressure, although the reactions in Group 4 occur under milder conditions. However, the choice of solvent can control the distribution of products in photochemical [2 + 2]-cycloaddition.[2403]

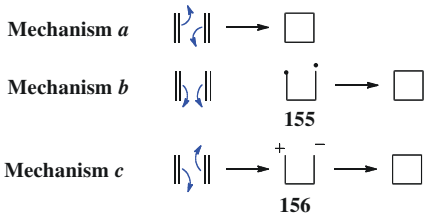
It has been found that certain [2 + 2]-cycloadditions that do not occur thermally can be made to take place without photochemical initiation using certain catalysts, usually transition metal compounds.[2404] Among the catalysts used are Lewis acids[2405] and phosphine–Ni complexes.[2406] The role of the catalyst is not certain and may be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or *s* bonds of the substrate.[2407] In such a case, the reaction would of course be a concerted $[2_s + 2_s]$ process.[2408] However, the available evidence is more consistent with nonconcerted mechanisms involving metal–carbon σ-bonded intermediates, at least in most cases.[2409] For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by Ir complexes.[2410] Photochemical[2411] $[_\pi 2 + _s 2]$-cycloadditions have also been reported. Visible light mediates cycloaddition in the presence of a Rh catalyst.[2412] Some reverse cyclobutane ring openings can also be catalytically induced (Reaction **18-38**).

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne[2413] bearing electron-withdrawing groups.[2414]

[2397] See Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* ***2005****, 127,* 3668.
[2398] Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1986****, 105,* 71-84.
[2399] Williams, J.K., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1962****, 84,* 2210.
[2400] Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* ***1973****, 38*, 1878.
[2401] Nagata, J.; Shirota, Y.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1087; Shirota, Y.; Yoshida, K.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1271.
[2402] Canales, E.; Corey, E.J. *J. Am. Chem. Soc.* ***2007****, 129,* 12686; Butenschön, H. *Angew. Chem. Int. Ed.* ***2008****, 47,* 3492; Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* ***2008****, 130,* 7532.
[2403] Ng, S.M.; Bader, S.J.; Snapper, M.L. *J. Am. Chem. Soc.* ***2006****, 128*, 7315.
[2404] Treutwein, J.; Hilt, G. *Angew. Chem. Int. Ed.* ***2008****, 47*, 6811.
[2405] Yamazaki, S.; Fujitsuka, H.; Yamabe, S.; Tamura, H. *J. Org. Chem.* ***1992****, 57*, 5610.
[2406] Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Tetrahedron* ***1974****, 30,* 405.
[2407] See Mango, F.D. *Top. Curr. Chem.* ***1974****, 45,* 39; *Tetrahedron Lett.* ***1973***, 1509.
[2408] See Bachrach, S.M.; Gilbert, J.C. *J. Org. Chem.* ***2004****, 69*, 6357; Ozkan, I.; Kinal, A. *J. Org. Chem.* ***2004****, 69*, 5390.
[2409] See Grubbs, R.H.; Miyashita, A.; Liu, M.M.; Burk, P.L. *J. Am. Chem. Soc.* ***1977****, 99,* 3863.
[2410] Fraser, A.R.; Bird, P.H.; Bezman, S.A.; Shapley, J.R.; White, R.; Osborn, J.A. *J. Am. Chem. Soc.* ***1973****, 95*, 597.
[2411] See Prinzbach, H.; Sedelmeier, G.; Martin, H. *Angew. Chem. Int. Ed.* ***1977****, 16*, 103.
[2412] Ischay, M.A.; Anzovino, M.E.; Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* ***2008****, 130,* 12886.
[2413] Gassman, P.G.; Mansfield, K.T. *J. Am. Chem. Soc.* ***1968****, 90,* 1517, 1524.
[2414] For a review, see Gassman, P.G. *Acc. Chem. Res.* ***1971****, 4,* 128.

These reactions are $[_{\pi}2 + {}_{s}2]$-cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems (e.g., bicyclo[1.1.0] butanes[2415] and bicyclo[2.1.0]pentanes). For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.[2416] The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism.

If dienes are involved in the reaction, the *Diels–Alder reaction* may compete, although most alkenes react with a diene either entirely by 1,2- or entirely by 1,4-addition. Three mechanisms have been proposed for [2 + 2]-cycloaddition.[2417]



Mechanism *a* is a concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**155**) and a diion (**156**) intermediate. As in Reaction **15-60**, a diradical intermediate must be a singlet. In searching for ways to tell which mechanism is operating in a given case, mechanism *c* is expected to be sensitive to changes in solvent polarity, while mechanisms *a* and *b* should be insensitive. Mechanism *a* is expected to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific. However, if the second step of these processes takes place very rapidly, before **155** or **156** have a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations, such rapid ring closure might be more likely here than in a [4 + 2]-cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[_{\pi}2_s + {}_{\pi}2_s]$ mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a $[_{\pi}2_s + {}_{\pi}2_a]$ mechanism is allowed (see above), and there is much evidence that ketenes and certain other linear molecules[2418] in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition, the molecules must approach each other in such a way (Fig. 15.12*a*) that the HOMO–LUMO overlap requires that the groups of one molecule project *into* the plane of the other. This does not happen with ordinary alkenes,[2419] but if one molecule is a ketene (Fig. 15.12*b*), a group on the carbon of the C=C unit is missing (relative to an alkene) and the $[_{\pi}2_s + {}_{\pi}2_a]$-reaction can take place.

[2415] Cairncross, A.; Blanchard, E.P. *J. Am. Chem. Soc.* ***1966****, 88,* 496.
[2416] Gassman, P.G.; Mansfield, K.T.; Murphy, T.J. *J. Am. Chem. Soc.* ***1969****, 91,* 1684.
[2417] For a review, see Bartlett, P.D. *Q. Rev. Chem. Soc.* ***1970****, 24,* 473. See Check, C.E.; Gilbert, T.M. *J. Org. Chem.* ***2005****, 70,* 9828.
[2418] See Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1984****, 106,* 1885.
[2419] See Bartlett, P.D.; Cohen, G.M.; Elliott, S.P.; Hummel, K.; Minns, R.A.; Sharts, C.M.; Fukunaga, J.Y. *J. Am. Chem. Soc.* ***1972****, 94,* 2899.

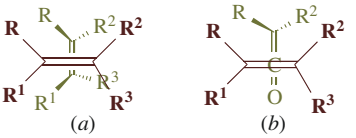
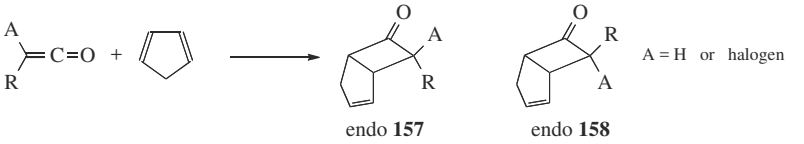


FIG. 15.12. Steric interactions in $[\pi 2_s + \pi 2_s]$-cycloaddition between (*a*) two alkene molecules and (*b*) a ketene and an alkene

Among the evidence[2420] for this mechanism[2421] is the following: (1) the reactions are stereospecific.[2422] (2) The isomer that forms is the *more hindered one*. Thus the reaction of methylketene plus cyclopentadiene gave only



endo **157** endo **158**

the endo product (**157**, A = H, R = CH_3).[2423] Even more remarkably, when haloalkyl ketenes RXC=C=O were treated with cyclopentadiene, the endo/exo ratio of the product (**157**, **158**, A = halogen) actually *increased* substantially when R was changed from Me to *i*Pr to *t*-Bu![2424] One would expect preferential formation of the exo products (**158**) from $[\pi 2_s + \pi 2_s]$-cycloadditions where the molecules approach each other face-to-face. However, a $[\pi 2_s + \pi 2_a]$-process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group, methyl in the figure, directed toward the alkene) must twist as shown in Fig. 15.13 (*tert*-butyl = larger; methyl = smaller group) in order for the + lobes to interact. This process swings the larger group (*tert*-butyl) into the endo position.[2425] The experimental results in which the amount of endo isomer increases with the increasing size of the R group appears to be contrary to what would be expected from steric hindrance considerations (called *masochistic steric effects*), but they are just what is predicted for a $[\pi 2_s + \pi 2_a]$ reaction. (3) There is only moderate polar solvent acceleration.[2426] (4) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.[2427] Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place

[2420] Also see Gheorghiu, M.D.; Pârvulescu, L.; Drâghici, C.; Elian, M. *Tetrahedron* ***1981****, 37 Suppl.*, 143. See, however, Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.* ***1983****, 105*, 2929.

[2421] See, however, Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1990****, 112,* 1754; Bernardi, F.; Bottoni, A.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* ***1990****, 112*, 2106; Valentí, E.; Pericàs, M.A.; Moyano, A. *J. Org. Chem.* ***1990****, 55*, 3582.

[2422] Bertrand, M.; Gras, J.L.; Goré, J. *Tetrahedron* ***1975****, 31*, 857; Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* ***1972****, 94*, 2870; Huisgen, R.; Mayr, H. *Tetrahedron Lett.* ***1975***, 2965, 2969.

[2423] Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* ***1970****, 53,* 417. See Rey, M.; Roberts, S.M.; Dreiding, A.S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* ***1982****, 65*, 703.

[2424] Brady, W.T.; Roe Jr., R. *J. Am. Chem. Soc.* ***1970****, 92*, 4618.

[2425] Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589

[2426] Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967****, 32*, 612; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4485, *Chem. Ber.* ***1969****, 102*, 3444; Sterk, H. *Z. NaturForsch. Teil B* ***1972****, 27,* 143.

[2427] Isaacs, N.S.; Stanbury, P. *J. Chem. Soc. Perkin Trans. 2,* ***1973***, 166.

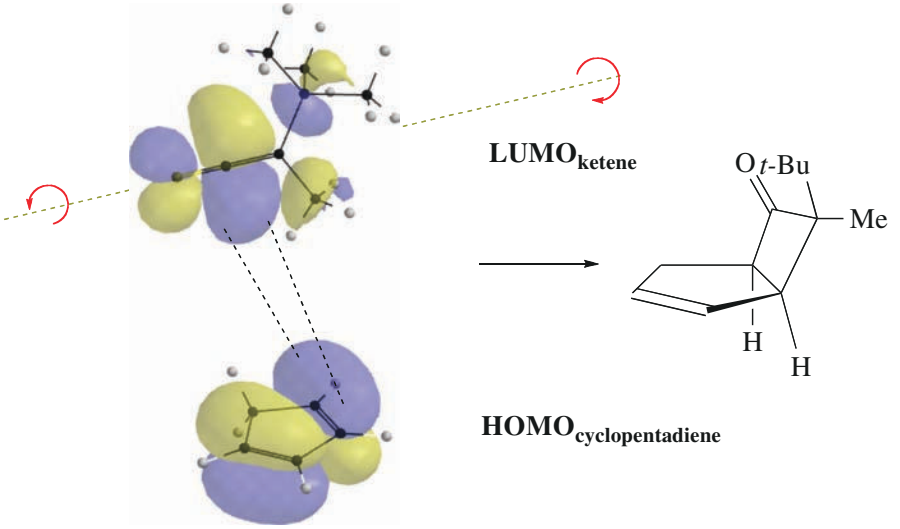
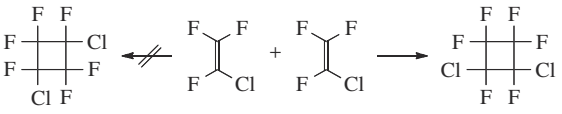


FIG. 15.13. Orbital overlap in the reaction of a ketene with cyclopentadiene. Here S and L represent small and large. [Reproduced from Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589 with permission from the Royal Society of Chemistry]

by the $[\pi 2_s + \pi 2_a]$ mechanism,[2428] but the evidence in these cases is more consistent with the diradical mechanism *b*.[2429]

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.[2430] These reactions are generally not stereospecific[2431] and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C{=}CFCl$ gives **159**, not **160**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other.[2432]



[2428] See Baldwin, J.E.; Roy, U.V. *Chem. Commun.* ***1969***, 1225; Moore, W.R.; Bach, R.D.; Ozretich, T.M. *J. Am. Chem. Soc.* ***1969***, *91*, 5918.

[2429] Pasto, D.J.; Yang, S.H. *J. Org. Chem.* ***1986***, *51*, 1676; Dolbier, D.W.; Seabury, M. *J. Am. Chem. Soc.* ***1987***, *109*, 4393; Dolbier, Jr., W.R.; Weaver, S.L. *J. Org. Chem.* ***1990***, *55*, 711; Becker, D.; Denekamp, C.; Haddad, N. *Tetrahedron Lett.* ***1992***, *33*, 827.

[2430] See, however, Roberts, D.W. *Tetrahedron* ***1985***, *41*, 5529.

[2431] Bartlett, P.D.; Hummel, K.; Elliott, S.P.; Minns, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2898.

[2432] See De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183; Doering, W. von E.; Guyton, C.A. *J. Am. Chem. Soc.* ***1978***, *100*, 3229.

The diion mechanism[2433] *c* has been reported for at least some of the reactions[2434] in categories 3 and 4,[2435] as well as some ketene dimerizations.[2436] The rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether, for example, was strongly influenced by changes in solvent polarity.[2437] Some of these reactions are nonstereospecific, but others are stereospecific.[2438] As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

Whether a given alkene reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the α positions of **155** or **156** help to stabilize a diradical, while donors (e.g., oxygen and nitrogen) favor a diion (they stabilize the positively charged end).[2439] A table in Ref. 2439 (see p. 451) shows which mechanism is more likely for [2 + 2]-cycloadditions of various pairs of alkenes.

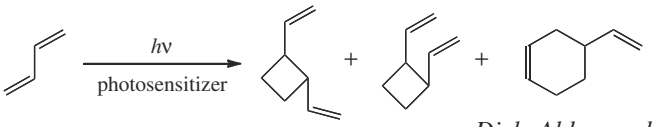
Thermal cleavage of cyclobutanes[2440] to give two alkene molecules (*cycloreversion*,[2441] the reverse of [2 + 2]-cycloaddition) operates by the diradical mechanism, and the $[_{\sigma}2_{s} + _{\sigma}2_{a}]$-pathway has not been found[2442] (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds. The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see Reaction **15-65**)[2443] or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (Sec. 2.K.ii).[2444]

Although thermal [2 + 2]-cycloaddition reactions are essentially limited to the cases described above, many (although by no means all) double-bond compounds react *when photochemically excited* (either directly or by a photosensitizer, see Sec. 7.A.vi,

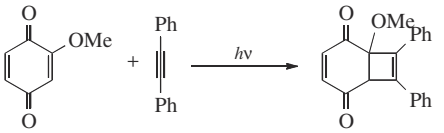
[2433] See Huisgen, R. *Acc. Chem. Res.* ***1977****, 10*, 117, 199; Huisgen, R.; Schug, R.; Steiner, G. *Bull. Soc. Chim. Fr.* ***1976***, 1813.
[2434] See Gompper, R. *Angew. Chem. Int. Ed.* ***1969****, 8,* 312.
[2435] The reactions of ketenes with enamines are apparently not concerted but take place by the diionic mechanism: Otto, P.; Feiler, L.A.; Huisgen, R. *Angew. Chem. Int. Ed.* ***1968****, 7,* 737.
[2436] See Moore, H.W.; Wilbur, D.S. *J. Am. Chem. Soc.* ***1978****, 100,* 6523.
[2437] Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966****, 88,* 5254. See also, Huisgen, R. *Pure Appl. Chem.* ***1980****, 52,* 2283.
[2438] Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* ***1973****, 95*, 5054, 5055.
[2439] Hall Jr., H.K. *Angew. Chem. Int. Ed.* ***1983****, 22*, 440.
[2440] See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966****, 4*, 147, see pp. 170–175, 180–183.
[2441] See Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed.* ***1982****, 21*, 225. See also, Reddy, G.D.; Wiest, O.; Hudlicky, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem.* ***1999****, 64,* 2860.
[2442] See Paquette, L.A.; Carmody, M.J. *J. Am. Chem. Soc.* ***1976****, 98,* 8175. See however Doering, W. von E.; Roth, W.R.; Breuckmann, R.; Figge, L.; Lennartz, H.; Fessner, W.; Prinzbach, H. *Chem. Ber.* ***1988****, 121*, 1.
[2443] See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 435–442.
[2444] D'Angelo, J.; Ficini, J.; Martinon, S.; Riche, C.; Sevin, A. *J. Organomet. Chem.* ***1979****, 177*, 265. See Hogeveen, H.; Kok, D.M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, ***1983***, pp. 981–1013.

category 5), even if they are not in the above categories.[2445] Simple alkenes absorb in the far-UV (Sec. 7.A.iii), which is difficult to reach experimentally, although this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes[2446] (especially to strained compounds, e.g., cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,[2447] α,β-unsaturated ketones,[2448] conjugated acids or acid derivatives, and quinones. Since these compounds, are conjugated, they absorb at longer wavelengths (Sec 7.A.iii). Both dimerizations and mixed additions are common. Some examples follow:



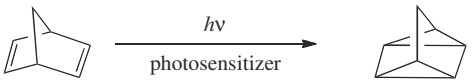
Diels-Alder product

Ref. 2449



Ref. 2450

See also, Section 7.A.vii (Reaction **7-9**). Photochemical [2 + 2]-cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.[2451] The cyclization of the quinone dimer shown above is one example. Other examples are



Quadricyclane

Ref. 2452

[2445] Demuth, M.; Mikhail, G. *Synthesis* ***1989***, 145; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 58–109; Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* ***1987***, *87,* 433; Wender, P.A. in Coyle, J. D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 163–188; Schreiber, S.L. *Science* ***1985***, *227*, 857; Baldwin, S.W. *Org. Photochem.* ***1981***, *5*, 123; Kricka, L.J.; Ledwith, A. *Synthesis* ***1974***, 539; Herndon, W.C. *Top. Curr. Chem.* ***1974***, *46,* 141; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2,* 1; Trecker, D.J. *Org. Photochem.* ***1969***, *2,* 63.

[2446] See Arnold, D.R.; Abraitys, V.Y. *Chem. Commun.* ***1967***, 1053; Yamazaki, H.; Cvetanovic, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520.

[2447] See Dilling, W.L. *Chem. Rev.* ***1969***, *69*, 845.

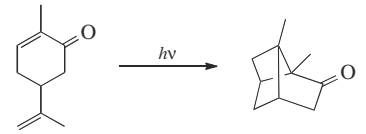
[2448] Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.* ***1993***, *93*, 3; Cossy, J.; Carrupt, P.; Vogel, P. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1369–1565; Weedon, A.C. in Horspool, W.M. *Synthetic Organic Photochemistry* Plenum, NY, ***1984***, pp. 61–143; Bauslaugh, P.G. *Synthesis* ***1970***, 287; Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1,* 50; Erickson, J.A.; Kahn, S.D. *Tetrahedron* ***1993***, *49*, 9699.

[2449] Liu, R.S.H.; Turro, N.J.; Hammond, G.S. *J. Am. Chem. Soc.* ***1965***, *87*, 3406; Cundall, R.B.; Griffiths, P.A. *Trans. Faraday Soc.* ***1965***, *61*, 1968; DeBoer, C.D.; Turro, N.J.; Hammond, G.S. *Org. Synth.* ***V***, 528.

[2450] Pappas, S.P.; Pappas, B.C. *Tetrahedron Lett.* ***1967***, 1597.

[2451] See Becker, D.; Haddad, N. *Org. Photochem.* ***1989***, *10,* 1-162; Crimmins, M.T. *Chem. Rev.* ***1988***, *88*, 1453; Oppolzer, W. *Acc. Chem. Res.* ***1982***, *15*, 135; Prinzbach, H. *Pure Appl. Chem.* ***1968***, *16,* 17.

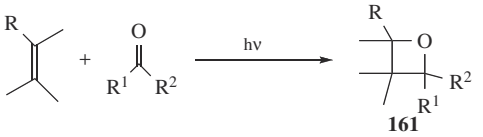
[2452] Hammond, G.S.; Turro, N.J.; Fischer, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4674; Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *15,* 197. See also, Cristol, S.J.; Snell, R.L. *J. Am. Chem. Soc.* ***1958***, *80*, 1950.



Carvone Carvonecamphor

Ref. 2453

It is obvious that many molecules can be constructed in this way that would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases, polymeric or other side products are obtained instead of the desired product.



161

The photochemical cycloaddition of a carbonyl, generally from an aldehyde or ketone and an alkene, is called the *Paternò–Büchi reaction*.[2454] This [2 + 2]-cycloaddition gives an oxetane (**161**) and the reaction is believed to proceed via a diradical intermediate. Silyl enol ethers react with aldehydes under nonphotochemical conditions using $ZnCl_2$ at 25°C or $SnCl_4$ at −78°C.[2455]

It is possible that some of these photochemical cycloadditions take place by a $[\pi 2_s + \pi 2_s]$-mechanism, which is of course allowed by orbital symmetry; when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state.[2456] The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,[2457] making it likely that the $[\pi 2_s + \pi 2_s]$-mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place.[2458] In one intramolecular case, the intermediate diradical has been trapped.[2459] Photosensitized $[2\pi + 2\pi]$-cycloadditions almost always involve the triplet state, and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism, the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state, which is of course a singlet. Thus, in order to conserve spin,[2460] the initially formed diradical must be a triplet; that is, the two electrons must have the same spin. Consequently, the second, or ring closing, step of the mechanism cannot take place at once, because a new bond cannot form

[2453] Ciamician, G.; Silber, P. *Ber.* ***1908****, 41*, 1928; Büchi, G.; Goldman, I.M. *J. Am. Chem. Soc.* ***1957****, 79,* 4741.
[2454] Paternò, E.; Chieffi, C. *Gazz. Chim. Ital.* ***1909****, 39*, 341; Büchi, G.; Inman, C.G.; Lipinsky, E.S. *J. Am. Chem. Soc.* ***1954****, 76*, 4327. See García-Expósito, E.; Bearpark, M.J.; Ortuño, R.M.; Robb, M.A.; Branchadell, V. *J. Org. Chem.* ***2002****, 67*, 6070.
[2455] Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* ***1999****, 1*, 1197.
[2456] Reactions between two excited molecules are extremely rare.
[2457] Yamazaki, H.; Cvetanovic, R.J.; Irwin, R.S. *J. Am. Chem. Soc.* ***1976****, 98*, 2198; Lewis, F.D.; Kojima, M. *J. Am. Chem. Soc.* ***1988****, 110*, 8660.
[2458] Maradyn, D.J.; Weedon, A.C. *Tetrahedron Lett.* ***1994****, 35*, 8107.
[2459] Becker, D.; Haddad, N.; Sahali, Y. *Tetrahedron Lett.* ***1989****, 30,* 2661.
[2460] This is an example of the *Wigner spin conservation rule* (Sec. 7.A.vi, category 5). Note that spin conservation is something entirely different from symmetry conservation.

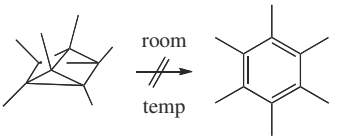
from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. The prediction is nonstereospecificity, and that is what is found.[2461] It has been believed that at least some [2 + 2] photocycloadditions take place by way of exciplex intermediates[2462] [an *exciplex*[2463] is an excited EDA complex (Sec. 7.A.vii) that is dissociated in the ground state; in this case one double bond is the donor and the other is the acceptor], but there is evidence against this.[2464]

In Reaction **15-60**, the principle of conservation of orbital symmetry was used to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable although highly strained. Quadricyclane and hexamethylprismane[2465] are thermodynamically much less stable (because they are much more strained), for example, than their corresponding isomeric dienes, norbornadiene and



Quadricyclane — Norbornadiene — Hexamethylprismane — **162** (A Dewar benzene)

hexamethylbicyclo[2.2.0]hexadiene (**162**).[2466] Yet the former two compounds can be kept indefinitely at room temperature, although in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a $_s2 + _s2$ process) and, as seen previously, a thermal process of this sort is forbidden by the *Woodward–Hoffmann rules*. The process is allowed photochemically, so both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.[2467] It is also possible to conceive of simple bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene (as shown below), which of course is far more stable than either hexamethylprismane or **162**. It has been calculated that hexamethylbenzene is at least 90 kcal mol^{-1} (380 kJ mol^{-1}) more stable than hexamethylprismane. A correlation diagram for this reaction[2468] discloses that it too is a symmetry-forbidden process. All three of these "forbidden" reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.[2468]



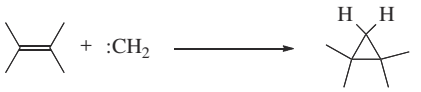
[2461] See, for example, Kramer, B.D.; Bartlett, P.D. *J. Am. Chem. Soc.* ***1972****, 94,* 3934.
[2462] See Caldwell, R.A.; Creed, D. *Acc. Chem. Res.* ***1980****, 13*, 45; Mattes, S.L.; Farid, S. *Acc. Chem. Res.* ***1982****, 15*, 80; Swapna, G.V.T.; Lakshmi, A.B.; Rao, J.M.; Kunwar, A.C. *Tetrahedron* ***1989****, 45*, 1777.
[2463] For a review of exciplexes, see Davidson, R.S. *Adv. Phys. Org. Chem.* ***1983****, 19*, 1–130.
[2464] Schuster, D.I.; Heibel, G.E.; Brown, P.B.; Turro, N.J.; Kumar, C.V. *J. Am. Chem. Soc.* ***1988****, 110*, 8261.
[2465] See Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967****, 6,* 78.
[2466] See Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967****, 6,* 518.
[2467] With transition metal catalysts: Landis, M.E.; Gremaud, D.; Patrick, T.B. *Tetrahedron Lett.* ***1982****, 23,* 375; Maruyama, K.; Tamiaki, H. *Chem. Lett.* ***1987***, 683.
[2468] See Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968****, 87,* 1185.

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[2469] These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the *Dewar* formula. Because of this, bicyclo[2.2.0]hexadiene is often called *Dewar benzene*. In the paragraph prior to Section 2.A, it was mentioned that Dewar formulas are canonical forms (although not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS **V**, 54, 235, 277, 297, 370, 393, 424, 459, 528; **VI**, 378, 571, 962, 1002, 1024, 1037; **VII**, 177, 256, 315; **VIII**, 82, 116, 306, 377; **IX**, 28, 275; **80**, 160. For the reverse reaction, see OS **V**, 734.

15-64 The Addition of Carbenes and Carbenoids to Double and Triple Bonds

***epi*-Methylene-addition**



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives by what can be considered as a formal [1 + 2]-cycloaddition.[2470] Many carbene derivatives [e.g., PhCH, ROCH,[2471] $Me_2C{=}C$, and $C(CN)_2$] have been added to double bonds, but the reaction is often performed with CH_2 itself, with halo and dihalocarbenes,[2472] and with carbalkoxycarbenes[2473] (generated from diazoacetic esters). Alkylcarbenes (HCR) have been added to alkenes,[2474] but more often these rearrange to give alkenes (Sec. 5.D.ii, category 4). The carbene can be generated in any of the ways normally used (Sec. 5.D.ii). However, most reactions in which a cyclopropane is formed by treatment of an alkene with a carbene "precursor" do not actually involve free carbene intermediates. In some cases, it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (Sec. 5.D.ii) is actually involved.

Carbene itself ($:CH_2$) is extremely reactive and gives many side reactions, especially insertion reactions (**12-21**), which greatly reduce yields. This competition is also true with Rh catalyzed diazoalkane cyclopropanations[2475] (see below). When: CH_2 must be added for preparative purposes, a free carbene is not used, but the *Simmons–Smith procedure*

[2469] Kobayashi, Y.; Kumadaki, I. Adv. Heterocycl. Chem. **1982**, 31, 169; Acc. Chem. Res. **1981**, 14, 76; van Tamelen, E.E. Acc. Chem. Res. **1972**, 5, 186; Angew. Chem. Int. Ed. **1965**, 4, 738; Schäfer, W.; Hellmann, H. Angew. Chem. Int. Ed. **1967**, 6, 518.

[2470] See Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S. pt. 1, pp. 307–373; Verhé, R.; De Kimpe, N. pt. 1, pp. 445–564; Marchand, A.P. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups,* pt. 1, Wiley, NY, ***1977***, pp. 534–607, 625–635;; Kirmse, W. *Carbene Chemistry* 2nd ed.; Academic Press, NY, ***1971***, pp. 85–122, 267–406. For a review of certain intramolecular additions, see Burke, S.D.; Grieco, P.A. *Org. React.* ***1979****, 26*, 361. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 135–153.

[2471] See Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968****, 7,* 588.

[2472] See Parham, W.E.; Schweizer, E.E. *Org. React.* ***1963****, 13,* 55.

[2473] See Dave, V.; Warnhoff, E.W. *Org. React.* ***1970****, 18,* 217.

[2474] See Frey, H.M. *J. Chem. Soc.* ***1962***, 2293.

[2475] Doyle, M.P.; Phillips, I.M. *Tetrahedron Lett.* ***2001****, 42*, 3155. For a review, see Merlic, C.A.; Zechman, A.L. *Synthesis* ***2003***, 1137.

(see **167**) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.[2476] Vinyldiazolactone is a vinylcarbene precursor for a reaction with alkenes to give spirolactones.[2477]

The absolute rate constant for addition of selected alkoxychlorocarbene to butenes has been measured to range from 330 to $1 \times 10^4\ M^{-1}\ s^{-1}$.[2478] Both entropy and enthalpy play a role in addition of some carbenes.[2479] Shown are a few of the many ways[2480] in which halocarbenes or carbenoids are generated,[2481] and most involve formal elimination (for the first two steps of the S_N1cB mechanism, see Sec. 10.G.iii):

$$CH_2Cl_2 + RLi \longrightarrow CHCl$$

$$N_2CHBr \xrightarrow{h\nu} CHBr$$

$$CHCl_3 + {}^-OH \longrightarrow CCl_2$$

$$PhHgCCl_2Br \xrightarrow{\Delta} CCl_2 \qquad \text{Ref. 2482}$$

$$Me_3SnCF_3 + NaI \longrightarrow CF_2 \qquad \text{Ref. 2483}$$

$$Me_2CBr_2 \xrightarrow{\text{electrolysis}} Me_2C: \qquad \text{Ref. 2484}$$

The reaction between $CHCl_3$ and HO^- is often carried out under phase-transfer conditions.[2485] It has been shown that the reaction between $PhCHCl_2$ and *t*-BuOK produces a carbenoid, but when the reaction is run in the presence of a crown ether, the carbene [Ph(Cl)C:] is formed instead.[2486] The reaction of iodoform and $CrCl_2$ leads to iodocyclopropanes upon reaction with alkenes.[2487] Dihalocyclopropanes are very useful compounds[2488] that can be reduced to cyclopropanes, treated with Mg or Na to give allenes (Reaction **18-3**), or converted to a number of other products.

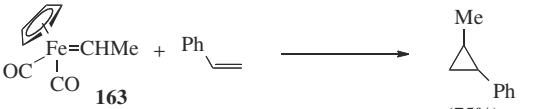
[2476] Moss, R.A. *Acc. Chem. Res.* ***1989****, 22,* 15; Kostikov, R.R.; Molchanov, A.P.; Khlebnikov, A.F. *Russ. Chem. Rev.* ***1989****, 58,* 654.
[2477] Bykowski, D.; Wu, K.-H.; Doyle, M.P. *J. Am. Chem. Soc.* ***2006****, 128*, 16038.
[2478] Moss, R.A.; Ge, C.-S.; Wlostowska, J.; Jang, E.G.; Jefferson, E.A.; Fan, H. *Tetrahedron Lett.* ***1995****, 36*, 3083.
[2479] Moss, R.A.; Wang, L.; Zhang, M.; Skalit, C.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2008****, 130,* 5634.
[2480] Seyferth, D.; Haas, C.K.; Dagani, D. *J. Organomet. Chem.* ***1976****, 104*, 9.
[2481] See also Kirmse, W. *Carbene Chemistry Carbene Chemistry* 2nd ed., Academic Press, NY, ***1971***, pp. 313–319; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 135–143.
[2482] See Seyferth, D. *Acc. Chem. Res.* ***1972****, 5,* 65; Larock, R.C. *Organomercurcury Compounds in Organic Synthesis* Springer, NY, ***1985***, pp. 341–380.
[2483] Seyferth, D. in Moss, R.A.; Jones, Jr., M. *Carbenes*, Vol. 2, Wiley, NY, ***1975***, pp. 101–158; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 237–270.
[2484] Léonel, E.; Paugam, J.P.; Condon-Gueugnot, S.; Nédélec, Y.-Y. *Tetrahedron* ***1998****, 54*, 3207.
[2485] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis* Academic Press, NY, ***1978***, pp. 224–268; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 18–43, 58–62. For a discussion of the mechanism, see Gol'dberg, Yu.Sh.; Shimanskaya, M.V. *J. Org. Chem. USSR* ***1984****, 20*, 1212.
[2486] Moss, R.A.; Lawrynowicz, W. *J. Org. Chem.* ***1984****, 49,* 3828.
[2487] Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* ***2003****, 125*, 12990.
[2488] Banwell, M.G.; Reum, M.E. *Adv. Strain Org. Chem.* ***1991****, 1,* 19–64; Kostikov, R.R.; Molchanov, A.P.; Hopf, H. *Top. Curr. Chem.* ***1990****, 155*, 41–80.

Alkenes of all types can be converted to cyclopropane derivatives by this reaction, but difficulty may be encountered with sterically hindered ones.[2489] Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[2490] Conjugated dienes give 1,2-addition to give a vinylcyclopropane.[2491] Addition of a second molar equivalent gives bicyclopropyl derivatives.[2492] 1,4-Addition is rare but has been reported in certain cases.[2493] Carbene adds to ketene to give cyclopropanone.[2494] Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:[2495]



A second equivalent gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.[2496]

Free carbenes can also be avoided by using transition metal–carbene complexes ($L_nM{=}CRR'$, L = a ligand, M = a metal),[2497] which add the group CRR′ to double bonds.[2498] An example is the reaction of iron carbene (**163**).[2499] These complexes can be isolated in some cases; in others they are generated *in situ* from appropriate precursors, of which diazo compounds are among the most important. Chromium complexes have been used for the cyclopropanation of alkenes.[2500]



163

Diazo compounds, including CH_2N_2 and other diazoalkanes, react with metals or metal salts (Cu, Pd,[2501] Ag,[2502] La,[2503] and Rh[2504] are commonly used) to give the carbene complexes that add:CRR′ to double bonds.[2505] Polymer-supported benzenesulfonyl azides

[2489] Dehmlow, E.V.; Eulenberger, A. *Liebigs Ann. Chem.* ***1979***, 1112.
[2490] Cairns, T.L.; McKusick, B.C. *Angew. Chem.* ***1961****, 73,* 520.
[2491] Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* ***1957****, 79,* 2542.
[2492] See Skattebøl, L. *J. Org. Chem.* ***1964****, 29*, 2951.
[2493] See Hudlicky, T.; Seoane, G.; Price, J.D.; Gadamasetti, K.G. *Synlett* ***1990***, 433; Lambert, J.B.; Ziemnicka-Merchant, B.T. *J. Org. Chem.* ***1990****, 55*, 3460.
[2494] Rothgery, E.F.; Holt, R.J.; McGee Jr., H.A. *J. Am. Chem. Soc.* ***1975****, 97*, 4971; Wasserman, H.H.; Berdahl, D. R.; Lu, T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group,* Wiley, NY, ***1987***, pt. 2, pp. 1455–1532.
[2495] Landor, S.R. in Landor, S.R. *The Chemistry of Allenes, Vol.* 2, Acaademic Press, NY, ***1982***, pp. 351–360; Binger, P.; Büch, H.M. *Top. Curr. Chem.* ***1987****, 135,* 77.
[2496] See Krapcho, A.P. *Synthesis* ***1978***, 77–126.
[2497] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,* Wiley, NY, ***1998***.
[2498] See Helquist, P. *Adv. Met.-Org. Chem.* ***1991****, 2,* 143; Brookhart, M.; Studabaker, W.B. *Chem. Rev.* ***1987****, 87,* 411; Syatkovskii, A.I.; Babitskii, B.D. *Russ. Chem. Rev.* ***1984****, 53,* 672.
[2499] Brookhart, M.; Tucker, J.R.; Husk, G.R. *J. Am. Chem. Soc.* ***1983****, 105*, 258.
[2500] Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M.A. *Org. Lett.* ***2002****, 4*, 4233.
[2501] Beaufort, L.; Demonceau, A.; Noels, A.F. *Tetrahedron* ***2005****, 61,* 9025. Also see Rodríguez-García, C.; Oliva, A.; Ortuño, R.M.; Branchadell, V. *J. Am. Chem. Soc.* ***2001****, 123*, 6157.
[2502] Thompson, J.L.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2007****, 129,* 6090.
[2503] Nishiyama, Y.; Tanimizu, H.; Tomita, T. *Tetrahedron Lett.* ***2007****, 48*, 6405,
[2504] See Panne, P.; DeAngelis, A.; Fox, J.M. *Org. Lett.* ***2008****, 10,* 2987.
[2505] See Adams, J.; Spero, D.M. *Tetrahedron* ***1991****, 47,* 1765; Maas, G. *Top. Curr. Chem.* ***1987****, 137, 75*; Doyle, M.P. *Chem. Rev.* ***1986****, 86,* 919; *Acc. Chem. Res.* ***1986****, 19,* 348; Heck, R.F. *Palladium Reagents in Organic Synthesis* Academic Press, NY, ***1985***, pp. 401–407; Wulfman, D.S.; Poling, B. *React. Intermed. (Plenum)* ***1980****, 1,* 321; Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966****, 7,* 128.

have been developed as a safe diazo-transfer reagent.[2506] Diazoketones and diazoesters react with alkenes to give the cyclopropane derivative, usually with a transition metal catalyst (e.g., a Cu complex).[2507] The Ru catalyst reaction of diazoesters with an alkyne gives a cyclopropene.[2508] An X-ray structure of an Os catalyst intermediate has been determined.[2509] Electron-rich alkenes react faster than simple alkenes.[2510]

Asymmetric cyclopropanation reactions are a growing area of interest,[2511] and chiral complexes have been used for enantioselective cyclopropane synthesis.[2512] Decomposition of diazoalkanes in the presence of chiral Rh[2513] Cu,[2514] Ir,[2515] Co,[2516] Au,[2517] or Ru[2518] complexes leads to optically active cyclopropanes. Diazosulfonate esters have been used in asymmetric cyclopropanations.[2519] The use of chiral additives or auxiliaries with a metal complex also leads to cyclopropanes enantioselectively.[2520] An important chiral species is $Rh_2(S\text{-DOSP})_4$,[2521] which leads to cyclopropanes with excellent enantioselectivity in carbene cyclopropanation reactions.[2522] Chiral organocatalysts have been used.[2523] The Cu catalyzed diazoester cyclopropanation was reported in an ionic liquid.[2524] Phosphonate esters have been incorporated into the diazo compound.[2525] *Fischer carbene* compounds (see Reaction **15-58**) react with enolate anions to

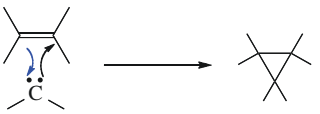
[2506] Green, G.M.; Peet, N.P.; Metz, W.A. *J. Org. Chem.* ***2001****, 66*, 2509.
[2507] Díaz-Requejo, M.M.; Belderraín, T.R.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2001****, 123*, 3167. See Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* ***2001***, 2151.
[2508] See Panne, P.; Fox, J.M. *J. Am. Chem. Soc.* ***2007****, 129,* 22.
[2509] Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* ***2001****, 123*, 4843.
[2510] See Davies, H.M.L.; Xiang, B.; Kong, N.; Stafford, D.G. *J. Am. Chem. Soc.* ***2001****, 123*, 7461.
[2511] Pellissier, H. *Tetrahedron* ***2008****, 64*, 7041.
[2512] Singh, V.K.; DattaGupta, A.; Sekar, G. *Synthesis* ***1997***, 137; Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* ***1996****, 37*, 4133.
[2513] Davies, H.M.L.; Rusiniak, L. *Tetrahedron Lett.* ***1998****, 39*, 8811; Haddad, N.; Galili, N. *Tetrahedron Asymmetry* ***1997****, 8*, 3367; Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* ***1997****, 53,* 9599; Fukuda, T.; Katsuki, T. *Tetrahedron* ***1997****, 53*, 7201.
[2514] Bayardon, J.; Holczknecht, O.; Pozzi, G.; Sinou, D. *Tetrahedron Asymmetry* ***2006****, 17*, 1568.
[2515] Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* ***2008****, 130*, 10327.
[2516] Chen, Y.; Ruppel, J.V.; Zhang, X.P. *J. Am. Chem. Soc.* ***2007****, 129*, 12074; Doyle, M.P. *Angew. Chem. Int. Ed.* ***2009****, 48*, 850.
[2517] Prieto, A.; Fructos, M.R.; Díaz-Requejo, M.M.; Pérez, P.J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A.M. *Tetrahedron* ***2009****, 65*, 1790.
[2518] Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *Chem. Commun.* ***2001***, 59. For a discussion of the mechanism, see Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* ***2004****, 126*, 442.
[2519] Ye, T.; Zhou, C. *New J. Chem.* ***2005****, 29,* 1159.
[2520] Ferreira, V.F.; Leão, R.A.C.; da Silva, F. de C.; Pinheiro, S.; Lhoste, P.; Sinou, D. *Tetrahedron Asymmetry* ***2007****, 18,* 1217; Miller, J.A.; Gross, B.A.; Zhuravel, M.A.; Jin, W.; Nguyen, S.B.T. *Angew. Chem. Int. Ed.* ***2005****, 44,* 3885.
[2521] Doyle, M.P. *Pure Appl. Chem.* ***1998****, 70* 1123; Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000****, 122*, 3063. See also, Davies, H.M.L.; Lee, G.H. *Org. Lett.* ***2004****, 6*, 2117.
[2522] Davies, H.M.L.; Townsend, R.J. *J. Org. Chem.* ***2001****, 66*, 6595.
[2523] Johansson, C.C.C.; Bremeyer, N.; Ley, S.V.; Owen, D.R.; Smith, S.C.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2006****, 45*, 6024.
[2524] Fraile, J.M.; García, J.I.; Herrerías, C.I.; Mayoral, J.A.; Carrié, D.; Vaultier, M. *Tetrahedron Asymmetry* ***2001****, 12*, 1891.
[2525] Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* ***2004****, 6*, 3211.

give cyclopropane derivatives.[2526] A Cr promoted cyclopropanation of conjugated amides has been reported.[2527]

Asymmetric, intramolecular cyclopropanation reactions have been reported.[2528] Note that the reaction of a diazoester with a chiral dirhodium catalyst leads to β-lactones with modest enantioselectivity.[2529]

Triple-bond compounds[2530] react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.[2531] Cyclopropenones (Sec. 2.K.i) are obtained by hydrolysis of dihalocyclopropenes.[2532]

Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the alkene increase the rate of the reaction, and electron-withdrawing groups decrease it,[2533] although the range of relative rates is not very great.[2534] As discussed in Section 5.D.i, carbenes in the singlet state, which is the most common state, react stereospecifically and syn,[2535] probably by a one-step mechanism,[2536] similar to mechanism *a* of Reactions **15-60** and **15-63**:



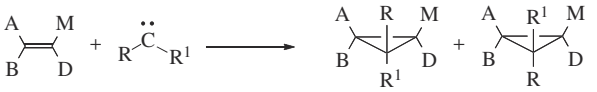
Infrared spectra of a carbene and the cyclopropane product have been observed in an Ar matrix at 12–45 K.[2537] Carbenes in the triplet state react nonstereospecifically,[2538] probably by a diradical mechanism, similar to mechanism *b* of Reactions **15-49** and **15-63**:



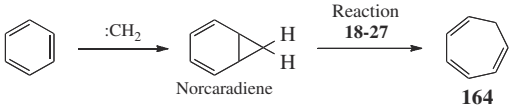
For carbenes or carbenoids of the type R—C—R′ there is another aspect of stereochemistry.[2539] When these species are added to all but symmetrical alkenes, two isomers

[2526] Barluenga, J.; Suero, M.G.; Pérez-Sánchez, I.; Flórez, J. *J. Am. Chem. Soc.* ***2008****, 130*, 2708.
[2527] Concellón, J.M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E.G.; García-Granda, S.; Diaz, M.R. *Org. Lett.* ***2008****, 10,* 349.
[2528] See Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* ***2003****, 125*, 2860.
[2529] Doyle, M.P.; May, E.J. *Synlett* ***2001***, 967.
[2530] See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 427–434; Closs, G.L. *Adv. Alicyclic Chem.* ***1966****, 1,* 53–127, see pp. 58–65.
[2531] Frey, H.M. *Chem. Ind. (London)* ***1960***, 1266.
[2532] Vol'pin, M.E.; Koreshkov, Yu.D.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 535.
[2533] Mitsch, R.A.; Rodgers, A.S. *Int. J. Chem. Kinet.* ***1969****, 1,* 439.
[2534] Moss, R.A. in Jones Jr., M.; Moss, R.A. *Carbenes*, Vol. 1, Wiley, NY, ***1973***, pp. 153–304. See also, Cox, D.P.; Gould, I.R.; Hacker, N.P.; Moss, R.A.; Turro, N.J. *Tetrahedron Lett.* ***1983****, 24,* 5313.
[2535] Ando, W.; Hendrick, M.E.; Kulczycki, Jr., A.; Howley, P.M.; Hummel, K.F.; Malament, D.S. *J. Am. Chem. Soc.* ***1972****, 94,* 7469.
[2536] See Giese, B.; Lee, W.; Neumann, C. *Angew. Chem. Int. Ed.* ***1982****, 21*, 310.
[2537] Nefedov, O.M.; Zuev, P.S.; Maltsev, A.K.; Tomilov, Y.V. *Tetrahedron Lett.* ***1989****, 30*, 763.
[2538] Skell, P.S.; Klebe, J. *J. Am. Chem. Soc.* ***1960****, 82*, 247. See also, Jones, Jr., M.; Tortorelli, V.J.; Gaspar, P.P.; Lambert, J.B. *Tetrahedron Lett*. ***1978***, 4257.
[2539] Moss, R.A. *Sel. Org. Transform.,* ***1970****, 1,* 35-88; Closs, G.L. *Top Stereochem.* ***1968****, 3,* 193–235. For a discussion of enantioselectivity in this reaction, see Nakamura, A. *Pure Appl. Chem.* ***1978****, 50,* 37.

are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



Which isomer is predominantly formed depends on R, R′, and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species (R′ = H), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show antistereoselectivity. When R = halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.

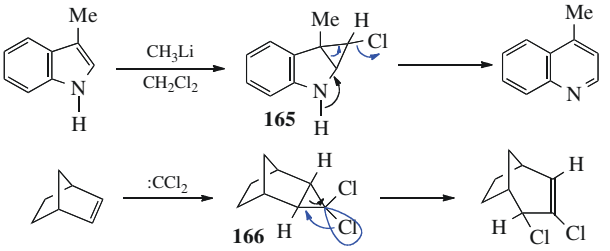


164

Carbenes are so reactive that they add to the "double bonds" of aromatic rings.[2540] The products are usually unstable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene (**164**),[2541] but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case[2542] (it undergoes an electrocyclic rearrangement, Reaction **18-27**), although certain substituted norcaradienes, [e.g., the product of addition of:$C(CN)_2$ to benzene],[2543] have been isolated.[2544] With:CH_2, insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding:CH_2 to benzene rings without the use of free carbene is the catalytic decomposition of diazomethane (CH_2N_2) in the aromatic compound as a solvent with CuCl or CuBr.[2545] By this method, better yields of cycloheptatrienes are obtained without insertion of side products. *Picosecond optical grating calorimetry* has been used to investigate the photochemical decomposition of diazomethane in benzene, and it appears that a transient is formed that is consistent with a weak complex between singlet methylene and benzene.[2546] Chlorocarbene (:CHCl) is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes[2547] via the initially formed adduct **165** in the case of the indole. In such cases, a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring

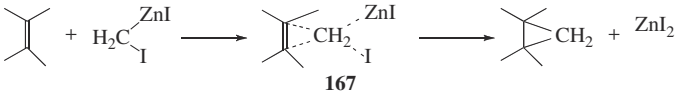
[2540] See Giese, C.M.; Hadad, C.M. *J. Org. Chem.* ***2002****, 67*, 2532.
[2541] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1951****, 75,* 297.
[2542] It has been detected by UV spectroscopy: Rubin, M.B. *J. Am. Chem. Soc.* ***1981****, 103,* 7791.
[2543] Ciganek, E. *J. Am. Chem. Soc.* ***1967****, 89*, 1454.
[2544] See Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987****, 26,* 559.
[2545] Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* ***1961****, 650,* 1; Müller, E.; Fricke, H. *Liebigs Ann. Chem.* ***1963****, 661*, 38; Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. *Liebigs Ann. Chem.* ***1961****, 675*, 63.
[2546] Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995****, 117*, 6635.
[2547] See Rees, C.W.; Smithen, C.E. *Adv. Heterocycl. Chem.* ***1964****, 3,* 57–78.

expansion can occur even with nonaromatic compounds, when the driving force is supplied by relief of strain (see Reaction **166**).[2548]



As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons–Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion of side products.[2549] This is known as a *carbenoid* reaction. Intramolecular variations are known.[2550] This procedure involves treatment of the double-bond compound with CH_2I_2 and a Zn—Cu couple and leads to cyclopropane derivatives in good yields.[2551] The Zn—Cu couple can be prepared in several ways,[2552] and heating Zn dust with CuCl in ether under nitrogen[2553] is particularly convenient. The reaction has also been done with unactivated Zn and ultrasound.[2554] When $TiCl_4$ is used along with Zn and CuCl, CH_2I_2 can be replaced by the cheaper CH_2Br_2.[2555]

The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn \cdot ZnI_2$, which is stable enough for isolable solutions.[2556] An X-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.[2557] The addition is stereospecifically syn, and a concerted mechanism[2558] is likely, perhaps involving **167**.[2559] An iodomethylzinc phosphate has also been used for cyclopropanation reactions.[2560] Diiodomethane gives cyclopropanes in a reaction mediated by indium.[2561]



[2548] Jefford, C.W.; Gunsher, J.; Hill, D.T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* ***VI***, 142. For a review of the addition of halocarbenes to bridged bicyclic alkenes see Jefford, C.W. *Chimia,* ***1970****, 24*, 357–363.

[2549] See Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* ***1973****, 20*, 1–131; Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974****, 12*, 83–134, see pp. 84–103.

[2550] Bull, J.A.; Charette, A.B. *J. Am. Chem. Soc.* ***2010****, 132,* 1895.

[2551] Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* ***1959****, 81,* 4256.

[2552] LeGoff, E. *J. Org. Chem.* ***1964****, 29*, 2048; Denis, J.M.; Girard, C.; Conia, J.M. *Synthesis* ***1972***, 549.

[2553] Rawson, R.J.; Harrison, I.T. *J. Org. Chem.* ***1970****, 35*, 2057.

[2554] Repic, O.; Lee, P.G.; Giger, U. *Org. Prep. Proced. Int.* ***1984****, 16,* 25.

[2555] Friedrich, E.C.; Lunetta, S.E.; Lewis, E.J. *J. Org. Chem.* ***1989****, 54,* 2388.

[2556] Blanchard, E.P.; Simmons, H.E. *J. Am. Chem. Soc.* ***1964****, 86,* 1337. For an analysis of the reaction by density functional theory, see Fang, W.-H.; Phillips, D.L.; Wang, D.-q.; Li, Y.-L. *J. Org. Chem.* ***2002****, 67*, 154.

[2557] Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* ***1991****, 113*, 723.

[2558] Dargel, T.K.; Koch, W. *J. Chem. Soc. Perkin Trans. 2,* ***1996***, 877.

[2559] Simmons, H.E.; Blanchard, E.P.; Smith, R.D. *J. Am. Chem. Soc.* ***1964****, 86,* 1347. For the transition state and intermediate see Bernardi, F.; Bottoni, A.; Miscione, G.P. *J. Am. Chem. Soc.* ***1997****, 119*, 12300.

[2560] Lacasse, M.-C.; Poulard, C.; Charette, A.B. *J. Am. Chem. Soc.* ***2005****, 127,* 12440.

[2561] Virender; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2005****, 46*, 37.

Asymmetric induction is possible when chiral additives are used.[2562] Chiral complexes also lead to enantioselectivity in the cyclopropanation reaction.[2563] Organocatalysts have been used.[2564]

With the *Simmons–Smith procedure*, as with free carbenes, conjugated dienes give 1,2-addition,[2565] and allenes give methylenecyclopropanes or spiropentanes.[2566]

An alternative way of carrying out the *Simmons–Smith reaction* is by treatment of the substrate with CH_2I_2 or another dihalomethane and Et_2Zn in ether.[2567] This method can be adapted to the introduction of RCH and ArCH by the use of $RCHI_2$ or $ArCHI_2$ instead of the dihalomethane.[2568] The reaction is compatible with other functionality in the carbenoid complex. The reaction of RCO_2CH_2I with diethyl zinc and an alkene under photolysis conditions give a cyclopropane.[2569] In another method, CH_2I_2 or $MeCHI_2$ is used along with an alane (R_3Al) to transfer CH_2 or CHMe.[2570] Titanium complexes have been used similarly.[2571] Samarium and CH_2I_2 has been used for the cyclopropanation of conjugated amides.[2572] For the conversion of enolate anions to cyclopropanols, CH_2I_2 has been used along with SmI_2.[2573] Diodomethane in the presence of isopropylmagnesium chloride has been used to cyclopropanate allyl alcohols.[2574]

The *Simmons–Smith reaction* is the basis of a method for the indirect α methylation of a ketone.[2575] The ketone (illustrated for cyclohexanone) is first converted to an enol ether, an enamine (Reaction **16-13**) or silyl enol ether[2576] (Reaction **12-17**), and cyclopropanation via the *Simmons–Smith reaction* is followed by hydrolysis to give the α methylated ketone. A related procedure using diethylzinc and diiodomethane allows ketones to be chain-extended by one carbon.[2577] In another variation, phenols can be ortho methylated in one laboratory step, by treatment with Et_2Zn and CH_2I_2.[2578]

Diazoesters react with amines with a Rh catalyst to give α-amino esters.[2579] Diazoesters also react with aldehydes and a Rh catalyst. The product is an α,β-epoxy ester.[2580]

[2562] Balsells, J.; Walsh, P.J. *J. Org. Chem.* ***2000****, 65*, 5005; Du, H.; Long, J.; Shi, Y. *Org. Lett.* ***2006****, 8,* 2827; Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* ***2005****, 46,* 2737.

[2563] Song, Z.; Lu, T.; Hsung, R.P.; Al-Rashid, Z.F.; Ko, C.; Tang, Y. *Angew. Chem. Int. Ed.* ***2007****, 46,* 4069; Shitama, H.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2008****, 47,* 2450; Zimmer, L.E.; Charette, A.B. *J. Am. Chem. Soc.* ***2009****, 131*, 15624.

[2564] Long, J.; Xu, L.; Du, H.; Li, K.; Shi, Y. *Org. Lett.* ***2009****, 11*, 5226.

[2565] Overberger, C.G.; Halek, G.W. *J. Org. Chem.* ***1963****, 28,* 867.

[2566] Charette, A.B.; Jolicoeur, E.; Bydlinski, G.A.S. *Org. Lett.* ***2001****, 3*, 3293.

[2567] See Zhao, C.; Wang, D.; Phillips, D.L. *J. Am. Chem. Soc.* ***2002****, 124*, 12903.

[2568] Friedrich, E.C.; Biresaw, G. *J. Org. Chem.* ***1982****, 47*, 1615.

[2569] Charette, A.B.; Beauchemin, A.; Fraancoeur, S. *J. Am. Chem. Soc.* ***2001****, 123*, 8139.

[2570] Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* ***1985****, 50,* 4412; *Org. Synth. 67,* 176.

[2571] Charette, A.B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* ***2001****, 123*, 12168.

[2572] Concellón, J.M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1917.

[2573] Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* ***1987****, 28*, 1307. See also, Molander, G.A.; Harring, L.S. *J. Org. Chem.* ***1989****, 54,* 3525.

[2574] Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* ***197****, 38*, 7349.

[2575] See Wenkert, E.; Mueller, R.A.; Reardon, Jr., E.J.; Sathe, S.S.; Scharf, D.J.; Tosi, G. *J. Am. Chem. Soc.* ***1970****, 92*, 7428 for the enol ether procedure; Kuehne, M.E.; King, J.C. *J. Org. Chem.* ***1973****, 38*, 304 for the enamine procedure; Conia, J.M. *Pure Appl. Chem.* ***1975****, 43,* 317–326 for the silyl ether procedure.

[2576] See Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* ***1976****, 41,* 2073; *Org. Synth.* ***VI***, 327.

[2577] Brogan, J.B.; Zercher, C.K. *J. Org. Chem.* ***1997****, 62*, 6444.

[2578] Lehnert, E.K.; Sawyer, J.S.; Macdonald, T.L. *Tetrahedron Lett.* ***1989****, 30*, 5215.

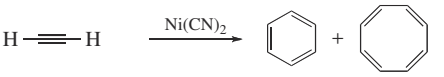
[2579] Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* ***2001****, 66*, 6729.

[2580] Doyle, M.P.; Hu, W.; Timmons, D.J. *Org. Lett.* ***2001****, 3*, 933.

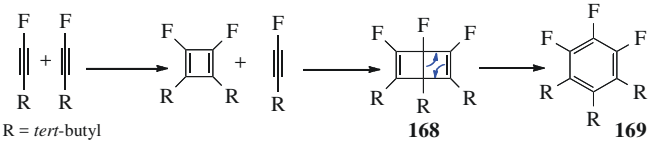
Diazoalkanes react similarly with aldehydes to give an alkene ($Me_3SiCH{=}N_2 + ArCHO \rightarrow ArCH{=}CHOSiMe_3$).[2581]

OS **V**, 306, 855, 859, 874; **VI**, 87, 142, 187, 327, 731, 913, 974; **VII**, 12, 200, 203; **VIII**, 124, 196, 321, 467; **IX**, 422; **76**, 86.

15-65 Trimerization and Tetramerization of Alkynes



Aromatic compounds can be prepared by cyclotrimerization of alkynes[2582] or triynes. Cyclotrimerization is possible by heating to 450–600 °C with no catalyst.[2583] The *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF gave 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**169**), which the first time was three adjacent *tert*-butyl groups put onto a benzene ring.[2584] The fact that this is a head-to-head joining allows formation of **169** from two alkynes. The fact that **168** (a *Dewar benzene*) was also isolated lends support to this scheme.[2585]



When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[2586] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes,[2587] and this reaction has been used to prepare very crowded molecules. Dialkylalkynes were trimerized over $CO_2(CO)_8$[2588] and over $Hg[Co(CO)_4]_2$ to give hexaisopropylbenzene.[2589] The six isopropyl groups are not free to rotate, but are lined up perpendicular to the plane of the benzene ring. Highly substituted benzene derivatives have also been prepared via cyclotrimeriztion using a Rh,[2590] Ni,[2591]

[2581] Dias, E.L.; Brookhart, M.; White, P.S. *J. Am. Chem. Soc.* ***2001****, 123*, 2442.
[2582] For a review, see Rubin, M.; Sromek, A.W.; Gevorgyan, V. *Synlett* ***2003***, 2265.
[2583] Kociolek, M.G.; Johnson, R.P. *Tetrahedron Lett.* ***1999****, 40*, 4141.
[2584] Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Valange, P. *Angew. Chem. Int. Ed.* ***1964****, 3*, 746; Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964****, 3,* 755.
[2585] See also, Wingert, H.; Regitz, M. *Chem. Ber.* ***1986****, 119,* 244.
[2586] See Winter, M.J. in Hartley, F.R.; Patai, S. The Chemistry of the Metal-Carbon Bond, Vol. 3, Wiley, NY, **1985**, pp. 259–294; Vollhardt, K.P.C. Angew. Chem. Int. Ed. **1984**, 23, 539; Acc. Chem. Res. **1977**, 10, 1; Maitlis, P.M. J. Organomet. Chem. **1980**, 200, 161; Reppe, W.; Kutepow, N.V.; Magin, A. Angew. Chem. Int. Ed. **1969**, 8, 727; Schore, N.E. Chem. Rev. **1988**, 88, 1081. For a list of reagents, with references, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley–VCH, NY, **1999**, pp. 198–201.
[2587] Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* ***1998****, 120*, 5130; Larock, R.C.; Tian, Q. *J. Org. Chem.* ***1998****, 63*, 2002.
[2588] Yong, L.; Butenschön, H. *Chem. Commun.* ***2002***, 2852; Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericàs, M.A.; Riera, A. *Org. Lett.* ***2001****, 3*, 3197. See also, Agenet, N.; Gandon, V.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* ***2007****, 129*, 8860.
[2589] See Hopff, H.; Gati, A. *Helv. Chim. Acta* ***1965****, 48,* 509.
[2590] See Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Chem. Lett.* ***2007****, 36,* 998.
[2591] Mori, N.; Ikeda, S.-i.; Odashima, K. *Chem. Commun.* ***2001***, 181.

Ti,[2592] Mo,[2593] Ru,[2594] Co,[2595] or a Pd[2596] catalyst. Alkynes react with allenes and a Ni catalyst to give highly substituted benzene derivatives.[2597] Conjugated ketones react with internal alkynes with Me_3Al and a Ni catalyst[2598] to give an aromatic ring fused to a cyclic ketone after reaction with DBU and air.[2599] N-Aryl chloroimines react with alkynes and a Rh catalyst to give quinolines,[2600] as do N-aryl alkynyl imines with a W complex.[2601]

Intramolecular cyclotrimerizations have been reported by condensation of a diyne[2602] with an alkyne in the presence of a Pd,[2603] Mo,[2604] Ni,[2605] Rh,[2606] Ir,[2607] Ag,[2608] Co,[2609] or Ru catalyst.[2610] Triynes have been similarly condensed with a Rh catalyst.[2611] Note that this type of cyclization has been labeled as a $[2+2+2]$-cycloaddition reaction, which is discussed in Reaction **15-66**. The internal cyclotrimerization of a triyne, utilizing a siloxy tether and a Co catalyst has been reported.[2612] Fused-ring aromatic compounds are prepared by this method. Similar results were obtained from diynes and allenes with a Ni catalyst.[2613] Solid-supported cyclotrimerizations have been reported.[2614] Endiynes are cyclized to bicyclic arenes using a Pd[2615] or Ru[2616] catalyst, as are yndienes with a Ru catalyst.[2617] Alkynyl biaryls are cyclized to phenanthrene derivatives using ICl.[2618] In the presence of $PhMe_2SiH$, CO, and a Rh catalyst, a nonconjugated triyne leads to a tricyclic compound in which a benzene ring is fused to two carbocyclic rings.[2619] Internal cyclotrimerization of an aryl alkynyl ketone where the aryl group has an *ortho*

[2592] Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2002****, 124*, 9682.
[2593] Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* ***1998****, 63*, 8606.
[2594] Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* ***2004****, 126*, 3712.
[2595] Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2002***, 576.
[2596] Gevorgyan, V.; Quan, L.G.; Yamamoto, Y. *J. Org. Chem.* ***2000****, 65*, 568. Also see Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2003****, 68*, 6836; Li, J.-H.; Xie, Y.-X. *Synth. Commun.* ***2004****, 34*, 1737.
[2597] Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* ***2001****, 3*, 4233.
[2598] Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* ***2002***, 2422.
[2599] Mori, N.; Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* ***1999****, 121*, 2722.
[2600] Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* ***2001****, 3*, 1109.
[2601] Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* ***2004****, 6*, 353.
[2602] See Kawathar, S.P.; Schreiner, P.R. *Org. Lett.* ***2002****, 4*, 3643.
[2603] Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* ***2001****, 66*, 2835. See also, Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* ***2003****, 68*, 5961.
[2604] Hara, R.; Guo, Q.; Takahashi, T. *Chem. Lett.* ***2000***, 140.
[2605] Jeevanandam, A.; Korivi, R.P.; Huang, I.-w.; Cheng, C.-H. *Org. Lett.* ***2002****, 4*, 807.
[2606] Witulski, B.; Zimmermann, A. *Synlett* ***2002***, 1855.
[2607] Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* ***2004****, 126*, 8382.
[2608] Zhao, J.; Hughes, C.O.; Toste, F.D. *J. Am. Chem. Soc.* ***2006****, 128*, 7436.
[2609] Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* ***2005***, 1474.
[2610] Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* ***2006****, 128*, 8336.
[2611] Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003****, 125*, 7784.
[2612] Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* ***2004****, 6*, 1519.
[2613] Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* ***2002****, 67*, 7724.
[2614] Young, D.D.; Senaiar, R.S.; Deiters, A. *Chemistry: European J.* ***2006****, 12*, 5563.
[2615] Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* ***2002****, 67*, 2653.
[2616] Odedra, A.; Wu, C.-J.; Pratap, T.B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* ***2005****, 127,* 3406.
[2617] Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* ***2005****, 127,* 4186.
[2618] Yao, T.; Campo, M.A.; Larock, R.C. *J. Org. Chem.* ***2005****, 70,* 3511.
[2619] Ojima, I.; Vu, A.T.; McCullagh, J.V.; Kinoshita, A. *J. Am. Chem. Soc.* ***1999****, 121*, 3230.

trimethylsiylalkyne substituent gives a tetracyclic naphthalene derivative with a fused cyclopentanone unit.[2620] Benzene derivatives with ortho alkyne units can be converted to naphthalene derivatives in aq NaOH with hydrazine, Te, $NaBH_4$ and sonication.[2621] Vinyl and alkyne substituents with a Ru catalyst lead to naphthalene derivatives.[2622] Cyclotrimerization occurs with alkynyl boronic esters.[2623]

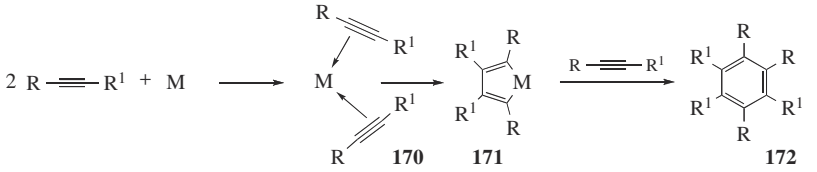
Imino and iodo substituents with a silyl alkyne and a Pd catalyst leads to an isoquinoline.[2624] Benzene derivatives having ortho imine and alkyne substituents give an isoquinoline when treated with iodine[2625] or with a Pd catalyst.[2626] Diynes with nitriles and a Ru catalyst lead to isoquinolines.[2627] Pyridines fused to carboxylic rings can be prepared by similar methodology using a cyanoamine and a Co catalyst.[2628] An isocyanate (Ar—N=C=O) reacts with a diyne and a Ru catalyst to give a bicyclic pyridone.[2629] Isocyanides and alkynes also react with a phosphine catalyst to give pyrroles.[2630] Ortho alkynyl and epoxy substituents leads to β-naphthols using a Ru catalyst.[2631]

Nitriles react with 2 molar equivalents of acetylene, in the presence of a Co catalyst, to give 2-substituted pyridines.[2632] Propargyl amines react with cyclohexanone derivatives and a Au complex to give tetrahydroquinolines.[2633] Treatment of alkynes with Cp_2ZrEt_2 followed by reaction with acetonitrile and then a second alkyne with a Ni catalyst gives a highly substituted pyridine.[2634] This reaction can be done intramolecularly using a photochemically induced reaction with a Co catalyst and *p*-TolCN to give pyridines incorporated into macrocycles.[2635] Diynes react with *N*-heterocyclic carbenes in the presence of a Ni catalyst to give pyridines.[2636] Alkynyl esters react with enamino esters with a $ZnBr_2$ catalyst to give substituted pyridines.[2637] α-Halo oxime ethers react with alkynes and *Grignard reagent*s, with a mixture of Pd and Cu catalysts, to give pyrimidines.[2638] Triketones fix nitrogen gas in the presence of $TiCl_4$ and Li metal to form bicyclic pyrrole derivatives.[2639]

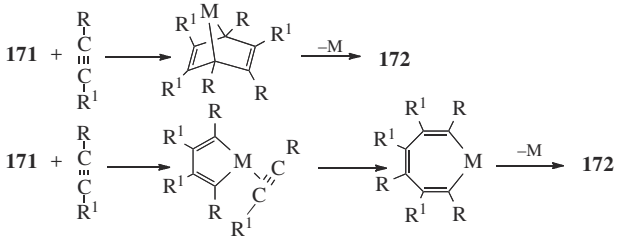
In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene (RC≡CH). The chief product is usually

[2620] Atienza, C.; Mateo, C.; de Frutos, Ó.; Echavarren, A.M. *Org. Lett.* ***2001****, 3*, 153.
[2621] Landis, C.A.; Payne, M.M.; Eaton, D.L.; Anthony, J.E. *J. Am. Chem. Soc.* ***2004****, 126*, 1338.
[2622] Klumpp, D.A.; Beauchamp, P.S.; Sanchez, Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001****, 42*, 5821.
[2623] Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* ***2004****, 6*, 3405.
[2624] Roesch, K.R.; Larock, R.C. *J. Org. Chem.* ***2002****, 67*, 86.
[2625] Huang, Q.; Hunter, J.A.; Larock, R.C. *Org. Lett.* ***2001****, 3*, 2973.
[2626] Dai, G.; Larock, R.C. *J. Org. Chem.* ***2003****, 68*, 920; Dai, G.; Larock, R.C. *Org. Lett.* ***2002****, 4*, 193.
[2627] Varela, J.A.; Castedo, L.; Saá, C. *J. Org. Chem.* ***2003****, 68*, 8595.
[2628] Boñaga, L.V.R.; Zhang, H.-C.; Maryanoff, B.E. *Chem. Commun.* ***2004***, 2394.
[2629] Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* ***2001****, 3,* 2117.
[2630] Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *Tetrahedron Lett.* ***2005****, 46*, 2563.
[2631] Madhusaw, R.J.; Lin, M.-Y.; Shoel, S.Md.A.; Liu, R.-S. *J. Am. Chem. Soc.* ***2004****, 126*, 6895.
[2632] Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 179.
[2633] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* ***2003****, 68*, 6959.
[2634] Takahashi, T.; Tsai, F.Y.; Kotora, M. *J. Am. Chem. Soc.* ***2000****, 122*, 4994.
[2635] Moretto, A.F.; Zhang, H.-C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2001****, 123*, 3157.
[2636] McCormick, M.M.; Duong, H.A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* ***2005****, 127*, 5030.
[2637] Bagley, M.C.; Dale, J.W.; Hughes, D.D.; Ohnesorge, M.; Philips, N.G.; Bower, J. *Synlett* ***2001***, 1523.
[2638] Kikiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2002****, 124*, 9032.
[2639] Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* ***1998****, 63*, 4832; Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem. Int. Ed.* ***1998****, 37*, 636.

the 1,2,4-isomer,[2640] with lesser amounts of the 1,3,15-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of the catalyzed



reaction to form benzenes[2641] is believed to go through a species **170** in which two molecules of alkyne coordinate with the metal, and another species (**171**), a five-membered heterocyclic intermediate.[2642] Such intermediates (where M = Rh, Ir, Zr,[2643] or Ni) have been isolated and are shown to give benzenes (**172**) when treated with alkynes.[2644] Note that this pathway accounts for the predominant formation of the 1,2,4-isomer. Two possibilities for the last step are a *Diels–Alder reaction,* and a ring expansion, each followed by extrusion of the metal:[2645]



In at least one case, the mechanism is different, going through a cyclobutadiene–nickel complex (see Sec. 2.K.ii), which has been isolated.[2646] Similar results were obtained with a Ti complex.[2647] Using a mixture of $PdCl_2$ and $CuCl_2$, however, aliphatic alkynes are converted to the 1,3,5-trialkyl benzene derivative.[2648]

Alkoxy chromium carbenes (*Fischer carbene complexes*, see Reaction **15-58**) react with phenylalkynes to give naphthalene derivatives.[2649] These Cr carbenes react with

[2640] See Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* ***2001****, 66*, 796.
[2641] See Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1986****, 108,* 5470; Lawrie, C.J.; Gable, K.P.; Carpenter, B.K. *Organometallics* ***1989****, 8,* 2274.
[2642] Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1981****, 103*, 6259; Kochi, J.K. *Organometallic Mechanisms and Catalysis* Academic Press, NY, ***1978***, pp. 428–432; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA ***1987***, pp. 870–877; Eisch, J.J.; Sexsmith, S.R. *Res. Chem. Intermed.* ***1990****, 13*, 149–192.
[2643] Takahahsi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* ***2002****, 124*, 388.
[2644] See Eisch, J.J.; Galle, J.E. *J. Organomet. Chem.* ***1975****, 96*, C23; McAlister, D.R.; Bercaw, J.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977****, 99,* 1666.
[2645] See, however, Bianchini, C.; Caulton, K.G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T.J.; Meli, A.; Peruzzini, M.; Raucher, D.J.; Streib, W.E.; Vizza, F. *J. Am. Chem. Soc.* ***1991****, 113,* 5127.
[2646] Mauret, P.; Alphonse, P. *J. Organomet. Chem.* ***1984****, 276,* 249. See also, Pepermans, H.; Willem, R.; Gielen, M.; Hoogzand, C. *Bull. Soc. Chim. Belg.* ***1988****, 97*, 115.
[2647] Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2001****, 123*, 7925.
[2648] Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* ***2001****, 66*, 3627.
[2649] Jackson, T.J.; Herndon, J.W. *Tetrahedron* ***2001****, 57*, 3859.

alkynyl boronates, cerium(IV) compounds, and then PhBr and a Pd catalyst to give a naphthoquinone.[2650] Diynes react to give cyclotrimerization.[2651] Note that vinyl Chromium carbenes react directly with alkynes to give spirocyclic compounds (spiro [4.4]nona-1,3,6-trienes).[2652] Benzofurans can be prepared using methoxy carbenes.[2653] Amino-substituted chromium carbenes react with alkynes and then silica to give substituted benzene derivatives that have an aminoalkyl ($—NR_2$) substituent.[2654] Imino-substituted Chromium carbenes react with alkynes to give pyrrole derivatives.[2655] Fischer carbene complexes react with alkynes to give the *Dötz benzannulation*,[2656] giving *p*-alkoxylphenol derivatives. Modification of this basic technique can lead to eight-membered ring carbocycles (see Reaction **15-66**).[2657]

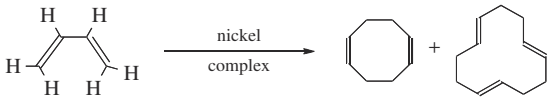
When benzene, in the gas phase, was adsorbed onto a surface of 10% rhodium-on-alumina, the reverse reaction took place, and acetylene was formed.[2658]

Heating ketones in the presence of $TlCl_3OTf$ leads to 1,3,5-trisubstituted arenes.[2659] Heating acetophenone with $TiCl_4$ gives 1,3,5-triphenylbenzene.[2660]

OS **VII**, 256; **IX**, 1; **80**, 93.

15-66 Other Cycloaddition Reactions

***cyclo*-[But-2-en-1,4-diyl]-1/4/addition**, and so on



Cycloaddition reactions other than [4 + 2], [3 + 2], or [2 + 2] are possible, often providing synthetically useful routes to cyclic compounds. Conjugated dienes can be dimerized or trimerized at the 1,4-positions (formally, [4 + 4] and [4 + 4 + 4] cycloadditions) by treatment with certain complexes or other transition metal compounds.[2661] Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.[2662] The relative amount of each product can be controlled by use of the proper catalyst. For example, Ni:P $(OC_6H_4$-*o*-$Ph)_3$ gives predominant dimerization, while Ni(cyclooctadiene)$_2$ gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise

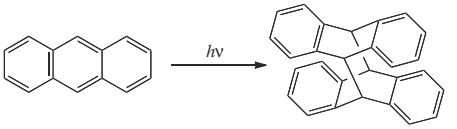
[2650] Davies, M.W.; Johnson, C.N.; Harrity, J.P.A. *J. Org. Chem.* ***2001****, 66*, 3525.
[2651] Jiang, M.X.-W.; Rawat, M.; Wulff, W.D. *J. Am. Chem. Soc.* ***2004****, 126*, 5970.
[2652] Schirmer, H.; Flynn, B.L.; de Meijere, A. *Tetrahedron* ***2000****, 56*, 4977.
[2653] Herndon, J.W.; Zhang, Y.; Wang, H.; Wang, K. *Tetrahedron Lett.* ***2000****, 41*, 8687.
[2654] Barluenga, J.; López, L.A.; Martínez, S.; Tomás, M. *Tetrahedron* ***2000****, 56*, 4967.
[2655] Campos, P.J.; Sampedro, D.; Rodríquez, M.A. *J. Org. Chem.* ***2003****, 68*, 4674.
[2656] Dötz, K.H. *Angew. Chem. Int. Ed.* ***1975****, 14*, 644.
[2657] Barluenga, J.; Aznar, F.; Palomero, M.A. *Angew. Chem. Int. Ed.* ***2000****, 39*, 4346.
[2658] Parker, W.L.; Hexter, R.M.; Siedle, A.R. *J. Am. Chem. Soc.* ***1985****, 107,* 4584.
[2659] Iranpoor, N.; Zeynizaded, B. *Synlett* ***1998***, 1079.
[2660] Li, Z.; Sun, W.-H.; Jin, X.; Shao, C. *Synlett* ***2001***, 1947.
[2661] Wilke, G. *Angew. Chem. Int. Ed.* ***1988****, 27,* 186; Heimbach, P.; Schenkluhn, H. *Top Curr. Chem.* ***1980****, 92*, 45; Baker, R. *Chem. Rev.* ***1973****, 73*, 487, see pp. 489–512; Semmelhack, M.F. *Org. React.* ***1972****, 19*, 115, pp. 128–143; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes, Vol. 2* Academic Press, NY, ***1974***, pp. 159–163; Heck, R.F. *Organotransition Metal Chemistry* Academic Press, NY, ***1974***, pp. 157–164.
[2662] See Rona, P. *Intra-Sci. Chem. Rep.* ***1971****, 5,* 105.

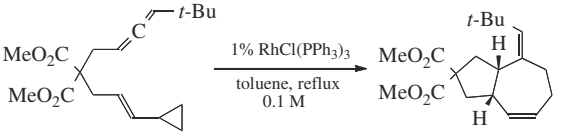
mechanisms involving metal–alkene complexes.[2663] The Rh catalyzed intramolecular cycloaddition of a furan with a conjugated diazoester gives a [3 + 4]-cycloadduct.[2664] The suprafacial thermal addition of an allylic cation to a diene (a [4 + 3] cycloaddition) is allowed by the *Woodward–Hoffmann rules* (this reaction would be expected to follow the same rules as the *Diels–Alder reaction*[2665]). Pyrroles react with allylic diazo compounds, in the presence of a Rh catalyst, to give bicyclic amines in a [4 + 3]-cycloaddition.[2666] A different [4 + 3]-cycloaddition involves the intramolecular reaction of a diene with an alkylidenecyclopropane unit, in the presence of a Pd catalyst, to give a seven-membered ring as part of a bicyclic system.[2667] A [3 + 2 + 2]-cycloaddition was reported with an alkyne and an alkene–alkylidenecyclopropane substrate, in the presence of a Rh catalyst.[2668] Reaction with a chiral Rh catalyst converts dienes and diazo compounds to cycloheptadienes.[2669] Chiral cations have been used in [4 + 3] cycloadditions.[2670] A [5 + 2]-cycloaddition of vinylcyclopropanes and alkenes, in the presence of a Rh catalyst, leads to seven-membered rings.[2671] The reaction of a conjugated carbonyl compound with a diazo ester, in the presence of a Cu catalyst, leads to a dihydropyran in what is labeled a [4 + 1]-cycloaddition.[2672] Dienes react with nitriles in a Ti mediated [4 + 1]-cycloaddition.[2673] Cycloheptatriene reacts with terminal alkynes, using a complex catalyst involves Co and Zn compounds, to give a bicyclic triene via a [6 + 2]-cycloaddition.[2674]

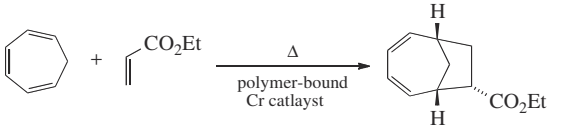
As seen in Reaction **15-60**, the *Woodward–Hoffmann rules* allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is $4n + 2$ and photochemically if the number is $4n$. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight membered or greater, concerted mechanisms, although allowed by orbital symmetry for the cases stated, become difficult to achieve. Due to the entropy factor the two ends of one system must simultaneously encounter the two ends of the other, unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct

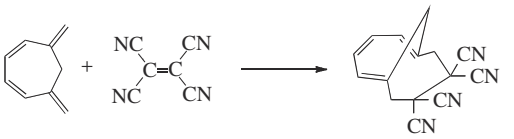
[2663] See Graham, G.R.; Stephenson, L.M. *J. Am. Chem. Soc.* ***1977****, 99,* 7098.
[2664] Davies, H.M.L.; Calvo, R.L.; Townsend, R.-J.; Ren, P.; Churchill, R.M. *J. Org. Chem.* ***2000****, 65*, 4261. For reviews of [3 + 4] cycloadditions see Mann, J. *Tetrahedron* ***1986****, 42*, 4611; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1984****, 23*, 1; ***1973****, 12*, 819; Noyori, R. *Acc. Chem. Res.* ***1979****, 12*, 61.
[2665] Garst, M.E.; Roberts, V.A.; Houk, K.N.; Rondan, N.G. *J. Am. Chem. Soc.* ***1984****, 106*, 3882.
[2666] Reddy, R.P.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2007****, 129*, 10312.
[2667] Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2007****, 129,* 11026.
[2668] Evans, P.A.; Inglesby, P.A. *J. Am. Chem. Soc.* ***2008****, 130,* 12838.
[2669] Deng, L.; Giessert, A.J.; Gerlitz, O.O.; Dai, X.; Diver, S.T.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2005****, 127,*1342.
[2670] Huang, J.; Hsung, R.P. *J. Am. Chem. Soc.* ***2005****, 127,* 50. See Harmata, M. *Chem. Commun.* ***2010***, 8886, 8904.
[2671] Wender, P.A.; Haustedt, L.O.; Lim, J.; Love, J.A.; Williams, T.J.; Yoon, J.-Y. *J. Am. Chem. Soc.* ***2006****, 128,* 6302.
[2672] Son, S.; Fu, G.C. *J. Am. Chem. Soc.* ***2007****, 129,* 1046.
[2673] Laroche, C.; Bertus, P.; Szymoniak, J. *Chem. Commun.* ***2005***, 3030.
[2674] Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* ***2005****, 7*, 2353.

[4 + 4]- or [4 + 4 + 4]-cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes. Some examples follows:

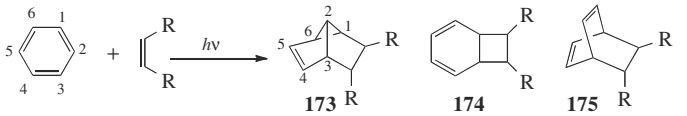
4 + 4 2  Ref.2675

5 + 2  Ref.2676

6 + 2  Ref.2677

8 + 2  Ref.2678

Benzene rings can undergo photochemical cycloaddition with alkenes.[2679] The major product is usually the 1,3 addition product (**173**, in which a three-membered ring has also been formed), although some of the 1,2-product (**174** Reaction **15-63**) is sometimes formed as well. Compound **174** is usually the main product where the alkene bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa. The 1,4-product (**175**) is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic alkenes bearing various groups.[2680]



[2675] Shönberg, A. *Preparative Organic Photochemistry* Springer, NY, ***1968***, pp. 97–99. Also see Zhu, M.; Qiu, Z.; Hiel, G.P.; Sieburth, S.Mc.N. *J. Org. Chem.* ***2002****, 67*, 3487.

[2676] Wender, P.A.; Gamber, G.G.; Scanio, M.J.C. *Angew. Chem. Int. Ed.* ***2001****, 40*, 3895; Wender, P.A.; Pedersen, T.M.; Scanio, M.J.C. *J. Am. Chem. Soc.* ***2002****, 124*, 15154; Wender, P.A.; Love, J.A.; Williams, T.J. *Synlett* ***2003***, 1295.

[2677] Rigby, J.H.; Mann, L.W.; Myers, B.J. *Tetrahedron Lett.* ***2001****, 42*, 8773. See Rigby, J.H.; Ateeq, H.S.; Charles, N.R.; Henshilwood, J.A.; Short, K.M.; Sugathapala, P.M. *Tetrahedron* ***1993****, 49*, 5495.

[2678] Farrant, G.C.; Feldmann, R. *Tetrahedron Lett.* ***1970***, 4979.

[2679] See Wender, P.A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* ***1990****, 62,* 1597; Gilbert, A. in Horspool, W.M. *Synthetic Organic Photochemistry,* Plenum, NY, ***1984***, pp. 1–60. For a review of this and related reactions, see McCullough, J.J. *Chem. Rev.* ***1987****, 87,* 811.

[2680] See the table in Wender, P.A.; Siggel, L.; Nuss, J.M. *Org. Photochem.* ***1989****, 10*, 357, pp. 384–415.

[2 + 2 + 2]-Cycloaddition reactions are known[2681] (also see Reaction **15-65**), usually with diynes, enynes, or intermolecular reactions of alkynes or alkenes with an alkyne, and facilitated by Ni[2682] Ru,[2683] or a Co catalyst.[2684] A mechanistic density functional study has been reported for this reaction.[2685] With a Co catalyst, an intramolecular [2 + 2 + 2]-cycloaddition of diynes with nitriles leads to bicyclic pyridines.[2686] Alkenyl isocyanates and alkynes react via [2 + 2 + 2]-cycloaddition, in the presence of a Ru catalyst, to form bicyclic conjugated lactams.[2687] Pyridines can also be prepared by metal-catalyzed [2 + 2 + 2]-cycloaddition.[2688] Alkynes and isocyanates react with CO in the presence of a Ru catalyst to give imides,[2689] and other [2 + 2 + 1]-cycloadditions are known,[2690] A Co catalyst is used for a [4 + 2 + 2]-cycloaddition of 1,3-butadiene and bicyclo[2.2.2]octa-2,5-diene.[2691] Eight-membered rings are produced by a Rh catalyzed [4 + 2 + 2] cycloaddition.[2692] Yne-dienes undergo [4 + 2 + 1]-cycloaddition in the presence of a Ni catalyst.[2693] Chromium catalysts are available for [6 + 4]-cycloadditions.[2694] Ene-diynes undergo [2 + 2 + 2 + 1]-cycloaddition to form seven-membered ring ketones, in the presence of CO and a Rh catalyst.[2695] Nickel catalyzed [2 + 2 + 2 + 2]-cycloadditions of alkynes lead to eight-membered rings.[2696]

Allenes and vinylcyclopropanes undergo [5 + 2]- and [5 + 2 + 1]-cycloadditions in the presence of a Rh catalyst.[2697] A reductive elimination step determines the selectivity for various substrates in Rh catalyzed catalyzed [5 + 2]-cycloadditions.[2698]

OS **VI**, 512; **VII**, 485; **X**, 1, 336.

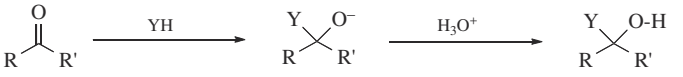
[2681] For a review, see Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* ***2005***, 4741.
[2682] Louie, J.; Gibby, J.E.; Farnsworth, M.V.; Tekavec, T.N. *J. Am. Chem. Soc.* ***2002****, 124*, 15188.
[2683] Cadierno, V.; García-Garrido, S.E.; Gimeno, J. *J. Am. Chem. Soc.* ***2006****, 128*, 15094; Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* ***2007****, 129,* 7730; Mallagaray, Á.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *Synlett* ***2010***, 2114.
[2684] Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem.* ***2008****, 73*, 5187.
[2685] Varela, J.A.; Rubín, S.G.; Castedo, L.; Saá, C. *J. Org. Chem.* ***2008****, 73,* 1320.
[2686] Boñaga, L.V.R.; Zhang, H.-C.; Moretto, A.F.; Ye, H.; Gauthier, D.A.; Li, J.; Leo, G.C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2005****, 127*, 3473.
[2687] Yu, R.T.; Rovis, T. *J. Am. Chem. Soc.* ***2006****, 128*, 2782; Yu, R.T.; Rovis, T. *J. Am. Chem. Soc.* ***2006****, 128,* 12370.
[2688] Varela, J.A.; Saá, C. *Synlett* ***2008***, 2571.
[2689] Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2006****, 128*, 14816.
[2690] Knölker, H.-J.; Braier, A.; Bröcher, D.J.; Jones, P.G.; Piotrowski, H. *Tetrahedron Lett.* ***1999***, *40,* 8075; Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* ***1999****, 121*, 7160.
[2691] Kiattansakul, R.; Snyder, J.K. *Tetrahedron Lett.* ***1999****, 40,* 1079.
[2692] Gilbertson, S.R.; DeBoef, B. *J. Am. Chem. Soc.* ***2002****, 124,* 8784; Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* ***2006****, 128,* 5354. For a computational study, see Baik, M.-H.; Baum, E.W.; Burland, M.C.; Evans, P.A. *J. Am. Chem. Soc.* ***2005****, 127,* 1602.
[2693] Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* ***2006****, 128,* 2609.
[2694] Kündig, E.P.; Robvieux, F.; Kondratenko, M. *Synthesis* ***2002***, 2053.
[2695] Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* ***2005****, 127*, 17756.
[2696] Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* ***2007****, 129,* 13402.
[2697] Wegner, H.A.; de Meijere, A.; Wender, P.A. *J. Am. Chem. Soc.* ***2005****, 127,* 6530; Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P.A.; Yu, Z.-X. *J. Am. Chem. Soc.* ***2007****, 129,* 10060.
[2698] Yu, Z.X.; Cheong, P.h.-Y.; Liu, P.; Legault, C.Y.; Wender, P.A.; Houk, K.N. *J. Am. Chem. Soc.* ***2008****, 130,* 2378.

CHAPTER 16

Addition to Carbon–Hetero Multiple Bonds

16.A. MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon–oxygen, carbon–nitrogen, and carbon–sulfur double bonds, as well as the carbon–nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon–carbon multiple bonds considered in Chapter 15.[1] Since C=O, C=N, and C≡N bonds are strongly polar, with the carbon always the positive end (except for isocyanides, see Sec. 16.B.iv), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds (the regiochemical preference). Nucleophilic attacking species always go to the carbon and electrophilic species to the oxygen or nitrogen. Additions to C=S bonds are much less common,[2] but in these cases the addition is sometimes in the other direction (reaction at sulfur is called *thiophilic addition* and addition to the carbon is called *carbophilic addition*).[3] For example, the reaction of phenyllithium with thiobenzophenone ($Ph_2C{=}S$) gives, after hydrolysis, benzhydryl phenyl sulfide (Ph_2CHSPh).[4]



1

The normal acyl addition of YH to a ketone gives an alkoxide, and hydrolysis gives **1**. Note that the product has a stereogenic carbon, but unless there is chirality in R or R′, or YH is optically active, the product must be a racemic mixture because there is no facial bias for addition to the carbonyl. The same holds true for C=N and C=S bonds. The stereochemistry of addition of a single YH to the carbon–nitrogen triple bond could be investigated, since the product can exist in (*E*) and (*Z*) forms (Sec. 4.K.i), but these reactions generally give imine products that undergo further reaction. Of course, if R or R′ *is* chiral, a mixture of diastereomers

[1] See Jencks, W.P. *Prog. Phys. Org. Chem.* ***1964****, 2,* 63

[2] See Schaumann, E. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1269–1367; Ohno, A. in Oae. S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 189–229; Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 219–240; Campaigne, E. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 917–959.

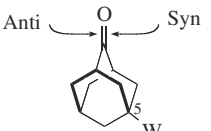
[3] See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338, pp. 261–267.

[4] See Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron* ***1978****, 34,* 2289.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

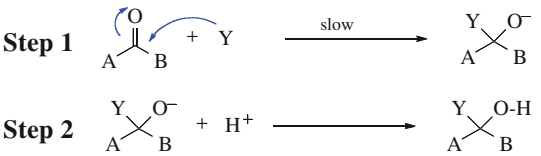
will result, and the stereochemistry of addition can be studied in such cases. *Cram's rule* or the *Felkin–Anh model* (Sec. 4.H) allows the direction of attack of Y to be predicted in many cases.[5] However, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.

In Section 15.B.iii, electronic effects were shown to play a part in determining which face of a carbon–carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantanones (**2**) electron-withdrawing (*–I*) groups W cause the attack to come from the syn face, while electron-donating groups cause it to come from the anti face.[6] In 5,6-disubstituted norborn-2-en-7-one systems, the carbonyl appears to tilt away from the π bond, with reduction occurring from the more hindered face.[7] An *ab initio* study of nucleophilic addition to 4-*tert*-butylcyclohexanones attempted to predict π-facial selectivity.[8]



2

The mechanistic picture is further simplified by the fact that free radical additions to carbon–heteroatom double bonds are not as prevalent (but see Reaction **16-31**).[9] In most cases, the nucleophile forms the first new bond to carbon, and these reactions are regarded as *nucleophilic additions*, which can be represented as:

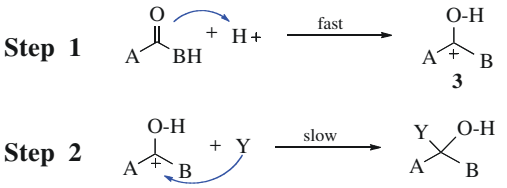


The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter the electrophilic atom is either hydrogen or carbon. Note that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (Sec. 16.A.i), but carbon groups (A, B = H, alkyl aryl, etc.) are poor leaving groups so that substitution does not compete with addition. For carboxylic acid derivatives, there are leaving groups (B = Cl, OR, NH_2, etc.) and acyl substitution predominates (Sec. 16.A.i). *The nature of A and B determines whether a nucleophilic attack at a carbon–heteroatom multiple bond will lead to substitution or addition.*

Both acids and bases can catalyze many of these reactions.[10] Bases catalyze the reaction by converting a reagent YH to the more powerful nucleophile Y^- (see Sec. 10.G.ii). Acids

[5] See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. Also see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 22; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521.
[6] See Laube, T.; Stilz, H.U. *J. Am. Chem. Soc.* ***1987***, *109*, 5876.
[7] Kumar, V.A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F.A.; Mehta, G. *Tetrahedron Lett.* ***1992***, *33*, 3069.
[8] Yadav, V.K.; Jeyaraj, D.A. *J. Org. Chem.* ***1998***, *63*, 3474. For a discussion of models, see Priyakumar, U.D.; Sastry, G.N.; Mehta, G. *Tetrahedron* ***2004***, *60*, 3465.
[9] See Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* ***1989***, *111*, 2674; Clerici, A.; Porta, O. *J. Org. Chem.* ***1989***, *54*, 3872; Cossy, J.; Pete, J.P.; Portella, C. *Tetrahedron Lett.* ***1989***, *30*, 7361.
[10] See Jencks, W.P.; Gilbert, H.F. *Pure Appl. Chem.* ***1977***, *49*, 1021.

catalyze it by converting the substrate to an heteroatom-stabilized cation (oxocarbenium ion **3** from C=O) in step 1, thus making it more attractive to nucleophilic attack and making the reverse reaction somewhat less favorable. Similar catalysis can also be achieved with metallic ions (e.g., Ag^+), which act as Lewis acids.[11]



In step 1 of the acid-catalyzed mechanism, the carbonyl reacts as a base with the proton to give **3**, which is known as an *oxocarbenium ion*. In Section 5.A.ii, it was pointed out that oxocarbenium ions are comparatively stable carbocations because the positive charge is delocalized on the oxygen by resonance.[12] Intermediate **3** then reacts with the nucleophile in step 2 to give the acyl addition product. The rate-determining step is usually the one involving nucleophilic attack. If one heteroatom (e.g., oxygen) stabilizes an adjacent carbocation, as in **3**, a second heteroatom (X) will stabilize an oxocarbenium ion (—X—C^+—X—) to a greater extent.[13]

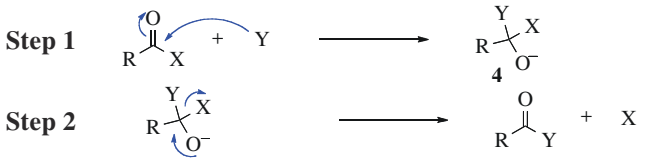
Reactivity factors for carbon–heteroatom multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.[14] If A and/or B are electron-donating groups (e.g., alkyl groups), rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule, but is lost on going to the intermediate. Double bonds in conjugation with the carbon–heteroatom multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4-addition (Sec. 15.A.ii). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

16.A.i. Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

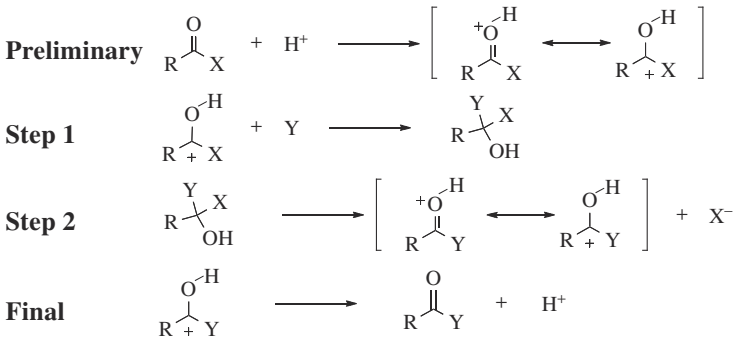
All the mechanisms discussed in previous chapters for substitution take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogues) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[15]*mechanism*.[16]

[11] Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1962***, 1190.
[12] See Brada, B.; Bundhoo, D.; Engels, B.; Hiberty, P.C. *Org. Lett.* ***2008***, *10,* 1951.
[13] Chamberland, S.; Ziller, J.W.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 5322.
[14] For a review of the reactivity of nitriles, see Schaefer, F.C. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 239–305.
[15] This mechanism has also been called the "addition–elimination mechanism".
[16] See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 209–223; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 463–554; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 375–452; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 237.

The IUPAC designation is $A_N + D_N$. The S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates (e.g., $RCO^+ BF_4^-$; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group (e.g., Cl^-);[17] and an SET mechanism has also been reported.[18] However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism discussed in Section 10.A.i. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y (**4**), and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:



When reactions are carried out in acid solution, there may also be a preliminary and a final step:



The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[19]

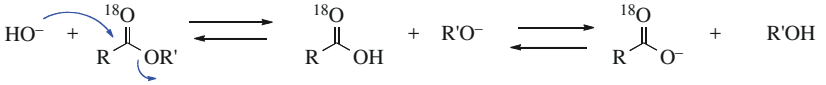
Evidence for the existence of the tetrahedral mechanism is as follows:[20]

1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.
2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant, but decreases with increasing hydroxylamine concentration.[21] This

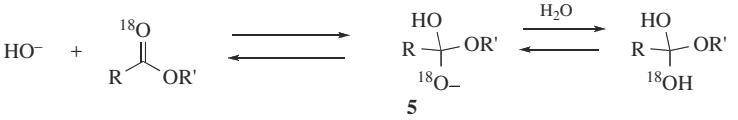
[17] Williams, A. *Acc. Chem. Res.* ***1989***, *22*, 387. See Bentley, T.W.; Koo, I.S. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1385. See, however, Buncel, E.; Um, I.H.; Hoz, S. *J. Am. Chem. Soc.* ***1989***, *111*, 971.
[18] Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Ortega, F. *J. Am. Chem. Soc.* ***1990***, *112*, 9336.
[19] SeeJencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; *Chem. Rev.* ***1972***, *72*, 705.
[20] Also see Guthrie, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 5892; Kluger, R.; Chin, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7382; O'Leary, M.H.; Marlier, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3300.
[21] Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1964***, *86*, 5616.

is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, *this cannot happen if there is only one step: there must be two steps, and hence an intermediate*. Similar kinetic behavior has been found in other cases as well;[22] in particular, plots of rate against pH are often bell-shaped.

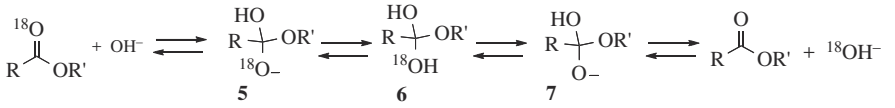
3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.[23] If this reaction proceeded by the normal S_N2 mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the carboxylic acid formed went back to the starting material:



On the other hand, if the tetrahedral mechanism operates



then the intermediate **5** reacts with an acid (e.g., water) and is converted to the conjugate acid, symmetrical intermediate **6**. In this intermediate, the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:



The intermediates **5** and **7** can now lose OR′ to give the carboxylic acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **5** reverts back to an ester, the ester will still be labeled, but if **7** reverts to an ester, the ^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. Experiments by Bender[24] found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[24] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **5** and **7** do not revert to an ester, but go entirely to an acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates, this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **5** loses OR′ before it can become

[22] Kevill, D.N.; Johnson, S.L. *J. Am. Chem. Soc.* ***1965***, *87*, 928; Leinhard, G.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3855; Schowen, R.L.; Jayaraman, H.; Kershner, L.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3373.

[23] Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, 4189.

[24] Bender, M.L.; Matsui, H.; Thomas, R.J.; Tobey, S.W. *J. Am. Chem. Soc.* ***1961***, *83*, 4193. See also, Shain, S.A.; Kirsch, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5848.

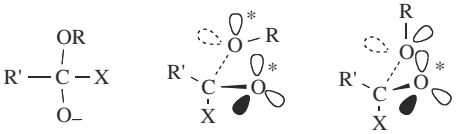
protonated to **6**.[25] Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[26] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate–^{18}O:



This reaction had previously been shown[27] to involve an intermediate by the kinetic methods mentioned above. Bender and Heck[26] showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen-exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O exchange measurements showed that there is a tetrahedral species present, but not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, but not necessarily tetrahedral. Bender and Heck's[26] results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated[28] or detected spectrally.[29]

Several studies have been made of the directionality of approach by the nucleophile.[30] Menger[30] has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.



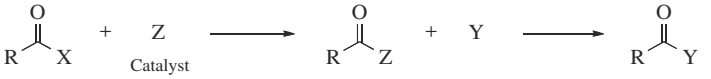
8 **A** **B**

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**4**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate **8** formed by attack of $^{-}$OR on a substrate R′COX. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals

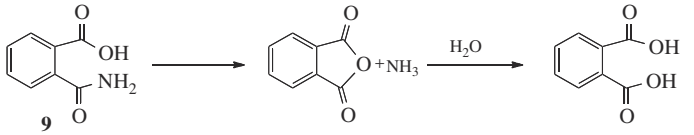
[25] For evidence for this possibility, see McClelland, R.A. *J. Am. Chem. Soc.* ***1984***, *106*, 7579.
[26] Bender, M.L.; Heck, H. d'A. *J. Am. Chem. Soc.* ***1967***, *89*, 1211.
[27] Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1965***, *87*, 4138.
[28] See Khouri, F.F.; Kaloustian, M.K. *J. Am. Chem. Soc.* ***1986***, *108*, 6683.
[29] See Capon, B.; Dosunmu, M.I.; Sanchez, M. de N de M. *Adv. Phys. Org. Chem.* ***1985***, *21*, 37; McClelland, R.A.; Santry, L.J. *Acc. Chem. Res.* ***1983***, *16*, 394; Capon, B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* ***1981***, *14*, 306. See also, van der Wel, H.; Nibbering, N.M.M. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 479, 491.
[30] See Menger, F.M. *Tetrahedron* ***1983***, 39, 1013; Liotta, C.L.; Burgess, E.M.; Eberhardt, W.H. *J. Am. Chem. Soc.* ***1984***, *106*, 4849.

marked ∗ are antiperiplanar to the C—X bond, but not from **B** because only the O^- has such an orbital. If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.[31] Free rotation in acyclic intermediates leads to many conformations, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.[32] More generally, the term *stereoelectronic* effects refers to any case in which orbital position requirements affect the course of a reaction. The backside attack in the S_N2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[33] There occur, in effect, two tetrahedral mechanisms:



(For an example, see Reaction **16-58**). When this happens internally, it is a neighboring-group mechanism at a carbonyl carbon.[34] For example, the hydrolysis of phthalamic acid (**9**) takes place as follows:



Evidence comes from comparative rate studies.[35] Thus **9** was hydrolyzed $\sim 10^5$ times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **9**) were hydrolyzed more slowly than benzamide. Other examples of neighboring-group participation at a carbonyl carbon have been reported.[36] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition, depending on the substituents, but the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OCOR, NH_2, and so on, the

[31] It has also been called the "antiperiplanar lone-pair hypothesis (ALPH)". For a reinterpretation of this factor in terms of the principle of least nuclear motion (see Reaction **15-10**), see Hosie, L.; Marshall, P.J.; Sinnott, M.L. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1121; Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113.

[32] Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Deslongchamps, *P. Stereoelectronic Effects in Organic Chemistry*, Pergamon, NY, ***1983***. See Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113; Gorenstein, D.G. *Chem. Rev.* ***1987***, *87*, 1047; Deslongchamps, *P. Heterocycles* ***1977***, *7*, 1271. Also see Ndibwami, A.; Deslongchamps, *P.Can. J. Chem.* ***1986***, *64*, 1788; Hegarty, A.F.; Mullane, M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 995. For evidence against the theory, see Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* ***1986***, 108, 5997; ***1987***, *109*, 522.

[33] See Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***, pp. 147–179; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 271. For a review where Z = a tertiary amine, see Cherkasova, E.M.; Bogatkov, S.V.; Golovina, Z.P. *Russ. Chem. Rev.* ***1977***, *46*, 246.

[34] Kirby, A.J.; Fersht, A.R. *Prog. Bioorg. Chem.* ***1971***, *1*, 1; Capon, B. *Essays Chem.* ***1972***, *3*, 127.

[35] Bender, M.L.; Chow, Y.; Chloupek, F.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5380.

[36] See Page, M.I.; Render, D.; Bernáth, G. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 867.

usual reaction is substitution. When X = OH, protonation to generate OH_2^+ is usually required before the group can be lost.

In both the S_N1 and S_N2 mechanisms, the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **4**, there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **4** will revert to the starting compounds. Thus there is a partitioning factor between **4** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[37] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 16.1, which shows the main reactions that proceed by the tetrahedral mechanism.

TABLE 16.1 The More Important Synthetic Reactions That Take Place by the Tetrahedral Mechanism.[a]

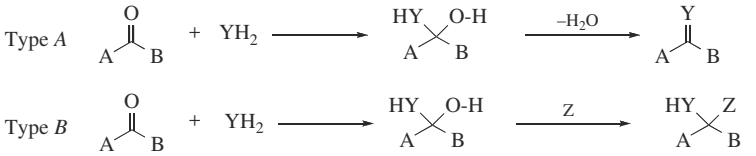
Reaction Number	Reaction
16-57	$RCOX + H_2O \longrightarrow RCOOH$
16-58	$RCOOCOR' + H_2O \longrightarrow RCOOH + R'COOH$
16-59	$RCO_2R' + H_2O \longrightarrow RCOOH + R'OH$
16-59	$RCONR'_{2'} + H_2O \longrightarrow RCOOH + R'_2NH\ (R' = H, alkyl, aryl)$
16-61	$RCOX + R'OH \longrightarrow RCO_2R'$
16-62	$RCOOCOR + R'OH \longrightarrow RCO_2R'$
16-63	$RCOOH + R'OH \longrightarrow RCO_2R'$
16-64	$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH$
16-66	$RCOX + R'COO^- \longrightarrow RCOOCOR'$
10-21	$RCOX + H_2O_2 \longrightarrow RCO_3H$
16-69	$RCOX + R'SH \longrightarrow RCOSR'$
16-72	$RCOX + NHR'_2 \longrightarrow RCONR'_2\ (R' = H, alkyl, aryl)$
16-73	$RCOOCOR + NHR'_2 \longrightarrow RCONR'_2\ (R' = H, alkyl, aryl)$
16-74	$RCOOH + NHR'_2 \xrightarrow[\text{agent}]{\text{coupling}} RCONR'_2\ (R' = H, alkyl, aryl)$
16-75	$RCO_2R' + NHR^2 \longrightarrow RCONR^2\ (R^2 = H, alkyl, aryl)$
16-79	$RCOOH + SOCl_2 \longrightarrow RCOCl$
19-39	$RCOX + LiAlH(O\text{-}t\text{-}Bu)_3 \longrightarrow RCHO$
19-41	$RCONR'_2 + LiAlH_4 \longrightarrow RCHO$
16-81	$RCOX + R_{2'}CuLi \longrightarrow RCOR'$
16-85	$2RCH_2CO_2R' \longrightarrow RCH_2COCHRCO_2R'$

[a]Catalysts are not shown.

[37] The compound RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

16.B. REACTIONS

Many of the reactions in this chapter are simple additions to carbon–hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. There are generally two types:



In type *A*, the initially formed adduct loses water (or, in the case of addition to C=NH, ammonia, etc.), and the net result of the reaction is the substitution of C=Y for C=O (or C=NH, etc.). In type *B* there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, which is often another YH moiety. This substitution is nucleophilic is most cases: Y usually has an unshared pair and S_N1 reactions occur very well on this type of compound (Sec. 10.G.i, category 2), even when the leaving group is as poor as OH or NH_2. In this chapter, reactions will be classified according to what is initially adding to the carbon–heteroatom multiple bond, even if subsequent reactions take place so rapidly that it is impossible to isolate the initial adduct.

Most of the reactions considered in this chapter can be reversed. In many cases, we will consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., **16-2** and **16-13**). For reactions that are reversible, the principle of microscopic reversibility (Sec. 6.H) applies.

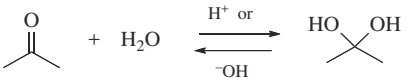
First, reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom will be discussed. Second, reactions in which carbon adds to the heteroatom will be discussed. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

16.B.i. Reactions in which Hydrogen or a Metallic Ion Adds to the Heteroatom

A. Attack by OH (Addition of H_2O)

16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates

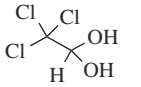
***O*-Hydro-*C*-hydroxy-addition**



The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.[38] These compounds are usually stable only in water solution and decompose on

[38] See Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 183–187; *Adv. Phys. Org. Chem.* ***1966****, 4,* 1; Le Hénaff, P. *Bull. Soc. Chim. Fr.* ***1968***, 4687.

distillation; that is, the equilibrium shifts back toward the carbonyl compound, usually via formation of an enol and tautomerization to the carbonyl. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20 °C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[39] It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[40] Since methyl, a $+I$ group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)[41] is a stable crystalline substance. In order for it to revert to chloral, ^-OH or H_2O must leave. This is made difficult by the electron-withdrawing character of the Cl_3C group and by the absence of a proton on the α carbon, which is required for loss of water to form an enol. Some other[42] polychlorinated and polyfluorinated aldehydes and ketones[43] and α-keto aldehydes also form stable hydrates, as do cyclopropanones.[44] In the last case,[45] formation of the hydrate relieves some of the *I* strain (Sec. 9.B) of the parent ketone.

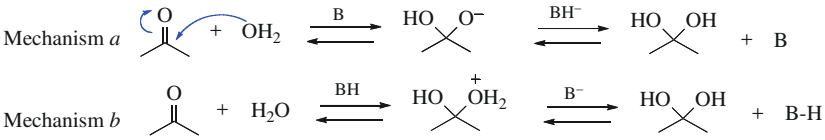


Chloral hydrate



Hydrate of cyclopropanone

The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:[46]



In mechanism *a*, as the H_2O attacks, the base pulls off a proton, and the net result is addition of ^-OH. This can happen because the base is already hydrogen bonded to the H_2O molecule before the attack. In mechanism *b*, because HB is already hydrogen bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way, B and HB accelerate the reaction even beyond the extent that they form ^-OH or H_3O^+ by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class e reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.[47] Thus the acid-catalyzed process here is a class e reaction, while the base-catalyzed process is a class n reaction.

[39] Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* ***1952****, 48,* 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* ***1960****, 56,* 1281.

[40] Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* ***1938****, 60*, 679.

[41] For a review of chloral, see Luknitskii, F.I. *Chem. Rev.* ***1975****, 75,* 259.

[42] Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* ***1976****, 98,* 3793.

[43] For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlin, E.M.; Zeifman, Yu.V.; Ching-Yun, C.; Knunyants, I.L. *Angew. Chem. Int. Ed.* ***1966****, 5*, 947.

[44] See Krois, D.; Lehner, H. *Monatsh. Chem.* ***1982****, 113,* 1019.

[45] Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* ***1967****, 89*, 1028. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974****, 47,* 73.

[46] Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1987****, 109,* 4675; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 662–680. A theoretical treatment is in Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* ***1995****, 117*, 4240.

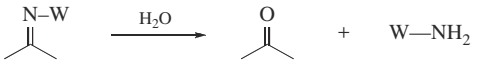
[47] Jencks, W.P. *Acc. Chem. Res.* ***1976****, 9*, 425.

For the reaction between ketones and H_2O_2, see **17-37**.

There are no OS references, but see OS **VIII**, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon–Nitrogen Double Bond[48]

Oxo-de-alkylimino-bisubstitution, and so on



Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones.[49] For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of *Schiff bases* (W = Ar) is more difficult and requires acid or base catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones (W = $NHCONH_2$) can also be hydrolyzed. Often a reactive aldehyde (e.g., formaldehyde), is added to combine with the liberated amine.

A number of reagents[50] have been used to cleave C=N bonds, especially those not easily hydrolyzable with acidic or basic catalysts or those that contain other functional groups that are attacked under these conditions.

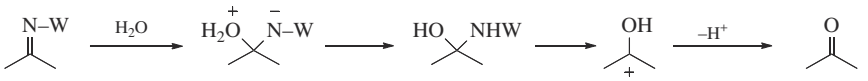
Oximes have been converted to the corresponding aldehyde or ketone[51] by treatment with aq phosphoric acid without an organic cosolvent,[52] periodic acid,[53] DABCO–Br_2,[54] NBS in water,[55] Chloramine-T[56] HCO_2H on SiO_2 with microwave irradiation,[57] and 20% I_2 in water containing SDS (sodium dodecyl sulfate)[58] or in an ionic liquid on SiO_2.[59] Transition metal compounds have been used, including those of Sb,[60] Co[61] Hg,[62] Bi,[63] Cu,[64] or Zn.[65] Oxidizing agents can be quite effective, including $KMnO_4$ on Al_2O_3,[66] tetraalkylammonium permanganates,[67] and quinolinium dichromate.[68] Alkaline H_2O_2[69] has also been used.

[48] For a review, see Khoee, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2003****, 35*, 527.
[49] For proton affinities of imines, see Hammerum, S.; Sølling, T.I. *J. Am. Chem. Soc.* ***1999****, 121*, 6002.
[50] For a list of reagents, with references, see Ranu, B.C.; Sarkar, D.C. *J. Org. Chem.* ***1988****, 53,* 878.
[51] For a review, see Corsaro, A.; Chiacchio, U.; Pistarà, V. *Synthesis* ***2001***, 1903.
[52] Bhar, S.; Guha, S. *Synth. Commun.* ***2005****, 35*, 1183.
[53] Li, Z.; Ding, R.-B.; Xing, Y.-L.; Shi, S.-Y. *Synth. Commun.* ***2005****, 35,* 2515.
[54] Heravi, M.M.; Derikvand, F.; Ghassemzadeh, M. *Synth. Commun.* ***2006****, 36*, 581.
[55] Bandgar, B.P.; Makone, S.S. *Org. Prep. Proceed. Int.* ***2000****, 32*, 391.
[56] Padmavathi, V.; Reddy, K.V.; Padmaja, A.; Venugopalan, P. *J. Org. Chem.* ***2003****, 68*, 1567.
[57] A solvent-free reaction. See Zhou, J.-F.; Tu, S.-J.; Feng, J.-C. *Synth. Commun.* ***2002****, 32*, 959.
[58] Gogoi, P.; Hazarika, P.; Konwar, D. *J. Org. Chem.* ***2005****, 70,* 1934.
[59] Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* ***2004****, 45*, 265.; Li, D.; Shi, F.; Deng, Y. *Tetrahedron Lett.* ***2004****, 45*, 6791.
[60] Narsaiah, A.V.; Nagaiah, K. *Synthesis* ***2003***, 1881.
[61] Mukai, C.; Nomura, I.; Kataoka, O.; Hanaoka, M. *Synthesis* ***1999***, 1872.
[62] De, S.K. *Synth. Commun.* ***2004****, 34*, 2289.
[63] See Arnold, J.N.; Hayes, P.D.; Kohaus, R.L.; Mohan, R.S. *Tetrahedron Lett.* ***2003****, 44*, 9173.
[64] Hashemi, M.M.; Beni, Y.A. *Synth. Commun.* ***2001****, 31*, 295; Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000****, 30,* 4129.
[65] Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000****, 30,* 4129.
[66] See Imanzadeh, G.H.; Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2003****, 33*, 735.
[67] Hajipour, A.R.; Mallakpour, S.E.; Khoee, E. *Synth. Commun.* ***2002****, 32*, 9.
[68] Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Azarm, M.; Mazidi, M.R. *Synth. Commun.* ***2001****, 31*, 435. See also, Zhang, G.-S.; Yang, D.-H.; Chen. M.-F. *Org. Prep. Proceed. Int.* ***1998****, 30*, 713.
[69] Ho, T. *Synth. Commun.* ***1980****, 10*, 465.

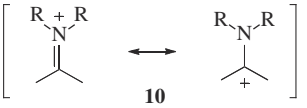
Phenylhydrazones can be converted to a ketone using Oxone and $KHCO_3$,[70] polymer-bound iodonium salts,[71] or $KMnO_4$ on wet SiO_2.[72] Dimethylhydrazones have been converted to ketones with $FeSO_4 \cdot 7\ H_2O$ in chloroform,[73] and Me_3SiCl/NaI in acetonitrile with 1% water.[74] Hydrazones (e.g., RAMP or SAMP, Reaction **10-68**, category 4) can be hydrolyzed with aq $CuCl_2$.[75] Tosylhydrazones can be hydrolyzed to the corresponding ketones with aq acetone and BF_3–etherate,[76] as well as with other reagents.[77]

Semicarbazones have been cleaved with ammonium chlorochromates on alumina[78] $(Bu_4N)_2S_2O_8$,[79] $Mg(HSO_4)_2$ on wet silica,[80] or by $SbCl_3$ with microwave irradiation.[81]

The hydrolysis of carbon–nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



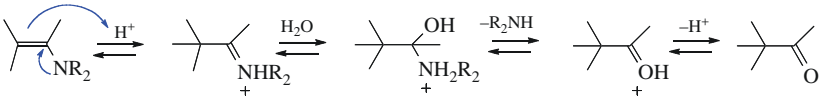
It is thus an example of reaction type *A* (see above). The sequence shown is generalized.[82] In specific cases, there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.[83] Which step is rate determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[84]



10

Iminium ions (**10**)[85] would be expected to undergo hydrolysis quite readily, since there is a resonance contributor with a positive charge on the carbon. Indeed, they react with water at room temperature.[86] Acid-catalyzed hydrolysis of enamines (the last step of the *Stork enamine reaction*, **10-69**, involves conversion to iminium ions).[87]

[70] Hajipour, A.R.; Mahboubghah, N. *Org. Prep Proceed. Int.* ***1999****, 31*, 112.
[71] Chen, D.-J.; Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* ***2001****, 31*, 3847.
[72] Hajipour, A.R.; Adibi, H.; Ruoho, A.E. *J. Org. Chem.* ***2003****, 68*, 4553.
[73] Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***1999****, 31*, 573.
[74] Kamal, A.; Ramana, K.V.; Arifuddin, M. *Chem. Lett.* ***1999***, 827.
[75] Enders, D.; Hundertmark, T.; Lazny, R. *Synth. Commun.* ***1999****, 29*, 27.
[76] Sacks, C.E.; Fuchs, P.L. *Synthesis* ***1976***, 456.
[77] See Chandrasekhar, S.; Reddy, Ch.R.; Reddy, M.V. *Chem. Lett.* ***2000***, 430; Jiricny, J.; Orere, D.M.; Reese, C.B. *Synthesis* ***1970***, 919.
[78] Zhang, G.-S.; Gong, H.; Yang, D.-H.; Chen, M.-F. *Synth. Commun.* ***1999****, 29*, 1165; Gong, H.; Zhang, G.-S. *Synth. Commun.* ***1999****, 29*, 2591.
[79] Chen, F.-E.; Liu, J.-P.; Fu, H.; Peng, Z.-Z.; Shao, L.-Y. *Synth. Commun.* ***2000****, 30*, 2295.
[80] Shirini, F.; Zolfigol, M.A.; Mallakpour, B.; Mallakpour, S.E.; Hajipour, A.R.; Baltork, I.M. *Tetrahedron Lett.* ***2002****, 43*, 1555.
[81] Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***2000****, 30*, 1651.
[82] For reviews of the mechanism, see Bruylants, A.; Feytmants-de Medicis, E. in Patai, S.*The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 465–504; Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group* pt. 1, Wiley, NY, ***1966***, pp. 199–205.
[83] See Sayer, J.M.; Conlon, E.H. *J. Am. Chem. Soc.* ***1980****, 102,* 3592.
[84] Cordes, E.H.; Jencks, W.P. *J. Am. Chem. Soc.* ***1963****, 85,* 2843.
[85] For a review of iminium ions, see Böhme, H.; Haake, M. *Adv. Org. Chem.* ***1976****, 9*, pt. 1, 107.
[86] Hauser, C.R.; Lednicer, D. *J. Org. Chem.* ***1959****, 24,* 46. For a study of the mechanism, see Gopalakrishnan, G.; Hogg, J.L. *J. Org. Chem.* ***1989****, 54*, 768.
[87] Sollenberger, P.Y.; Martin, R.B. *J. Am. Chem. Soc.* ***1970****, 92,* 4261. For a review of enamine hydrolysis see Stamhuis, E.J.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 165–180.



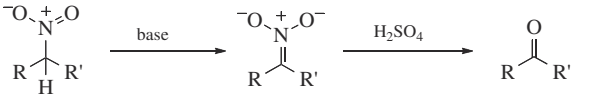
The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (Reaction **10-6**).

OS **I**, 217, 298, 318, 381; **II**, 49, 223, 234, 284, 310, 333, 395, 519, 522; **III**, 20, 172, 626, 818; **IV**, 120; **V**, 139, 277, 736, 758; **VI**, 1, 358, 640, 751, 901, 932; **VII**, 8; **65**, 108, 183; **67**, 33; **76**, 23.

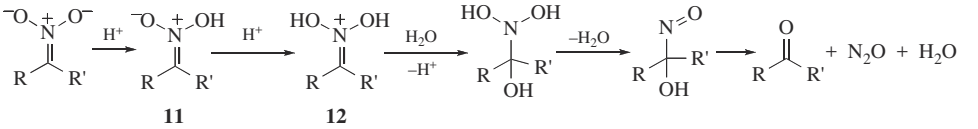
OS **II**, 24; **IV**, 819; **V**, 273; **VI**, 910.

16-3 Hydrolysis of Aliphatic Nitro Compounds

Oxo-de-hydro,nitro-bisubstitution



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.[88] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **16-2**, this reaction involves hydrolysis of a C=N double bond. A possible mechanism involves initial formation of the *aci form* of the nitro compound (**11**):[89]



Intermediates of type **12** have been isolated in some cases.[90]

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods.[91] Among these are treatment of the nitro compound with basic H_2O_2 in an ionic liquid,[92] or 30% H_2O_2—K_2CO_3,[93] DBU in acetonitrile,[94] or CAN.[95]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for their preparation.[96] Both the *Nef reaction* and the hydroxamic acid process involve the *aci form*; the difference in products arises from

[88] See Pinnick, H.W. *Org. React.* ***1990****, 38*, 655; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 220–231, 416–419.

[89] Hawthorne, M.F. *J. Am. Chem. Soc.* ***1957****, 79,* 2510. Also see van Tamelen, E.E.; Thiede, R.J. *J. Am. Chem. Soc.* ***1952****, 74*, 2615; Sun, S.F.; Folliard, J.T. *Tetrahedron* ***1971****, 27,* 323.

[90] Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* ***1977****, 42*, 2091.

[91] For a review, see Ballini, R.; Petrini, M. *Tetrhaedron* ***2004****, 60*, 1017.

[92] Bortolini, O.; De Nino, A.; Garofalo, A.; Maiuolo, L.; Russo, B. *Synth. Commun.* ***2010****, 40,* 2483.

[93] Olah, G.A.; Arvanaghi, M.; Vankar, Y.D.; Prakash, G.K.S. *Synthesis* ***1980***, 662.

[94] Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetahedron Lett.* ***2002****, 43*, 5233.

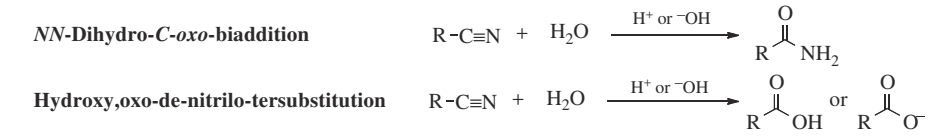
[95] Olah, G.A.; Gupta, B.G.B. *Synthesis* ***1980***, 44.

[96] See Sosnovsky, G.; Krogh, J.A. *Synthesis* ***1980***, 654.

higher acidity. For example, a difference in sulfuric acid concentration from 2 to 15.5 M changes the product from the aldehyde to the hydroxamic acid.[97] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated *aci form* of the nitro compound is further protonated.

OS **VI**, 648; **VII**, 414. See also, OS **IV**, 573.

16-4 Hydrolysis of Nitriles



Nitriles can be hydrolyzed to give either amides or carboxylic acids.[98] The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is readily formed. When the acid is desired,[99] the reagent of choice is aq NaOH containing ~ 6–12% H_2O_2, but acid-catalyzed hydrolysis is also carried out. The reaction of nitriles with TFA–acetic acid–sulfuric acid, followed by treatment with water gives the corresponding amide.[100] A Rh catalyzed hydrolysis with aq isopropyl alcohol leads to the amide.[101] A "dry" hydrolysis of nitriles has been reported.[102] Enzymatic hydrolysis to give the amide was reported with nitrilase (ZmNIT2).[103] Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.[104]

Hydrolysis of cyanohydrins [RCH(OH)CN] is usually carried out under acidic conditions, because basic solutions cause competing reversion of the cyanohydrin to the aldehyde and CN^-. However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.[105]

There are a number of procedures for stopping at the amide stage,[106] among them the use of concentrated H_2SO_4; 2 molar equivalents of chlorotrimethylsilane followed by H_2O,[107] aq NaOH with PEG-400 and microwave irradiation,[108] heating on neutral alumina,[109] or dry HCl followed by H_2O. The same result can also be obtained by use

[97] Kornblum, N.; Brown, R.A. *J. Am. Chem. Soc.* ***1965****, 87,* 1742. See also, Edward, J.T.; Tremaine, P.H. *Can J. Chem.* ***1971****, 49,* 3483, 3489, 3493.

[98] See Zil'berman, E.N. *Russ. Chem. Rev.* ***1984****, 53,* 900; Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970****, [14] 5,* 11, 23.

[99] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1986–1987.

[100] Moorthy, J.N.; Singhal, N. *J. Org. Chem.* ***2005****, 70*, 1926.

[101] Goto, A.; Endo, K.; Saito, S. *Angew. Chem. Int. Ed.* ***2008****, 47*, 3607.

[102] Chemat, F.; Poux, M.; Berlan, J. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1781; ***1994***, 2597.

[103] Mukherjee, C.; Zhu, D.; Biehl, E.R.; Parmar, R.R.; Hua, L. *Tetrahedron* ***2006****, 62,* 6150. Also see Black, G.W.; Gregson, T.; McPake, C.B.; Perry, J.J.; Zhang, M. *Tetrahedron Lett.* ***2010****, 51*, 1639.

[104] Rounds, W.D.; Eaton, J.T.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988****, 29*, 6557.

[105] Jammot, J.; Pascal, R.; Commeyras, A. *Tetrahedron Lett.* ***1989****, 30,* 563.

[106] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 119–125. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1988–1990.

[107] Basu, M.K.; Luo, F.-T. *Tetrahedron Lett.* ***1998****, 39*, 3005.

[108] Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1713.

[109] Wligus, C.P.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1995****, 36*, 3469.

of water and certain metal ions or complexes[110] including an In,[111] Au,[112] or a Ru catalyst.[113] Other reagents include MnO_2/SiO_2 with microwave irradiation,[114] or $Hg(OAc)_2$ in HOAc.[115] The reaction of ferric nitrate and an amine generates the amide.[116]

Nitriles are converted to thioamides [$ArC(=S)NH_2$] with ammonium sulfide [$(NH_4)_2S$] in methanol, with microwave irradiation.[117] Thioamides are also prepared using phosphorus pentasulfide.[118]

Thiocyanates are converted to thiocarbamates in a similar reaction:[119] R—S—C≡N + H_2O → R—S—CO— NH_2. Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates: $R_2NCN \rightarrow [R_2NCOOH] \rightarrow R_2NH$.

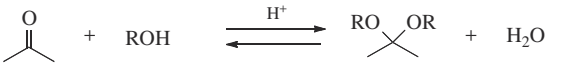
OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; III; 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932; **76**, 169. Also see, OS **III**, 609; **IV**, 359, 502; **66**, 142.

B. Attack by OR (Addition of ROH)

16-5 The Addition of Alcohols to Aldehydes and Ketones

Dialkoxy-de-oxo-bisubstitution

Dithioalkyl-de-oxo-bisubstitution



Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[120] Lewis acid derivatives of Ti,[121] Cu,[122] In,[123] Ru,[124] or Co[125] can be used in conjunction with alcohols. Organocatalysts have been used for this conversion under acid-free conditions.[126] This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid.[127] With small unbranched aldehydes the equilibrium lies to the right. If ketals or acetals of larger molecules must be prepared the equilibrium must be shifted, usually by removal of water. This can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent (e.g., Al_2O_3 or a molecular sieve).[128] The reaction is not

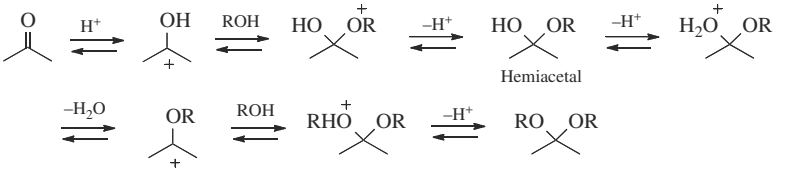
[110] See McKenzie, C.J.; Robson, R. *J. Chem. Soc., Chem. Commun.* ***1988***, 112.
[111] Kim, E.S.; Lee, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* ***2010****, 51*, 1589.
[112] Ramón, R.S.; Marion, N.; Nolan, S.P. C*hemistry: Eur. J.* ***2009****, 15*, 8695.
[113] See Polshettiwar, V.; Varma, R.S. *Chemistry: Eur. J.* ***2009****, 15*, 1582.
[114] For a solvent-free reaction. See Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***2002****, 32*, 1731.
[115] Plummer, B.F.; Menendez, M.; Songster, M. *J. Org. Chem.* ***1989****, 54,* 718.
[116] Allen, C.L.; Lapkin, A.A.; Williams, J.M.J. *Tetrahedron Lett.* ***2009****, 50*, 4262.
[117] Bagley, M.C.; Chapaneri, K.; Glover, C.; Merritt, E.A. *Synlett* ***2004*** 2615.
[118] Kaboudin, B.; Elhamifar, D. *Synthesis* ***2006***, 224.
[119] Zil'berman, E.N.; Lazaris, A.Ya. *J. Gen. Chem. USSR* ***1963****, 33*, 1012.
[120] For reviews, see Meskens, F.A.J. *Synthesis* ***1981***, 501; Schmitz, E.; Eichhorn, I. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 309–351.
[121] Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* ***2001****, 57*, 217.
[122] Kumar, R.; Chakraborti, A.K. *Tetrahedron Lett.* ***2005****, 46*, 8319.
[123] Gregg, B.T.; Golden, K.C.; Quin, J.F. *Tetrahedron* ***2008****, 64*, 3287.
[124] De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004****, 45*, 8141.
[125] Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2004****, 45*, 4917.
[126] Kotke, M.; Schreiner, P.R. *Tetrahedron* ***2006****, 62,* 434.
[127] See Heravi, M.M.; Tajbakhsh, M.; Habibzadeh, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001****, 132*, 985.
[128] For many examples of each of these methods, see Meskens, F.A.J. *Synthesis* ***1981***, 501, pp. 502–505.

catalyzed in either direction by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This reaction is therefore a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope.

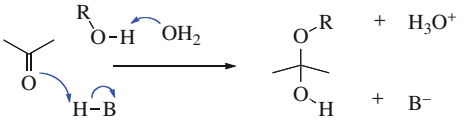
Most aldehydes are easily converted to acetals,[129] but the reaction with ketones is more difficult, presumably for steric reasons. While the reaction often fails, many ketals, especially from cyclic ketones, have been made in this manner.[130] Many functional groups may be present without being affected. 1,2- and 1,3-Diols form cyclic acetals and ketals (1,3-dioxolanes[131] and 1,3-dioxanes,[132] respectively), and these are often used to protect aldehydes and ketones. Chiral dioxolanes have been prepared from chiral diols.[133] Dioxolanes have been prepared from ketones in ionic liquids.[134] Ketones are converted with dimethyl ketals by electrolysis with NaBr in methanol.[135] Intramolecular reactions are possible in which a keto diol or an aldehyde diol generates a bicyclic ketal or acetal.

The conversion of acetals back to aldehydes or ketones is accomplished by many reagents, including aq acid. Heating with water under microwave irradiation converts acetals to the corresponding carbonyl compound.[136] Transition metal compounds of Bi[137] catalyze this conversion as well.

The mechanism for acetal/ketal formation involves initial formation of a *hemiacetal*,[138] and it is the reverse of that given for acetal hydrolysis:



In a study of the acid-catalyzed formation of the hemiacetal, Grunwald[139] showed that the data best fit a mechanism in which the three steps shown here are actually all concerted; that is, the reaction is simultaneously catalyzed by acid and base, with water acting as the base:[140]



[129] For other methods, see Ott, J.; Tombo, G.M.R.; Schmid, B.; Venanzi, L.M.; Wang, G.; Ward, T.R. *Tetrahedron Lett.* ***1989****, 30,* 6151, Liao, Y.; Huang, Y.; Zhu, F. *J. Chem. Soc., Chem. Commun.* ***1990***, 493.

[130] High pressure has been used to improve the results with ketones: Dauben, W.G.; Gerdes, J.M.; Look, G.C. *J. Org. Chem.* ***1986****, 51,* 4964. For other methods, see Otera, J.; Mizutani, T.; Nozaki, H. *Organometallics* ***1989****, 8,* 2063; Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* ***1988***, 233.

[131] See Gopinath, R.; Haque, Sk.J.; Patel, B.K. *J. Org. Chem.* ***2002****, 67*, 5842.

[132] Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* ***2004****, 45*, 4963; Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* ***2002***, 1296.

[133] Kurihara, M.; Hakamata, W. *J. Org. Chem.* ***2003****, 68*, 3413.

[134] See Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* ***2004****, 69*, 3582.

[135] Elinson, M.N.; Feducovich, S.K.; Dmitriev, D.E.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron Lett.* ***2001****, 42*, 5557.

[136] Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Tagarelli, A.; Sindona, G. *Tetrahedron Lett.* ***2007****, 48*, 8623.

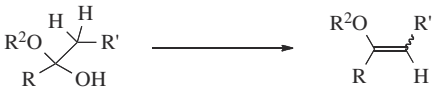
[137] Bailey, A.D.; Baru, A.R.; Tasche, K.K.; Mohan, R.S. *Tetrahedron Lett.* ***2008****, 49,* 691.

[138] For a review of hemiacetals, see Hurd, C.D. *J. Chem. Educ.* ***1966****, 43,* 527.

[139] Grunwald, E. *J. Am. Chem. Soc.* ***1985****, 107*, 4715.

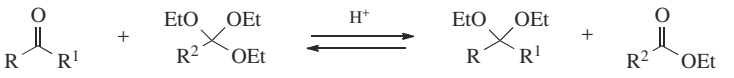
[140] See Grunwald, E. *J. Am. Chem. Soc.* ***1985****, 107*, 4710; Leussing, D.L. *J. Org. Chem.* ***1990****, 55,* 666.

Hemiacetals themselves are no more stable than the corresponding hydrates (Reaction **16-1**). If the original aldehyde or ketone has an α hydrogen, it is possible to lose water from the hemiacetal, and enol ethers can be prepared in this manner:



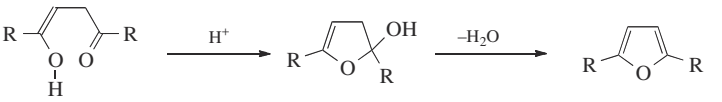
Similarly, treatment with an anhydride and a catalyst can give an enol ester (see Reaction **16-6**).[141] As with hydrates, it is noted that hemiacetals of cyclopropanones[142] and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, transacetalation is possible (see Reaction **10-13**). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,[143] in the presence of an acid catalyst (shown for an ortho ester):



This method is useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. Alternatively, the substrate is treated with an alkoxysilane ($ROSiMe_3$) in the presence of trimethylsilyl trifluoromethanesulfonate.[144] Formic acid reacts with alcohols to give orthoformates.

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds:



Similarly, 1,5-diketones give pyrans. Conjugated 1,4-diketones (e.g., 1,4-diphenylbut-2-en-1, 4-dione) are converted to 2,5-diphenylfuran with formic acid, 5% Pd/C, PEG-200, and a sulfuric acid catalyst with microwave irradiation.[145] Note that alkynyl ketones are converted to furans with palladium(II) acetate.[146]

OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **VIII**, 357. Also see, OS **IV**, 558, 588; **V**, 25; **VIII**, 415.

[141] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 1484–1485.

[142] See Salaun, J. *Chem. Rev.* ***1983****, 83,* 619.

[143] See DeWolfe, R.H. *Carboxylic Ortho Ester Derivatives*, Academic Press, NY, ***1970***, pp. 154–164. See Karimi, B.; Ebrahimian, G.R.; Seradj, H. *Org. Lett.* ***1999****, 1*, 1737; Leonard, N.M.; Oswald, M.C.; Freiberg, D.A.; Nattier, B.A.; Smith, R.C.; Mohan, R.S. *J. Org. Chem.* ***2002****, 67*, 5202.

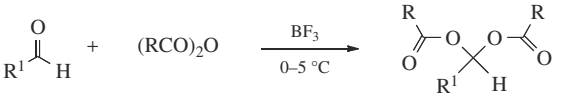
[144] Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1985***, 743. See also, Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* ***1987****, 60*, 775.

[145] Rao, H.S.P.; Jothilingam, S. *J. Org. Chem.* ***2003****, 68*, 5392.

[146] Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* ***2001****, 66,* 6014. See Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* ***2000****, 41*, 9195.

16-6 Acylation of Aldehydes and Ketones

O-Acyl-*C*-acyloxy-addition

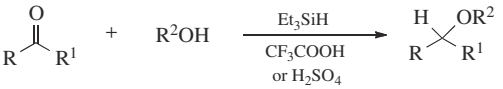


Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of proton acids,[147] NBS,[148] ceric ammonium nitrate,[149] BF_3, $LiBF_4$,[150] and Lewis acid compounds of Fe,[151] In,[152] Cu,[153] Bi,[154] W,[155] or Zr.[156] *N*-Chlorosuccinimide with thiourea is a highly efficient catalyst.[157] Silica supported perchloric acid is useful for the preparation of acylals.[158] Conjugated aldehydes are converted to the corresponding acylal by reaction with acetic anhydride and a $FeCl_3$ catalyst.[159] The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.[160]

OS **IV**, 489.

16-7 Reductive Alkylation of Alcohols

C-Hydro-*O*-alkyl-addition



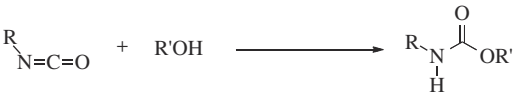
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid[161] or by hydrogenation in alcoholic acid in the presence of a Pt catalyst.[162] The process can formally be regarded as addition of ROH to give a hemiacetal [$RR'C(OH)OR^2$], followed by reduction of the OH. In this respect, it is similar to Reaction **16-17**. Homoallylic ethers are formed by the Fe catalyzed reaction of acetals and aldehydes,[163] and by reactions in ionic liquids.[164] The In catalyzed reaction of aldehydes with allyltriethoxysilane leads to the corresponding ether.[165]

[147] See Olah, G.A.; Mehrotra, A.K. *Synthesis* ***1982***, 962.
[148] Karimi, B.; Seradj, H.; Ebrahimian, G.R. *Synlett* ***2000***, 623
[149] Roy, S.C.; Banerjee, B. *Synlett* ***2002***, 1677.
[150] Yadav, J.S.; Reddy, B.V.S.; Venugapal, C.; Ramalingam, V.T. *Synlett* ***2002***, 604.
[151] Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001****, 123*, 3671; Wang, C.; Li, M. *Synth. Commun.* ***2002****, 32*, 3469.
[152] Smith, B.M.; Graham, A.E. *Tetrahedron Lett.* ***2006****, 47,* 9317.
[153] Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* ***2000***, 359.
[154] Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* ***2004****, 60*, 3675.
[155] A solvent-free reaction. See Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* ***2002****, 32*, 669.
[156] Smitha, G.; Reddy, Ch.S. *Tetrahedron* ***2003****, 59*, 9571.
[157] Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* ***2009****, 50*, 4199.
[158] Kamble, V.T.; Jamode, V.S.; Joshi, N.S.; Biradar, A.V.; Deshmukh, R.Y. *Tetrahedron Lett.* ***2006****, 47,* 5573.
[159] Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001****, 123*, 3671.
[160] Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* ***1969****, 25,* 1679.
[161] Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* ***1972****, 94*, 3659.
[162] Gooßen, L.J.; Linder, C. *Synlett* ***2006***, 3489. For another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* ***1972****, 8,* 902.
[163] Spafford, M.J.; Anderson, E.D.; Lacey, J.R.; Palma, A.C.; Mohan, R.S. *Tetrahedron Lett.* ***2007****, 48,* 8665.
[164] Anzalone, P.W.; Mohan, R.S. *Synthesis* ***2005***, 2661.
[165] Yang, M.-S.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Jiang, J.-X. *Tetrahedron Lett.* ***2008****, 49*, 253.

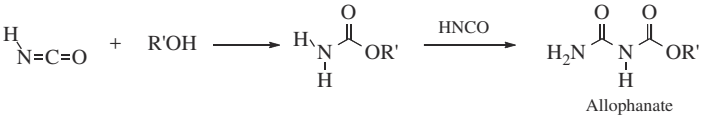
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone → dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.[166]

16-8 The Addition of Alcohols to Isocyanates

N-Hydro-*C*-alkoxy-addition



The reaction of an isocyanate with alcohols gives a carbamate (a substituted urethane). This is an excellent reaction of wide scope that gives good yields. Isocyanic acid (HNCO) gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives *allophanates*.



Allophanate

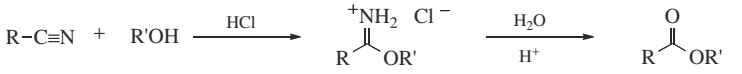
The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.[167] Combining compounds with two NCO groups with compounds containing two OH groups makes polyurethanes. Cyclic carbamates (e.g., 1,3-oxazine-2-ones), are generated by the reaction of an isocyanate with an oxetane, in the presence of a Pd catalyst.[168] Isothiocyanates similarly give thiocarbamates (RNHCSOR′),[169] but they react slower than the corresponding isocyanates. Isocyanates react with LiAlHSeH and then iodomethane to give the corresponding selenocarbonate (RNHCOSeMe).[170]

The details of the mechanism are poorly understood,[171] but the oxygen of the alcohol certainly attacks the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[172] Metallic compounds, can also catalyze the addition of ROH to isocyanates[173] by light,[174] or, for tertiary ROH, by lithium alkoxides[175] or *n*-butyllithium.[176]

OS **I**, 140; **V**, 162; **VI**, 95, 226, 788, 795.

16-9 Alcoholysis of Nitriles

Alkoxy,oxo-de-nitrilo-tersubstitution



[166] Sassaman, M.B.; Kotian, K.D.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* ***1987****, 52*, 4314. See also, Kikugawa, Y. *Chem. Lett.* ***1979***, 415.
[167] Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* ***2004****, 45*, 4769.
[168] Larksarp, C.; Alper, H. *J. Org. Chem.* ***1999****, 64,* 4152.
[169] See Walter, W.; Bode, K. *Angew. Chem. Int. Ed.* ***1967****, 6,* 281. See also, Wynne, J.H.; Jensen, S.D.; Snow, A.W. *J. Org. Chem.* ***2003****, 68*, 3733.
[170] Koketsu, M.; Ishida, M.; Takakura, N.; Ishihara, H. *J. Org. Chem.* ***2002****, 67*, 486.
[171] See Satchell, D.P.N.; Satchell, R.S.*Chem. Soc. Rev.* ***1975****, 4*, 231.
[172] See Donohoe, G.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1671 and references cited therein. See also, Sivakamasundari, S.; Ganesan, R. *J. Org. Chem.* ***1984****, 49,* 720.
[173] See Kim, Y.H.; Park, H.S. *Synlett* ***1998***, 261; Duggan, M.E.; Imagire, J.S. *Synthesis* ***1989***, 131.
[174] McManus, S.P.; Bruner, H.S.; Coble, H.D.; Ortiz, M. *J. Org. Chem.* ***1977****, 42,* 1428.
[175] Bailey, W.J.; Griffith, J.R. *J. Org. Chem.* ***1978****, 43,* 2690.
[176] Nikoforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* ***1989***, 489.

The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.[177] The salt can be converted to the free imino ester by treatment with a weak base (e.g., sodium bicarbonate) or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aq HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[178]

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst (e.g., dry HCl or $AlCl_3$), to give carbamates:[179]

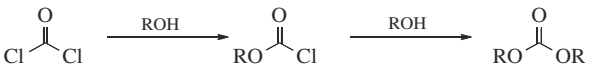
$$ClCN + 2ROH \xrightarrow[\text{or } AlCl_3]{HCl} ROCONH_2 + RCl$$

ROH can also be added to nitriles in another manner (Reaction **16-91**).

OS **I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **VIII**, 415.

16-10 The Formation of Carbonates and Xanthates

Di-*C*-alkoxy-addition; *S*-Metallo-*C*-alkoxy-addition



The reaction of phosgene with an alcohol generates haloformic esters, and reaction with a second equivalent of alcohol gives a carbonate. This reaction is related to the acyl addition reactions of acyl chlorides in Reaction **16-98**. An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$; CbzCl) from phosgene and benzyl alcohol. When CbzCl reacts with an amine, the product is the benzyl carbamate, *N*-Cbz, which is widely used for protection of amino groups during peptide synthesis. When an alcohol reacts with certain alkyl halides (e.g., benzyl chloride) and CO_2, in the presence of Cs_2CO_3 and tetrabutylammonium iodide, a mixed carbonate is formed.[180]

The addition of alcohols to carbon disulfide (S=C=S) in the presence of a base produces xanthates.[181] The base is often HO^-, but in some cases better results can be obtained by using methylsulfinyl carbanion ($MeSOCH_2^-$).[182] If an alkyl halide (RX) is present, the xanthate ester (ROCSSR′) can be produced directly. In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts ($ROCO_2^-$).

OS **V**, 439; **VI**, 207, 418; **VII**, 139.

[177] See Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970****, [14] 5,* 23, see pp. 24–26. Imino esters: see Neilson, D.G. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 385–489.

[178] Schaefer, F.C.; Peters, G.A. *J. Org. Chem.* ***1961****, 26,* 412.

[179] See Fuks, R.; Hartemink, M.A. *Bull. Soc. Chim. Belg.* ***1973****, 82,* 23.

[180] Kim, S.i.; Chu, F.; Dueno, E.E.; Jung, K.W. *J. Org. Chem.* ***1999****, 64*, 4578.

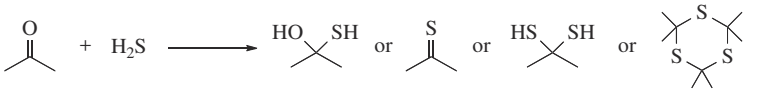
[181] See Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 316–367.

[182] Meurling, P.; Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand.* ***1972****, 26*, 279.

C. Sulfur Nucleophiles

16-11 The Addition of H_2S and Thiols to Carbonyl Compounds

***O*-Hydro-*C*-mercapto-addition, thioxo-de-oxo-bisubstitution, dimercapto-de-oxo-bisubstitution, and carbonyl-trithiane transformation**



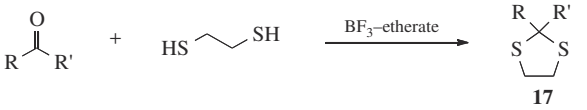
13 **14** **15** **16**

The addition of H_2S to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **16**.[183] *gem*-Dithiols (**15**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[184] They have been prepared by the treatment of ketones with H_2S under pressure[185] and under mild conditions with HCl as a catalyst.[186] A much more useful application is the addition of thiols to aldehydes and ketones to give hemi-mercaptals [CH(OH)SR] and dithioacetals [$CH(SR)_2$] (Reaction **16-5**). This reaction is generally not a good route to thioketones (**14**). α-Hydroxythiols (**13**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[187] Apparently *gem*-hydroxy thiols (e.g., **13**) are rather unstable and quite difficult to prepare.

Thiols add to aldehydes and ketones to initially give hemi-mercaptals and dithioacetals. Hemi-mercaptals are ordinarily unstable,[188] but they are usually more stable than the corresponding hemiacetals and can be isolated in certain cases.[189] The isolated product of this reaction is most often the dithioacetal, which like the acetals obtained by reaction with an alcohol, are stable in the presence of base. However, a sufficiently strong base can remove a proton from the carbon between the sulfur atoms (—S—CHR—S—)[190] to form the corresponding carbanion (see Reaction **10-71**). The pK_a of such protons is typically 31–37,[191] requiring a strong base, and deprotonation is often quite slow. The reaction of aldehydes or ketones with thiols most commonly uses a Lewis acid catalyst (e.g., boron trifluoride etherate, $BF_3{\cdot}OEt_2$)[192] to give the dithioacetal[193] or dithioketal. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of $TiCl_4$,[194] $SiCl_4$,[195] $LiBF_4$,[196] $Al(OTf)_3$,[197] tosic acid on silica gel in dichloromethane,[198]

[183] Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962****, 27,* 3760.
[184] For **15**, see Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963****, 2,* 370.
[185] Cairns, T.L.; Evans, G.L.; Larchar, A.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1952****, 74*, 3982.
[186] Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962****, 27*, 3760; Demuynck, M.; Vialle, J. *Bull. Soc. Chim. Fr.* ***1967***, 1213.
[187] Harris Jr., J.F. *J. Org. Chem.* ***1960****, 25,* 2259.
[188] See, for example, Fournier, L.; Lamaty, G.; Nata, A.; Roque, J.P. *Tetrahedron* ***1975****, 31*, 809.
[189] For example, see Field, L.; Sweetman, B.J. *J. Org. Chem.* ***1969****, 34,* 1799.
[190] Truce, W.E.; Roberts, F.E. *J. Org. Chem.* ***1963****, 28,* 961.
[191] Streitwieser Jr., A.; Caldwell, R.A.; Granger, M.R. *J. Am. Chem. Soc.* ***1964****, 86,* 3578; Streitwieser, Jr., A.; Maskornick, M.J.; Ziegler, G.R. T*etrahedron Lett.* ***1971***, 3927; Ward, H.R.; Lawler, R.G. *J. Am. Chem. Soc.* ***1967****, 89,* 5517.
[192] Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* ***1978****, 26,* 3743; Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* ***1975***, 2643.
[193] See Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, N.K. *Tetrahedron Lett.* ***2001****, 42*, 4425.
[194] Kumar, V.; Dev, S. *Tetrahedron Lett.* ***1983****, 24,* 1289.
[195] Ku, B.; Oh, D.Y. *Synth. Commun.* ***1989***, 433.
[196] This reaction is done neat, see Kazaraya, K.; Tsuji, S.; Sato, T. *Synlett* ***2004***, 1640.
[197] A solvent-free reaction. Firouzabadi, H.; Iranpoor, N.; Kohmarch, G. *Synth. Commun.* ***2003****, 33*, 167.
[198] Ali, M.H.; Goretti Gomes, M. *Synthesis* ***2005***, 1326.

and oxalic acid promotes the reaction.[199] Similarly reactions that use 1,2-ethanedithiol or 1,3-propanedithiol lead to 1,3-dithiolanes (**17**)[200] or 1,3-dithianes.[201] 3-(1,3-Dithian-2-ylidene)pentane- 2,4-dione has been used as a thioacetalization reagent for reactions in water.[202]



17

Dithioacetals and dithioketals are used as protecting groups for aldehydes and ketones, and after subsequent reactions involving the R or R′ group, deprotection regenerates the carbonyl.[203] Simple hydrolysis is the most common method for converting thiocarbonyls to carbonyls, but there are a variety of reagents for this conversion.[204] Lewis acids (e.g., aluminum chloride, $AlCl_3$) and mercuric salts are common reagents (the *Corey–Seebach procedure*).[205] Other reagents include $BF_3{\cdot}OEt_2$ in aq THF containing mercuric oxide (HgO),[206] ceric ammonium nitrate $[Ce(NH_4)_2(NO_3)_6]$,[207] chlorotrimethylsilane and H_2O_2,[208] $PhI(OAc)_2$ in aq acetone,[209] and Cu salts.[210] When aldehydes and ketones react with mercapto–alcohols, mixed acetals or ketals are formed.

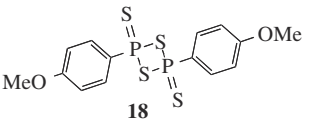
Thioamides are converted to amides with *Caro's acid* (H_2SO_5) on SiO_2.[211] The use of 2-mercaptoethanol ($HSCH_2CH_2OH$), for example, leads to an oxathiolane[212] and 3-mercaptopropanol ($HSCH_2CH_2CH_2OH$) leads to an oxathiane. Alternatively, the dithioketal can be desulfurized with Raney nickel (Reaction **14-27**), giving the overall conversion C=O → CH_2 (Reaction **19-70**).

Thioketones (**14**) can be prepared from certain ketones (e.g., diaryl ketones) by treatment with H_2S and an acid catalyst, usually HCl. They are often unstable and usually trimerize (to **16**) or react with air. Thioaldehydes[213] are even less stable and simple ones[214] apparently have never been isolated, although *tert*-BuCHS has been prepared in solution, where it exists for several hours at 20 °C.[215] A high-yield synthesis of thioketones involves

[199] Miyake, H.; Nakao, Y.; Sasaki, M. *Chem. Lett.* ***2007****, 36,* 104.
[200] See Kamal, A.; Chouhan, G. *Synlett* ***2002***, 474. For a review, see Olsen, R.K.; Currie, Jr., J.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 521–532.
[201] See Laskar, D.D.; De, S.K. *Tetrahedron Lett.* ***2004****, 45*, 1035, 2339.
[202] Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* ***2005****, 70*, 4535.
[203] See Ganguly, N.C.; Datta, M. *Synlett* ***2004***, 659.
[204] Corsaro, A.; Pistarà, V. *Tetrahedron* ***1998****, 54*, 15027.
[205] Seebach, D.; Corey, E.J. J. *Org. Chem.* ***1975****, 40*, 231; Seebach, D. *Synthesis* ***1969***, 17.
[206] Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971****, 36*, 366.
[207] Ho, T.–L.; Ho, H.C.; Wong, C.M. *J. Chem. Soc., Chem. Commun.* ***1972***, 791a.
[208] Bahrami, K.; Khodaei, M.M.; Tajik, M. *Synthesis* ***2010***, 4282.
[209] Shi, X.-X.; Wu, Q.-Q. *Synth. Commun.* ***2000****, 30*, 4081.
[210] Besra, R.C.; Rudrawar, S.; Chakraborti, A.K. *Tetrahedron Lett.* ***2005****, 46,* 6213; Oksdath-Mansilla, G.; Peñéñory, A.B. *Tetrahedron Lett.* ***2007****, 48,* 6150.
[211] Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000****, 30*, 2353.
[212] See Ballini, R.; Bosica, G.; Maggi, R. ; Mazzacani, A.; Righi, P.; Sartori, G. *Synthesis* ***2001***,1826; Mondal, E.; Sahu, P.R.; Khan, A.T. *Synlett* ***2002***, 463.
[213] See Usov, V.A.; Timokhina, L.V.; Voronkov, M.G. *Russ. Chem. Rev.* ***1990****, 59,* 378.
[214] See Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1241, and references cited in these papers.
[215] Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* ***1983****, 105*, 1683. See also, Baldwin, J.E.; Lopez, R.C.G. *J. Chem. Soc., Chem. Commun.* ***1982***, 1029.

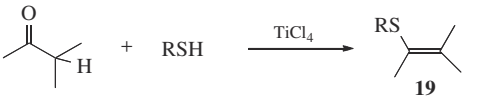
treatment of acyclic[216] ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide[217] (**18**, known as *Lawesson's reagent*).[218] Thioketones can also be prepared by treatment of ketones with P_4S_{10},[219] P_4S_{10} and hexamethyldisiloxane,[220] P_4S_{10} on alumina,[221] and from oximes or various types of hydrazone (overall conversion C=N–→ C=S).[222] Reagent **18** converts the C=O groups of amides and carboxylic esters[223] to C=S groups.[224] Lactones react with **18** in the presence of hexamethyldisiloxane an microwave irradiation to give the thiolactone.[225]

Other reagents may be used for this transformation including $POCl_3$ followed by $S(TMS)_2$, which converts lactams to thiolactams.[226] Treatment with triflic anhydride, and then H_2S[227] or aq $S(NH_4)_2$[228] converts amides to thioamides, as does the microwave assisted reaction with $PSCl_2/H_2O/Et_3N$, without solvent.[229] Carboxylic acids (RCOOH) can be converted directly to dithiocarboxylic esters (RCSSR′),[230] in moderate yield, with P_4S_{10} and a primary alcohol (R′OH).[231]



18

If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether (**19**) by treatment with a thiol in the presence of $TiCl_4$.[232] Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, $RCOR' + R^2SH \rightarrow RR'CHSR^2$,[233] in a reductive alkylation reaction, analogous to Reaction **16-7**.



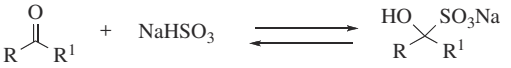
19

OS **II**, 610; **IV**, 927; **VI**, 109; **VII**, 124, 372. Also see, OS **III**, 332; **IV**, 967; **V**, 780; **VI**, 556; **VIII**, 302.

[216] Cyclopentanone and cyclohexanone gave different products: Scheibye, S.; Shabana, R.; Lawesson, S.; Rømming, C. *Tetrahedron* ***1982****, 38,* 993.
[217] See Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.
[218] See Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis* ***2003***, 1929. For a study of the mechanism, see Rauchfuss, T.B.; Zank, G.A. *Tetrahedron Lett.* ***1986****, 27*, 3445. See Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* ***2007****, 107*, 5210. For reactions with fluorous Lawesson's reagent, see Kaleta, Z.; Makowski, B.T.; Soós, T.; Dembinski, R. *Org. Lett.* ***2006****, 8,* 1625.
[219] See Scheeren, J.W.; Ooms, P.H.J.; Nivard, R.J.F. *Synthesis* ***1973***, 149.
[220] Curphey, T.J. *J. Org. Chem.* ***2002****, 67*, 6461.
[221] Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* ***2004****, 45*, 6255.
[222] See Okazaki, R.; Inoue, K.; Inamoto, N. *Tetrahedron Lett.* ***1979***, 3673.
[223] For a review of thiono esters RC(=S)OR', see Jones, B.A.; Bradshaw, J.S. *Chem. Rev.* ***1984****, 84*, 17.
[224] Yde, B.; Yousif, N.M.; Pedersen, U.S.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* ***1984****, 40*, 2047; Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.
[225] Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M. *Tetrahedron Lett.* ***2003****, 44*, 6647.
[226] Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* ***1994****, 59*, 348.
[227] Charette, A.B.; Chua, P. *Tetrahedron Lett.* ***1998****, 39*, 245.
[228] Charette, A.B.; Grenon, M. *J. Org. Chem.* ***2003****, 68*, 5792.
[229] Pathak, U.; Pandey, L.K.; Tank, R. *J. Org. Chem.* ***2008****, 73,* 2890.
[230] For a review of dithiocarboxylic esters, see Kato, S.; Ishida, M. *Sulfur Rep.,* ***1988****, 8,* 155.
[231] Davy, H.; Metzner, P. *Chem. Ind. (London)* ***1985***, 824.
[232] Mukaiyama, T.; Saigo, K. *Chem. Lett.* ***1973***, 479.
[233] Kikugawa, Y. *Chem. Lett.* ***1981***, 1157.

16-12 Formation of Bisulfite Addition Products

O-Hydro-*C*-sulfonato-addition



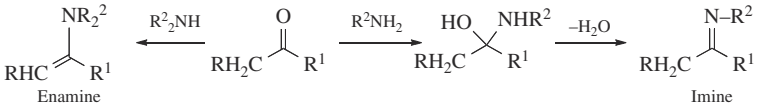
Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite ($NaHSO_3$). Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base)[234] and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.[235]

OS **I**, 241, 336; **III**, 438; **IV**, 903; **V**, 437.

D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

16-13 The Addition of Amines to Aldehydes and Ketones

Alkylimino-de-oxo-bisubstitution



The addition of ammonia[236] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*,[237] but these compounds are generally unstable. In addition, many imines with a hydrogen on the nitrogen spontaneously polymerize.[238]

In contrast to ammonia, primary, secondary, and tertiary amines can add to aldehydes[239] and ketones to give different kinds of products. Primary amines give imines[240] and secondary amines give enamines (for reactions, see **10-69**). Such imines are stable enough for isolation, but in some cases, especially with simple R groups, they rapidly decompose

[234] For cleavage with ion-exchange resins, see Khusid, A.Kh.; Chizhova, N.V. *J. Org. Chem. USSR* ***1985,*** *21*, 37. For a discussion of the mechanism, see Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1978,*** *100,* 1228.

[235] The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara, T.; Wakabayashi, T.; Taya, K. *Chem. Lett.* ***1981***, 1657.

[236] For a review of this reagent in organic synthesis, see Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

[237] These compounds have been detected by ^{13}C NMR: Chudek, J.A.; Foster, R.; Young, D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1285.

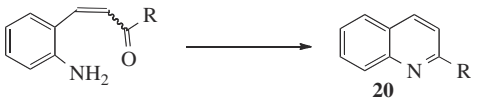
[238] Methanimine $CH_2{=}NH$ is stable in solution for several hours at –95° C, but rapidly decomposes at –80° C: Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouv. J. Chim.,* ***1982,*** *6*, 121. See also, Bock, H.; Dammel, R. *Chem. Ber.* ***1987,*** *120*, 1961.

[239] For a review of the reactions between amines and formaldehyde, see Farrar, W.V. *Rec. Chem. Prog.,* ***1968,*** *29,* 85. For a synthesis of imines, see Kwon, M.S.; Kim, S.; Park, S.; Bosco, W.; Chidrala, R.K.; Park, J. *J. Org. Chem.* ***2009,*** *74,* 2877; Kim, J.W.; He, J.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* ***2009,*** *38*, 920.

[240] See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond,* Wiley, NY, ***1970***, pp. 64–83; Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 600–614. Also see Ku, Y.-Y.; Grieme, T.; Pu, Y.-M.; Bhatia, A.V.; King, S.A. *Tetrahedron Lett.* ***2005,*** *46*, 1471; Guzen, K.P.; Guarezemini, A.S.; Órfão, A.T.G.; Cella, R.; Pereira, C.M.P.; Stefani, H.A. *Tetrahedron Lett.* ***2007,*** *48,* 1845.

or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them.[241] Even sterically hindered imines can be prepared.[242] The initial N-substituted hemiaminals[243] lose water to give the stable *Schiff bases*.

In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[244] In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent (e.g., $TiCl_4$),[245] or by addition of a molecular sieve.[246] Imines have been formed from aldehydes and amines in an ionic liquid.[247]



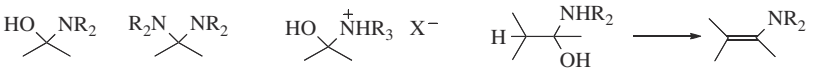
20

The reaction is often used to effect ring closure.[248] The *Friedländer quinoline synthesis*[249] is an example where ortho alkenyl aniline derivatives give the quinoline (**20**).[250] The alkene derivative can be prepared *in situ* from an aldehyde and a suitably functionalized ylid.[251] Pyrylium ions react with ammonia or primary amines to give pyridinium ions[252] (see Reaction **10-57**). Primary amines react with 1,4-diketones, with microwave irradiation, to give N-substituted pyrroles.[253] Similar reactions in the presence of Montmorillonite KSF[254] or by simply heating the components with tosic acid[255] have been reported.

The reaction of secondary amines with ketones leads to enamines (see **10-69**).[256] When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**21**) cannot lose water in the same way since the iminium ion intermediate does not have a proton on nitrogen, and in some cases it is possible to isolate them.[257] However, they are generally unstable, and under the reaction conditions usually react further. If no α hydrogen is present, **21** is converted to the more stable *aminal* (**22**).[258]

[241] See Lai, J.T. *Tetrahedron Lett.* ***2002****, 43*, 1965.
[242] Love, B.E.; Ren, J. *J. Org. Chem.* ***1993****, 58*, 5556.
[243] See Forlani, L.; Marianucci, E.; Todesco, P.E. *J. Chem. Res. (S)* ***1984***, 126.
[244] See Eisch, J.J.; Sanchez, R. *J. Org. Chem.* ***1986****, 51,* 1848.
[245] Weingarten, H.; Chupp, J.P.; White, W.A. *J. Org. Chem.* ***1967****, 32,* 3246.
[246] See Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972****, 91*, 605.
[247] Andrade, C.K.Z.; Takada, S.C.S.; Alves, L.M.; Rodrigues, J.P.; Suarez, P.A.Z.; Branda, R.F.; Soares, V.C.D. *Synlett* ***2004***, 2135.
[248] For a review, see Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* ***1987****, 43*, 5171.
[249] See Cheng, C.; Yan, S. *Org. React.* ***1982****, 28,* 37.
[250] See Yadav, J.S.; Reddy, B.V.S.; Premalatha, K. *Synlett* ***2004***, 963.
[251] Hsiao, Y.; Rivera, N.R.; Yasuda, N.; Hughes, D.L.; Reider, P.J. *Org. Lett.* ***2001****, 3*, 1101.
[252] See Zvezdina, E.A.; Zhadonva, M.P.; Dorofeenko, G.N. *Russ. Chem. Rev.* ***1982****, 51*, 469.
[253] Danks, T.N. *Tetrahedron Lett.* ***1999****, 40*, 3957.
[254] Banik, B.K.; Samajdar, S.; Banik, I. *J. Org. Chem.* ***2004****, 69*, 213.
[255] Klappa, J.J.; Rich, A.E.; McNeill, K. *Org. Lett.* ***2002****, 4*, 435.
[256] See Hodgson, D.M.; Bray, C.D.; Kindon, N.D.; Reynolds, N.J.; Coote, S.J.; Um, J.M.; Houk, K.N. *J. Org. Chem.* ***2009****, 74*, 1019.
[257] See Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* ***1962***, 1843.
[258] Duhamel, P. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 849–907.

However, if an α hydrogen is present, water (from **21**) or RNH_2 (from **22**) can be lost in that direction to give an enamine (**24**).[259] This is the most common method[260] for the preparation of enamines and usually takes place when an aldehyde



21 **22** (aminal) **23** **24**

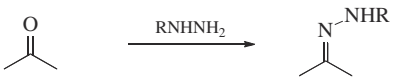
or ketone containing an α hydrogen is treated with a secondary amine.[261] The water is usually removed azeotropically or with a drying agent,[262] and molecular sieves can also be used.[263] Silyl carbamates (e.g., $Me_2NCO_2SiMe_3$) have been used to convert ketones to enamines.[264] Stable primary enamines have also been prepared.[265] Enamino–ketones have been prepared from diketones and secondary amines using low-molecular-weight amines in water,[266] or using microwave irradiation on silica gel.[267] Enamines have been prepared by the reaction of an aldehyde, a secondary amine, and a terminal alkyne in the presence of AgI at 100 °C,[268] AgI in an ionic liquid,[269] CuI with microwave irradiation,[270] or a Au catalyst.[271]

Tertiary amines can only give salts (**23**).

OS **I**, 80, 355, 381; **II**, 31, 49, 65, 202, 231, 422; **III**, 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV**, 210, 605, 638, 824; **V**, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **VI**, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; **VII**, 8, 135, 144, 473; **VIII**, 31, 132, 403, 451, 456, 493, 586, 597. Also see, OS **IV**, 283, 464; **VII**, 197; **VIII**, 104, 112, 241.

16-14 The Addition of Hydrazine Derivatives to Carbonyl Compounds

Hydrazono-de-oxo-bisubstitution



The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second equivalent of carbonyl compound to give an *azine*. This type

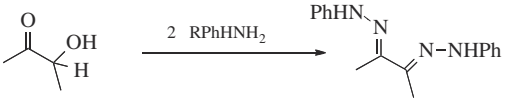
[259] See Haynes, L.W.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd. ed., Marcel Dekker, NY, ***1988***, pp. 103–163; Pitacco, G.; Valentin, E. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 623–714.
[260] For another method, see Katritzky, A.R.; Long, Q.; Lue, P.; Jozwiak, A. *Tetrahedron* ***1990***, *46*, 8153.
[261] Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.* ***2006***, *71*, 7481.
[262] See Nilsson, A.; Carlson, R. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 523.
[263] See Carlson, R.; Nilsson, A.; Strömqvist, M. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 7.
[264] Kardon, F.; Mörtl, M.; Knausz, D. *Tetrahedron Lett.* ***2000***, *41*, 8937.
[265] Erker, G.; Riedel, M.; Koch, S.; Jödicke, T.; Würthwein, E.-U. *J. Org. Chem.* ***1995***, *60*, 5284.
[266] Stefani, H.A.; Costa, I.M.; Silva, D. de O. *Synthesis* ***2000***, 1526.
[267] Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 5071.
[268] Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* ***2003***, *5*, 4473.
[269] Li, Z.; Wei, C.; Chen, L.; Varma, R.S.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 2443.
[270] Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* ***2004***, *6*, 1001.
[271] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 9584.

of product is especially important for aromatic aldehydes:

$$ArCH{=}N{-}NH_2 + ArCHO \longrightarrow \underset{\text{An azine}}{ArCH{=}N-N{=}CHAr}$$

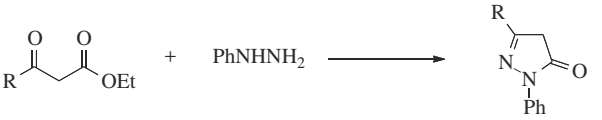
However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[272] Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,[273] are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[274] Since these are usually solids, they make excellent derivatives and were commonly employed for this purpose in the past, before the advent of modern spectroscopy methods. Cyclic hydrazones are known,[275] as are conjugated hydrazones.[276] Azides react with *N,N*-dimethylhydrazine and ferric chloride to give the *N,N*-dimethylhydrazone.[277] Alkenes react with CO/H_2, phenylhydrazine and a diphosphine catalyst to give a regioisomeric mixture of phenylhydrazones that favored "anti-Markovnikov" addition.[278] Oximes are converted to hydrazones with water and hydrazine in refluxing ethanol.[279]

α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:



An osazone

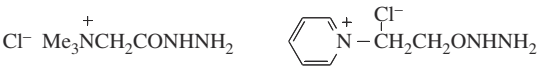
Osazones are particularly important in carbohydrate chemistry, and the *osazone test*[280] with phenylhydrazine is used to test for the presence of sugars with an adjacent sterogenic carbon. In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones*, respectively (the latter is illustrated for β-keto esters). No azines are formed under these conditions.



A pyrazolone

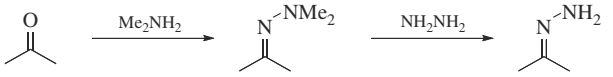
Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide ($NH_2NHCONH_2$), in which case the hydrazone is called a semicarbazone: *Girard's reagents T and P* are hydrazones that are water soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.[281]

[272] See Day, A.C.; Whiting, M.C. *Org. Synth.* ***VI***, 10.
[273] See Behforouz, M.; Bolan, J.L.; Flynt, M.S. *J. Org. Chem.* ***1985****, 50*, 1186.
[274] For a review of arylhydrazones, see Buckingham, J. *Q. Rev. Chem. Soc.* ***1969****, 23*, 37.
[275] Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* ***1998****, 39*, 2157.
[276] Palacios, F.; Aparicio, D.; de los Santos, J.M. *Tetrahedron Lett.* ***1993****, 34*, 3481.
[277] Barrett, I.C.; Langille, J.D.; Kerr, M.A. *J. Org. Chem.* ***2000****, 65*, 6268.
[278] Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M. *Tetrahedron Lett.* ***2004****, 45*, 869.
[279] Pasha, M.A.; Nanjundaswamy, H.M. *Synth. Commun.* ***2004****, 34*, 3827.
[280] See Mester, L.; El Khadem, H.; Horton, D. *J. Chem. Soc., C* ***1970***, 2567.
[281] See Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1991****, 56,* 1419.



Girard's reagent T Girard's reagent P

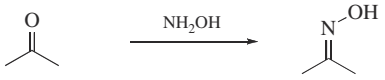
Simple *N*-unsubstituted hydrazones can be obtained by an exchange reaction. The *N,N*-dimethylhydrazone is prepared first and then treated with hydrazine:[282]



OS **II**, 395; **III**, 96, 351; **IV**, 351, 377, 536, 884; **V**, 27, 258, 747, 929; **VI**, 10, 12, 62, 242, 293, 679, 791; **VII**, 77, 438. Also see, OS **III**, 708; **VI**, 161; **VIII**, 597.

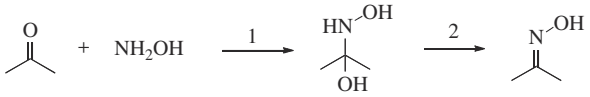
16-15 The Formation of Oximes

Hydroxyimino-de-oxo-bisubstitution



In a reaction very much like **16-14**, oximes can be prepared by the addition of hydroxylamine (NH_2OH) to aldehydes or ketones. Derivatives of hydroxylamine [e.g., H_2NOSO_3H and $HON(SO_3Na)_2$] have also been used. For hindered ketones (e.g., 2,2,4,4-tetramethyl-3-pentanone), high pressures (as high as 10,000 atm) may be necessary.[283] The reaction of hydroxylamine with unsymmetrical ketones or with aldehydes leads to a mixture of (*E*)- and (*Z*)-isomers. For aromatic aldehydes, heating with K_2CO_3 led to the (*E*)- isomer, whereas heating with $CuSO_4$ gave the (*Z*)-hydroxylamine.[284] Hydroxylamines react with ketones in ionic liquids[285] and on silica gel.[286]

It has been shown[287] that the rate of formation of oximes is at a maximum at a pH that depends on the substrate but is usually ~ 4. The rate also decreases as the pH is either raised or lowered from this point (a bell-shaped curve). In Section 16.A.i, bell-shaped curves like this were shown to be caused by changes in the rate-determining step in many cases. In this case, at low pH values step 2 is rapid (because it is acid catalyzed), and



25

step 1 is slow (and rate determining), because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate $^+NH_3OH$ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and consequently so does the reaction rate, until the maximum rate is reached at ~ pH 4. As the rising pH causes an increase in the rate of step 1, it also causes a *decrease* in

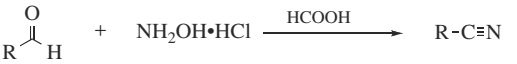
[282] Newkome, G.R.; Fishel, D.L. *J. Org. Chem.* ***1966****, 31*, 677.
[283] Jones, W.H.; Tristram, E.W.; Benning, W.F. *J. Am. Chem. Soc.* ***1959****, 81,* 2151.
[284] Sharghi, H.; Sarvari, M.H. *Synlett* ***2001***, 99.
[285] Ren, R.X.; Ou, W. *Tetrahedron Lett.* ***2001****, 42*, 8445.
[286] Hajipour, A.R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* ***1999****, 29*, 1697.
[287] Jencks, W.P. *J. Am. Chem. Soc.* ***1959****, 81*, 475; *Prog. Phys. Org. Chem.* ***1964****, 2*, 63.

the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above ~ 4, step 2 becomes rate determining, and although the rate of step 1 is still increasing (as it will until essentially all the NH_2OH is unprotonated), it is now step 2 that determines the rate. This step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond ~ 4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[288] There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: > pH ~ 10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate determining.[289] Still a third change in the rate-determining step has been found at ~ pH 1, showing that at least in some cases step 1 actually consists of two steps: formation of a zwitterion (e.g., $HOH_2N^+—C—O^-$ in the case shown above) and conversion of this to **25**.[290] The intermediate **25** has been detected by NMR in the reaction between NH_2OH and acetaldehyde.[291]

OS **I**, 318, 327; **II**, 70, 204, 313, 622; **III**, 690, **IV**, 229; **V**, 139, 1031; **VII**, 149. See also, OS **VI**, 670.

16-16 The Conversion of Aldehydes to Nitriles

Nitrilo-de-hydro,oxo-tersubstitution



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,[292] $KF—Al_2O_3$,[293] or $NaHSO_4{\cdot}SiO_2$ with microwave irradiation.[294] Heating in *N*-methylpyrrolidinone (NMP) is also effective with aryl aldehydes[295] and heating on dry alumina with aliphatic aldehyde.[296] The reaction is a combination of **16-15** and **17-29**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably, NH_2OSO_2OH.[297] Treatment with hydroxylamine and NaI[298] or certain carbonates[299] also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, although the *Schmidt reaction* (**18-16**) may compete.[300] Microwave irradiation has been used with $NH_2OH{\cdot}HCl$ and another reagent, which includes phthalic anhydride[301] or H—Y zeolite.[302] The reaction of an aldehyde with hydroxylamine followed by diethyl

[288] See Cockerill, A.F.; Harrison, R.G.in Patai, S. *The Chemistry of Functional Groups, Supplement A,* pt. 1, Wiley, NY, ***1977***, pp. 288–299; Sollenberger, P.Y.; Martin, R.B.in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 367–392. For isotope effect studies, see Rossi, M.H.; Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1990****, 55*, 1300.

[289] Sayer, J.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1972****, 94,* 3262.

[290] Sayer, J.M.; Edman, C. *J. Am. Chem. Soc.* ***1979****, 101*, 3010.

[291] Cocivera, M.; Effio, A. *J. Am. Chem. Soc.* ***1976****, 98*, 7371.

[292] Olah, G.A.; Keumi, T. *Synthesis* ***1979***, 112.

[293] Movassagh, B.; Shokri, S. *Tetrahedron Lett.* ***2005****, 46*, 6923.

[294] Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.

[295] Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis* ***1999***, 586; Chakraborti, A.K.; Kaur, G. *Tetrahedron* ***1999****, 55*, 13265.

[296] Sharghi, H.; Sarvari, M.H. *Tetrahedron* ***2002****, 58*, 10323.

[297] Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* ***1976****, 59,* 2786.

[298] Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* ***2003***, 1841.

[299] Bose, D.S.; Goud, P.R. *Synth. Commun.* ***2002****, 32*, 3621.

[300] See Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* ***1989***, 105.

[301] Veverková, E.; Toma, Š. *Synth. Commun.* ***2000****, 30*, 3109.

[302] Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* ***2002***, 625.

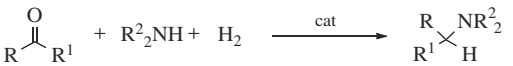
cholorophosphate ($EtOPOCl_2$) gives the nitrile.[303] Heating with hydroxylamine in DMSO[304] and using hydroxylamine and oxalyl chloride[305] have been used. *tert*-Butanesulfinyl imines are also used for the conversion of aldehydes to nitriles.[306] Other reagents include trimethylsilyl azide,[307] hydroxylamine hydrochloride/$MgSO_4$/TsOH,[308] or I_2 with aq ammonia,[309] The reaction of a conjugated aldehyde with ammonia, CuCl, and 50% H_2O_2 gave the conjugated nitrile.[310] Aldehydes with IBX (*o*-iodoxybenzoic acid) and liquid ammonia gives the nitrile.[311] Tetrabutylammonium tribromide in aq ammonia has also been used.[312] Trichloroisocyanuric acid with a catalytic amount of TEMPO (Sec. 5.C.i) converts aldehydes to nitriles at 0 °C in dichloromethane.[313] Aromatic aldehydes are converted to the nitrile by heating 2.2 molar equivalents of $NaN(SiMe_3)_2$ in 1,3-dimethylimidazolidin-2-one, in a sealed tube.[314] The aldehydes employed had a hydroxy substituent.

In a related reaction, the reaction of primary alcohols with iodine in ammonia water gives the corresponding nitrile.[315] Upon treatment with 2 molar equivalents of dimethylaluminum amide (Me_2AlNH_2), carboxylic esters give nitriles: $RCO_2R' \rightarrow RCN$.[316] This is likely a combination of Reaction **16-75** and **17-30** (see Reaction **19-5**).

OS **V**, 656.

16-17 Reductive Alkylation of Ammonia or Amines

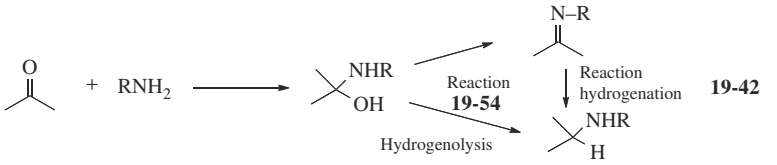
Hydro,dialkylamino-de-oxo-bisubstitution



When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen gas and an appropriate catalyst (e.g., Rh or Ir; heterogeneous or homogeneous),[317] *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[318] The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:[319] In this regard, the reaction of an aldehyde

[303] Zhu, J.-L.; Lee, F.-Y.; Wu, J.-D.; Kuo, C.-W.; Shia, K.-S. *Synlett* ***2007***, 1317.
[304] Chill, S.T.; Mebane, R.C. *Synth. Commun.* ***2009****, 39,* 3601.
[305] Movassagh, B.; Fazeli, A. *Synth. Commun.* ***2007****, 37,* 625.
[306] Tanuwidjaja, J.; Peltier, H.M.; Lewis, J.C.; Schenkel, L.B.; Ellman, J.A. *Synthesis* ***2007***, 3385.
[307] Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* ***1987****, 43,* 693.
[308] Ganboa, I.; Palomo, C. *Synth. Commun.* ***1983****, 13,* 219.
[309] Talukdar, S.; Hsu, J.-L.; Chou, T.-C.; Fang, J.-M. *Tetrahedron Lett.* ***2001****, 42*, 1103.
[310] Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* ***2000****, 41*, 6749.
[311] Arote, N.D.; Bhalerao, D.S.; Akamanchi, K.G. *Tetrahedron Lett.* ***2007****, 48,* 3651. Also see Zhu, C.; Ji, L.; Wei, Y. *Synthesis* ***2010***, 3121.
[312] Zhu, Y.-Z.; Cai, C. *Monat. Chemie* ***2010****, 141,* 637.
[313] Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.
[314] Hwu, J.R.; Wong, F.F. *Eur. J. Org. Chem.* ***2006***, 2513.
[315] Mori, N.; Togo, H. *Synlett* ***2005***, 1456. Also see Reddy, K.R.; Maheswari, C.U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M.L. *Tetrahedron Lett.* ***2009****, 50*, 2050.
[316] Wood, J.L.; Khatri, N.A.; Weinreb, S.M. *Tetrahedron Lett.* ***1979***, 4907.
[317] See Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* ***2003****, 68*, 4067; Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* ***2003****, 68*, 4120.
[318] See Rylander, P.N. *Hydrogenation Methods* Academic Press, NY, ***1985***, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* ***1980****, 49*, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals* Academic Press, NY, ***1967***, pp. 291–303.
[319] See Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1964***, 1366, 1374, 1584, 1594.

with an amine to give an iminium salt (**16-31**) can be followed in a second chemical step of reduction of the C=N unit (**19-42**) using $NaBH_4$ or a variety of other reagents.[320]



Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 molar equivalents of ammonia and 1 molar equivalent of aldehyde or ketone, and 1 molar equivalent of primary amine and 1 molar equivalent of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways. In general, they are prepared from primary or secondary amines.[321] The method is seldom carried out with 3 molar equivalents of ammonia and 1 molar equivalent of carbonyl compound. When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products. Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. The reaction is compatible with amino acids, giving the N-alkylated amino acid.[322] Other reducing agents[323] can be used instead of hydrogen and a catalyst, among them boranes,[324] $PhSiH_3$ with 2% Bu_2SnCl_2,[325] triethylsilane with an Ir[326] or an In catalyst,[327] zinc and HCl, or Zn (with formaldehyde for reductive methylation),[328] and polymethylhydrosiloxane.[329] Several hydride reducing agents can be used, including

[320] See Bhattacharyya, S. *Synth. Commun.* ***2000****, 30,* 2001.
[321] Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines* Macmillan, NY, ***1965***, pp. 44–52.
[322] Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* ***2000****, 41*, 8225.
[323] For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 835–840.
[324] Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* ***2008****, 73*, 1297. For a reaction using ammonia-borane, see Ramachandran, P.V.; Gagare, P.D.; Sakavuyi, K.; Clark. P. *Tetrahedron Lett.* ***2010****, 51*, 3167. 1,2,3-Triazole-boranes have also been used: Liao, W.; Chen, Y.; Liu, Y.; Duan, H.; Petersen, J.L.; Shi, X. *Chem. Commun.* ***2009***, 6436.
[325] Apodaca, R.; Xiao, W. *Org. Lett.* ***2001****, 3*, 1745. For a Mo-catalzyed reaction see Smith, C.A.; Cross, L.E.; Hughes, K.; Davis, R.E.; Judd, D.B.; Merritt, A.T. *Tetrahedron Lett.* ***2009****, 50*, 4906.
[326] Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2005****, 70*, 2195; Lee, O.-Y.; Law, K.-L.; Ho, C.-Y; Yang, D. *J. Org. Chem.* ***2008****, 73,* 8829.
[327] Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* ***2009****, 11*, 3302.
[328] da Silva, R.A.; Estevam, I.H.S.; Bieber, L.W. *Tetrahedron Lett.* ***2007****, 48,* 7680.
[329] Chandrasekhar, S.; Reddy, Ch.R.; Ahmed, M. *Synlett* ***2000***, 1655.

$NaBH_4$,[330] $NaBH_4$ with $Ti(OiPr)_4$[331] or $NiCl_2$,[332] $NaBH_4/H_3BO_4$,[333] BER,[334] polymer-bound triethylammonium acetoxyborohydride,[335] $LiBH_4$,[336] $ZnBH_4$-*N*-methylpiperidine,[337] $ZrBH_4$,[338] $NaBH_3CN$,[339] or sodium triacetoxyborohydride,[340] Aldehydes and primary amines react with allylic halides, in the presence of Zn dust, to give a homoallylic secondary amine.[341] A *Hantzsch dihydropyridine* in conjunction with a Sc catalyst has been used,[342] and the use of a *Hantzsch ester* in a reductive amination is sometimes called a hydrogen-bond catalyzed reaction.[343] The reaction of an aldehyde and an amine in isopropyl alcohol, in the presence of Ni nanoparticles, undergoes reductive amination via hydrogen transfer.[344]

Formic acid is an effective reagent for reductive amination[345] in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH_2PO_3 to give the N-methylated tertiary amine[346] and microwave irradiation has also been used.[347] Conjugated aldehydes are converted to alkenyl-amines with the amine/silica gel followed by reduction with zinc borohydride.[348] In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler–Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.[349] It is possible to use ammonium (or amine) salts of formic acid,[350] or formamides, as a substitute for the *Wallach conditions*. This method is called the *Leuckart reaction*,[351] and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A Rh catalyzed variation has been reported.[352]

[330] Gribble, G.W.; Nutaitis, C.F. *Synthesis* ***1987***, 709. For the use of an ionic liquid-water system, see Nagaiah, K.; Kumar, V.N.; Rao, R.S.; Reddy, B.V.S.; Narsaiah, A.V.; Yadav, J.S. *Synth. Commun.* ***2006****, 36*, 3345.

[331] Neidigh, K.A.; Avery, M.A.; Williamson, J.S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 2527; Bhattacharyya, S. *J. Org. Chem.* ***1995****, 60*, 4928.

[332] Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 503.

[333] This is a solvent-free reaction. See Cho, B.T.; Kang, S.K. *Synlett* ***2004***, 1484.

[334] Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* ***1993****, 23*, 1595.

[335] Bhattacharyya, S.; Rana, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003****, 44*, 4957.

[336] Cabral, S.; Hulin, B.; Kawai, M. *Tetrahedron Lett.* ***2007****, 48,* 7134.

[337] Alinezhad, H.; Tajbakhsh, M.; Zamani, R. *Synlett* ***2006***, 431.

[338] Heydari, A.; Khaksar, S.; Esfandyari, M.; Tajbakhsh, M. *Tetrahedron* ***2007****, 63,* 3363.

[339] Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* ***1990****, 55,* 2552. See also, Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* ***1990****, 31,* 5547. See Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979****, 11,* 201; Lane, C.F. *Synthesis* ***1975***, 135. See also, Grenga, P.N.; Sumbler, B.L.; Beland, F.; Priefer, R. *Tetrahedron Lett.* ***2009****, 50*, 6658.

[340] Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* ***1996****, 61*, 3849.

[341] Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* ***2007****, 72*, 3149.

[342] Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* ***2004****, 60*, 6649.

[343] Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* ***2006****, 8,* 741.

[344] Alonso, F.; Riente, P.; Yus, M. *Synlett* ***2008***, 1289.

[345] For a microwave induced reaction see Torchy, S.; Barbry, D. *J. Chem. Res. (S)* ***2001***, 292.

[346] Davis, B.A.; Durden, D.A. *Synth. Commun.* ***2000****, 30*, 3353.

[347] Barbry, D.; Torchy, S. *Synth. Commun.* ***1996****, 26*, 3919.

[348] Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* ***1998****, 63*, 370.

[349] Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* ***2002****, 32*, 457.

[350] For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkaufer, R.E. *Synthesis* ***1988***, 91. See Byun, E.; Hong, B.; De Castro, K.A.; Lim, M.; Rhee, H. *J. Org. Chem.* ***2007****, 72*, 9815.

[351] Moore, M.L. *Org. React.* ***1949****, 5*, 301; Awachie, P.I.; Agwada, V.C. *Tetrahedron* ***1990****, 46,* 1899 and references cited therein; Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J.M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* ***1996****, 37,* 8177; Lejon, T.; Helland, I. *Acta Chem. Scand.* ***1999****, 53*, 76.

[352] Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* ***2002****, 67*, 8685. See Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* ***2004****, 36*, 99.

Allylic silanes react with aldehydes and carbamates, in the presence of Bi catalysts,[353] or BF_3·OEt_2[354] to give the corresponding allylic *N*-carbamoyl derivative. The reaction can be done with aromatic amines in the presence of vinyl ethers and a Cu complex to give β-amino ketones.[355] Reductive amination of an aryl amine and an aryl aldehyde that contains an ortho conjugated ketone substituent gives the amine, which adds 1,4- (Reaction **15-AA**) to the α,β-unsaturated ketone unit to give a bicyclic amine.[356] Alternative methods of reductive alkylation have been developed. Alkylation of an imine formed *in situ* is also possible.[357]

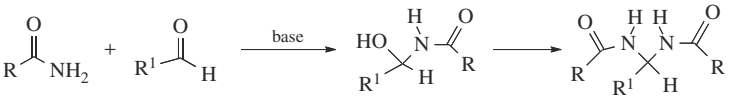
Enantioselective reductive amination reactions are known, generating chiral amines. Ketones and anilines react in the presence of an organocatalyst and a catalytic amount of a chiral phosphoric acid to give the chiral amine.[358] The reaction of an aldehyde with a chiral amine initiated a reaction that gave a chiral primary amine.[359] A Yb catalyzed reaction with a ketone gave a chiral secondary amine.[360] Aldehydes react with *N*-diphenylphosphinoylimines and Et_2Zn, in the presence of a chiral Cu precatalyst, to give a chiral amine.[361] Asymmetric biocatalytic reductive amination reactions are known.[362] Asymmetric reductive amination has been attempted using a *Hantzsch ester* mediated reaction.[363]

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Azo compounds react with aldehydes, in the presence of proline, and subsequent reduction with $NaBH_4$ gives the chiral hydrazine derivative.[364]

OS **I**, 347, 528, 531; **II**, 503; **III**, 328, 501, 717, 723; **IV**, 603; **V**, 552; **VI**, 499; **VII**, 27.

16-18 Addition of Amides to Aldehydes

Alkylamido-de-oxo-bisubstitution

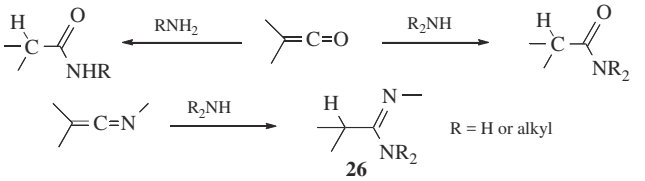


Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $RCONH^-$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.[365] If the R′ group contains an α hydrogen, water may split out.

[353] Ollevier, T.; Ba, T. *Tetrahedron Lett.* ***2003****, 44*, 9003.
[354] Billet, M.; Klotz, P.; Mann, A. *Tetrahedron lett.* ***2001****, 42*, 631.
[355] Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* ***1999****, 64*, 6833.
[356] Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* ***1999****, 1*, 1579.
[357] See Choudary, B.M.; Jyothi, K.; Madhi, S.; Kantam, M.L. *Synlett* ***2004***, 231; Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* ***2003***, 883.
[358] Storer, R.I.; Carrera, D.E.; Ni, Y.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2006****, 128*, 84. See Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* ***2006****, 128,* 13074.
[359] Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* ***2006****, 128,* 11038.
[360] Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* ***2008****, 73,* 1297.
[361] Côté, A.; Charette, A.B. *J. Org. Chem.* ***2005****, 70,* 10864.
[362] Koszelewski, D.; Lavandera, I.; Clay, D.; Guebitz, G.M.; Rozzell, D.; Kroutil, W. *Angew. Chem. Int. Ed.* ***2008****, 47,* 9337.
[363] Wakchaure, V.N.; Nicoletti, M.; Ratjen, L.; List, B. *Synlett* ***2010***, 2708.
[364] List, B. *J. Am. Chem. Soc.* ***2002****, 124*, 5656; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002****, 124*, 6254.
[365] Challis, B.C.; Challis, J.A. in Zabicky, J.*The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* ***1965****, 14,* 52, pp. 91–95, 104–112; Gilbert, E.E. *Synthesis* ***1972***, 30.

Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with $TsNH_2$ (e.g., with trifluoroacetic anhydride, TFAA) in CH_2Cl_2 at reflux,[366] or with $TiCl_4$ in refluxing dichloroethane,[367] to give the *N*-tosylimine (Ts—N=CHPh). In a similar manner, the reaction of $TolSO_2Na$ + $PhSO_2Na$ with an aldehyde in aq formic acid gives the *N*-phenylsulfonyl imine.[368] The reaction of an aldehyde with Ph_3P=NTs and a ruthenium catalyst gives the *N*-tosyl imine.[369]

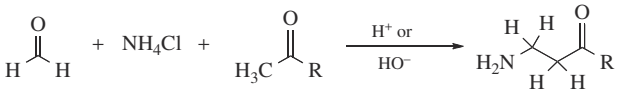
Primary and secondary amines add to ketenes to give, respectively, *N*-substituted and *N, N*-disubstituted amides:[370] and to ketenimines to give amidines, (**26**).[371]



26

16-19 The Mannich Reaction

Acyl,amino-de-oxo-bisubstitution, and so on



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[372] This can formally be considered as an addition of ammonia to give H_2NCH_2OH, followed by a nucleophilic substitution. The reaction can be carried out with salts of primary or secondary amines,[373] or with amides[374] rather than ammonia, in which cases the product is substituted on the nitrogen with R, R^2, and RCO, respectively. The product is referred to as a *Mannich base*. The imine can be generated *in situ*, and the reaction of a ketone, formaldehyde, and diethylamine with microwave irradiation gave the *Mannich* product, a β-amino ketone.[375] Many active hydrogen compounds give the reaction, including ketones and aldehydes, esters, nitroalkanes,[376] and nitriles as well as ortho-carbon atoms of phenols, the carbon of terminal alkynes, the oxygen of alcohols and the sulfur of thiols.[377]

[366] Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* ***2003****, 44*, 1231.
[367] Ram, R.N.; Khan, A.A. *Synth. Commun.* ***2001****, 31*, 841.
[368] Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* ***2000***, 75.
[369] Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004****, 45*, 4341.
[370] Tidwell, T.T. *Acc. Chem. Res.* ***1990****, 23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975****, 4*, 231. For an enantioselective reaction, see Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002****, 124*, 10006.
[371] Stevens, C.L.; Freeman, R.C.; Noll, K. *J. Org. Chem.* ***1965****, 30*, 3718.
[372] Tramontini, M.; Angiolini, L. *Tetrahedron* ***1990****, 46*, 1791; Gevorgyan, G.A.; Tramontini, M. *Synthesis* ***1973***, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin, NY, ***1972***, pp. 654–660; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1985****, 54,* 495.
[373] Agababyan, A.G.; Gevorgyan, G.A.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1982****, 51,* 387.
[374] Hellmann, H. *Angew. Chem.* ***1957****, 69,* 463; *Newer Methods Prep. Org. Chem.* ***1963****, 2,* 277.
[375] Gadhwal, S.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synlett* ***2000***, 341.
[376] Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* ***2001****, 42*, 4673. See Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 117–130.
[377] see Massy, D.J.R. *Synthesis* ***1987***, 589; Dronov, V.I.; Nikitin, Yu.E. *Russ. Chem. Rev.* ***1985****, 54*, 554

Arylamines do not normally give the reaction, but hydrazines can be used.[378] Vinylogous *Mannich reactions* are known[379] (see Sec. 6.B for vinylogy).

The *Mannich base* product can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and an active compound, for example,

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogen atoms, the *Mannich base* may condense with one or two additional molecules of aldehyde and ammonia or amine, for example,

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_2CHCOR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_3CHCOR$$

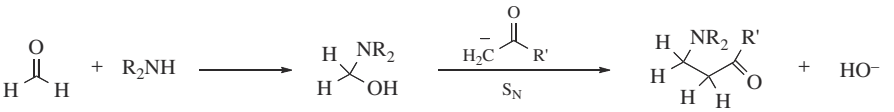
Another reaction consists of condensation of the *Mannich base* with excess formaldehyde:

$$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$$

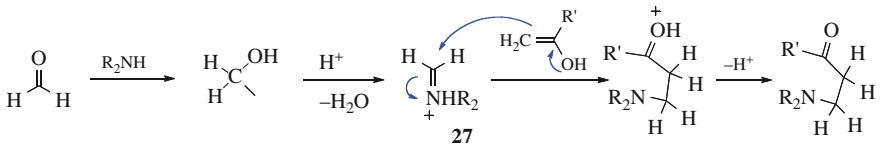
Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times, they are side products.

When the *Mannich base* contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to α,β-unsaturated aldehydes, ketones, esters, and so on.

Studies of the reaction kinetics have led to the following proposals for the mechanism of the *Mannich reaction*.[380] The base-catalyzed reaction:



The acid-catalyzed reaction:



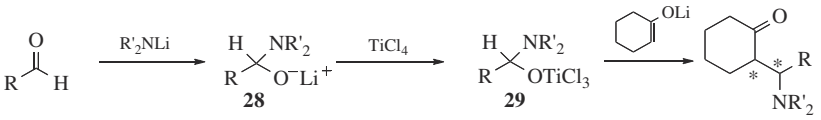
According to this mechanism, it is the free amine, not the salt that reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to what happens in Reaction **12-4**. There is kinetic evidence for the intermediacy of the iminium ion (**27**).[381]

When an unsymmetrical ketone is used as the active-hydrogen component, two products are possible. Regioselectivity has been obtained by treatment of the ketone with

[378] El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* ***2003****, 68*, 8733.
[379] Bur, S.; Martin, S.F. *Tetrahedron* ***2001****, 57*, 3221; Martin, S.F. *Acc. Chem. Res.* ***2002****, 35*, 895.
[380] Cummings, T.F.; Shelton, J.R. *J. Org. Chem.* ***1960****, 25,* 419.
[381] Benkovic, S.J.; Benkovic, P.A.; Comfort, D.R. *J. Am. Chem. Soc.* ***1969****, 91,* 1860.

preformed iminium ions:[382] the use of $Me_2N^+{=}CH_2$ CF_3COO^- in CF_3COOH gives substitution at the more highly substituted position, while with $(i\text{Pr})_2N^+{=}CH_2$ ClO_4^- the reaction takes place at the less highly substituted position.[383] The preformed iminium compound dimethyl(methylene)ammonium iodide ($CH_2{=}N^+Me_2$ I^-), called an *Eschenmoser's salt*,[384] has also been used in *Mannich reactions*.[385] The analogous chloride salt has been condensed with an imine to give a β,β′-dimethylamino ketone after acid hydrolysis.[386]

Another type of preformed reagent (**29**) has been used to carry out diastereoselective *Mannich reactions*. The lithium salts (**28**) are treated with $TiCl_4$ to give **29**, which is then treated with the enolate anion of a ketone.[387] The Pd catalyzed Mannich reaction of enol ethers to imines is also known.[388] The reaction of silyl enol ethers and imines[389] is catalyzed by HBF_4 in aq methanol.[390] Similarly, silyl enol ethers react with aldehydes and aniline in the presence of $InCl_3$ to give the β-amino ketone.[391]



Enantioselective *Mannich reactions* are known.[392] Chiral catalysts are commonly used,[393] including proline,[394] proline derivatives, or proline analogues,[395] a Pybox-La catalyst,[396] chiral aminosulfonamides,[397] or Cinchona alkaloids,[398] and other chiral amines.[399] Chiral

[382] See Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971****, 10,* 330.
[383] Jasor, Y.; Luche, M.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Chem. Commun.* ***1974***, 253; Gaudry, M.; Jasor, Y.; Khac, T.B. *Org. Synth.* ***VI***, 474.
[384] Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971****, 10,* 330.
[385] See Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* ***1980****, 45,* 524, and references cited therein.
[386] Arend, M.; Risch, N. *Tetrahedron Lett.* ***1999****, 40*, 6205.
[387] Seebach, D.; Schiess, M.; Schweizer, W.B. *Chimia* ***1985****, 39,* 272. See also, Katritzky, A.R.; Harris, P.A. *Tetrahedron* ***1990****, 46*, 987.
[388] See Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* ***1999****, 121*, 5450.
[389] See Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chemistry: European J.* ***2006****, 12*, 5082.
[390] Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* ***2001****, 42*, 4025.
[391] Loh, T.-P.; Wei, L.L. *Tetrahedron Lett.* ***1998****, 39*, 323.
[392] See Córdova, A. *Acc. Chem. Res.* ***2004****, 37*, 102; Marques, M.M.B. *Angew. Chem. Int. Ed.* ***2006****, 45*, 348; Ibrahem, I.; Córdova, A. *Chem. Commun.* ***2006***, 1760; Amedjkouh, M.; Brandberg, M. *Chem. Commun.* ***2008***, 3043.
[393] See Rodríguez, B.; Bolm, C. *J. Org. Chem.* ***2006****, 71,* 2888.
[394] List, B.; Pojarliev, P.; Biller, W.T.; Martin, H.J. *J. Am. Chem. Soc.* ***2004****, 124*, 827; Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem. Int. Ed.* ***2004****, 43,* 6528; Yang, J.W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* ***2007****, 46,* 609.
[395] Mitsumori, S.; Zhang, H.; Cheong, P.H.-Y.; Houk, K.N.; Tanaka, F.; Barbas, III, C.F. *J. Am. Chem. Soc.* ***2006****, 128,* 1040; Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, III, C.F. *J. Am. Chem. Soc.* ***2006****, 128,* 9630. See also, Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q.-Y.; Yamaguchi, J.; Uchimaru, T. *Chemistry: Asian J.* ***2008****, 3,* 225.
[396] Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007****, 129*, 9588; Cutting, G.A.; Stainforth, N.E.; John, M.P.; Kociok-Köhn, G.; Willis, M.C. *J. Am. Chem. Soc.* ***2007****, 129,* 10632.
[397] Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* ***2005****, 127*, 16408; Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* ***2008****, 64,* 1197.
[398] Lou, S.; Taoka, B.M.; Ting, A.; Schaus, S.E. *J. Am. Chem. Soc.* ***2005****, 127*, 11256; Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* ***2006****, 128,* 6048.
[399] Haurena, C.; LeGall, E.; Sengmany, S.; Martens, T. *Tetrahedron* ***2010****, 66,* 9902.

Brønsted acids are also used as catalysts,[400] as well as chiral ammonium salts.[401] Chiral diamine[402] or phosphine-imine[403] ligands have been used, and chiral dinuclear zinc compounds.[404] Chiral auxiliaries on the carbonyl fragment can be used.[405] Chiral imines, in the form of chiral hydrazones, have been used with silyl enol ethers and a Sc catalyst.[406] Chiral amines react with aldehydes, with silyl enol ethers and an $InCl_3$ catalyst in ionic liquids, to give the *Mannich* product with good enantioselectivity.[407] A chiral thiourea catalyst has been used with a vinylogous *Mannich reaction*[408] (see Sec. 6.B for vinylogy).

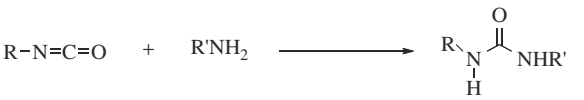
The reaction of nitroalkanes and amines, usually in the presence of a metal catalyst (e.g., CuBr), [409] has been called the nitro-*Mannich reaction*.[410] An asymmetric nitro-*Mannich reaction* used a Cu—Sm catalyst,[411] a Cu catalyst,[412] or a chiral thiourea catalyst.[413]

Also See, **11-22**.

OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also, OS **VIII**, 358.

16-20 The Addition of Amines to Isocyanates

***N*-Hydro-*C*-alkylamino-addition**



Ammonia and primary and secondary amines can be added to isocyanates[414] to give substituted ureas.[415] Isothiocyanates give thioureas.[416] This is an excellent method for the preparation of ureas and thioureas. These compounds are often used as derivatives for primary and secondary amines. Isocyanic acid (HNCO) also gives the reaction; usually its salts (e.g., NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of this acid.[417]

OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **VIII**, 26.

[400] Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* ***2007****, 129*, 3790; Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* ***2007****, 129,* 6756; Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* ***2007***, 1441.

[401] Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* ***2008****, 130,* 10878.

[402] Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* ***2002****, 124*, 5640; Trost, B.M.; Terrell, C.R. *J. Am. Chem. Soc.* ***2003****, 125*, 338.

[403] Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007****, 129,* 500.

[404] Trost, B.M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* ***2006****, 128,* 2778.

[405] Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* ***2004****, 6*, 1721.

[406] Jacobsen, M.F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* ***2004****, 69*, 4792.

[407] Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003****, 44*, 2409.

[408] Liu, T.-Y.; Cui, J.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* ***2007****, 129,* 1878.

[409] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2005***, *127*, 3672.

[410] Anderson, J.C.; Blake, A.J.; Howell, G.P.; Wilson, C. *J. Org. Chem.* ***2005****, 70*, 549.

[411] Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007****, 129,* 4900.

[412] Anderson, J.C.; Howell, G.P.; Lawrence, R.M.; Wilson, C.S. *J. Org. Chem.* ***2005****, 70,* 5665.

[413] Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* ***2008****, 130,* 8606.

[414] For a review of the mechanism, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975****, 4*, 231.

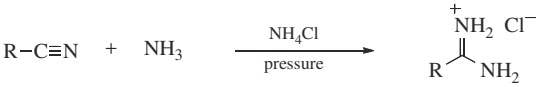
[415] See Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* ***1985****, 54*, 249.

[416] Herr, R.J.; Kuhler, J.L.; Meckler, H.; Opalka, C.J. *Synthesis* ***2000***, 1569.

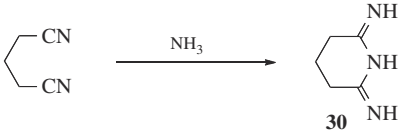
[417] See Shorter, J. *Chem. Soc. Rev.* ***1978****, 7,* 1. See also, Williams, A.; Jencks, W.P. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1753, 1760; Hall, K.J.; Watts, D.W. *Aust. J. Chem.* ***1977****, 30*, 781, 903.

16-21 The Addition of Ammonia or Amines to Nitriles

N-Hydro-*C*-amino-addition



Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[418] Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines (**30**).[419]



30

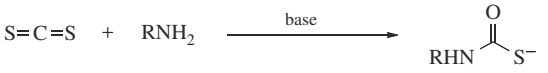
Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[420] Ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide [$MeAl(Cl)NR_2$; R = H or Me).[421] The addition of ammonia to cyanamide (NH_2CN) gives guanidine [$(NH_2)_2C{=}NH$]. Guanidines can also be formed from amines.[422]

If water is present, in the presence of a Ru[423] or a Pt catalyst,[424] the addition of a primary or secondary amine to a nitrile gives an amide: $RCN + R^1NHR^2 + H_2O \rightarrow RCONR^1R^2 + NH_3$ (R^2 may be H). When benzonitrile reacts with $H_2PO_3Se^-$ in aq methanol, a selenoamide [$Ph(C{=}Se)NH_2$], is formed after treatment with aq potassium carbonate.[425]

OS **I**, 302 [but also see, OS **V**, 589]; **IV**, 245, 247, 515, 566, 769. See also, OS **V**, 39.

16-22 The Addition of Amines to Carbon Disulfide and Carbon Dioxide

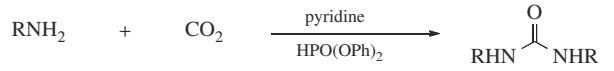
S-Metallo-*C*-alkylamino-addition



Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.[426] This reaction is similar to **16-10**. Hydrogen sulfide can be eliminated from the product, directly or indirectly, to give isothiocyanates (RNCS). Isothiocyanates can be obtained directly by the reaction of primary amines and CS_2 in

[418] For reviews of amidines, see Granik, V.G. *Russ. Chem. Rev.* ***1983****, 52,* 377; Gautier, J.; Miocque, M.; Farnoux, C.C. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 283–348.
[419] Elvidge, J.A.; Linstead, R.P.; Salaman, A.M. *J. Chem. Soc.* ***1959***, 208.
[420] Grivas, J.C.; Taurins, A. *Can. J. Chem.* ***1961****, 39,* 761.
[421] Garigipati, R.S. *Tetrahedron Lett.* ***1990****, 31,* 1969.
[422] Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A. *Tetrahedron Lett.* ***2002****, 43*, 1401.
[423] Murahashi, S.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* ***1986****, 108*, 7846.
[424] Cobley, C.J.; van den Heuvel, M.; Abbadi, A.; de Vries, J.G. *Tetrahedron Lett.* ***2000****, 41*, 2467.
[425] Kamiński, R.; Glass, R.S.; Skowrońska, A. *Synthesis* ***2001***, 1308.
[426] Dunn, A.D.; Rudorf, W. *Carbon Disuphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 226–315; Katritzky, A.R.; Faid-Allah, H.; Marson, C.M. *Heterocycles* ***1987****, 26,* 1657; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, see pp. 804–812; Katritzky, A.R.; Marson, C.M.; Faid-Allah, H. *Heterocycles* ***1987****, 26*, 1333.

pyridine in the presence of dicyclohexylcarbodiimide.[427] A tosyl chloride mediated preparation of isothiocyanates is also known.[428] Aniline derivatives react with CS_2 and NaOH, and then ethyl chloroformate to give the aryl isothiocyanate.[429] In the presence of diphenyl phosphite and pyridine, primary amines add to CO_2 and to CS_2 to give, respectively, symmetrically substituted ureas and thioureas:[430] Isoselenoureas [$R_2NC(=NR^1)SeR^2$] can also be formed.[431]

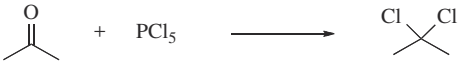


OS **I**, 447; **III**, 360, 394, 599, 763; **V**, 223.

E. Halogen Nucleophiles

16-23 The Formation of *gem*-Dihalides from Aldehydes and Ketones

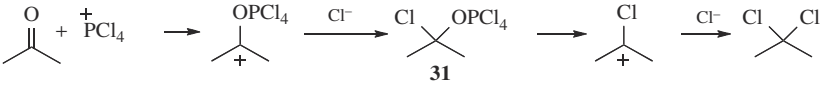
Dihalo-de-oxo-bisubstitution



Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides[432] by treatment with PCl_5. The reaction fails for perhalo ketones.[433] If the aldehyde or ketone has an α hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product, as shown,[434] or even the main product.[435] Phosphorus pentabromide (PBr_5) does not give good yields of *gem*-dibromides,[436] but these can be obtained from aldehydes, by the use of Br_2, and triphenyl phosphite.[437] *gem*-Dichlorides can be prepared by reacting an aldehyde with $BiCl_3$.[438]



The mechanism of *gem*-dichloride formation involves initial attack on PCl_4^+, which is present in solid PCl_5, by the carbonyl oxygen, followed by addition of Cl^- to the carbon:[439]



31

[427] Jochims, J.C. *Chem. Ber.* ***1968****, 101,* 1746.; Molina, P.; Alajarin, M.; Arques, A. *Synthesis* ***1982***, 596.
[428] Wong, R.; Dolman, S.J. *J. Org. Chem.* ***2007****, 72,* 3969.
[429] Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. *Org. Prep. Proceed. Int.* ***2000****, 32*, 571.
[430] Fournier, J.; Bruneau, C.; Dixneuf, P.H.; Lécolier, S. *J. Org. Chem.* ***1991****, 56,* 4456. See Chiarotto, I.; Feroci, M. *J. Org. Chem.* ***2003****, 68*, 7137; Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* ***2003****, 68*, 7289.
[431] Asanuma, Y.; Fujiwara, S.-i.; Shi-ike, T.; Kambe, N. *J. Org. Chem.* ***2004****, 69*, 4845.
[432] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 719–722.
[433] Farah, B.S.; Gilbert, E.E. *J. Org. Chem.* ***1965****, 30,* 1241.
[434] See Nikolenko, L.N.; Popov, S.I. *J. Gen. Chem. USSR* ***1962****, 32*, 29.
[435] See Newman, M.S.; Fraenkel, G.; Kirn, W.N. *J. Org. Chem.* ***1963****, 28*, 1851.
[436] See Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* ***1986***, 122.
[437] Hoffmann, R.W.; Bovicelli, P. *Synthesis* ***1990***, 657. See also, Lansinger, J.M.; Ronald, R.C. *Synth. Commun.* ***1979****, 9,* 341.
[438] Kabalka, G.W.; Wu, Z. *Tetrahedron Lett.* ***2000****, 41*, 579.
[439] Newman, M.S. *J. Org. Chem.* ***1969****, 34*, 741.

This chloride ion may come from PCl_6^-, which is also present in solid PCl_5. There follows a two-step S_N1 process. Alternatively, **31** can be converted to the product without going through the chlorocarbenium ion, by an S_Ni process.

This reaction has sometimes been performed on carboxylic esters, though these compounds very seldom undergo any addition to the C=O bond. An example is the conversion of $F_3CCOOPh$ to F_3CCCl_2OPh.[440] However, formates commonly give the reaction.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride (SF_4),[441] including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous HF.[442] Carboxylic acids, acyl chlorides, and amides react with SF_2 to give 1,1,1-trifluorides. In these cases, the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, but more vigorous conditions are required. In this case, the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from RCO_2R'[443] and then converted to the trifluoride. Anhydrides can react in either manner. Both types of intermediate are isolable under the right conditions, and SF_4 even converts CO_2 to CF_4. A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride (SeF_4) gives similar reactions, but atmospheric pressure and ordinary glassware can be used.[444] Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (**DAST**, Et_2NSF_3), and CF_2Br_2 in the presence of zinc.[445] The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5. Some dithianes can be converted to *gem*-difluorides with a mixture of fluorine and iodine in acetonitrile.[446] Oximes give *gem*-difluorides with $NO^+BF_4^-$ and pyridinium polyhydrogen fluoride.[447]

Treatment with hydrazine to give the hydrazone, and then $CuBr_2$/*t*-BuOLi, generated the *gem*-dibromide.[448] Oximes give *gem*-dichlorides upon treatment with chlorine and $BF_3{\cdot}OEt_2$, and then HCl.[449]

In a related process, α-halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. The addition of HX to an aldehyde or

[440] Clark, R.F.; Simons, J.H. *J. Org. Chem.* ***1961****, 26,* 5197.
[441] Wang, C.J. *Org. React.* ***1985****, 34*, 319; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974****, 21*, 1.
[442] Muratov, N.N.; Mohamed, N.M.; Kunshenko, B.V.; Burmakov, A.I.; Alekseeva, L.A.; Yagupol'skii, L.M. *J. Org. Chem. USSR* ***1985****, 21*, 1292.
[443] See Bunnelle, W.H.; McKinnis, B.R.; Narayanan, B.A. *J. Org. Chem.* ***1990****, 55*, 768.
[444] Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974****, 96,* 925.
[445] Hu, C.-M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 335.
[446] Chambers, R.D.; Sandford, G.; Atherton, M. *J. Chem. Soc., Chem. Commun.* ***1995***, 177.
[447] York, C.; Prakash, G.K.S.; Wang, Q.; Olah, G.A. *Synlett* ***1994***, 425.
[448] Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* ***1996***, 273.
[449] Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* ***1993****, 58*, 1939.

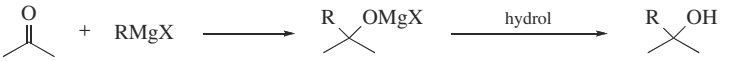
ketone gives α-halo alcohols, which are usually unstable, although exceptions are known, especially with perfluoro and perchloro species.[450]

OS **II**, 549; **V**, 365, 396, 1082; **VI**, 505, 845; **VIII**, 247. Also see, OS **I**, 506. For α-haloethers, see OS **I**, 377; **IV**, 101 (see, however, OS **V**, 218), 748; **VI**, 101.

F. Attack at Carbon by Organometallic Compounds[451]

16-24 The Addition of Grignard Reagents and Organolithium Reagents to Aldehydes and Ketones

***O*-Hydro-*C*-alkyl-addition**



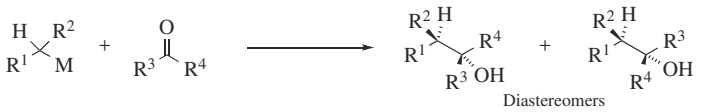
Organomagnesium compounds, commonly known as *Grignard reagents* (RMgX), are formed by the reaction of alkyl, vinyl, or aryl halides with magnesium metal, usually in ether solvents (e.g., diethyl ether or THF; Reaction **12-38**). Halogen–Mg exchange can generate a *Grignard reagent* by reaction of aryl halides with reactive aliphatic *Grignard reagents*.[452] Microwave irradiation has been used to facilitate the formation of *Grignard reagents* from aryl chlorides that are slow to react otherwise.[453]

The addition of *Grignard reagents* to aldehydes and ketones[454] is known as the *Grignard reaction.*[455] The initial product of reaction with a carbonyl is a magnesium alkoxide, requiring a hydrolysis step to generate the final alcohol product. Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope. In many cases, the hydrolysis step is carried out with dilute HCl or H_2SO_4, but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (Reaction **17-1**). In such cases (and often for other alcohols as well), an aqueous solution of ammonium chloride is used instead of a strong acid. *Grignard reagents* have been used in solid-phase synthesis.[456] Ionic liquids have been used for the *Grignard reaction*.[457]

Transition metal catalysts can promote 1,2-addition of Grignard reagents to ketones. A catalytic amount of Zn(II) compounds promote the reaction, for example.[458] In the presence of a catalytic amount of $InCl_3$, *Grignard reagents* react to give a mixture of 1,2- and 1,4-addition products with the 1,4-product predominating, but there was an increased 1,2-addition relative to the uncatalyzed reaction.[459]

[450] For example, see Clark, D.R.; Emsley, J.; Hibbert, F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1107.
[451] See Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vols. 2–4, Wiley, NY, ***1985–1987***.
[452] Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* ***2004****, 6,* 4905.
[453] Gold, H.; Larhed, M.; Nilsson, P. *Synlett* ***2005***, 1596.
[454] See Leung, S.S.-W.; Streitwieser, A. *J. Org. Chem.* ***1999****, 64*, 3390.
[455] See Eicher, T. in Patai, S. *The Chemistry of the Carbonyl Group,* pt. 1, Wiley, NY, ***1966***, pp. 621–693; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 138–528; Stowell, J.C. *Chem. Rev.* ***1984****, 84,* 409. For a computational study of this reaction, see Yamazaki, S.; Yamabe, S. *J. Org. Chem.* ***2002****, 67*, 9346.
[456] Franzén, R.G. *Tetrahedron* ***2000****, 56*, 685.
[457] Handy, S.T. J. Org. Chem. **2006**, 71, 4659.
[458] Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* ***2006****, 128,* 9998; Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* ***2010****, 75*, 5008; Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* ***2010***, 2674.
[459] Kelly, B.G.; Gilheany, D.G. *Tetrahedron Lett.* ***2002****, 43*, 887.

Diastereoselective addition[460] has been carried out with achiral reagents and chiral substrates,[461] similar to the reduction shown in Reaction **19-36**.[462] Because the attacking atom in this case is carbon, diastereoselective addition is possible with an achiral substrate and an optically active reagent.[463] The use of suitable reactants creates, in the most general case, two new stereogenic centers, so the product can exist as two pairs of enantiomers, as shown. Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.[464]



Asymmetric *Grignard reactions* are possible under certain circumstances.[465] Chiral ligands with a chiral Cu catalyst[466] or a chiral Ti complex[467] give alcohols with good enantioselectivity. An interesting method formed using an alkylmagnesium halide, dibutylmagnesium (Bu_2Mg) and a chiral diamine, and subsequent reaction with an aldehyde led to the alcohol derived from acyl addition of a butyl group with good enantioselectivity.[468] N-Heterocyclic carbenes have been used as organocatalysts for asymmetric *Grignard reactions*.[469] Aryl iodides undergo halogen–magnesium exchange when pretreated with PhMgCl, and subsequent reaction with an aldehyde gives the alcohol.[470]

The reaction of aldehydes or ketones with alkyl and aryl *Grignard reagents* was done in the earliest work without preliminary formation of RMgX, by mixing RX, the carbonyl compound, and magnesium metal in an ether solvent. This approach preceded Grignard's work, and is now known as the *Barbier reaction*.[471] The organolithium analogue of this process is also known.[472] Yields were generally satisfactory. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.[473] Modern versions of the

[460] Yamamoto, Y.; Maruyama, K. *Heterocycles* ***1982****, 18*, 357. Also see Tomoda, S.; Senju, T. *Tetrahedron* ***1999****, 55*, 3871. See Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. *J. Org. Chem.* ***2003****, 68*, 4546.

[461] See Reetz, M.T. *Angew. Chem. Int. Ed.* ***1984****, 23*, 556. See also, Keck, G.E.; Castellino, S. *J. Am. Chem. Soc.* ***1986****, 108,* 3847.

[462] See Soai, K.; Niwa, S.; Hatanaka, T. *Bull. Chem. Soc. Jpn.* ***1990****, 63,* 2129. Also see Hoffmann, R.W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* ***1988****, 121*, 2225; Paquette, L.A.; Learn, K.S.; Romine, J.L.; Lin, H. *J. Am. Chem. Soc.* ***1988****, 110*, 879; Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* ***1989****, 54,* 1570.

[463] See Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* ***1984****, 106*, 7970. See Greeves, N.; Pease, J.E. *Tetrahedron Lett.* ***1996****, 37,* 5821; Zweifel, G.; Shoup, T.M. *J. Am. Chem. Soc.* ***1988****, 110,* 5578.

[464] See Masuyama, Y.; Takahara, J.P.; Kurusu, Y. *Tetrahedron Lett.* ***1989****, 30,* 3437.

[465] Luderer, M.R.; Bailey, W.F.; Luderer, M.R.; Fair, J.D.; Dancer, R.J.; Sommer, M.B. *Tetrahedron Asymm.* ***2009****, 20*, 981.

[466] Cotton, H.K.; Norinder, J.; Bäckvall, J.-E. *Tetrahedron* ***2006****, 62,* 5632; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* ***2005****, 44,* 4435; López, F.; van Zijl, A.W.; Minnaard, A.J.; Feringa, B.L. *Chem. Commun.* ***2006***, 409.

[467] Muramatsu, Y.; Harada, T. *Angew. Chem. Int. Ed.* ***2008****, 47,* 1088.

[468] Yong, K.H.; Taylor, N.J.; Chong, J.M. *Org. Lett.* ***2002****, 4*, 3553.

[469] Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem. Int. Ed.* ***2010****, 49,* 3037.

[470] Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* ***2005****, 70,* 2445.

[471] Barbier, P. *Compt. Rend.,* ***1899****, 128,* 110. See Blomberg, C.; Hartog, F.A. *Synthesis* ***1977***, 18; Molle, G.; Bauer, P. *J. Am. Chem. Soc.* ***1982****, 104,* 3481. For a list of Barbier-type reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1125–1134.

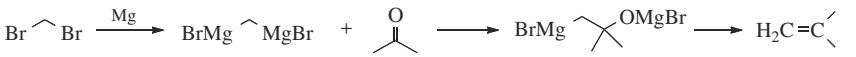
[472] Guijarro, A.; Yus, M. *Tetrahedron Lett.* ***1993****, 34*, 3487; de Souza-Barboza, J.D.; Pétrier, C.; Luche, J. *J. Org. Chem.* ***1988****, 53,* 1212.

[473] Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* ***1988****, 29*, 3887.

Barbier reaction employ other metals and/or reaction conditions, and will be discussed in Reaction **16-25**. However, Mg–*Barbier reactions* are catalyzed by other metal complexes (e.g., Cu compounds).[474] Some transition metal compounds are stable in water, so some *Grignard–Barbier reactions* can be done in water.[475] A retro-*Barbier reaction* has been reported in which a cyclic tertiary alcohol was treated to an excess of bromine and potassium carbonate to give 6-bromo-2-hexanone from 1-methylcyclopentanol.[476]

The reaction of RMgX or RLi with α,β-unsaturated aldehydes or ketones can proceed via 1,4-addition as well as normal 1,2-addition (see *Michael addition* in Reaction **15-25**).[477] In general, alkyllithium reagents give less 1,4 addition than the corresponding *Grignard reagents*.[478] In a compound containing both an aldehyde and a ketone, it is possible to add RMgX chemoselectively to the aldehyde without significantly disturbing the carbonyl of the ketone group[479] (see also, Reaction **16-24**). *Grignard reagents* have been shown to add to some conjugated cyclic ketones with an α,β-OTf group via 1,2-addition, followed by cleavage to give an alkynyl ketone.[480]

In some cases, a *Grignard reaction* can be performed intramolecularly.[481] For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.[482] Other four- and five-membered ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a δ- or ε-halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenyporphine[483] (see Reaction 16-25).



The gem-disubstituted Mg compounds formed from CH_2Br_2 or CH_2I_2 (Reaction **12-38**) react with aldehydes or ketones to give alkenes in moderate-to-good yields.[484] *Wittig-type reactions* also produce alkenes and are discussed in Reaction **16-44**. The reaction could not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium also have produced alkenes.[485]

Organolithium reagents (RLi), prepared from alkyl halides and Li metal or by exchange of an alkyl halide with a reactive organolithium (Reaction **12-38**) react with aldehydes and ketones by acyl addition to give the alcohol,[486] after hydrolysis. Organolithium reagents are more basic than the corresponding *Grignard reagent*, which leads to problems of

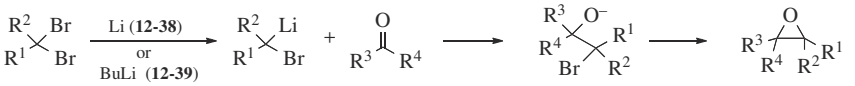
[474] Erdik, E.; Koçoğlu, M. *Tetrahedron Lett.* ***2007****, 48,* 4211.
[475] Li, C.-J. *Tetrahedron* ***1996****, 52*, 5643.
[476] Zhang, W.-C.; Li, C.-J. *J. Org.Chem.* ***2000****, 65*, 5831.
[477] For a discussion of the mechanism of this reaction, see Holm, T. *Acta Chem. Scand.* ***1992****, 46*, 985.
[478] An example was given in Reaction **15-25**.
[479] Vaskan, R.N.; Kovalev, B.G. *J. Org. Chem. USSR* ***1973****, 9,* 501.
[480] Kamijo, S.; Dudley, G.B. *J. Am. Chem. Soc.* ***2005****, 127,* 5028.
[481] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1134–1135.
[482] Leroux, Y. *Bull. Soc. Chim. Fr.* ***1968***, 359.
[483] Corey, E.J.; Kuwajima, I. *J. Am. Chem. Soc.* ***1970****, 92*, 395. For another method, see Molander, G.A.; McKie, J. A. *J. Org. Chem.* ***1991****, 56*, 4112, and references cited therein.
[484] Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G.*Tetrahedron* ***1970****, 26,* 1281.
[485] See Piotrowski, A.M.; Malpass, D.B.; Boleslawski, M.P.; Eisch, J.J. *J. Org. Chem.* ***1988****, 53,* 2829; Tour, J.M.; Bedworth, P.V.; Wu, R. *Tetrahedron Lett.* ***1989****, 30,* 3927; Lombardo, L. *Org. Synth. 65*, 81.
[486] For a study of *Hammett* ρ values, see Maclin, K.M.; Richey, Jr., H.G. *J. Org. Chem.* ***2002****, 67*, 4370.

deprotonation in some cases. Organolithium reagents are generally more nucleophilic, however, and can add to hindered ketones with relative ease when compared to the analogous *Grignard reagent*.[487] These reagents tend to form aggregates, which influences the reactivity and selectivity of the addition reaction.[488] The addition of lithium amide–butyllithium mixed aggregates has been studied.[489]

Alkyl, vinyl,[490] and aryl organolithium reagents can be prepared and undergo acyl addition. Structural variations are also possible, including enantioselective 1,2-addition.[491] 1-Bromo-1-lithioethene was prepared, and reacts with an aldehyde to give an allylic alcohol bearing a vinyl bromide unit.[492] An interesting variation of the fundamental acyl addition reaction of organolithium reagents treated an aldehyde with an acyl-lithio amide [LiC(=O)N(Me)CH_2Me] to give an α-hydroxy amide derivative.[493]

As with the reduction of aldehydes and ketones (Reaction **19-36**), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.[494] Chiral secondary alcohols have been obtained with high enantioselectivity by addition of *Grignard* and organolithium compounds to aromatic aldehydes, in the presence of optically active amino alcohols as ligands.[495]

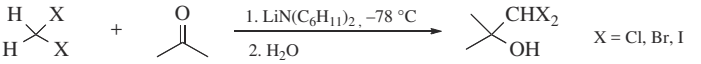
An interesting variation is the reaction of methyllithium and CH_2I_2 with an aliphatic aldehyde to give an epoxide.[496] A lithio-epoxide was formed by treating an epoxide with *sec*-butyllithium in the presence of sparteine,[497] or with *n*-butyllithium/TMEDA,[498] and subsequent reaction with an aldehyde led to an epoxy alcohol. Alkylidene oxetanes react with lithium, and then with an aldehyde to give a conjugated ketone.[499] The reaction of *gem*-dihalides with a carbonyl compound and Li or BuLi give epoxides[500] (see also, Reaction **16-46**).



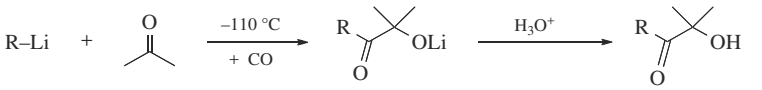
In other uses of *gem*-dihalo compounds, aldehydes and ketones add the CH_2I group [$R_2CO \rightarrow R_2C(OH)CH_2I$] when treated with CH_2I_2 in the presence of SmI_2,[501] and the

[487] Lecomte, V.; Stéphan, E.; Le Bideau, F.; Jaouen, G. *Tetrahedron* ***2003****, 59*, 2169.
[488] See Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* ***2002****, 58*, 4717.
[489] Liu, J.; Li, D.; Sun, C.; Williard, P.G. *J. Org. Chem.* ***2008****, 73*, 4045.
[490] For a discussion of selectivity, see Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* ***2002****, 4,* 4735.
[491] Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron Asymmetry* ***2006****, 17,* 2021.
[492] Novikov, Y.Y.; Sampson, P. *J. Org. Chem.* ***2005****, 70*, 10247.
[493] Cunico, R.F. *Tetrahedron Lett.* ***2002****, 43*, 355.
[494] See Solladié, G. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 157–199, 158–183; Nógrádi, M. *Stereoselective Synthesis* VCH, NY, ***1986***, pp. 160–193; Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* ***1991****, 30*, 49.
[495] Schön, M.; Naef, R. *Tetrahedron Asymmetry* ***1999****, 10*, 169; Arvidsson, P.I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron Asymmetry* ***1999****, 10*, 527.
[496] Concellón, J.M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* ***2001****, 57*, 8983.
[497] Hodgson, D.M.; Reynolds, N.J.; Coote, S.J. *Org. Lett.* ***2004****, 6*, 4187.
[498] Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* ***2004****, 6*, 4191.
[499] Hashemsadeh, M.; Howell, A.R. *Tetrahedron Lett.* ***2000****, 41*, 1855, 1859.
[500] Cainelli, G.; Tangari, N.; Umani-Ronchi, A. *Tetrahedron* ***1972****, 28,* 3009, and references cited therein.
[501] Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* ***1986****, 27*, 3243.

CHX_2 group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.[502]

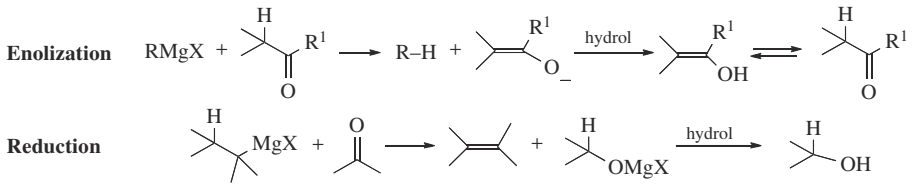


It is possible to add an acyl group to a ketone to give (after hydrolysis) an α-hydroxy ketone.[503] This can be done by adding RLi and CO to the ketone at −110 °C:[504]



When the same reaction is carried out with carboxylic esters ($R'COOR^2$), α-diketones ($RCOCOR'$) are obtained.[503]

Most aldehydes and ketones react with most *Grignard reagents*, but there are several potential side reactions[505] that occur mostly with hindered ketones and with bulky *Grignard reagents*. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α hydrogen, and the latter requires that the *Grignard reagent* have a β hydrogen:



Enolization is an acid–base reaction (**12-24**) in which a proton is removed from the α carbon by the *Grignard reagent*, which is a strong base. The carbonyl compound is converted to its enolate anion, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol (e.g., β-keto esters).

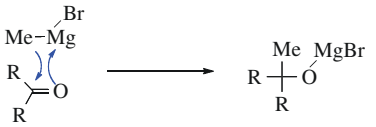
The carbonyl compound can be reduced to an alcohol (Reaction **16-24**) by the *Grignard reagent*, which itself undergoes elimination to give an alkene. The *Grignard reagent* must have a β-carbon that bears a hydrogen atom.

Two other side reactions are condensation (between enolate ion and excess ketone) and *Wurtz-type coupling* (**10-64**). Addition of *Grignard reagents* to ketones cannot be used to prepare highly hindered tertiary alcohols (e.g., triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol) or they can be prepared only in extremely low yields, because reduction and/or enolization become prominent.[506] However, these alcohols can

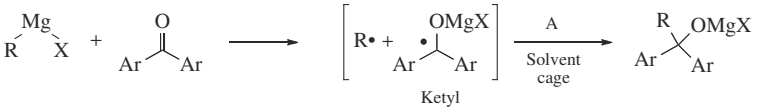
[502] Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977****, 50,* 1588.
[503] See Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C.; Archer, C.M. *Isr. J. Chem.* ***1984****, 24,* 167.
[504] Seyferth, D.; Weinstein, R.M.; Wang, W. *J. Org. Chem.* ***1983****, 48*, 1144; Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C. *Tetrahedron Lett.* ***1983****, 24,* 4907.
[505] Lajis, N. Hj.; Khan, M.N.; Hassan, H.A. *Tetrahedron* ***1993****, 49*, 3405.
[506] Whitmore, F.C.; George, R.S. *J. Am. Chem. Soc.* ***1942****, 64,* 1239.

be prepared by the use of alkyllithium reagents at –80 °C[507] because enolization and reduction are much less important.[508] Other methods of increasing the degree of addition at the expense of reduction include complexing the *Grignard reagent* with $LiClO_4$ or $Bu_4N^+Br^-$,[509] or using benzene or toluene instead of ether as solvent.[510] Both reduction and enolization can be avoided by adding $CeCl_3$ to the *Grignard reagent*.[511]

There has been controversy regarding the mechanism of addition of *Grignard reagents* to aldehydes and ketones.[512] The reaction is difficult to study because of the variable nature of the species present in the *Grignard* solution (Sec. 5.B.ii) and because the presence of small amounts of impurities in the Mg seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.[513] There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair. A detailed mechanism of this type has been proposed by Ashby *et al.*,[514] based on the discovery that this reaction proceeds by two paths: one first order in MeMgBr and the other first order in Me_2Mg.[515] According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl carbon, though the exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[516]



The other type of mechanism is a SET process[517] with a ketyl intermediate:[518]



This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for strictly aliphatic ones.

[507] Bartlett P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968****, 90,* 4421. See also, Lomas, J.S. *Nouv. J. Chim.,* ***1984****, 8*, 365; Molle, G.; Briand, S.; Bauer, P.; Dubois, J.E. *Tetrahedron* ***1984****, 40*, 5113.

[508] Buhler, J.D. *J. Org. Chem.* ***1973****, 38,* 904.

[509] Chastrette, M.; Amouroux, R. *Chem. Commun.* ***1970***, 470; *Bull. Soc. Chim. Fr.* ***1970***, 4348. See also, Richey, Jr., H.G.; DeStephano, J.P. *J. Org. Chem.* ***1990****, 55,* 3281.

[510] Canonne, P.; Foscolos, G.; Caron H.; Lemay, G. *Tetrahedron* ***1982****, 38,* 3563.

[511] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* ***1989****, 111*, 4392.

[512] See Holm, T. *Acta Chem. Scand. Ser. B* ***1983****, 37,* 567; Ashby, E.C. *Pure Appl. Chem.* ***1980****, 52*, 545; Ashby, E. C.; Laemmle, J.; Neumann, H.M. *Acc. Chem. Res.* ***1974****, 7,* 272. Also see Ashby, E.C.; Laemmle, J. *Chem. Rev.* ***1975****, 75*, 521; Solv'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987****, 56*, 465.

[513] See, for example, Ashby, E.C.; Neumann, H.M.; Walker, F.W.; Laemmle, J.; Chao, L. *J. Am. Chem. Soc.* ***1973****, 95*, 3330.

[514] Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1972****, 94*, 5421.

[515] Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971****, 93*, 4601; Laemmle, J.; Ashby, E.C.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971****, 93,* 5120.

[516] Ashby, E.C.; Yu, S.H.; Roling, P.V. *J. Org. Chem.* ***1972****, 37*, 1918. See also, Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M.L. *Tetrahedron* ***1980****, 36,* 3403.

[517] For a review, see Dagonneau, M. *Bull. Soc. Chim. Fr.* ***1982***, II-269.

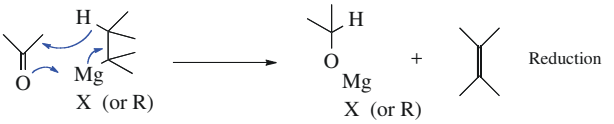
[518] See Walling, C. *J. Am. Chem. Soc.* ***1988****, 110*, 6846.

Among the evidence[519] for the SET mechanism are ESR spectra[520] and the fact that $Ar_2C(OH)C(OH)Ar_2$ side products are obtained (from dimerization of the ketyl; see *pinacol coupling* in Reaction **19-76**).[521] In the case of addition of RMgX to benzil (PhCOCOPh), ESR spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.[522] Note that a separate study failed to observe freely defusing radicals in the formation of *Grignard reagents*.[523] Carbon isotope effect studies with $Ph^{14}COPh$ showed that the rate-determining step with most *Grignard reagents* is the carbon–carbon bond-forming step (marked *A*), although it is the initial electron-transfer step with allylmagnesium bromide.[524] In the formation of *Grignard reagents* from bromocyclopropane, diffusing cyclopropyl radical intermediates were found.[525] The concerted versus stepwise mechanism has been probed with chiral *Grignard reagents*.[526]

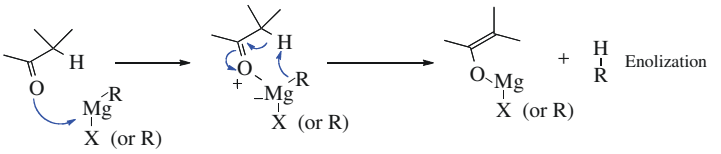
Note that there are similarities in reactivity for the $S_{RN}1$ (see Sec. 13.A.iv) and *Grignard mechanisms*.[527] Experimental evidence from this work suggests a linear rather than a chain mechanism.

Mechanisms for the addition of organolithium reagents have been investigated much less.[528] Addition of a cryptand that binds Li^+ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.[529]

There is general agreement that the mechanism leading to reduction[530] is usually as follows:



There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:[531]



[519] Also see Holm, T. *Acta Chem. Scand. Ser. B* ***1988****, 42*, 685; Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* ***1983****, 105*, 2922; Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1991****, 56*, 2573.

[520] Maruyama, K.; Katagiri, T. *Chem. Lett.* ***1987***, 731, 735; *J. Phys. Org. Chem.* ***1988****, 1*, 21.

[521] See Holm, T.; Crossland, I. *Acta Chem. Scand.* ***1971****, 25*, 59.

[522] Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* ***1986****, 108,* 6263; *J. Phys. Org. Chem.* ***1989****, 2,* 205. See also, Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* ***1991****, 4,* 158.

[523] Walter, R.I. *J. Org. Chem.* ***2000****, 65*, 5014.

[524] Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* ***1989****, 111*, 4912.

[525] Garst, J.F.; Ungváry, F. *Org. Lett.* ***2001****, 3*, 605.

[526] Hoffmann, RW.; Hölzer, B. *Chem. Commun.* ***2001***, 491.

[527] Bodineau, N.; Mattalia, J.-M.; Hazimeh, H.; Handoo, K.L.; Timokhin, V.; Négrel, J.-C.; Chanon, M. *Eur. J. Org. Chem.* ***2010***, 2476.

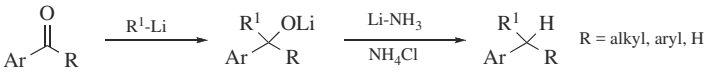
[528] See Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1989****, 54,* 4706.

[529] Perraud, R.; Handel, H.; Pierre, J. *Bull. Soc. Chim. Fr.* ***1980***, II-283.

[530] See Cabaret, D.; Welvart, Z. *J. Organomet. Chem.* ***1974****, 80*, 199; Holm, T. *Acta Chem. Scand.* ***1973****, 27,* 1552; Morrison, J.D.; Tomaszewski, J.E.; Mosher, H.S.; Dale, J.; Miller, D.; Elsenbaumer, R.L. *J. Am. Chem. Soc.* ***1977****, 99*, 3167; Okuhara, K. *J. Am. Chem. Soc.* ***1980****, 102,* 244.

[531] Pinkus, A.G.; Sabesan, A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 273.

Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.[532]

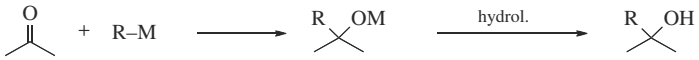


A similar reaction has been carried out with *N,N*-disubstituted amides: $RCONR_2' \rightarrow RR^2CHNR_2'$.[533]

OS **I**, 188; **II**, 406, 606; **III**, 200, 696, 729, 757; **IV**, 771, 792; **V**, 46, 452, 608, 1058; **VI**, 478, 537, 542, 606, 737, 991, 1033; **VII**, 177, 271, 447; **VIII**, 179, 226, 315, 343, 386, 495, 507, 556; **IX**, 9, 103, 139, 234, 306, 391, 472; **75**, 12; **76**, 214; **X**, 200.

16-25 Addition of Other Organometallics to Aldehydes and Ketones

O **-Hydro-*C*-alkyl-addition**



A variety of organometallic reagents other than RMgX and RLi add to aldehydes and ketones. A simple example is formation of Na, or K alkyne anions (e.g., RC≡C-M, Reaction **16-38**), which undergo acyl addition to ketones or aldehydes to give the propargylic alcohol.[534] In the reaction with terminal acetylenes,[535] sodium acetylides are the most common reagents (when they are used, While Na is the metal of choice for the addition of acetylenic groups, vinylic alanes (prepared as in Reaction **15-17**) are the reagents of choice for the addition of vinylic groups.[536] The reagent $Me_3Al/^{-}C{\equiv}CH\ Na^{+}$ also adds to aldehydes to give the ethynyl alcohol.[537] A solvent-free reaction was reported that mixed a ketone, a terminal alkyne and potassium *tert*-butoxide.[538] The reaction is often called the *Nef reaction*, but Li,[539] Mg, and other metallic acetylides have also been used. A particularly convenient reagent is the lithium acetylide–ethylenediamine complex,[540] a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of a base, so that the acetylide is generated *in situ*. This procedure is called the *Favorskii reaction*, not to be confused with the *Favorskii rearrangement* (**18-7**).[541] Zinc(II) chloride facilitates the addition of a terminal alkyne to an aldehyde to give a propargylic alcohol.[542] Zinc(II) triflate can also be

[532] Lipsky, S.D.; Hall, S.S. *Org. Synth.* ***VI***, 537; McEnroe, F.J.; Sha, C.; Hall, S.S. *J. Org. Chem.* ***1976****, 41*, 3465.
[533] Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* ***1985****, 50,* 3885.
[534] See Guillarme, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* ***2006****, 106,* 2355.
[535] Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 207–241; Ried, W. *Newer Methods Prep. Org. Chem.* ***1968****, 4,* 95.
[536] Newman, H. *Tetrahedron Lett.* ***1971***, 4571. See Jacob, III, P.; Brown, H.C. *J. Org. Chem.* ***1977****, 42*, 579.
[537] Joung, M.J.; Ahn, J.H.; Yoon, N.M. *J. Org. Chem.* ***1996****, 61*, 4472.
[538] Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 185.
[539] See Midland, M.M. *J. Org. Chem.* ***1975****, 40,* 2250, for the use of amine-free monolithium acetylide.
[540] Beumel Jr., O.F.; Harris, R.F. *J. Org. Chem.* ***1963****, 28,* 2775.
[541] See Kondrat'eva, L.A.; Potapova, I.M.; Grigina, I.N.; Glazunova, E.M.; Nikitin, V.I. *J. Org. Chem. USSR* ***1976****, 12*, 948.
[542] Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2002****, 43*, 8323

used for alkyne addition to aldehydes,[543] and in the presence of a chiral ligand leads to good enantioselectivity in the propargyl alcohol product.[544]

The reagents Et_3Al, Et_2Zn, and a terminal alkyne react with ketones, and in the presence of a cinchona alkaloid gives the alkynyl alcohol in moderate ee.[545] Other enantioselective alkynylation reactions are known using various catalysts.[546] Terminal alkynes add to aryl aldehydes in the presence of $InBr_3$ and NEt_3,[547] SmI_2,[548] or Me_2Zn.[549] A Zn mediated reaction using iodoalkynes is known.[550] Catalytically generated zinc acetylides add to aldehydes.[551] An In catalyzed addition of alkynes to aldehydes used a catalytic amount of BINOL and gave the alkynyl alcohol with high enantioselectivity.[552] Other enantioselective addition reactions of terminal alkynes are known.[553] The reaction with In is compatible with the presence of a variety of other functional groups in the molecule, including phosphonate,[554] propargylic sulfides.[555]

Many organometallic reagents have been reported for the addition of allylic groups,[556] and there are enantioselective reactions.[557] One of the most common methods is the *Barbier reaction* noted in Reaction **16-24**, which includes metals and metal compounds other than Mg or Li, although the method is not limited to allylic compounds. Common reagents are allylic In compounds,[558] which add to aldehydes or ketones in various solvents,[559] Enantioselective In mediated *Barbier reactions* are known.[560] Indium reacts with allylic bromides and ketones in water[561] and in aqueous media. The reaction of a

[543] Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***2000****, 122*, 1806.

[544] Boyall, D.; Frantz, D.E.; Carreira, E.M. *Org. Lett.* ***2002****, 4*, 2605.; Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* ***2004****, 6*, 1193; Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* ***2002***, 1524. For an example using zinc(II) diflate, see Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* ***2002***, 2098.

[545] Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* ***2005****, 70*, 1084.

[546] See Li, H.; Huang, Y.; Jin, W.; Xue, F.; Wan, B. *Tetrahedron Lett.* ***2008****, 49,* 1686; Mao, J.; Bao, Z.; Guo, J.; Ji, S. *Tetrahedron* ***2008****, 64,* 9901; Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron Asymmetry* ***2007****, 18,* 2668.

[547] Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* ***2003****, 44*, 4171.

[548] Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2001***, 627.

[549] Wolf, C.; Liu, S. *J. Am. Chem. Soc.* ***2006****, 128,* 10996; Cozzi, P.G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* ***2005****, 70,* 5733.

[550] Srihari, P.; Singh, V.K.; Bhunia, D.C.; Yadav, J.S. *Tetrahedron Lett.* ***2008****, 49*, 7132.

[551] Downey, C.W.; Mahoney, B.D.; Lipari, V.R. *J. Org. Chem.* ***2009****, 74,* 2904.

[552] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005****, 127*, 13760.

[553] Ekström, J.; Zaitsev, S.B.; Adolfsson, H. *Synlett* ***2006***, 885.

[554] Ranu, B.C.; Samanta, S.; Hajra, A. *J. Org. Chem.* ***2001****, 66*, 7519.

[555] Mitzel, T.M.; Palomo, C.; Jendza, K. *J. Org. Chem.* ***2002****, 67*, 136.

[556] For a list of reagents and references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1156–1170. Also see Gajewski, J.J.; Bocian, W.; Brichford, N.L.; Henderson, J.L. *J. Org. Chem.* ***2002****, 67*, 4236.

[557] See Denmark, S.E.; Fu, J. *Chem. Rev.* ***2003****, 103*, 2763.

[558] For a review, see Cintas, P. *Synlett* ***1995***, 1087.

[559] Yi, X.-H.; Haberman, J.X.; Li, C.-J. *Synth. Commun.* ***1998****, 28*, 2999; Lloyd-Jones, G.C.; Russell, T. *Synlett* ***1998***, 903; Li, C.-J.; Lu, Y.-Q. *Tetrahedron Lett.* ***1995****, 36*, 2721.

[560] Hirayama, L.C.; Gamsey, S.; Knueppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* ***2005****, 46,* 2315; Haddad, T.D.; Hirayama, L.C.; Taynton, P.; Singaram, B. *Tetrahedron Lett.* ***2008****, 49,* 508; Preite, M.D.; Pérez-Carvajal, A. *Synlett* ***2006***, 3337. For an example in ionic liquids, see Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* ***2005****, 46,* 4573. For an example with propargylic halides, see Lacie, C. Hirayama, L.C.; Dunham, K.K.; Singaram, B. *Tetrahedron Lett.* ***2006****, 47,* 5173.

[561] Chan, T.H.; Yang, Y. *J. Am. Chem. Soc.* ***1999****, 121*, 3228; Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* ***1998****, 63*, 1836; Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* ***1996****, 7*, 1535.

propargyl halide, In, and an aldehyde in aq THF leads to an allenic alcohol.[562] When allyl iodide is mixed with In and TMSCl, reaction with a conjugated ketone proceed by 1,4-addition, but in the presence of 10% CuI, the major product is that of 1,2-addition.[563] Allyl bromide reacts with Mn/TMSCl and an In catalyst in water to give the homoallylic alcohols from aldehydes.[564] Indium metal is used for the acyl addition of allylic halides with a variety of aldehydes and ketones, including aliphatic aldehydes,[565] aryl aldehydes,[566] and α-keto esters.[567] Elimination of the homoallylic alcohol to a conjugated diene can accompany the addition in some cases.[568]

Allyl bromide reacts with a ketone and Sm[569] or SmI_2,[570] to give the homoallylic alcohol. Other metals can be used with allylic halides to give homoallylic alcohols from aldehydes or ketones,[571], including Zn,[572] La,[573] or Mg-Cd[574] and compounds of Ti,[575] Mn,[576] Fe,[577] Ga,[578] Ge,[579] Zr,[580] Nb,[581] Cd,[582] Sb,[583] Te,[584] Ba,[585] Ce,[586] Nd,[587] Hg,[588] Bi,[589] In,[590] and Pb.[591]

[562] Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003****, 125*, 13042.
[563] Lee, P.H.; Ahn, H.; Lee. K.; Sung, S.-y.; Kim, S. *Tetrahedron Lett.* ***2001****, 42*, 37.
[564] Augé, J.; Lubin-Germain, N.; Thiaw-Woaye, A. *Tetrahedron Lett.* ***1999****, 40*, 9245.
[565] Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* ***2001****, 42*, 8701.
[566] Khan, F.A.; Prabhudas, B. *Tetrahedron* ***2000****, 56*, 7595.
[567] Kumar, S.; Kaur, P.; Chimni, S.S. *Synlett* ***2002***, 573.
[568] Kumar, V.; Chimni, S.; Kumar, S. *Tetrahedron Lett.* ***2004****, 45,* 3409.
[569] Basu, M.K.; Banik, B.K. *Tetrahedron Lett.* ***2001****, 42*, 187.
[570] Hélion, F.; Namy, J.-L. *J. Org. Chem.* ***1999****, 64*, 2944.
[571] See Knochel, P.; Rao, S.A. *J. Am. Chem. Soc.* ***1990****, 112,* 6146; Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn.* ***1990****, 63*, 1738; Marton, D.; Tagliavini, G.; Zordan, M.; Wardell, J.L. *J. Organomet. Chem.* ***1990****, 390,* 127; Wang, W.; Shi, L.; Xu, R.; Huang, Y. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 424.
[572] Wang, J.-x.; Jia, X.; Meng, T.; Xin, L. *Synthesis* ***2005***, 2838.
[573] In water: Bian, Y.-J.; Zhang, J.-Q.; Xia, J.-P.; Li, J.-T. *Synth. Commun.* ***2006****, 36*, 2475.
[574] Narsaiah, A.V.; Reddy, A.R.; Rao, Y.G.; Kumar, E.V.; Prakasham, R.S.; Reddy, B.V.S.; Yadav, J.S. *Synthesis* ***2008***, 3461.
[575] See Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* ***2005***, 775; Estévez, R.E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J.M.; Robles, R.; Gansäuer, A.; Cuerva, J.M.; Oltra, J.E. *Chemistry: Eur. J.* ***2009****, 15*, 2774.
[576] Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2001****, 57*, 8807; Berkessel, A.; Menche, D.; Sklorz, C.A.; Schröder, M.; Paterson, I. *Angew. Chem. Int. Ed.* ***2003****, 42*, 1032.
[577] Chan, T.C.; Lau, C.P.; Chan, T.H. *Tetrahedron Lett.* ***2004****, 45*, 4189.
[578] Wang, Z.; Yuan, S.; Li, C.-J. *Tetrahedron Lett.* ***2002****, 43*, 5097.
[579] Hashimoto, Y.; Kagoshima, H.; Saigo, K. *Tetrahedron Lett.* ***1994****, 35*, 4805.
[580] Hanzawa, Y.; Tabuchi, N.; Saito, K.; Noguchi, S.; Taguchi, T. *Angew. Chem. Int. Ed.* ***1999****, 38*, 2395.
[581] Andrade, C.K.Z.; Azevedo, N.R.; Oliveira, G.R. *Synthesis* ***2002***, 928.
[582] Zheng, Y.; Bao, W.; Zhang, Y. *Synth. Commun.* ***2000****, 30*, 3517.
[583] Li, L.-H.; Chan, T.H. *Can. J. Chem.* ***2001****, 79*, 1536.
[584] See Avilov, D.V.; Malasare, M.G.; Arslancan, E.; Dittmer, D.L. *Org. Lett.* ***2004****, 6*, 2225.
[585] Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1994****, 116,* 6130.
[586] Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* ***1999****, 40*, 9115.
[587] Evans, W.J.; Workman, P.S.; Allen, N.T. *Org. Lett.* ***2003****, 5*, 2041.
[588] Chan, T.H.; Yang, Y. *Tetrahedron Lett.* ***1999****, 40*, 3863.
[589] Smith, K.; Lock, S.; El-Hiti, G.A.; Wada, M.; Miyoshi, N. *Org. Biomol. Chem.* ***2004****, 2*, 935; Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* ***2004***, 1171.
[590] Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* ***2005***, 1010; Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* ***2005***, 1318; Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* ***2005***, 4217; Masuyama, Y.; Chiyo, T.; Kurusu, Y. *Synlett* ***2005***, 2251.
[591] Zhou, J.-Y.; Jia, Y.; Sun, G.-F.; Wu, S.-H. *Synth. Commun.* ***1997****, 27*, 1899.

In addition, $BiCl_3/NaBH_4$,[592] Mg—$BiCl_3$,[593] and $CrCl_2/NiCl_2$,[594] have been used. Allylic alcohols have been converted to organometallic reagents with diethylzinc and a Pd[595] or a Ru catalyst,[596] leading to the homoallylic alcohol upon reaction with an aldehyde. Allylic acetates add to aldehydes in the presence of a Ru catalyst.[597]

Enantioselective reactions are known.[598] A Cu catalyzed reaction is known that proceeds with good enantioselectivity.[599] Allylzinc bromide adds to aldehydes under solvent-free conditions.[600] A chiral Cr–Mn complex has been used with allylic bromides in conjunction with trimethylsilyl chloride.[601] Reagents of the type R—Yb have been prepared from RMgX.[602] The alkyl group of trialkyl aluminum compounds (e.g., $AlEt_3$) add to aldehydes, enantioselectively in the presence of chiral transition metal complexes.[603] Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in the presence of ketones.[604] Organomanganese compounds are also chemoselective in this way.[605] In a related reaction, organocerium reagents, generated from cerium chloride ($CeCl_3$ and a *Grignard reagent* or an organolithium reagent) gives an organometallic reagent that adds chemoselectively.[606] Aryl halides that have a pendant ketone unit react with a Pd catalyst to give cyclization via acyl addition.[607]

As noted in Reaction **16-24**, enolate formation and reduction complicate some *Grignard reactions*. One way to avoid complications is to add $(RO)_3TiCl$, $TiCl_4$,[608] $(RO)_3ZrCl$, or $(R_2N)_3TiX$ to the *Grignard* or organolithium reagent. This produces organotitanium or organozirconium compounds that are much more selective than *Grignard* or organolithium reagents.[609] An important advantage of these reagents is that they do not react with NO_2 or CN functions that may be present in the substrate, as *Grignard* and organolithium reagents do. The reaction of a β-keto amide with $TiCl_4$, for example, gives a complex that allows selective reaction of the ketone unit with MeMgCl—$CeCl_3$ to give the corresponding alcohol.[610] Premixing an allylic *Grignard reagent* with $ScCl_3$ prior to reaction with the

[592] Ren, P.-D.; Shao, D.; Dong, T.-W. *Synth. Commun.* ***1997****, 27*, 2569.
[593] Wada, M.; Fukuma, T.; Morioka, M.; Takahashi, T.; Miyoshi, N. *Tetrahedron Lett.* ***1997****, 38*, 8045.
[594] Taylor, R.E.; Ciavarri, J.P. *Org. Lett.* ***1999****, 1*, 467.
[595] Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***2003****, 42*, 3392.
[596] Wang, M.; Yang, X.-F.; Li, C.-J. *Eur. J. Org. Chem.* ***2003***, 998.
[597] Denmark, S.E.; Nguyen, S.T. *Org. Lett.* ***2009****, 11*, 781.
[598] Appelt, H.R.; Limberger, J.B.; Weber, M.; Rodrigues, O.E.D.; Oliveira, J.S.; Lüdtke, D.S.; Braga, A.L. *Tetrahedron Lett.* ***2008****, 49,* 4956.
[599] Fandrick, D.R.; Fandrick, K.R.; Reeves, J.T.; Tan, Z.; Tang, W.; Capacci, A.G.; Rodriguez, S.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *J. Am. Chem. Soc.* ***2010****, 132,* 7600.
[600] Zhang, Y.; Jia, X.; Wang, J.-X. *Eur. J. Org. Chem.* ***2009***, 2983.
[601] Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* ***2003****, 125*, 1140.
[602] Matsubara, S.; Ikeda, T.; Oshima, K.; Otimoto, K. *Chem. Lett.* ***2001***, 1226.
[603] Lu, J.-F.; You, J.-S.; Gau, H.-M. *Tetrahedron Asymmetry* ***2000****, 11*, 2531.
[604] Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986*** (monograph), pp. 75–86. See also, Kim, S.-H.; Rieke, R.D. *Tetrahedron Lett.* ***1999****, 40*, 4931.
[605] Cahiez, G.; Figadere, B. *Tetrahedron Lett.* ***1986****, 27*, 4445. See Soai, K.; Watanabe, M.; Koyano, M. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 2124.
[606] Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem. Int. Ed.* ***1993****, 32*, 1061; Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* ***1994****, 35*, 6713.
[607] Quan, L.G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000****, 122*, 4827.
[608] See Reetz, M.T.; Kyung, S.H.; Hüllmann, M. *Tetrahedron* ***1986****, 42,* 2931.
[609] Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986***. See Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed.* ***1983****, 22,* 31; Reetz, M.T. *Top. Curr. Chem.* ***1982****, 106*, 1.
[610] Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* ***2001****, 42*, 6093.

aldehyde gives direct acyl addition without allylic rearrangement as the major product, favoring the *trans*-alkene unit.[611]

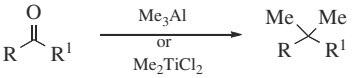
Allyltin compounds readily add to aldehydes and ketones.[612] Maleic acid promotes the reaction in aqueous media.[613] Allylic bromides react with Sn to generate the organometallic *in situ*, which then adds to aldehydes.[614] Allylic chlorides react with aldehydes in the presence of ditin compounds (e.g., $Me_3Sn—SnMe_3$ and a Pd catalyst).[615] Allyltrialkyltin compounds[616] and tetraallyltin react with aldehydes or ketones in the presence of BF_3—etherate,[617] or compounds of Cu,[618] Ce,[619] Bi,[620] Pb,[621] Ag[622] Cd,[623] Cr,[624] Pd,[625] Re,[626] Gd,[627] Ti,[628] Rh,[629] Zr,[630] Co,[631] or La.[632] Propargylic tin compounds react with aldehydes to give the alcohol, with good antiselectivity.[633] Tetraallyltin reacts via 1,2-addition to conjugated ketones in refluxing methanol.[634] Tetraallyltin reacts with aldehydes in ionic liquids[635] and on wet silica.[636] In addition, allyltributyltin adds to aldehydes in ionic liquids with $InCl_3$.[637] Tetraallyltin adds to ketones or aldehydes to give homoallylic alcohols with good enantioselectivity in the presence of a chiral Ti complex[638] or a chiral In

[611] Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* ***2003****, 44*, 1007.
[612] Marshall, J.A.; Palovich, M.R. *J. Org. Chem.* ***1998****, 63*, 4381; Zha, Z.; Qiao, S.; Jiang, J.; Wang, Y.; Miao, Q.; Wang, Z. *Tetrahedron* ***2005****, 61*, 2521. See Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* ***2002****, 124*, 13442; Masuyama, Y.; Ito, T.; Tachi, K.; Ito, A.; Kurusu, Y. *Chem. Commun.* ***1999***, 1261. Also see Li, G.-l.; Zhao, G. *J. Org. Chem.* ***2005****, 70,* 4272.
[613] Li, G.-l.; Zhao, G. *Synlett* ***2005***, 2540.
[614] Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003****, 125*, 2958; Andres, P.C.; Peatt, A.C.; Raston, C.L. *Tetraheron Lett.* ***2002****, 43*, 7541.
[615] Wallner, O.A.; Szabó, K.J. *J. Org. Chem.* ***2003****, 68*, 2934.
[616] See Issacs, N.S.; Maksimovic, L.; Rintoul, G.B.; Young, D.J. *J. Chem. Soc., Chem. Commun.* ***1992***, 1749; Isaacs, N.S.; Marshall, R.L.; Young, D.J. *Tetrahedron Lett.* ***1992****, 33*, 3023.
[617] Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* ***1979***, 919. For a review, see Yamamoto, Y. *Aldrichimica Acta* ***1987****, 20,* 45.
[618] Kalita, H.R.; Borah, A.J.; Phukan, P. *Tetrahedron Lett.* ***2007****, 48*, 5047.
[619] Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Reddy, J.S.S. *Tetrahedron* ***2005****, 61*, 879.
[620] Choudary, B.M.; Chidara, S.; Sekhar, Ch.V.R. *Synlett* ***2002***, 1694.
[621] Shibata, I.; Yoshimura, N.; Yabu, M.; Baba, A. *Eur. J. Org. Chem.* ***2001***, 3207.
[622] Yanagisawa, A.; Nakashima, H.; Nakatsuka, Y.; Ishiba, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1129.
[623] Kobayashi, S.; Aoyama, N.; Manabe, K. *Synlett* ***2002***, 483.
[624] Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *Tetrahedron* ***2006****, 62,* 5116.
[625] Zhang, T.; Shi, M.; Zhao, M. *Tetrahedron* ***2008****, 64*, 2412.
[626] Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Tetrahedron Lett.* ***2005****, 46*, 787.
[627] Lingaiah, B.V.; Ezikiel, G.; Yakaiah, T.; Reddy, G.V.; Rao, P.S. *Tetrahedron Lett.* ***2006****, 47,* 4315.
[628] Kii, S.; Maruoka, K. *Tetrahedron Lett.* ***2001****, 42*, 1935.
[629] Andrade, C.K.Z.; Azevedo, N.R. *Tetrahedron Lett.* ***2001****, 42*, 6473.
[630] Kurosa, M.; Lorca, M. *Tetrahedron Lett.* ***2002****, 43*, 1765.
[631] Chaudhuri, M.K.; Dehury, S.K.; Hussain, S. *Tetrahedron Lett.* ***2005****, 46,* 6247. Also see Tang, L.; Ding, L.; Chang, W.-X.; Li, J. *Tetrahedron Lett.* ***2006****, 47,* 303.
[632] Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002****, 43*, 319.
[633] Savall, B.M.; Powell, N.A.; Roush, W.R. *Org. Lett.* ***2001****, 3,* 3057.
[634] Khan, A.T.; Mondal, E. *Synlett* ***2003***, 694.
[635] Gordon, C.M.; McCluskey, A. *Chem. Commun.* ***1999***, 1431.
[636] Jin, Y.Z.; Yasuda, N.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* ***2003****, 44*, 8765.
[637] Lu, J.; Ji, S.-J.; Qian, R.; Chen, J.-P.; Liu, Y.; Loh, T.-P. *Synlett* ***2004***, 534.
[638] Kim, J.G.; Waltz, K.M.; Garcia, I.F.; Kwiatkowski, D.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004****, 126*, 12580.

complex.[639] Allylic alcohols and homoallylic alcohols add to aldehydes in the presence of $Sn(OTf)_2$[640] In/$InCl_3$,[641] or with a Rh catalyst.[642]

The tin compound can be prepared *in situ* using an α-iodo ketone with an aldehyde and Bu_2SnI_2—LiI.[643] A similar addition occurs with $(allyl)_2SnBr_2$ in water.[644] Asymmetric induction has been reported.[645] The use of a chiral Rh[646] or Ti[647] catalyst leads to enantioselective addition of allyltributyltin to aldehydes. Allyltributyltin reacts with aldehydes in the presence of $SiCl_4$ and a chiral phosphoramide to give the homoallylic alcohol with moderate enantioselectivity.[648] Tetravinyltin adds to ketones in the presence of an In catalyst.[649] Allenyl tin compounds (CH_2=C=$CHSnBu_3$) also react with aldehydes in the presence of BF_3•OEt_2 to give a 2-dienyl alcohol.[650] Selectfluor has been used to induce 1,2-addition of the allyl group of allyltributyltin to a conjugated aldehyde.[651]

Both aluminum and titanium reagents have been used. Aluminum catalysts, (e.g., [methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)], MABR), facilitate addition of allyltributyltin to aldehydes.[652] Triphenylaluminum reacts with aryl aldehydes in the presence of a Ti catalyst.[653] Trimethylaluminum[654] and dimethyltitanium dichloride[655] exhaustively methylate ketones to give *gem*-dimethyl compounds[656] (see also, Reaction **10-63**):



The Ti reagent also dimethylates aromatic aldehydes.[657] Triethylaluminum reacts with aldehydes, however, to give the mono-ethyl alcohol, and in the presence of a chiral additive the reaction proceeds with good asymmetric induction.[658] A complex of Me_3Ti•MeLi has

[639] Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* ***2005****, 7*, 159; Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* ***2005****, 7,* 2743.
[640] Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-i. *J. Am. Chem. Soc.* ***1998****, 120*, 6609.
[641] Jang, T.-S.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. *Synthesis* ***2003***, 775.
[642] Masuyama, Y.; Kaneko, Y.; Kurusu, Y. *Tetrahedron Lett.* ***2004****, 45*, 8969.
[643] Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* ***2002****, 4*, 301.
[644] Chan, T.H.; Yang, Y.; Li, C.J. *J. Org. Chem.* ***1999****, 64*, 4452.
[645] Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* ***1996,*** *118*, 4723; Motoyama, Y.; Nishiyama, H. *Synlett* ***2003***, 1883; Xia, G.; Shibatomi, K.; Yamamoto, H. *Synlett* ***2004***, 2437; Jennequin, T.; Wencel-Delord, J.; Rix, D.; Daubignard, J.; Crévisy, C.; Mauduit, M. *Synlett* ***2010***, 1661.
[646] Moloyama, Y.; Narusawa, H.; Nishiyama, H. *Chem. Commun.* ***1999***, 131.
[647] Doucet, H.; Santelli, M. *Tetrahedron Asymmetry* ***2000****, 11*, 4163.
[648] Denmark, S.E.; Wynn, T. *J. Am. Chem. Soc.* ***2001****, 123*, 6199.
[649] Zhang, X.; Chen, D.; Liu, X.; Feng, X. *J. Org. Chem.* ***2007****, 72,* 5227.
[650] Luo, M.; Iwabuchi, Y.; Hatakeyama, S. *Chem. Commun.* ***1999***, 267; Yu, C.-M.; Lee, S.-J.; Jeon, M. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3557.
[651] Liu, J.; Wong, C.-H. *Tetrahedron Lett.* ***2002****, 43,* 3915.
[652] Marx, A.; Yamamoto, H. *Synlett* ***1999***, 584.
[653] Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* ***2006****, 128,* 14808.
[654] Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974****, 27*, 1655. See also, Jeffery, E.A.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974****, 27,* 2569. For discussions of the mechanism of this reaction, see Ashby, E.C.; Smith, R.S. *J. Organomet. Chem.* ***1982****, 225*, 71. See Maruoka, H.; Yamamoto, H. *Tetrahedron* ***1988****, 44,* 5001.
[655] Reetz, M.T.; Westermann, J.; Kyung, S. *Chem. Ber.* ***1985****, 118*, 1050.
[656] See Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* ***1989****, 30,* 1581.
[657] Reetz, M.T.; Kyung, S. *Chem. Ber.* ***1987****, 120*, 123.
[658] Chan, A.S.C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* ***1997****, 119*, 4080.

been shown to be selective for 1,2-addition with conjugated ketones, in the presence of nonconjugated ketones.[659]

Chiral amides react with aldehydes in the presence of $TiCl_4$ to give syn-selective addition products.[660] Titanium-catalyzed enantioselective additions are also known.[661] High %ee values have been obtained with organometallics,[662] including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the Ti,[663] allylic boron compounds, and organozinc compounds. Chiral dendritic Ti catalysts have been used to give moderate enantioselectivity.[664]

Organozinc compounds add to aldehydes and ketones. An example is the reaction of an alkylzinc chloride (RZnCl) to give the corresponding alcohol.[665] Enantioselective reaction of a carbonyl with a dialkylzinc is possible when chiral catalysts are employed,[666] or when chiral ligands[667] are employed.[668] A comparison of the stereoselectivity for reactions of diphenylzinc and diethylzinc has been reported.[669] Dialkylzinc reagents, in the presence of a chiral Ti complex[670] a Zn complex,[671] an Al complex,[672] a chiral Cr complex,[673] a chiral Schiff base,[674] or a chiral bis(sulfonamide[675] and other chiral complexes[676] react with aldehydes or ketones to give

[659] Markó, I.E.; Leung, C.W. *J. Am. Chem. Soc.* ***1994****, 116*, 371.
[660] Crimmins, M.T.; Chaudhary, K. *Org. Lett.* ***2000*** *2*, 775.
[661] Walsh, P.J. *Acc. Chem. Res.* ***2003****, 36*, 739.
[662] See Takai, Y.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* ***1990****, 55,* 1707.
[663] Wang, J.; Fan, X.; Feng, X.; Quian, Y. *Synthesis* ***1989***, 291; Riediker, M.; Duthaler, R.O. *Angew. Chem. Int. Ed.* ***1989****, 28*, 494; Riediker, M.; Hafner, A.; Piantini, U.; Rihs, G.; Togni, A. *Angew. Chem. Int. Ed.* ***1989****, 30,* 499.
[664] Fan, O.-H.; Liu, G.-H.; Chen, X.-M.; Deng, G.-J.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001****, 12*, 1559.
[665] Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* ***2007****, 129,* 5376.
[666] Costa, A.M.; García, C.; Carroll, P.J.; Walsh, P.J. *Tetrahedron* ***2005****, 61*, 6442; Roudeau, R.; Pardo, D.G.; Cossy, J. *Tetrahedron* ***2006****, 62*, 2388; Parrott, II, R.W.; Dore, D.D.; Chandrashekar, S.P.; Bentley, J.T.; Morgan, B.S.; Hitchcock, S.R. *Tetrahedron Asymmetry* ***2008****, 19,* 607; Hatano, M.; Miyamoto, T.; Ishihara, K. *Synlett* ***2006***, 1762. See Ianni, J.C.; Annamalai, V.; Phuan, P.-W.; Panda, M.; Kozlowski, M.C. *Angew. Chem. Int. Ed.* ***2006****, 45,* 5502. For organocatalysts, see Kang, Y.-f.; Liu, L.; Wang, R.; Ni, M.; Han, Z.-j. *Synth. Commun.* ***2005****, 35,* 1819; Hui, A.; Zhang, J.; Wang, Z. *Synth. Commun.* ***2008****, 38,* 2374; Godoi, M.; Alberto, E.E.; Paixão, M.W.; Soares, L.A.; Schneider, P.H.; Braga, A.L. *Tetrahedron* ***2010****, 66*, 1341; Wu, Z.-L.; Wu, H.-L.; Wu, P.-Y.; Uang, B.-J. *Tetrahedron Asymm.* ***2009****, 20*, 1556; Banerjee, S.; Ferrence, G.M.; Hitchcock, S.R. *Tetrahedron Asymm.* ***2010****, 21*, 837.
[667] Zhu, H.J.; Jiang, J.X.; Saebo, S.; Pittman, Jr., C.U. *J. Org. Chem.* ***2005****, 70,* 261; Bisai, A.; Singh, P.K.; Singh, V.K. *Tetrahedron* ***2007****, 63,* 598; Burguete, M.I.; Escorihuela, J.; Luis, S.V.; Lledós, A.; Ujaque, G. *Tetrahedron* ***2008****, 64,* 9717; Bulut, A.; Aslan, A.; Izgü, E.Ç.; Dogan, Ö *Tetrahedron Asymmetry* ***2007****, 18,* 1013; Qin, Y.-C.; Pu, L. *Angew. Chem. Int. Ed.* ***2005****, 45,* 273; Park, J.K.; Lee, H.G.; Bolm, C.; Kim, B.M. *Chemistry: European J.* ***2005****, 11,* 945.
[668] See Dean, M.A.; Hitchcock, S.R. *Tetrahedron Asymmetry* ***2008****, 19,* 2563.
[669] Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2005****, 127,* 1548.
[670] For a review, see Pu, L. *Tetrahedron* ***2003****, 59*, 9873. See Li, Z.-B.; Pu, L. *Org. Lett.* ***2004****, 6*, 1065; Dahmen, S. *Org. Lett.* ***2004****, 6*, 2113; Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron Asymmetry* ***2004****, 15*, 3155; Lu, G.; Li, X.; Jia, X.; Chan, W.L.; Chan, A.S.C. *Angew. Chem. Int. Ed.* ***2003****, 42*, 5057; Xu, Z.; Wang, R.; Xu, J.; Da, C.-s.; Yan, W.-j.; Chen, C. *Angew. Chem. Int. Ed.* ***2003****, 42*, 5747.
[671] Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* ***2007****, 9,* 4535.
[672] Wieland, L.C.; Deng, H.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005****, 127*, 1545. Alse see Friel, D. K.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008****, 130,* 9942.
[673] Cozzi P.G.; Kotrusz, P. *J. Am. Chem. Soc.* ***2006****, 128*, 4940.
[674] Tanaka, T.; Yasuda, Y; Hayashi, M. *J. Org. Chem.* ***2006****, 71,* 7091.
[675] With $Ti(OiPr)_4$, see Jeon, S.-J.; Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2005****, 127*, 16416; Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L.K.; Walsh, P.J. *J. Org. Chem.* ***2005****, 70,* 448. See Huang, Z.; Lai, H.; Qin, Y. *J. Org. Chem.* ***2007****, 72,* 1373.
[676] Milburn, R.R.; Hussain, S.M.S.; Prien, O.; Ahmed, Z.; Snieckus, V. *Org. Lett.* ***2007****, 9,* 4403.

the corresponding alcohol with good enantioselectivity.[677] High enantioselectivity was obtained from R_2Zn reagents (R = alkyl)[678] and aromatic[679] aldehydes by the use of a small amount of various catalysts.[680] The enantioselectivity is influenced by additives (e.g., LiCl).[681] Silica-immobilized chiral ligands[682] can be used in conjunction with dialkylzinc reagents, and polymer-supported ligands have been used.[683]

Propargylic acetate adds to aldehydes with good antiselectivity in the presence of Et_2Zn and a Pd catalyst.[684] With other organometallic compounds, active metals (e.g., alkylzinc reagents)[685] are useful and compounds, such as alkylmercurys, do not react. Dimethylzinc and diethylzinc are probably the most common reagents. An intramolecular version is possible by reaction of an allene–aldehyde with dimethylzinc. Aryl halides react with Zn–Ni complexes to give acyl addition of the aryl group to an aldehyde.[686] The reaction of an allylic halide and Zn[687] or Zn/TMSCl[688] leads to acyl addition of aldehydes.

Organochromium compounds add to aldehydes or ketones.[689] The reaction of an organochromium reagent with an aldehyde or ketone is known as the *Nozaki–Hiyama reaction*. In the original version, a Cr(II) solution was prepared by reduction of chromic chloride by $LiAlH_4$. This product was subsequently treated with an aldehyde and an allylic halide.[690] The coupling of allylic halides and aldehydes or ketones in the presence of a Cr catalyst and a chiral ligand gives products with good enantioselectivity.[691] Enantioselective coupling reactions catalyzed by Cr compounds are of increasing interest.[692] The organochromium reagent may be derived from vinyl halides, triflates, or aryl derivatives.[693]

[677] See Braga, A.L.; Paixão, M.W.; Westermann, B.; Schneider, P.H.; Wessjohann, L.A. *J. Org. Chem.* ***2008****, 73,* 2879.
[678] See Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2001****, 123*, 2464.
[679] See Soai, K.; Yokoyam, S.; Hayasaka, T. *J. Org. Chem.* ***1991****, 56*, 4264.
[680] Pu, L.; Yu, H.-B. *Chem. Rev.* ***2001****, 101*, 757. See also, Danilova, T.I.; Rozenberg, V.I.; Starikova, Z.A.; Bräse, S. *Tetrahedron Asymmetry* ***2004****, 15*, 223; Scarpi, D.; Lo Galbo, F.; Occhiato, E.G.; Guarna, A. *Tetrahedron Asymmetry* ***2004****, 15*, 1319; Sibi, M.P.; Stanley, L.M. *Tetrahedron Asymmetry* ***2004****, 15*, 3353; Tseng, S.-L.; Yang, T.-K. *Tetrahedron Asymmetry* ***2004****, 15*, 3375; Harada, T.; Kanda, K.; Hiraoka, Y.; Marutani, Y.; Nakatsugawa, M. *Tetrahedron Asymmetry* ***2004****, 15*, 3879.
[681] Sosa-Rivadeneyra, M.; Muñoz-Muñiz, O.; de Parrodi, C.A.; Quintero, L.; Juaristi, E. *J. Org. Chem.* ***2003****, 68*, 2369; García, C.; La Rochelle, L.K.; Walsh, P.J. *J. Am. Chem. Soc.* ***2002****, 124*, 10970.
[682] Fraile, J.M.; Mayoral, J.A.; Servano, J.; Pericàs, M.A.; Solà, L.; Castellnou, D. *Org. Lett.* ***2003****, 5*, 4333.
[683] See Lipshutz, B.H.; Shin, Y.-J. *Tetrahedron Lett.* ***2000****, 41,* 9515.
[684] Marshall, J.A.; Adams, N.D. *J. Org. Chem.* ***1999****, 64*, 5201.
[685] See Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974****, 12*, 103. See Sjöholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc., Chem. Commun.* ***1994***, 1217; Jones, P.R.; Desio, P.J. *Chem. Rev.* ***1978****, 78,* 491.
[686] Majumdar, K.K.; Cheng, C.-H. *Org. Lett.* ***2000****, 2*, 2295.
[687] See Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* ***2002****, 58*, 7381.
[688] Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobyashi, J.-i. *Synlett* ***2002***, 2116.
[689] For a reaction of aliphatic halides, mediated by Cr(II), see Wessjohann, L.A.; Schmidt, G.; Schrekker, H.S. *Tetrahedron* ***2008****, 64*, 2134.
[690] Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. J. Am. Chem. Soc. **1977**, 99, 3179. See Takai, K. Org. React. **2004**, 64, 253.
[691] Miller, J.J.; Sigman, M.S. *J. Am. Chem. Soc.* ***2007****, 129*, 2752; Hargaden, G.C.; O'Sullivan, T.P,; Guiry, P.J. *Org. Biomol. Chem.* ***2008****, 6*, 562; Huang, X.-R.; Chen, C. *Tetrahedron Asymm.* ***2010****, 21*, 2999.
[692] Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2006****, 128,* 2554; Shimada, Y.; Katsuki, T. *Chem. Lett.* ***2005****, 34,* 786.
[693] Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1983****, 24,* 5281.

Other metals facilitate addition of groups to an aldehyde, including the coupling of an alkene to an aldehyde using a Ni catalyst.[694] Vinyl bromides react with $NiBr_2/CrCl_3$/TMSCl to give a reagent that adds to aldehydes to give the allylic alcohol.[695] Vinyl complexes generated from alkynes and SmI_2 add intramolecularly, and eight-membered rings have been formed in this way.[696] Vinyl reagents are formed *in situ* via organozirconium compounds with Me_2Zn, Ti compounds, and terminal alkynes.[697]

Lithium dimethylcopper (Me_2CuLi) reacts with aldehydes[698] and with certain ketones[699] to give the expected alcohols. The RCu(CN)ZnI reagents also react with aldehydes, in the presence of BF_3–etherate, to give secondary alcohols. Vinyltellurium compounds react with $BF_3{\cdot}OEt_2$ and cyanocuprates [R(2-thienyl)$CuCNLi_2$] to give a reagent that adds 1,2- to the carbonyl of a conjugated ketone.[700] Vinyl tellurium compounds also react with *n*-butyllithium to give a reagent that adds to nonconjugated ketones.[701] In conjunction with $BeCl_2$, organolithium reagents add to conjugated ketones. In THF, 1,4- addition is observed, but in diethyl ether the 1,2-addition product is formed.[702]

Alkenes and alkynes add to aldehydes or ketones via the π bond by conversion to a reactive organometallic. A radical-type addition is possible using alkenes with BEt_3. Alkynes add to aldehydes elsewhere in the same molecule in the presence of BEt_3 and a Ni catalyst to give a cyclic allylic alcohol.[703] Alkene aldehydes react similarly using Me_3SiOTf.[704] In a similar manner, dienes[705] or alkynes[706] add to aldehydes in the presence of a Ni catalyst. Allenes add to aldehydes in the presence of a Ni catalyst, using a chiral imidazolinyl carbene ligand, and the product is trapped as the triethylsilyl ether by addition of Et_3SiI.[707] Ketenimines add to aldehydes, in the presence of $SiCl_4$ and an achiral ligand, to give the β-cyanohydrin with good enantioselectivity.[708] Allylic acetates react with ketones to give the homoallylic alcohol under electrochemical conditions that include bipyridyl, tetrabutylammonium tetrafluoroborate, and $FeBr_2$.[709] Terminal alkynes react with Zr complexes and Me_2Zn to give an allylic tertiary alcohol.[710] Internal alkynes also give allylic alcohols in the presence of BEt_3 and a Ni catalyst.[711] Reaction of an aldehyde containing a conjugated diene unit with diethylzinc and a Ni catalyst leads to cyclic

[694] Ng, S.-S.; Ho, C.-Y.; Jamison, T.F. *J. Am. Chem. Soc.* ***2006****, 128,* 11513.
[695] Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Mochizuki, M.; Tanaka, H. *Tetrahedron Lett.* ***2000****, 41*, 81.
[696] Hölemann, A.; Reissig, H.-U. *Synlett* ***2004***, 2732.
[697] Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2005****, 127*, 8355.
[698] See Reetz, M.T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* ***1994****, 35*, 1969.
[699] See Matsuzawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989****, 30,* 1975.
[700] Araújo, M.A.; Barrientos-Astigarraga, R.E.; Ellensohn, R.M.; Comasseto, J.V. *Tetrahedron Lett.* ***1999****, 40*, 5115.
[701] Dabdoub, M.J.; Jacob, R.G.; Ferreira, J.T.B.; Dabdoub, V.B.; Marques, F.de.A. *Tetrahedron Lett.* ***1999****, 40*, 7159.
[702] Krief, A.; de Vos, M.J.; De Lombart, S.; Bosret, J.; Couty, F. *Tetrahedron Lett.* ***1997****, 38*, 6295.
[703] Miller, K.M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004****, 126*, 4130.
[704] Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* ***2001***, 1042. For a reaction using a Ni catalyst, see Ng, S.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2005****, 127*, 14194.
[705] Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* ***2004****, 6*, 1131.
[706] Chaulagain, M.R.; Sormunen, G.J.; Montgomery, J. *J. Am. Chem. Soc.* ***2007****, 129*, 9568; Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2008****, 130,* 14052.
[707] Ng, S.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2005****, 127,* 7320.
[708] Denmark, S.E.; Wilson, T.W.; Burk, M.T.; Heemstra, Jr., J.R. *J. Am. Chem. Soc.* ***2007****, 129,* 14864.
[709] Durandetti, M.; Meignein, C.; Périchon, J. *J. Org. Chem.* ***2003****, 68*, 3121.
[710] Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004****, 126*, 6538.
[711] Miller, K.M.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004****, 126*, 15342.

alcohols having a pendant allylic unit.[712] A similar reaction was reported using a Cu catalyst.[713] The intramolecular addition of an alkene to an aldehyde leads to a saturated cyclic alcohol using $PhSiH_3$ and a Co catalyst.[714]

Aryl halides react with a Ni complex under electrolytic conditions to add the aryl group to aldehydes.[715] The C position of an indole adds to aldehydes in the presence of a Pd catalyst.[716] The addition of trifluoromethyl to an aldehyde was accomplished photochemically using CF_3I and $(Me_2N)_2C{=}C(NMe_2)_2$.[717] α-Iodo phosphonate esters react with aldehydes and SmI_2 to give a β-hydroxy phosphonate ester.[718] Addition to the allene in the presence of a Ni catalyst[719] or a $CeCl_3$ catalyst[720] is followed by addition of the intermediate organometallic to the aldehyde to give the cyclic product.

Intramolecular addition of a conjugated ester (via the β-carbon) to an aldehyde generates a cyclic ketone.[721] This type of coupling has been called the *Stetter reaction*,[722] which actually involves the addition of aldehydes to activated double bonds (Reaction **15-34**), mediated by a catalytic amount of thiazolium salt in the presence of a weak base. The intramolecular addition of the allene moiety to an aldehyde is catalyzed by a Pd complex in the presence of $Me_3SiSnBu_3$.[723] A highly enantio- and diastereoselective intramolecular *Stetter reaction* has been developed.[724] Alkynyl aldehydes react with silanes (e.g., Et_3SiH) and a nickel catalyst to give a cyclic compound having a silyl ether and an exocyclic vinylidene unit.[725] Alkene-aldehydes give cyclic alcohols via intramolecular addition of the C=C unit to the carbonyl under electrolytic conditions using a phase-transfer catalyst.[726] A similar cyclization was reported using $SnCl_4$.[727] Vinylidene cycloalkanes react with aldehydes in the presence of a Pd catalyst to give a homoallylic alcohol where addition occurs at the carbon exocyclic to the ring.[728] Allenes react with benzaldehyde using $HCl{-}SnCl_2$ with a Pd catalyst.[729] Silyl allenes react with aldehydes in the presence of a chiral Sc catalyst to give homopropargylic alcohols with good enantioselectivity.[730] Intramolecular addition of an allene to aldehyde via addition of phenyl when treated with PhI and a Pd catalyst.[731] Allenes add to ketones to give homoallylic alcohols in the

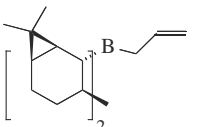
[712] Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* ***2001****, 3*, 2181.
[713] Agapiou, K.; Cauble, D.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2004****, 126*, 4528.
[714] Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001****, 123*, 5112.
[715] Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *Org. Lett.* ***2001****, 3*, 2073.
[716] Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* ***2001***, 1443.
[717] Aït-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier, Jr., W.R. *Org. Lett.* ***2001****, 3*, 4271.
[718] Orsini, F.; Caselli, A. *Tetrahedron Lett.* ***2002****, 43*, 7255.
[719] Montgomery, J.; Song, M. *Org. Lett.* ***2002****, 4*, 4009.
[720] Fischer, S.; Groth, U.; Jeske, M.; Schütz, T. *Synlett* ***2002***, 1922.
[721] Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004****, 126*, 8876.
[722] Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed* ***1973****, 12,* 81; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991****, 40*,407; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004****, 126,* 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. See Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004****, 126*, 2314.
[723] Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed.* ***2002****, 41*, 343.
[724] Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2005****, 127,* 6284.
[725] Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* ***1999****, 121*, 6098.
[726] Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.
[727] Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* ***2001****, 3*, 4205.
[728] Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* ***2000****, 2*, 4059.
[729] Chang, H.-M.; Cheng, C.-H. *Org. Lett.* ***2000****, 2*, 3439.
[730] Evans, D.A.; Sweeney, Z.K.; Rovis, T.; Tedrow, J.S. *J. Am. Chem. Soc.* ***2001****, 123*, 12095.
[731] Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* ***2002****, 67*, 4376.

presence of SmI_2 and HMPA.[732] Alkenes having an allylic methyl group in the presence of BF_3•OEt_2 add to formaldehyde to give a homoallylic alcohol.[733] Conjugated dienes react with aldehyde via acyl addition of a terminal carbon of the diene, in the presence of Ni $(acac)_2$ and Et_2Zn.[734]

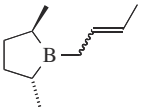
Although organoboranes do not generally add to aldehydes and ketones,[735] allylic boranes are exceptions.[736] When they add, an allylic rearrangement always takes place. Allylic rearrangements may take place with the other reagents as well. The use of a chiral catalyst leads to asymmetric induction[737] and chiral allylic boranes have been prepared.[738] Addition of trialkylboranes to aldehydes is catalyzed by a Ni complex.[739] Note that chloroboranes (R_2BCl) react with aldehydes via acyl addition of the alkyl group, giving the corresponding alcohol after treatment with water.[740] Treatment with catecholborane gives addition to the conjugated ketone, and subsequent cyclization of the resulting organometallic at the nonconjugated ketone gives a cyclic alcohol with a pendant ketone unit, after treatment with methanol.[741] In the presence of Ru[742] Cu,[743] Ni,[744] or Pd[745] compounds, $RB(OH)_2$ and arylboronic acids [$ArB(OH)_2$, see Reaction **12-28**] add to aldehydes to give the corresponding alcohol. Arylboronic acids add to aldehydes in the presence of a chiral ligand to give an alcohol with good enantioselectivity.[746] An enantioselective intramolecular reaction of an arylboronic acid to a pendant ketone moiety used a Pd catalyst.[747] Polymer-bound aryl borates add an aryl group to aldehydes in the presence of a Rh catalyst.[748] An intramolecular version of the phenylboronic acid induced reaction is known, where a molecule with ketone and conjugated ketone units is converted to a cyclic alcohol using a chiral Rh catalyst.[749] Allylic boronates add to aldehydes,[750] and

[732] Hölemann, A.; Reißig, H.-U. *Chem. Eur. J.* ***2004****, 10*, 5493.
[733] Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* ***2002****, 4*, 1667.
[734] Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* ***2002****, 4*, 2715.
[735] See Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989****, 30,* 5153.
[736] See Hoffmann, R.W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* ***1990****, 62,* 1993; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents* Academic Press, NY, ***1988***, pp. 310–318; Bubnov, Yu.N. *Pure Appl. Chem.* ***1987****, 21*, 895; Buynak, J.D.; Geng, B.; Uang, S.; Strickland, J.B. *Tetrahedron Lett.* ***1994****, 35*, 985.
[737] Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004****, 126*, 8910. For an enantioselective reaction with an alkoxyboranes, see Lou, S.; Moquist, P.N.; Schaus, S.E. *J. Am. Chem. Soc.* ***2006****, 128*, 12660.
[738] See Schneider, U.; Ueno. M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2008****, 130,* 13824.
[739] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2005****, 7,* 4689.
[740] Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2002****, 58*, 3243.
[741] Huddleston, R.R.; Cauble, D.F.; Krische, M.J. *J. Org. Chem.* ***2003****, 68*, 11.
[742] Ueda, M.; Miyaura, N. *J. Org. Chem.* ***2000****, 65*, 4450 and references cited therein; Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* ***2006****, 8,* 1479. See Son, S.U.; Kim, S.B.; Reingold, J.A.; Carpenter, G.B.; Sweigart, D.A. *J. Am. Chem. Soc.* ***2005****, 127,* 12238.
[743] Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* ***2009****, 74,* 943.
[744] Zhou, L.; Du, X.; He, R.; Ci, Z.; Bao, M. *Tetrahedron Lett.* ***2009****, 50*, 406.
[745] Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* ***2005****, 7*, 4153.
[746] Ji, J.-X.; Wu, J.; Au-Yeung, T.T.-L.; Yip, C.-W.; Haynes, R.K.; Chan, A.S.C. *J. Org. Chem.* ***2005****, 70,* 1093; Wu, P.-Y.; Wu, H.-L.; Uang, B.-J. *J. Org. Chem.* ***2006****, 71,* 833; Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2008****, 47,* 4351; Braga, A.L.; Lüdtke, D.S.; Vargas, F.; Paixão, M.W. *Chem. Commun.* ***2005***, 2512; Schmidt, F.; Rudolph, J.; Bolm, C. *Synthesis* ***2006***, 3625; Jagt, R.B.C.; Toullec, P.Y.; de Vries, J.G.; Feringa, B.L.; Minnaard, A.J. *Org. Biomol. Chem.* ***2006****, 4,* 773; Jumde, V.R.; Facchetti, S.; Iuliano, A. *Tetrahedron Asymm.* ***2010****, 21*, 2775.
[747] Liu, G.; Lu, X. J. Am. Chem. Soc. **2006**, 128, 6504.
[748] See Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* ***2005***, 840.
[749] Cauble, D.F.; Gipson, J.D.; Krische, M.J. *J. Am. Chem. Soc.* ***2003****, 125*, 1110.
[750] See Gravel, M.; Lachance, H.; Lu, X.; Hall, D.G. *Synthesis* ***2004***, 1290; Bouffard, J.; Itami, K. *Org. Lett.* ***2009****, 11*, 4410.

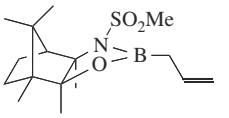
there are enantioselective reactions.[751]



32



33



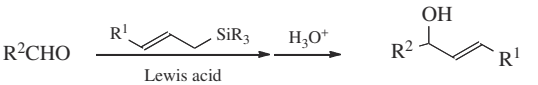
34

A number of optically active allylic boron compounds have been used, including[752] B-allylbis(2-isocaranyl)borane (**32**),[753] (*E*)- and (*Z*)-crotyl-(*R*,*R*)-2,5-dimethylborolanes (**33**),[754] and the borneol derivative **34**,[755] all of which add an allyl group to aldehydes, with good enantioselectivity. A recyclable 10-TMS-9-borabicyclo[3.3.2]decane has been used for asymmetric allyl and crotyl addition to aldehydes.[756] Where the substrate possesses an aryl group or a triple bond, using a metal carbonyl complex of the substrate enhances enantioselectivity.[757]

Potassium alkynyltrifluoroborates (Reaction **12-28**) react with aldehydes and a secondary amine, in an ionic liquid, to give a propargylic amine.[758] Allylic trifluoroborates (Reaction **12-28**) react with aldehydes to give the homoallylic alcohol. The Pd catalyzed reaction of aryl aldehydes with $PhBF_3K$ gave a diaryl alcohol.[759] A Ru catalyzed reaction of aryltrifluoroborates led to sterically hindered diaryl ketones.[760] Aliphatic aldehydes react with this reagent, in the presence of $BF_3{\cdot}OEt_2$, to give the homoallylic alcohol with allylic rearrangement and a preference for the syn diastereomer.[761] Aryl aldehydes react as well.[762]

16-26 Addition of Trialkylallylsilanes to Aldehydes and Ketones

***O*-Hydro-*C*-alkyl-addition**



Allylic trialkyl, trialkoxy, and trihalosilanes add to aldehydes to give the homoallylic alcohols in the presence of a Lewis acid[763] (including $TaCl_5$[764] and $YbCl_3$[765]), fluoride

[751] Chai, Z.; Liu, X.-Y.; Zhang, J.-K.; Zhao, G. *Tetrahedron Asymmetry* ***2007****, 18*, 724; Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2007****, 46,* 5909; Hall, D.G. *Synlett* ***2007***, 1644. See Barnett, D.S.; Moquist, P.N.; Schaus, S.E. *Angew. Chem. Int. Ed.* ***2009****, 48*, 8679.

[752] See Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.* ***1990****, 112*, 6339; Brown, H.C.; Randad, R.S. *Tetrahedron Lett.* ***1990****, 31*, 455; Stürmer, R.; Hoffmann, R.W. *Synlett* ***1990***, 759.

[753] Racherla, U.S.; Brown, H.C. *J. Org. Chem.* ***1991****, 56,* 401, and references cited therein.

[754] Garcia, J.; Kim, B.M.; Masamune, S. *J. Org. Chem.* ***1987****, 52*, 4831.

[755] Reetz, M.T.; Zierke, T. *Chem. Ind. (London)* ***1988***, 663.

[756] Burgos, C.H.; Canales, E.; Matos, K.; Soderquist, J.A. *J. Am. Chem. Soc.* ***2005****, 127*, 8044.

[757] Roush, W.R.; Park, J.C. *J. Org. Chem.* ***1990****, 55*, 1143.

[758] Kabalka, G.W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* ***2004****, 45*, 729.

[759] Kuriyama, M.; Shimazawa, R.; Enomoto, T.; Shirai, R. *J. Org. Chem.* ***2008****, 73,* 6939.

[760] Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* ***2008****, 73*, 7800.

[761] Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999****, 40*, 4289.

[762] Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.

[763] Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989****, 37,* 57, pp. 113–125, 290–328; Parnes, Z.N.; Bolestova, G.I. *Synthesis* ***1984***, 991, see pp. 997–1000. See Aggarwal, V.K.; Vennall, G.P. *Tetrahedron Lett.* ***1996****, 37*, 3745.

[764] Chandrasekhar, S.; Mohanty, P.K.; Raza, A. *Synth. Commun.* ***1999****, 29*, 257.

[765] Fang, X.; Watkin, J.G.; Warner, B.P. *Tetrahedron Lett.* ***2000****, 41*, 447.

ion,[766] proazaphosphatranes,[767] or a catalytic amount of iodine.[768] A Ru catalyst has been used in conjunction with an arylsilane and an aldehyde.[769] Allyl(trimethoxy)silane adds an allyl group to aldehydes using a CdF_2[770] catalyst or a chiral AgF complex.[771] Allyltrichlorosilanes have also been used in addition reactions with aldehydes.[772] Hünig's base (iPr$_2$NEt) and a sulfoxide have also been used to facilitate the addition of an allyl group to an aldehyde from allyltrichlorosilane.[773] The mechanism of this reaction has been examined.[774]

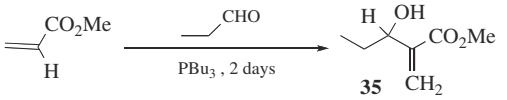
Allyltrichlorosilane reacts with aldehydes in the presence of certain additives to give the corresponding alcohol,[775] and the reaction proceeds with good enantioselectivity by addition of a chiral additive.[776] Other chiral additives have been used,[777] as well as chiral catalysts,[778] and chiral complexes of allyl silanes.[779] Trimethoxyallylsilanes react with aldehydes in the presence of a Cu catalyst and a chiral ligand to give the chiral alcohol.[780] Chiral allylic silyl derivatives add to aldehydes to give the chiral homoallylic alcohol.[781]

Allylic silanes react with *gem*-diacetates in the presence of $InCl_3$ to give a homoallylic acetate[782] or with dimethyl acetals and TMSOTf in an ionic liquid to give the homoallylic methyl ether.[783] Allylic alcohols can be treated with TMS—Cl and NaI, and then Bi to give an organometallic reagent that adds to aldehydes.[784]

[766] See Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* ***2002***, 45.
[767] Wang, Z.; Kisanga, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 6459.
[768] Yadav, J.S.; Chand, P.K.; Anjaneyulu, S. *Tetrahedron Lett.* ***2002***, *43*, 3783.
[769] Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* ***2002***, 298.
[770] Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2003***, 676.
[771] Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3701.
[772] Kobayashi, S.; Nishio, K. *J. Org. Chem.* ***1994***, *59*, 6620.
[773] Massa, A.; Malkov, A.V.; Kocovský, P.; Scettri, A. *Tetrahedron Lett.* ***2003***, *44*, 7179.
[774] Bottoni, A.; Costa, A.L.; Di Tommaso, D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* ***1997***, *119*, 12131; Denmark, S.E.; Weber, E.J.; Wilson, T.; Willson, T.M. *Tetrahedron* ***1989***, *45*, 1053; Keck, G.E.; Andrus, M.B.; Castellino, S. *J. Am. Chem. Soc.* ***1989***, *111,* 8136.
[775] Malkov, A.V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovský, P. *J. Org. Chem.* ***2003***, *68*, 9659.
[776] Malkov, A.V.; Ramírez-López, P.; Biedermannová (née Bendová), L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kocovský, P. *J. Am. Chem. Soc.* ***2008***, *130*, 5341; Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* ***2006***, *71,* 1458; Denmark, S.E.; Fu, J.; Coe, D.M.; Su, X.; Pratt, N.E.; Griedel, B.D. *J. Org. Chem.* ***2006***, *71,* 1513; Denmark, S.E.; Fu, J.; Lawler, M.J. *J. Org. Chem.* ***2006***, *71,* 1523; Traverse, J.F.; Zhao, Y.; Hoveyda, A.H.; Snapper, M.L. *Org. Lett.* ***2005***, *7,* 3151; Malkov, A.V.; Bell, M.; Castelluzzo, F.; Kocovský, P. *Org. Lett.* ***2005***, *7,* 3219; Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M.B. *Tetrahedron Lett.* ***2006***, *47,* 8611; De Sio, V.; Massa, A.; Scettri, A. *Org. Biomol. Chem.* ***2010***, *8,* 3055; Oh, Y.S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Asymm.* ***2010***, *21*, 1833.
[777] Angell, R.M.; Barrett, A.G.M.; Braddock, D.C.; Swallow, S.; Vickery, B.D. *Chem. Commun.* ***1997***, 919.
[778] Malkov, A.V.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem Int. Ed.* ***2003***, *42*, 3802.
[779] Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* ***1999***, *55*, 977
[780] Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M *J. Am. Chem. Soc.* ***2005***, *127,* 4138; Yamamoto, H.; Wadamoto, M. *Chemistry: Asian J.* ***2007***, *2,* 692.
[781] Kubota, K.; Leighton, J.L. *Angew. Chem. Int. Ed.* ***2003***, *42*, 946; Hackman, B.M.; Lombardi, P.J.; Leighton, J. L. *Org. Lett.* ***2004***, *6*, 4375.
[782] Yadav, J.S.; Reddy, B.V.S.; Madhuri, Ch.; Sabitha, G. *Chem. Lett.* ***2001***, 18.
[783] Zerth, H.M.; Leonard, N.M.; Mohan, R.S. *Org. Lett.* ***2003***, *5*, 55.
[784] Miyoshi, N.; Nishio, M.; Murakami, S.; Fukuma, T.; Wada, M. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 689.

16-27 Addition of Conjugated Alkenes to Aldehydes (the Baylis–Hillman Reaction)[785]

O-Hydro-*C*-alkenyl-addition



35

In the presence of a base[786] (1,4-diazabicyclo[2.2.2]octane, DABCO) or trialkylphosphines, conjugated carbonyl compounds (ketones, esters, including lactones)[787] thioesters,[788] and amides[789]) add to aldehydes via the α carbon to give α-alkenyl-β-hydroxy esters or amides. This sequence is called the *Baylis–Hillman reaction (or Morita–Baylis–Hillman)*,[790] and a simple example is the formation of **35**.[791] Mechanistic investigations of the reaction have been reported.[792] Methyl vinyl ketone gave other products in the *Baylis–Hillman reaction*, whereas conjugated esters do not.[793] Methods that are catalytic in base have been developed for the *Baylis–Hillman reaction*.[794] Both microwave irradiation[795] and ultrasound[796] have been used to induce the reaction.[797] *Baylis–Hillman reactions* have been done in aqueous acidic media.[798] There is a protein-catalyzed reaction.[799] Under certain conditions, rate enhancements have been observed.[800] The reaction has been done in ionic liquids[801] and PEG[802] or sulfolane,[803] and without an organic solvent.[804] Rate

[785] See Basavaiah, D.; Rao, A.J.; Satyanarayana, T. *Chem. Rev.* ***2003****, 103*, 811.
[786] See Luo, S.; Mi, X.; Xu, H.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004****, 69*, 8413.
[787] See Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* ***2003****, 44*, 2991.
[788] See Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Coltart, D.M. *Org. Lett.* ***2008****, 10,* 4819.
[789] See Faltin, C.; Fleming, E.M.; Connon, S.J. *J. Org. Chem.* ***2004****, 69*, 6496.
[790] Baylis, A.B.; Hillman, M.E.D. Ger. Offen. 2,155,133 *Chem. Abstr.,* ***1972****, 77*, 34174q [U.S. Patent 3,743,668]; Drewes, S.E.; Roos, G.H.P. *Tetrahedron* ***1988****, 44*, 4653. For a review, see Basavaiah, D.; Rao, P.D.; Hyma, R.S. *Tetrahedron* ***1996****, 52*, 8001.
[791] Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997****, 62*, 1521. Also see, Drewes, S.E.; Rohwer, M.B. *Synth. Commun.* ***1997****, 27*, 415.
[792] Robiette, R.; Aggarwal, V.K.; Jeremy N; Harvey, J.N. *J. Am. Chem. Soc.* ***2007****, 129,* 15513 (computational); Roy, D.; Sunoj, R.B. *Org. Lett.* ***2007****, 9,* 4873 (computational). Price, K.E.; Broadwater, S.J.; Walker, B.J.; McQuade, D.T. *J. Org. Chem.* ***2005****, 70*, 3980.
[793] Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* ***2001***, 833.
[794] Pereira, S.I.; Adrio, J.; Silva, A.M.S.; Carretero, J.C. *J. Org. Chem.* ***2005****, 70,* 10175; Lin, Y.-S.; Liu, C.-W.; Tsai, T.Y.-R. *Tetrahedron Lett.* ***2005****, 46,* 1859; Zhao, S.-H.; Chen, Z.-B. *Synth. Commun.* ***2005****, 35*, 3045. For an ionic-liquid immobilizied base, see Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* ***2005****, 70,* 2338. See Aggarwal, V. K.; Emme, I.; Fulford, S.Y. *J. Org. Chem.* ***2003****, 68*, 692.
[795] Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V. *Synlett* ***1994***, 444.
[796] Coelho, F.; Almeida, W.P.; Veronese, D.; Mateus, C.R.; Lopes, E.C.S.; Rossi, R.C.; Silveira, G.P.C.; Pavam, C. H. *Tetrahedron* ***2002****, 58*, 7437.
[797] For improved procedures: Zhao, S.-H.; Bie, H.-Y.; Chen, Z.-B. *Org. Prep. Proceed. Int.* ***2005****, 37*, 231.
[798] Caumul, P.; Hailes, H.C. *Tetrahedron Lett.* ***2005****, 46*, 8125.
[799] Reetz, M.T.; Mondière, R.; Carballeira, J.D. *Tetrahedron Lett.* ***2007****, 48*, 1679.
[800] See Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997****, 62*, 1521; Luo, S.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004****, 69*, 555; Cai, J.; Park, K.S.; Kim, J.; Choo, H.; Chong, Y. *Synlett* ***2007***, 395. For a discussion of salt effects, see Kumar, A.; Pawar, S.S. *Tetrahedron* ***2003****, 59*, 5019.
[801] Rosa, J.N.; Afonso, C.A.M.; Santos, A.G. *Tetrahedron* ***2001****, 57*, 4189. For an example in a chiral ionic liquid, see Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* ***2004****, 45*, 6425.
[802] Chandrasekhar, S.; Narsihmulu, Ch.; Saritha, B.; Sultana, S.S. *Tetrahedron Lett.* ***2004****, 45*, 5865.
[803] Krishna, P.R.; Manjuvani, A.; Kannan, V.; Sharma, G.V.M. *Tetrahedron Lett.* ***2004****, 45*, 1183.
[804] Asano, K.; Matsubara, S. *Synthesis* ***2009***, 3219.

acceleration occurs with bis(arylthio)ureas in a DABCO promoted reaction.[805] Transition metal compounds can facilitate the *Baylis–Hillman reaction*,[806] and BF_3•OEt_2 has been used.[807] A sila variation is known, involving the reaction of vinylsilanes and aldehydes.[808] An *aza-Balyis–Hillman reaction* is discussed in Reaction **16-31**.

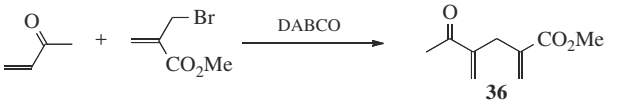
An intramolecular version of the *Baylis–Hillman reaction* generated cyclopentenone derivatives from alkyne-aldehydes and a Rh catalyst.[809] Other intramolecular cyclization reactions are known.[810] Cyclization of a conjugated ester using DABCO, where the "alcohol" group contained an aldehyde unit (an α-hydroxy aldehyde derivative) gave a lactone with a hydroxy unit at C-3 relative to the carbonyl and an α-vinylidene.[811]

Enantioselective *Baylis–Hillman reactions*[812] are possible using a chiral auxiliary via an amide[813] or ester.[814] Organocatalysts can be used to give products with good enantioselectivity.[815] Sugars have been used as ester auxiliaries, and in reaction with aryl aldehydes and 20% DABCO gave the allylic alcohol with modest enantioselectivity.[816]

Another variation is the *Rauhut–Currier cyclization* reaction,[817] which involves the reaction of a conjugated carbonyl with the allylic site of a second conjugated system. Intramolecular variations of this latter method are known.[818] With the boron trifluoride induced reaction between an aldehyde and a conjugated ketone, a saturated β-hydroxy ketone was formed with good antiselectivity.[819] The coupling of aldehydes with conjugated ketones used $TiCl_4$,[820] dialkylaluminum halides,[821] and with (polymethyl)hydrosiloxane and a Cu catalyst.[822] Conjugated esters were coupled to aldehydes with DABCO and a La catalyst.[823] Aldehydes are coupled to conjugated esters with a chiral quinuclidine catalyst and a Ti catalyst, as well as in the presence of tosylamine, the final product was the allylic *N*-tosylamine formed with modest enantioselectivity.[824]

[805] Maher, D.J.; Connon, S.J. *Tetrahedron Lett.* ***2004****, 45*, 1301.
[806] See Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* ***2007****, 9,* 927.
[807] Walsh, L.M.; Winn, C.L.; Goodman, J.M. *Tetrahedron Lett.* ***2002****, 43*, 8219.
[808] Chuprakov, S.; Malyshev, D.A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2007****, 129*, 14868.
[809] Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2001****, 123*, 11492.
[810] Keck, G.E.; Welch, D.S. *Org. Lett.* ***2000****, 4*, 3687.
[811] Krishna, P.R.; Kannan, V.; Sharma, G.V.M. *J. Org. Chem.* ***2004****, 69*, 6467.
[812] See Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* ***2007****, 46,* 4614; Also see, Markó, I.E.; Giles, P. R.; Hindley, N.J. *Tetrahedron* ***1997****, 53*, 1015.
[813] Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *J. Am. Chem. Soc.* ***1997****, 119*, 4317.
[814] See Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P.W. *Tetrahedron Asymmetry* ***2003****, 14*, 971.
[815] Imbriglio, J.E.; Vasbinder, M.M.; Miller, S.J. *Org. Lett.* ***2003****, 5*, 3741. See also, Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* ***2005****, 7,* 4293; Berkessel, A.; Roland, K.; Neudörfl, J.M. *Org. Lett.* ***2006****, 8,* 4195; Lattanzi, A. *Synlett* ***2007***, 2106.
[816] Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2001****, 12*, 847.
[817] Rauhut, M. M.; Currier, H. *U.S. Patent 307499919630122,* American Cyanamid Co., ***1963***.
[818] Aroyan, C.E.; Miller, S.J. *J. Am. Chem. Soc.* ***2007****, 129*, 256.
[819] Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N.R.; Reddy, M.S. *Tetrahedron Lett.* ***2003****, 44*, 2583.
[820] Li, G.; Wei, H.-X.; Gao, J.J.; Caputo, T.D. *Tetrahedron Lett.* ***2000****, 41*, 1; Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* ***2000****, 2,* 2397.
[821] Pei, W.; Wei, H.X.; Li, G. *Chem. Commun.* ***2002***, 2412.
[822] Arnold, L.A.; Imbos, R.; Mandoli, A.; de Vries, A.H.M.; Naasz, R.; Feringa, B.L. *Tetrahedron* ***2000****, 56*, 2865.
[823] Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* ***2003****, 68*, 915.
[824] Balan, D.; Adolfsson, H. *Tetrahedron Lett.* ***2003****, 44*, 2521.

Alkyl halides are coupled with conjugated carbonyls to give the alkylated derivative in what is known as *Morita–Baylis–Hillman alkylation.*[825] α-Bromomethyl esters react with conjugated ketones and DABCO to give a coupling product, (**34**).[826] A similar DBU induced reaction was reported using α-bromomethyl esters and conjugated nitro compounds.[827]



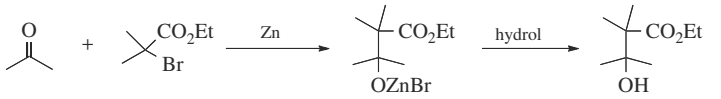
36

The reaction can be modified to give additional products, as with the reaction of *o*-hydroxybenzaldehyde and methyl vinyl ketone with DABCO, where the initial *Baylis–Hillman product* cyclized via conjugate addition of the phenolic oxygen to the conjugated ketone (Reaction **15-31**).[828] Aldehydes and conjugated esters can be coupled with a sulfonamide to give an allylic amine.[829]

See OS ***2010***, 87, 201

16-28 The Reformatsky Reaction

***O*-Hydro-*C*-α-ethoxycarbonylalkyl-addition**



The *Reformatsky reaction*[830] is very similar to Reaction **16-24**. An aldehyde or ketone is treated with Zn and a halide; the halide is usually an α-halo ester or a vinylog (see Sec. 6. B) of an α-halo ester (e.g., RCHBrCH=CHCOOEt), although α-halo nitriles,[831] α-halo ketones,[832] and α-halo *N,N*-disubstituted amides have also been used. Especially high reactivity can be achieved with activated Zn,[833] and with Zn and ultrasound.[834] The reaction is catalytic in Zn in the presence of iodine and ultrasound.[835] Metals other than Zn can be used, including In,[836] Mn,[837] low valent Ti,[838] metal compounds of Ti,[839] Sn,[840]

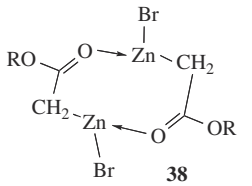
[825] Krafft, M.E.; Haxell, T.F.M.; Seibert, K.A.; Abboud, K.A. *J. Am. Chem. Soc.* ***2006****, 128*, 4174; Krafft, M.E.; Haxell, T.F.N. *J. Am. Chem. Soc.* ***2005****, 127,* 10168; Krafft, M.E.; Seibert, K.A.; Haxell, T.F.N.; Hirosawa, C. *Chem. Commun.* ***2005***, 5772.
[826] Basavaiah, D.; Sharada, D.S.; Kumaragurubaran, N.; Reddy, R.M. *J. Org. Chem.* ***2002****, 67*, 7135.
[827] Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* ***2004****, 60*, 4995.
[828] Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1331.
[829] Balan, D.; Adolfsson, H. *J. Org. Chem.* ***2002****, 67*, 2329.
[830] See Fürstner, A. *Synthesis* ***1989***, 571; Rathke, M.W. *Org. React.* ***1975****, 22,* 423; Gaudemar, M. *Organomet. Chem. Rev. Sect. A* ***1972****, 8,* 183; Ocampo, R.; Dolbier Jr., W.R. *Tetrahedron* ***2004****, 60*, 9325.
[831] Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N. *Tetrahedron Lett.* ***1990****, 31*, 2205; Zheng, J.; Yu, Y.; Shen, Y. *Synth. Commun.* ***1990****, 20*, 3277.
[832] See Huang, Y.; Chen, C.; Shen, Y. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 2855.
[833] Rieke, R.D.; Uhm, S.J. *Synthesis* ***1975***, 452; Bouhlel, E.; Rathke, M.W. *Synth. Commun.* ***1991****, 21*, 133.
[834] Han, B.; Boudjouk, P. *J. Org. Chem.* ***1982****, 47,* 5030.
[835] Ross, N.A.; Bartsch, R.A. *J. Org. Chem.* ***2003****, 68*, 360.
[836] Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* ***1994****, 67*, 1126.
[837] Suh, Y.S.; Rieke, R.D. *Tetrahedron Lett.* ***2004****, 45*, 1807.
[838] Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* ***1994***, 1225.
[839] See Parrish, J.D.; SheHon, D.R.; Little, R.D. *Org. Lett.* ***2003****, 5*, 3615.
[840] Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* ***1999***, 689.

Sm[841] or Sc.[842] The use of additives (e.g., Ge[843] or Me_2Zn)[844] can lead to highly selective reactions.[845] A combination of Zn and an α-bromo ester can be used in conjunction with BF_3•OEt_2, followed by reaction with dibenzoyl peroxide.[846] The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic, or contain various functional groups. Solvents used are generally ethers, including Et_2O, THF, and 1,4-dioxane, although the reaction can be done in water[847] using dibenzoyl peroxide and $MgClO_4$.

With the use of chiral auxiliaries[848] or chiral catalysts,[849] good enantioselectivity[850] can be achieved.

Dialkylzinc compounds are an alternative source of Zn in the *Reformatsky reaction*. The reaction of an α-bromo ester, an aldehyde, and diethylzinc in THF with a Rh catalyst, gave a β-hydroxy ester.[851]

Formally, the reaction is somewhat analogous to the *Grignard reaction* (**16-24**), with $EtO_2C—C—ZnBr$ (**37**) as an intermediate analogous to RMgX.[852] There *is* an intermediate derived from Zn and the ester, the structure of which has been shown to be **38**, by X-ray crystallography of the solid intermediate prepared from *t*-$BuOCOCH_2Br$ and Zn.[853] As can be seen, it has some of the characteristics of **37**.



38 R = *t*-Bu

After hydrolysis, the alcohol is the usual product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an alkene. By the use of Bu_3P along with Zn, the alkene can be made the main product,[854] making this an alternative to the *Wittig reaction* (**16-44**). The alkene is also the product when K_2CO_3/$NaHCO_3$ is used

[841] Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* ***1995***, 197; Arime, T.; Takahashi, H.; Kobayashi, S.; Yamaguchi, S.; Mori, N. *Synth. Commun.* ***1995****, 25*, 389; Park, H.S.; Lee, I.S.; Kim, Y.H. *Tetrahedron Lett.* ***1995****, 36*, 1673; Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* ***1987****, 109*, 6556.

[842] Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* ***1998****, 39*, 8465.

[843] Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org.Chem.* ***1998****, 63*, 691.

[844] Cozzi, P.G. Angew. Chem. Int. Ed. **2006**, 45, 2951.

[845] Cozzi, P.G. Angew. Chem. Int. Ed. **2007**, 46, 2568.

[846] Chattopadhyay, A.; Salaskar, A. *Synthesis* ***2000***, 561.

[847] Bieber, L.W.; Malvestiti, I.; Storch, E.C. *J. Org. Chem.* ***1997****, 62*, 9061.

[848] See Orsini, F.; Sello, G.; Manzo, A.M.; Lucci, E.M. *Tetrahedron Asymmetry* ***2005****, 16,* 1913.

[849] Kloetzing, R.J.; Thaler, T.; Knochel, P. *Org. Lett.* ***2006****, 8,* 1125; Shin, E.-k.; Kim, H.J.; Kim, Y.; Kim, Y.; Park, Y.S. *Tetrahedron Lett.* ***2006****, 47,* 1933; Emmerson, D.P.G.; Hems, W.P.; Davis, B.G. *Tetrahedron Asymmetry* ***2005****, 16,* 213; Fernández-Ibáñez, M.A.; Maciá, B.; Minnaard, A.J.; Feringa, B.L. *Angew. Chem. Int. Ed.* ***2008****, 47,* 1317; *Chem. Commun.* ***2008***, 2571; Cozzi, P.G.; Mignogna, A.; Zoli, L. *Pure Appl. Chem.* ***2008****, 80*, 891.

[850] See Ribeiro, C.M.R.; de S. Santos, E.; de O. Jardim, A.H.; Maia, M.P.; da Silva, F.C.; Moreira, A.P.D.; Ferreira, V.F. *Tetrahedron Asymmetry* ***2002****, 13*, 1703.

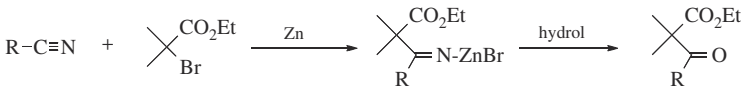
[851] Kanai, K.; Wakabyashi, H.; Honda, T. *Org. Lett.* ***2000****, 2*, 2549.

[852] See Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P.; Fakultatea, K.; Unibertsitatea, E.H.; Lecea, B. *Tetrahedron Lett.* ***1993****, 34*, 6111.

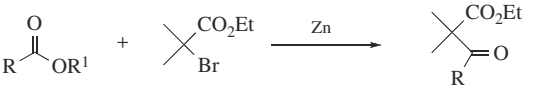
[853] Dekker, J.; Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M.; Spek, A.L. *Organometallics* ***1984****, 3,* 1403.

[854] Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* ***1988****, 29,* 6119. For another method, see Huang, Y.; Shi, L.; Li, S.; Wen, X. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 2397.

with 2% PEG–telluride.[855] Since *Grignard reagents* cannot be formed from α-halo esters, the method is quite useful, but competing reactions sometimes lead to low yields. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles[856]:



Carboxylic esters have also been used as substrates, but then, as might be expected (Sec. 16.A), the result is substitution and not addition:



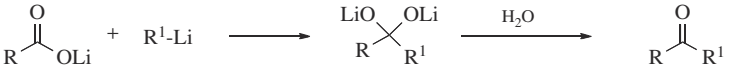
The product in this case is the same as with the corresponding nitrile, though the pathways are different. The reaction is compatible with amine substituents, and α-(*N,N*-dibenzyl) amino aldehydes have been used to prepare β-hydroxy-γ-(*N,N*-dibenzylamino) esters with good antiselectivity.[857]

For an alternative approach involving ester enolates, see Reaction **16-36**.

OS **3**, 408; **4**, 120, 444; **6**, 598; **IX**, 275.

16-29 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[858] The carboxylate salt is formed by reaction of the carboxylic acid with 1 molar equivalent of R^1Li. The R′ group may be aryl or primary, secondary, or tertiary alkyl and R may be alkyl or aryl. The compounds MeLi and PhLi have been employed most often. Tertiary alcohols are side products. Lithium acetate can be used, but generally gives low yields. Using R(PrNH)Mg, carboxylic acid salts react to form ketones.[859]

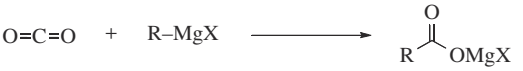
A variation of this transformation reacts the acid with lithium naphthalenide in the presence of 1-chlorobutane. The product is the ketone.[860] A related reaction treats the lithium carboxylate with lithium metal and the alkyl halide, with sonication, to give the ketone.[861] Phenylboronic acid (Reaction **12-28**) reacts with aryl carboxylic acids in the presence of a Pd catalyst and disuccinoyl carbonate to give a diaryl ketone.[862]

OS **V**, 775.

[855] Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* ***2002****, 67*, 3096.
[856] See Hannick, S.M.; Kishi, Y. *J. Org. Chem.* ***1983****, 48,* 3833.
[857] Andrés, J.M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* ***2001****, 57*, 8521.
[858] See Jorgenson, M.J. *Org. React.* ***1970****, 18,* 1; Rubottom, G.M.; Kim, C. *J. Org. Chem.* ***1983****, 48,* 1550.
[859] Ohki, M.; Asaoka, M. *Chem. Lett.* ***2009****, 38*, 856.
[860] Alonso, F.; Lorenzo, E.; Yus, M. *J. Org. Chem. ,* ***1996****, 61*, 6058.
[861] Aurell, M.J.; Danhui, Y.; Einhorn, J.; Einhorn, C.; Luche, J.L. *Synlett* ***1995***, 459. Also see, Aurell, M.J.; Einhorn, C.; Einhorn, J.; Luche, J.L. *J. Org. Chem.* ***1995****, 60*, 8.
[862] Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2001***, 2084.

16-30 The Addition of Organometallic Compounds to CO_2 and CS_2

C-Alkyl-*O*-halomagnesio-addition



Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone,[863] but the product is the salt of a carboxylic acid. The reaction is usually performed by adding the *Grignard reagent* to dry ice. Many carboxylic acids have been prepared in this manner, and this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi,[864] RNa, RCaX, RBa,[865] etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO_2 to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also, Reaction **16-42**).

Aryl organoboronates react with CO_2, in the presence of a Ru catalyst, to give the corresponding aryl carboxylic acid.[866] Aryl and alkenyl boronic esters are carboxylated in the presence of a Cu catalyst.[867] Vinyl halides react with CO and water, with a Pd catalyst in an ionic liquid, to give the conjugated carboxylic acid.[868] Organozinc compounds are carboxylated with CO_2 and a Ni catalyst.[869] Metal-free carboxylation of organozinc reagents is also known.[870] In the presence of CO_2 and an organocatalyst, aromatic aldehydes are converted to the corresponding carboxylic acid.[871] Direct carboxylation of aryl bromides is possible using CO_2 and a Pd catalyst.[872] Allenes are converted to β,γ-unsaturated acids with CO_2 in the presence of Et_2Zn.[873]

When chiral additives (e.g., (−)-sparteine) have added to the initial reaction with the organolithium reagent, quenching with CO_2 produces carboxylic acids with good asymmetric induction.[874]

In a closely related reaction, *Grignard reagents* add to CS_2 to give salts of dithiocarboxylic acids.[875] These salts can be trapped with amines to form thioamides.[876] Two other reactions are worthy of note. (1) Lithium dialkylcopper reagents react with

[863] See Volpin, M.E.; Kolomnikov, I.S. *Organomet. React.* ***1975****, 5*, 313; Sneeden, R.P.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 137–173; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 913–948. For a more general review, see Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* ***1981****, 50*, 63.

[864] For a kinetic study, see Nudelman, N.S.; Doctorovich, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1233.

[865] Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* ***1992***, 593.

[866] Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2006****, 128*, 8706.

[867] Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* ***2008****, 10*, 2697.

[868] Zhao, X.; Alper, H.; Yu, Z. J. *Org. Chem.* ***2006****, 71*, 3988.

[869] Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2008****, 10*, 2681.

[870] Kobayashi, K.; Kondo, Y. *Org. Lett.* ***2009****, 11,* 2035.

[871] Nair, V.; Varghese, V.; Paul, R.P.; Jose, A.; Sinu, C.R.; Menon, R.S. *Org. Lett.* ***2010****, 12,* 2653.

[872] Correa, A.; Martín, R. *J. Am. Chem. Soc.* ***2009****, 131,* 15974.

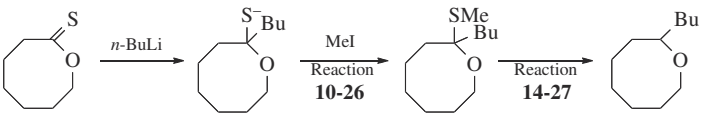
[873] North, M. *Angew. Chem. Int. Ed.* ***2009****, 48*, 4104.

[874] Park, Y.S.; Beak, P. *J. Org. Chem.* ***1997****, 62*, 1574.

[875] See Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K. *Synthesis* ***1983***, 605.

[876] Katritzky, A.R.; Moutou, J.-L.; Yang, Z. *Synlett* ***1995***, 99.

dithiocarboxylic esters to give tertiary thiols.[877] (2) Thiono lactones can be converted to cyclic ethers,[878] for example:



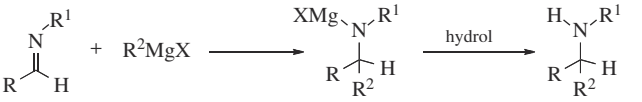
This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, e.g., Reaction **16-63**) by reaction **16-11**.

A terminal alkyne can be converted to the anion under electrolytic conditions, in the presence of CO_2, to give propargylic acids ($R—C{\equiv}C—CO_2H$).[879]

OS **I**, 361, 524; **II**, 425; **III**, 413, 553, 555; **V**, 890, 1043; **VI**, 845; **IX**, 317.

16-31 The Addition of Organometallic Compounds to C=N Compounds

***N*-Hydro-*C*-alkyl-addition**



Aldimines can be converted to secondary amines by treatment with *Grignard reagents*.[880] Ketimines generally react with *Grignard reagents* to give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[881] The solvent and the aggregation state of the organolithium play a role in the addition, however.[882] For the addition of an organometallic compound to an imine to give a primary amine, R′ in RCH=NR′ would have to be H, and such compounds are seldom stable. However, the conversion has been done for R = aryl, by the use of the masked reagents $(ArCH{=}N)_2SO_2$ [prepared from an aldehyde, RCHO, and sulfamide, $(NH_2)_2SO_2$]. Addition of R^2MgX or R^2Li to these compounds gives $ArCHR^2NH_2$ after hydrolysis.[883] An intramolecular version of the addition of organolithium reagents is known that gave 2-phenylpyrrolidine.[884] *Grignard reagents* add to imines in the presence of various transition metal catalysts, including $Sc(OTf)_3$[885] or Cp_2ZrCl_2.[886] Alkynes add to imines yielding propargylic amines.[887]

[877] Bertz, S.H.; Dabbagh, G.; Williams, L.M. *J. Org. Chem.* ***1985****, 50*, 4414.
[878] Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Veale, C.A.; Furst, G.T. *J. Am. Chem. Soc.* ***1987****, 109*, 2504.
[879] Köster, F.; Dinjus, E.; Duñach, E. *Eur. J. Org. Chem.* ***2001***, 2507.
[880] See Harada, K. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 266–272; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1204–1227; Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* ***1996****, 37*, 4187; Bambridge, K.; Begley, M.J.; Simpkins, N.S. *Tetrahedron Lett.* ***1994****, 35*, 3391.
[881] Huet, J. *Bull. Soc. Chim. Fr.* ***1964***, 952, 960, 967, 973.
[882] Qu, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2005****, 127,* 10820; *J. Am. Chem. Soc.* ***2006****, 128,* 9355.
[883] Davis, F.A.; Giangiordano, M.A.; Starner, W.E. *Tetrahedron Lett.* ***1986****, 27*, 3957.
[884] Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* ***2001****, 66*, 6207.
[885] Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* ***2001***, 1859.
[886] Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* ***2001***, 3677.
[887] Zani, L.; Bolm, C. *Chem. Commun.* ***2006***, 4263.

When chiral additives are used in conjunction with the organolithium reagent, chiral amines are produced[888] with good asymmetric induction.[889] Chiral auxiliaries have been used in addition reactions of organometallic compounds to imines,[890] and to oxime derivatives.[891] Transition metal asymmetric alkylation of imines uses metal compounds of Cu.[892] Chiral catalysts lead to enantioselective addition of alkynes to imines to give the amine.[893] Chiral *N*-sulfinylimines reaction with lithium silanes give the α-silylsulfinylamine.[894]

Zinc metal reacts with allylic bromides to form an allylic zinc complex, which reacts with imines to give the homoallylic amine.[895] This reaction is catalyzed by TMSCl.[896] Dialkylzinc reagents add to functionalized imines to give the functionalized amine, often with transition metal catalysts (e.g., Ni compounds).[897] Dialkylzinc reagents add to *N*-tosyl imines to give the alkylated tosylamine.[898] In the presence of a chiral ligand, the metal-catalyzed reaction proceeds with good enantioselectivity.[899] With a Cu catalyst and a chiral ligand the product is formed with good enantioselectivity.[900] The reaction of imines (e.g., $ArN{=}CHCO_2Et$), where R = a chiral benzylic substituent and $ZnBr_2$, followed by R′ZnBr leads to a chiral α-amino ester.[901] Terminal alkynes add to imines using $ZnCl_2$ and TMSCl, and with a chiral ligand attached to nitrogen the reaction proceeds with some enantioselectivity.[902] Dimethylzinc has been used to mediate the addition of terminal alkynes to *N*-tosylimines.[903]

[888] For a review see Enders, D.; Reinhold, U. *Tetrahedron Asymmetry,* ***1997****, 8*, 1895.

[889] Denmark, S.E.; Stiff, C.M. *J. Org. Chem.* ***2000****, 65*, 5875; Chrzanowska, M.; Sokołowska, J. *Tetrahedron Asymmetry* ***2001****, 12*, 1435.

[890] See Friestad, G.K.; Mathies, A.K. *Tetrahedron* ***2007****, 63,* 2541; Ferraris, D. *Tetrahedron* ***2007****, 63,* 9581.

[891] Dieter, R.K.; Datar, R. *Can. J. Chem.* ***1993****, 71*, 814.

[892] Yamada, K.-i.; Tomioka, K. *Chem. Rev.* ***2008****, 108,* 2874.

[893] Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* ***2008****, 49,* 379; Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2007****, 18,* 396; Liu, B.; Huang, L.; Liu, J.; Zhong, Y.; Li, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2007****, 18,* 2901; Zani, L.; Eichhorn, T.; Bolm, C. *Chem.: Eur. J.* ***2007****, 13,* 2587; Ding, H.; Friestad, G.K. *Synthesis* ***2005***, 2815; Zhou, C.-Y.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2010****, 132*, 10955.

[894] Ballweg, D.M.; Miller, R.C.; Gray, D.L.; Scheidt, K.A. *Org. Lett.* ***2005****, 7,* 1403.

[895] Lee, C.-L.K.; Ling, H.-Y.; Loh, T.-P. *J. Org. Chem.* ***2004****, 69,* 7787. See van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R.M.; Broxterman, Q.B. *Org. Lett.* ***2001****, 3*, 3943.

[896] Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* ***2003****, 68*, 6444.

[897] Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* ***2006****, 8*, 139; Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron* ***2007****, 63,* 1167.

[898] See Dickstein, J.S.; Fennie, M.W.; Norman, A.L.; Paulose, B.J.; Kozlowski, M.C. *J. Am. Chem. Soc.* ***2008****, 130*, 15794; Gao, F.; Deng, M.; Qian, C. *Tetrahedron* ***2005****, 61,* 12238.

[899] See Fu, P.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008****, 130,* 5530; Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* ***2006****, 8,* 979; Basra, S.; Fennie, M.W.; Kozlowski, M.C. *Org. Lett.* ***2006****, 8,* 2659; Charette, A.B.; Boezio, A.A.; Côté, A.; Moreau, E.; Pytkowicz, J.; Desrosiers, J.-N.; Legault, C. *Pure Appl. Chem.* ***2005****, 77*,1259.

[900] Fujihara, H.; Nagai, K.; Yomioka, K. *J. Am. Chem. Soc.* ***2000****, 122*, 12055. See Wang, C.-J.; Shi, M. *J. Org. Chem.* ***2003****, 68*, 6229.

[901] Chiev, K.P.; Roland, S.; Mangeney, P. *Tetrahedron Asymmetry* ***2001****, 13*, 2205.

[902] Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2003****, 44,* 6767.

[903] Zani, L.; Alesi, S.; Cozzi, P.G.; Bolm, C. *J. Org. Chem.* ***2006****, 71,* 1558.

Other organometallic compounds add to aldimines,[904] including Sn,[905] Sm,[906] Ge,[907] Zr,[908] Ga metal with ultrasound,[909] Yb with Me_3SiCl,[910] and In.[911] Catalytic amounts of the metal compound can be used with an allylic stannane.[912] Catalytic enantioselective addition reactions with these organometallics are well known,[913] including reactions in an ionic liquid.[914] Aryltrialkylstannanes add the aryl group to N-tosyl imines using a Rh catalyst and sonication.[915] Allylic halides react with imines in the presence of In metal[916] or $InCl_3$[917] to give the homoallylic amine, and with N-sulfonyl imines to give the homoallylic sulfonamide.[918] In this latter reaction, antiselectivity was observed when the reaction was done in water, and syn selectivity when done in aq THF.[919] Aryl iodides add to *N*-aryl imines in the presence of a Rh catalyst.[920] Arylation of *N*-tosyl ketimines proceeds with good enantioselectivity using a Rh catalyst.[921] Propargylic halides add to imines in the presence of In metal, in aq THF.[922]

Terminal alkynes react with aryl aldehydes and aryl amines to give propargylic amine without a catalyst.[923] Alternatively, with an Ir[924] or a Cu catalyst[925] they also lead to a propargylic amine.[926] Terminal alkynes add to *N*-substituted imines to give a propargylic amine with good enantioselectivity using a chiral Cu complex.[927] Lithium alkyne anions add to chiral *N*-sulfinylimines, in the presence of Me_3Al, to give the chiral propargyl

[904] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 847–863.
[905] Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998****, 120*, 4242; Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* ***1997***, 1099.
[906] See Kim, B.; Han, R.; Park, R.; Bai, K.; Jun, Y.; Baik, W. *Synth. Commun.* ***2001****, 31*, 2297.
[907] Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* ***1999***, 2191.
[908] With a Cu catalyst, see Sato, A.; Ito, H.; Okada, M.; Nakamura, Y.; Taguchi, T. *Tetrahedron Lett.* ***2005****, 46*, 8381.
[909] Andrews, P.C.; Peatt, A.C.; Raston, C.L. *Tetrahedron Lett.* ***2004****, 45*, 243.
[910] Su, W.; Li, J.; Zhang, Y. *Synth. Commun.* ***2001****, 31,* 273.
[911] Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G.R.; Lloyd-Jones, G.C.; Shepperson, I.R. *J. Am. Chem. Soc.* ***2007****, 129,* 3846. With a Cu catalyst, see Black, D.A.; Arndtsen, B.A. *Org. Lett.* ***2006****, 8,* 1991.
[912] **Al**: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* ***2003****, 125*, 3720. **La**: Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002****, 43*, 323. **Nb**: Andrade, C.K.Z.; Oliveira, G.R. *Tetrahedron Lett.* ***2002****, 43*, 1935; Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1157. **Pd**: Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004****, 69*, 3562. **Ta**: Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2004****, 69*, 2185. **Zr**: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2001****, 40*, 1896.
[913] See Kobayashi, Sh.; Ishitani, H. *Chem. Rev.* ***1999****, 99*, 1069.
[914] Chowdari, N.S.; Ramachary, D.B.; Barbas, III, C.F. *Synlett* ***2003***, 1906.
[915] Ding, R.; Zhao, C.H.; Chen, Y.J.; Lu, L.; Wang, D.; Li, C.J. *Tetrahedron Lett.* ***2004****, 45*, 2995.
[916] Choucair, B.; Léon, H.; Miré, M.-A.; Lebreton, C.; Mosset, P. *Org. Lett.* ***2000****, 2*, 1851. See Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* ***2003****, 68*, 1309.
[917] Under electrolysis conditions, see Hilt, G.; Smolko, K.I.; Waloch, C. *Tetrahedron Lett.* ***2002****, 43*, 1437.
[918] Lu, W.; Chan, T.H. *J. Org. Chem.* ***2000****, 65*, 8589.
[919] Lu, W.; Chan, T.H. *J. Org. Chem.* ***2001****, 66*, 3467.
[920] Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* ***2000****, 122*, 12043.
[921] Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* ***2010****, 132,* 13168.
[922] Prajapati, D.; Laskar, D.D.; Gogoi, B.J.; Devi, G. *Tetrahedron Lett.* ***2003****, 44*, 6755.
[923] Li, C.-J.; Wei, C. *Chem. Commun.* ***2002***, 268.
[924] Fischer, C.; Carreira, E.M. *Synthesis* ***2004***, 1497.
[925] Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* ***2003****, 9*, 2797.
[926] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2002****, 124*, 5638.
[927] See Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* ***2006****, 71*, 2064.

compound.[928] Diynes add to *N*-sulfinyl imines in the presence of a chiral Rh catalyst to give the corresponding allylic sulfinylamine.[929] Alkenes add to N-sulfonyl imines in the presence of a chiral Rh catalyst to give the alkylated sulfonamide.[930]

Triethylaluminum adds an ethyl group to an imine in the presence of a Eu catalyst. Reaction with $PhSnMe_3$ and *N*-tosylimines with a Rh catalyst leads to addition of a phenyl group to the carbon of the C=N bond.[931] Other *N*-sulfonyl imines react similarly to give the corresponding sulfonamide, and in the presence of a chiral ligand the reaction proceeds to good enantioselectivity.[932] *N*-Tosyl imines also react with dialkylzinc reagents, giving the sulfonamide with modest enantioselectivity.[933] *N*-Sulfinyl imines [$R_2CH{=}NS(=O)R'$][934] react with Grignard reagents at carbon to give the corresponding *N*-sulfinylamine.[935] Furan derivatives add via C-2 with good enantioselectivity using a chiral phosphoric acid catalyst.[936] Alkenes add to *N*-tosyl imines with a Yb catalyst[937] and allenes add to *N*-carbamoyl imines in the presence of a V catalyst.[938] *N*-Carbamoyl imines, formed *in situ*, react with allylic silanes in the presence of an iodine catalyst.[939] *N*-Carbamoyl imines add acetonitrile (via carbon) using DBU and a Ru catalyst.[940]

Arylboronates (Reaction **12-28**) add to *N*-sulfonyl imines in the presence of a Rh catalyst to give the corresponding sulfonamide.[941] Chiral Cu complexes have also been used for effective allylation of ketimines.[942] Aryl boronic acids (Reaction **12-28**) add the aryl group to *N*-tosyl imines using a Rh[943] or Pd[944] catalyst. Arylboronic acids react similarly, and in the presence of a chiral Rh[945] or Ir[946] catalyst give a chiral sulfinamide or sulfonamide. Allylic boronates also add to aldehydes, and subsequent treatment with ammonia gives the homoallylic amine.[947] Vinyl boronates add to nitrones in the presence of Me_2Zn, transferring the vinyl group to the C=N unit.[948] Potassium allyltrifluoroborates react with *N*-tosyllimines in the presence of a Pd catalyst.[949]

[928] Patterson, A.W.; Ellman, J.A. *J. Org. Chem.* ***2006****, 71,* 7110.
[929] Kong, J.-R.; Cho, C.-W.; Krische, M.J. *J. Am. Chem. Soc.* ***2005****, 127*, 11269.
[930] Komanduri, V.; Grant, C.D.; Krische, M.J. *J. Am. Chem. Soc.* ***2008****, 130,* 12592.
[931] Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* ***1999****, 40*, 9259.
[932] Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* ***2000****, 122*, 976.
[933] Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* ***2003****, 68*, 9723.
[934] See Ellman, J.A.; Owens, T.D.; Tang, T.P. *Acc. Chem. Res.* ***2002****, 35,* 984.
[935] Tang, T.P.; Volkman, S.K.; Ellman, J.A. *J. Org. Chem.* ***2001****, 66*, 8772.
[936] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* ***2004****, 126*, 11804. See also, Spanedda, M.V.; Ourévitch, M.; Crouse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* ***2004****, 45*, 5023.
[937] Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* ***2003****, 68*, 3112.
[938] Trost, B.M.; Jonasson, C. *Angew. Chem. Int. Ed.* ***2003****, 42*, 2063.
[939] Phukan, P. *J. Org. Chem.* ***2004****, 69*, 4005.
[940] Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004****, 126*, 13632.
[941] Ueda, M.; Saito, A.; Miyaura, N. *Synlett* ***2000***, 1637.
[942] Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2006****, 128,* 7687.
[943] Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* ***2006****, 8*, 2567; Trincado, M.; Ellman, J.A. *Angew. Chem. Int. Ed.* ***2008****, 47,* 5623; Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett* ***2007***, 2213.
[944] Zhang, Q.; Chen, J.; Liu, M.; Wu, H.; Cheng, J.; Qin, C.; Su, W.; Ding, J. *Synlett* ***2008***, 935.
[945] Weix, D.J.; Shi, Y.; Ellman, J.A. *J. Am. Chem. Soc.* ***2005****, 127,* 1092; Beenen, M.A.; Weix, D.J.; Ellman, J.A. *J. Am. Chem. Soc.* ***2006****, 128,* 6304; Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2007****, 129,* 5336.
[946] Ngai, M.-Y.; Barchuk, A.; Krische, M.J. *J. Am. Chem. Soc.* ***2007****, 129,* 12644.
[947] Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004****, 126*, 7182.
[948] Pandya, A.; Pinet, S.U.; Chavant, P.Y.; Vallée, Y. *Eur. J. Org. Chem.* ***2003***, 3621.
[949] Solin, N.; Wallner, O.A.; Szabó, K.J. *Org. Lett.* ***2005****, 7,* 689.

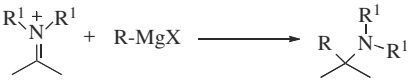
Allylic silanes (e.g., allyltrimethylsilane) add to *N*-substituted imines in the presence of a Pd catalyst to give the homoallylic amine.[950] Similar results are obtained when the allylic silane and imine are treated with a catalytic amount of tetrabutylammonium fluoride.[951] Allylic trichlorosilanes add to hydrazones to give homoallylic hydrazine derivatives with excellent antiselectivity[952] and with good enantioselectivity using a chiral ligand.[953] Chiral allylic silane derivatives have been developed, and add to hydrazones with good enantioselectivity.[954]

There is an *aza-Balyis–Hillman reaction* that converts imines and conjugated carbonyl derivatives to the α-amino conjugated derivative.[955] *N*-Tosyl imines can be used in place of aldehydes, and the reaction of the imine, a conjugated ester and DABCO gave the allylic *N*-tosylimine.[956] A "double *Baylis–Hillman*" *reaction* has also been reported using *N*-tosylimines and conjugated ketones.[957] The use of chiral catalysts leads enantioselective product formation.[958] An enantioselective aza-*Baylis–Hillman reaction*[959] was reported using as chiral reaction medium.[960] Aldehydes add via the α carbon using proline, to give β-amino aldehydes with good selectivity to give chiral β-amino aldehydes.[961]

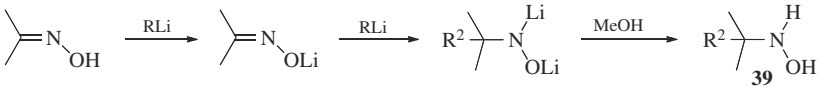
Silyl enol ethers add to hydrazones in the presence of ZnF_2 and a chiral ligand to give chiral β-hydrazino ketones.[962] Similar addition to imine derivatives was accomplished using ketene silyl acetals and Amberlyst-15.[963] Alternatively, an imine is reacted first with $Zn(OTf)_2$ and then with a ketene silyl acetal.[964]

Nitro compounds add to *N*-carbamoyl imines with a chiral diamine catalyst with some enantioselectivity.[965] Nitro compounds add via carbon using a Cu catalyst, and with good enantioselectivity when a chiral ligand is used.[966] The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $ClCH{=}NMe_2^+\ Cl^-$ to give oximes: $RCH{=}N(O)OLi + R'MgX \rightarrow RR'C{=}NOH$.[967]

[950] Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***1999****, 64*, 2614.
[951] See Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004****, 69*, 735.
[952] Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2001****, 123*, 9493.
[953] Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* ***2003****, 125*, 6610.
[954] Berger, R.; Duff, K.; Leighton, J.L. *J. Am. Chem. Soc.* ***2004****, 126*, 5686.
[955] Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* ***2009****, 109*, 1. See Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* ***2005****, 127,* 3680; Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* ***2005****, 127,* 3790; Gajda, A.; Gajda, T. *J. Org. Chem.* ***2008****, 73,* 8643.
[956] Xu, Y.-M.; Shi, M. *J. Org. Chem.* ***2004****, 69*, 417.
[957] Shi, M.; Xu, Y.-M. *J. Org. Chem.* ***2003****, 68*, 4784.
[958] Qi, M.-J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron* ***2008****, 64,* 1181; Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas III, C.F. *Angew. Chem. Int. Ed.* ***2007****, 46,* 1878.
[959] See Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* ***2007****, 46,* 4614.
[960] Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C.W.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* ***2006****, 45*, 3689.
[961] Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N.S.; Turner, J.M.; Thayumanavan, R.; Barbas, III, C.F. *J. Org. Chem.* ***2003****, 68*, 9624; Chowdari, N.S.; Suri, J.T.; Barbas, III, C.F. *Org. Lett.* ***2004****, 6,* 2507.
[962] Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004****, 126*, 7768. For a similar reaction using a Bi catalyst, see Ollevier, T.; Nadeau, E. *J. Org. Chem.* ***2004****, 69*, 9292.
[963] Shimizu, M.; Itohara, S.; Hase, E. *Chem. Commun.* ***2001***, 2318.
[964] Ishimaru, K.; Kojima, T. *J. Org. Chem.* ***2003****, 68*, 4959.
[965] Nugent, B.M.; Yoder, R.A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004****, 126*, 3418.
[966] Nishiwaki, N.; Knudson, K.R.; Gothelf, K.V.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001****, 40*, 2992.
[967] Fujisawa, T.; Kurita, Y.; Sato, T. *Chem. Lett.* ***1983***, 1537.



Iminium salts[968] give tertiary amines directly, via 1,2-addition to the C=N unit. Chloroiminium salts [ClCH=NR_2'Cl^-, generated *in situ* from an amide ($HCONR_2$') and phosgene ($COCl_2$)] react with 2 molar equivalents of a *Grignard reagent* RMgX, one adding to the C=N and the other replacing the Cl, to give tertiary amines R_2CHNR_2'.[969]



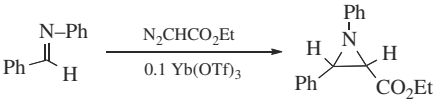
Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give 1,2-addition when treated with *Grignard reagents*, while some gave reductions and others gave miscellaneous reactions. Organocerium reagents add to hydrazones.[970] Indium metal promotes the addition of alkyl iodides to hydrazones.[971] A hydrazone can be formed *in situ* by reacting an aldehyde with a hydrazine derivative. In the presence of tetrallyltin and a Sc catalysts, homoallylic hydrazine derivatives are formed.[972] Hydrazone derivatives react with iodoalkenes in the presence of $InCl_3$ and $Mn_2(CO)_{10}$ under photochemical conditions to give the hydrazine derivative.[973] Ketene dithioacetals add to hydrazones using a chiral Zr catalyst to give a pyrazolidine.[974] Oximes can be converted to hydroxylamines (**39**) by treatment with 2 molar equivalents of an alkyllithium reagent, followed by methanol.[975] Oxime ethers add an allyl group upon reaction with allyl bromide and In metal in water.[976] Nitrones [$R_2C{=}N^+(R')—O^-$] react with allylic bromides and Sm to give homoallylic oximes,[977] and with terminal alkynes and a Zn catalyst to give propargylic oximes.[978] *Grignard reagents* also add to nitrones.[979] Nitrones react with $CH_2{=}CHCH_2InBr$ in aq DMF to give the homoallylic oxime[980] and silyl ketene acetals add in the presence of a chiral Ti catalyst to good enantioselectivity.[981]

Allylic alcohols add to imines in the presence of a Pd catalyst to give the homoallylic amine.[982]

OS **IV**, 605; **VI**, 64. Also see, OS **III**, 329.

[968] Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988,*** pp. 275–356.
[969] Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* ***1985***, 2178.
[970] Denmark, S.E.; Edwards, J.P.; Nicaise, O. *J. Org. Chem.* ***1993****, 58*, 569.
[971] Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* ***2004****, 60*, 4227.
[972] Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* ***2001***, 1140.
[973] Friedstad, G.K.; Qin, J. *J. Am. Chem. Soc.* ***2001****, 123*, 9922.
[974] Yamshita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004****, 126*, 11279.
[975] Richey Jr., H.G.; McLane, R.C.; Phillips, C.J. *Tetrahedron Lett.* ***1976***, 233.
[976] Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* ***2003****, 68*, 3348.
[977] Laskar, D.D.; Prajapati, D.; Sandu, J.S. *Tetrahedron Lett.* ***2001****, 42*, 7883.
[978] Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***1999****, 121*, 11245. See Pinet, S.; Pandya, S.U.; Chavant, P.Y.; Ayling, A.; Vallee, Y. *Org. Lett.* ***2002****, 4,* 1463.
[979] See Merino, P.; Tejero, T. *Tetrahedron* ***2001****, 57*, 8125.
[980] Kumar, H.M.S.; Anjaneyulu, S.; Reddy, E.J.; Yadav, J.S. *Tetrahedron Lett.* ***2000****, 41*, 9311.
[981] Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* ***2002****, 124*, 2888.
[982] Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* ***2005****, 7,* 637.

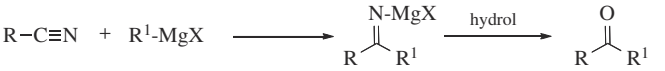
16-32 Addition of Carbenes and Diazoalkanes to C=N Compounds



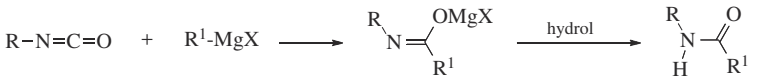
In the presence of metal catalysts [e.g., $Yb(OTf)_3$], diazoalkanes add to imines to generate aziridines.[983] The reaction is somewhat selective for the cis-diastereomer. The use of chiral additives in this reaction leads to aziridines enantioselectively.[984] Imines can be formed by the reaction of an aldehyde and an amine, and subsequent treatment with Me_3SiI and butyllithium gives an aziridine.[985] *N*-Tosyl imines react with diazoalkenes to form *N*-tosyl aziridines, with good cis selectivity[986] and modest enantioselectivity in the presence of a chiral Cu catalyst,[987] but give excellent enantioselectivity with a chiral Rh catalyst[988] or with the use of an organocatalyst.[989] Note that *N*-tosyl aziridines are formed by the reaction of an alkene with PhI=NTs and a Cu catalyst.[990] *N*-Acylimines react with diazoesters via C—H insertion using a Pt catalyst.[991] The reaction of alkenes with diazo compounds is discussed in Reaction **15-53**.

16-33 The Addition of Grignard Reagents to Nitriles and Isocyanates

Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)



***N*-Hydro-*C*-alkyl-addition**



Ketones can be prepared by addition of *Grignard reagents* to nitriles, followed by hydrolysis of the initially formed imine anion. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[992] Yields can be improved by the use of Cu(I) salts[993] or by using benzene containing 1 equiv of ether as the

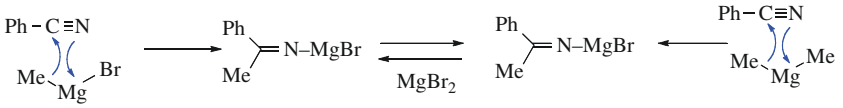
[983] See Nagayama, S.; Kobayashi, S. *Chem Lett.* ***1998***, 685. Also see, Rasmussen, K.G.; Jørgensen, K.A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1401.
[984] See Janardanan, D.; Sunoj, R.B. *J. Org. Chem.* ***2008****, 73,* 8163.
[985] Reetz, M.T.; Lee, W.K. *Org. Lett.* ***2001****, 3*, 3119.
[986] Krumper, J.R.; Gerisch, M.; Suh, J.M.; Bergman, R.G.; Tilley, T.D. *J. Org. Chem.* ***2003****, 68*, 9705; Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004****, 126*, 1612.
[987] Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2293.
[988] Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001****, 40*, 1433.
[989] Lu, Z.; Zhang, Y.; Wulff, W.D. *J. Am. Chem. Soc.* ***2007****, 129,* 7185. Also see Branco, P.S.; Raje, V.P.; Dourado, J.; Gordo, J. *Org. Biomol. Chem.* ***2010****, 8,* 2968.
[990] Handy, S.T.; Czopp, M. *Org. Lett.* ***2001****, 3*, 1423.
[991] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* ***2005****, 127,* 9360.
[992] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 767–845.
[993] Weiberth, F.J.; Hall, S.S. *J. Org. Chem.* ***1987****, 52*, 3901.

solvent, rather than ether alone.[994] In general, the ketimine salt does not react with *Grignard reagents*: Hence, tertiary alcohols or tertiary alkyl amines are not often side products.[995] By careful hydrolysis of the salt, it is sometimes possible to isolate ketimines ($RR'C{=}NH$),[996] especially when R and R′ = aryl. The addition of *Grignard reagents* to the C≡N group is normally slower than to the C=O group, and cyano group containing aldehydes add the *Grignard reagent* without disturbing the CN group.[997] Organolithium reagents add to nitriles, mediated by LiBr, to form N-acetyl enamines.[998] Other metal compounds have been used, including Sm with allylic halides[999] and organocerium compounds (e.g., $MeCeCl_2$).[1000] Allylic halides react with an excess of Zn metal in the presence of 40% $AlCl_3$ and in the presence of a nitrile, to give homoallylic ketones after hydrolysis.[1001]

Addition of *Grignard reagents*[1002] or organolithium reagents[1003] to ω-halo nitriles leads to 2-substituted cyclic imines.

The *Blaise reaction* is the reaction of the organozinc reagent derived from a α-bromoester with Zn metal and a nitrile to give the corresponding β-ketoester.[1004]

The following mechanism has been proposed for the reaction of the methyl *Grignard reagent* with benzonitrile[1005]:



Arylboronic acids add to nitriles in the presence of a Pd catalyst.[1006] Aryl and alkenylboronic acids add to isocyanates in the presence of a Pd[1007] or Rh[1008] catalyst.

Arenes add to nitriles in the presence of a Pd catalyst in DMSO/trifluoroacetic acid to give a diaryl ketone.[1009]

The addition of *Grignard reagents* to isocyanates gives, after hydrolysis, *N*-substituted amides.[1010] This is a very good reaction and can be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[1011]

[994] Canonne, P.; Foscolos, G.B.; Lemay, G. *Tetrahedron Lett.* ***1980***, 155.
[995] See Gauthier, R.; Axiotis, G.P.; Chastrette, M. *J. Organomet. Chem.* ***1977****, 140,* 245.
[996] Pickard, P.L.; Toblert, T.L. *J. Org. Chem.* ***1961****, 26*, 4886.
[997] Cason, J.; Kraus, K.W.; McLeod, Jr., W.D. *J. Org. Chem.* ***1959****, 24,* 392.
[998] Savarin, C.G.; Boice, G.N.; Murry, J.A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* ***2006****, 8,* 3903.
[999] Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* ***1997****, 27*, 1495.
[1000] Ciganek, E. *J. Org. Chem.* ***1992****, 57*, 4521.
[1001] Lee, A.S.-Y.; Lin, L.-S. *Tetrahedron Lett.* ***2000****, 41*, 8803.
[1002] Fry, D.F.; Fowler, C.B.; Dieter, R.K. *Synlett* ***1994***, 836.
[1003] Gallulo, V.; Dimas, L.; Zezza, C.A.; Smith, M.B. *Org. Prep. Proceed. Int.* ***1989****, 21*, 297.
[1004] Blaise, E.E. *Compt. Rend.* ***1901****, 132*, 478; Rao, H.S.P.R.; Rafi, S.; Padmavathy, K. *Tetrahedron* ***2008****, 64,* 8037.
[1005] Ashby, E.C.; Chao, L.; Neumann, H.M. *J. Am. Chem. Soc.* ***1973****, 95*, 4896, 5186.
[1006] Zhao, B.; Lu, X. *Tetrahedron Lett.* ***2006****, 47*, 6765.
[1007] Kianmehr, E.; Rajabi, A.; Ghanbari, M. *Tetrahedron Lett.* ***2009****, 50*, 1687.
[1008] Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* ***2007***, 3577.
[1009] Zhou, C.; Larock, R.C. *J. Am. Chem. Soc.* ***2004****, 126*, 2302.
[1010] See Screttas, C.G.; Steele, B.R. *Org. Prep. Proced. Int.* ***1990****, 22,* 271.
[1011] Cooke, Jr., M.P.; Pollock, C.M. *J. Org. Chem.* ***1993****, 58*, 7474. For another method, see Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* ***1986****, 27,* 501.

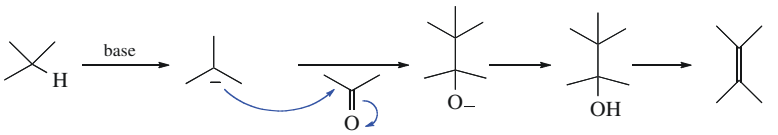
Isothiocyanates give *N*-substituted thioamides. Other organometallic compounds add to isocyanates. Vinyltin reagents lead to conjugate amides.[1012]

Note that terminal alkynes add to the carbon of an isonitrile in the presence of a uranium complex, giving a propargylic imine.[1013]

OSCV **III**, 26, 562; **V**, 120, 520.

G. Carbon Attack by Active Hydrogen Compounds

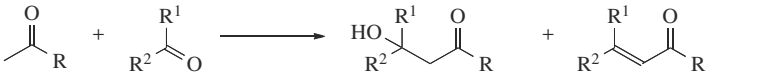
Reactions **16-34**–**16-50** are base-catalyzed condensations (although some of them are also catalyzed to acids).[1014] In Reactions **16-34**–**16-44**, a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.2 illustrates the differences. Reaction **16-50** is an analogous reaction involving addition to C≡N.

16-34 The Aldol Condensation[1015]

***O*-Hydro-*C*-(α-acylalkyl)-addition; α-Acylalkylidine-de-oxo-bisubstitution**



(if an α-H was present)

In the *aldol reaction* or *aldol condensation*[1016] the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[1017] Although acid-catalyzed aldol reactions are known,[1018] the most common form of the reaction uses a base. There is evidence that an SET mechanism can intervene when the substrate is an aromatic

[1012] Niestroj, M.; Neumann, W.P.; Thies, O. *Chem. Ber.* ***1994****, 127*, 1131.

[1013] Barnea, E.; Andrea, T.; Kapon, M.; Berthet, J.-C.; Ephritikhine, M.; Eisen, M.S. *J. Am. Chem. Soc.* ***2004****, 126*, 10860.

[1014] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, , pp. 629–682; Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 567–619. See also, Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.

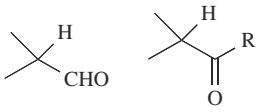
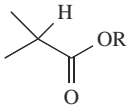
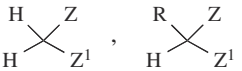
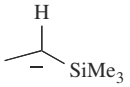
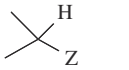
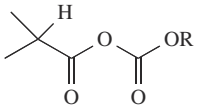
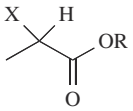
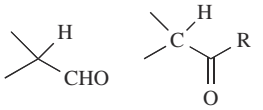
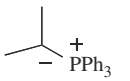
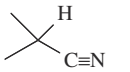
[1015] See Mahrwald, R. *Modern Aldol Reactions*, 2 Volume Set, Wiley, NJ, ***2004***; Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 816–823. For a treatise that discloses Aleksandr Borodin as the discoverer of the aldol condensation, see Podlech, J. *Angew. Chem. Int. Ed.* ***2010****, 49*, 6490.

[1016] This reaction is also called the *aldol condensation*, although, strictly speaking, this term applies to the formation only of the α,β-unsaturated product, and not the aldol.

[1017] See Thebtaranonth, C.; Thebtaranonth, Y. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 199–280, 99–212; Hajos, Z.G. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, ***1979***; pp. 1–84; Nielsen, A.T.; Houlihan, W.J. *Org. React.* ***1968****, 16,* 1.

[1018] See Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* ***1998****, 120*, 413.

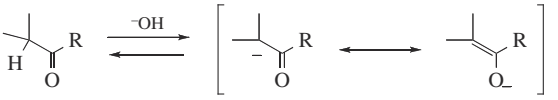
TABLE 16.2 Base-Catalyzed Condensations Showing the Active-Hydrogen Components and the Carbonyl Compounds

Reaction Number	Reaction	Active Hydrogen Component	Carbonyl Component	Subsequent Reaction
16-34	*Aldol*		Aldehyde, ketone	Dehydration may follow
16-36			Aldehyde, ketone (usually without α-hydrogens)	Dehydration may follow
16-38	*Knoevenagel*	 and similar molecules	Aldehyde, ketone (usually without α-hydrogens)	Dehydration usually follows
16-41	*Peterson*		Aldehyde, ketone	Dehydration may follow
16-42		 Z = COR, COOR, NO_2	CO_2, CS_2	
16-39	*Perkin*		Aromatic aldehyde	Dehydration usually follows
16-40	*Darzen's*		Aldehyde, ketone	Epoxidation
16-43	*Tollen's*		Formaldehyde	Crossed-Cannizzaro reaction follows
16-44	*Wittig*		Aldehyde, ketone	Dehydration always follows
16-50	*Thorpe*		Nitrile	

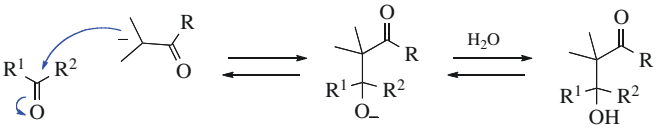
ketone.[1019] Although hydroxide was commonly used in early versions of this reaction, stronger bases [e.g., alkoxides (RO^-) or amides (R_2N^-)] are also common. Amine bases have been used to catalyze the aldol condensation.[1020] Hydroxide ion is not a strong

[1019] Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986****, 51*, 472.
[1020] Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* ***2007****, 129*, 7258. See Erkkilä, A.; Pihko, P.M. *J. Org. Chem.* ***2006****, 71,* 2538.

enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion; that is, the equilibrium lies well to the left, for both aldehydes



and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



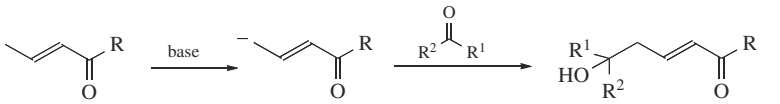
This equilibrium lies further to the right with alkoxide relative to hydroxide, but the equilibrium still lies predominantly to the left. With amide bases, and particularly with aprotic solvents, the equilibrium usually lies much more to the right when compared with alkoxides or hydroxide. Protic solvents, (e.g., water or alcohol) are acidic enough to react with the enolate anion and shift the equilibrium to the left. As noted, in an aprotic solvent (e.g., ether or THF), with a strong amide base (e.g., LDA, sec. Sec. 8.F, category 7), the equilibrium lies more to the right.[1021] A variety of amide bases can be used to deprotonate the ketone or aldehyde, and in the case of an unsymmetrical ketone removal of the more acidic proton leads to the kinetic enolate anion.[1022] Note that a polymer-bound amide base has been used[1023] and solid-phase chiral lithium amides are known.[1024] A polymer-supported phosphoramide has been used as a catalyst for the aldol condensation.[1025]

The product of an aldol condensation is a β-hydroxy aldehyde (called an *aldol*) or a β-hydroxy ketone, which in some cases is dehydrated during the course of the reaction. An aldol is readily isolated unless the substrate is an aromatic aldehyde or ketone when the reaction is done in aprotic solvents with a mild workup procedure. The aldol reaction has been done in ionic liquids.[1026] Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the C=O bond; so that this is a method of preparing α,β-unsaturated aldehydes and ketones, as well as β-hydroxy aldehydes and ketones. One-pot procedures have been reported to give the conjugated product.[1027] The entire reaction is an equilibrium (including the dehydration step), and α,β-unsaturated and β-hydroxy aldehydes and ketones can be cleaved by treatment with $^{-}$OH (the *retrograde aldol reaction*). The retro-aldol condensation has been exploited for crossed-aldol reactions.[1028] A vinylogous (Sec. 6.B) aldol reaction is known[1029] as is a

[1021] See Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* ***2001****, 42*, 7383.
[1022] See Zhao, P.; Lucht, B.L.; Kenkre, S.L.; Collum, D.B. *J. Org. Chem.* ***2004****, 69*, 242; Zhao, P.; Condo, A.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2004****, 126*, 3113.
[1023] Seki, A.; Ishiwata, F.; Takizawa, Y.; Asami, M. *Tetrahedron* ***2004****, 60*, 5001.
[1024] Johansson, A.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron Asymmetry* ***2003****, 14*, 1261.
[1025] Flowers, II, R.A.; Xu, X.; Timmons, C.; Li, G. *Eur. J. Org. Chem.* ***2004***, 2988.
[1026] Zheng, X.; Zhang, Y. *Synth. Commun.* ***2003***, 161.
[1027] Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* ***2002****, 67*, 4615.
[1028] See Simpura, I.; Nevalainen, V. *Angew. Chem. Int. Ed.* ***2000****, 39*, 3422.
[1029] See Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* ***2000****, 100*, 1929; Casiraghi, G.; Zanardi, E.; Rassu, G. *Pure Appl. Chem.* ***2000****, 72*, 1645; Denmark, S.E.; Heemstra, Jr., J.R.; Beutner, G.L. *Angew. Chem. Int. Ed.* ***2005****, 44,* 4782.

'double' aldol.[1030] Enzyme-mediated aldol reactions have been reported using two aldehydes, including formaldehyde.[1031]

Under the principle of vinylogy (Sec. 6.B), the active hydrogen can be one in the γ position of an α,β-unsaturated carbonyl compound:



The scope of the aldol reaction may be discussed under five headings:

1. *Reaction between Two Molecules of the Same Aldehyde*. Homo-coupling. Hydroxide or alkoxide bases are used in protic solvents,[1032] and the reaction is quite feasible. Nowadays, the use of dialkylamide bases in aprotic solvents (e.g., ether or THF) is more common. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.
2. *Reaction between Two Molecules of the Same Ketone*. Homo-coupling. With hydroxide or alkoxide bases in protic solvents the equilibrium lies well to the left,[1033] and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (e.g., See OS **I**, 199). As with aldehydes, the use of dialkylamide bases (e.g., LDA or lithium hexamethyldisilazide, Sec. 8.F., category 7) in aprotic solvents (e.g., ether or THF) are more common. Unsymmetrical ketones condense on the side that has the most hydrogens with dialkylamide bases in aprotic solvents, but on the side with the fewest hydrogens with alkoxide bases in alcohol solvents.
3. *Reaction between Two Different Aldehydes*. Cross-coupling. In protic solvents with an alkoxide base, this will produce a mixture of four products (eight, if the alkenes are counted). However, if one aldehyde does not have an α hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed-aldol reaction is often called the *Claisen–Schmidt reaction*.[1034] The crossed-aldol reaction is readily accomplished using amide bases in aprotic solvent. The first aldehyde is treated with LDA in THF at –78 °C, for example, to form the enolate anion. Subsequent treatment with a second aldehyde leads to the mixed-aldol product. The crossed aldol of two aldehydes has been done using potassium *tert*-butoxide and $Ti(OBu)_4$.[1035]
4. *Reaction between Two Different Ketones*. Cross-coupling. This is seldom attempted with hydroxide or alkoxide bases in protic solvents since similar considerations apply to those discussed for aldehydes. This reaction is commonly done with amide bases in aprotic solvents, but with somewhat more difficulty than with aldehydes.

[1030] See Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* ***2002****, 124*, 10759.
[1031] Demir, A.S.; Ayhan, P.; Igdir, A.C.; Duygu, A.N. *Tetrahedron* ***2004****, 60*, 6509.
[1032] For discussions of equilibrium constants in aldol reactions, see Guthrie, J.P.; Wang, X. *Can. J. Chem.* ***1991****, 69*, 339; Guthrie, J.P. *J. Am. Chem. Soc.* ***1991****, 113,* 7249, and references cited therein.
[1033] The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple, S.R.; Allerhand, A. *J. Am. Chem. Soc.* ***1987****, 109,* 6609.
[1034] For an aqueous version, see Buonora, P.T.; Rosauer, K.G.; Dai, L. *Tetrahedron Lett.* ***1995****, 36*, 4009.
[1035] Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetraehdron Lett.* ***2000****, 41*, 4415.

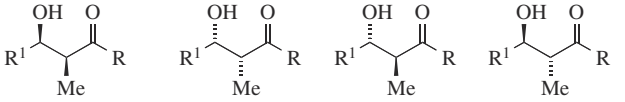
5. *Reaction between an Aldehyde and a Ketone.* This is usually feasible with hydroxide or alkoxides bases in protic solvents when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself.[1036] This is also called the *Claisen–Schmidt reaction*. Even when the aldehyde has an α hydrogen, it is generally the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. Mixtures are usually produced, however. If the ketone or the aldehyde is treated with an amide base in aprotic solvents, a second aldehyde or ketone can be added to give the aldolate with high regioselectivity. The reaction can be also made regioselective by preparing an enol derivative of the ketone separately[1037] and then adding this to the aldehyde (or ketone). Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),[1038] and enol borinates ($R'CH{=}CR^2{-}OBR_2$),[1039] which can be synthesized by Reaction **15-27** or directly from an aldehyde or ketone[1040]. Preformed metallic enolates are also used. For example, lithium enolates[1041] (prepared by Reaction **12-23**) react with the substrate in the presence of $ZnCl_2$.[1042] In this case, the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.[1043] Other metallic enolates can be used for aldol reactions, either preformed or generated *in situ* with a catalytic amount of a metal compound. Compounds used for this purpose include metal complexes of Mg,[1044] Ti,[1045] Zr,[1046] Pd,[1047] In,[1048] Sn,[1049] La,[1050] and Sm,[1051] all of which give products with moderate-to-excellent diastereoselectivity[1052] and regioselectivity. α-Alkoxy ketones react with lithium enolates particularly fast.[1053] A bis(aldol) condensation has been reported with epoxy ketones and aldehydes using SmI_2.[1054]

There are discussions that relate to the transition state of the aldol condensation. There is experimental evidence for chair-like transition states in the aldol reactions of methyl

[1036] See Kad, G.L.; Kaur, K.P.; Singh, V.; Singh, J. *Synth. Commun.* ***1999****, 29*, 2583.
[1037] See Mukaiyama, T. *Isr. J. Chem.* ***1984****, 24,* 162; Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 264–276.
[1038] Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* ***1985****, 58*, 2427.
[1039] See Hooz, J.; Oudenes, J.; Roberts, J.L.; Benderly, A. *J. Org. Chem.* ***1987****, 52*, 1347; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* ***1988****, 29*, 1041. For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 324–333. For an *ab initio* study see Murga, J.; Falomir, E.; Carda, M.; Marco, J.A. *Tetrahedron* ***2001****, 57*, 6239.
[1040] See Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* ***1992****, 33*, 3421.
[1041] See Arnett, E.M.; Fisher, F.J.; Nichols, M.A.; Ribeiro, A.A. *J. Am. Chem. Soc.* ***1990****, 112*, 801.
[1042] House, H.O.; Crumrine, D.S.; Teranishi, A.Y.; Olmstead, H.D. *J. Am. Chem. Soc.* ***1973****, 95*, 3310.
[1043] It has been contended that such stabilization is not required: Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* ***1979****, 101*, 7723.
[1044] Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004****, 60,* 11829.
[1045] See Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* ***1998***, 262.
[1046] Evans, D.A.; McGee, L.R. *Tetrahedron Lett.* ***1980****, 21*, 3975; *J. Am. Chem. Soc.* ***1981****, 103,* 2876.
[1047] Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* ***1989****, 111*, 4126.
[1048] See Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2001****, 57*, 4231.
[1049] Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* ***1998***, 958.
[1050] Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* ***1993***, 371.
[1051] Yokoyama, Y.; Mochida, K. *Synlett* ***1996***, 445; Sasai, H.; Arai, S.; Shibasaki, M. *J. Org.Chem.* ***1994****, 59*, 2661. Also see, Bao, W.; Zhang, Y.; Wang, J. *Synth. Commun.* ***1996****, 26*, 3025.
[1052] For a review, see Mahrwald, R. *Chem. Rev.* ***1999****, 99*, 1095.
[1053] Das, G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990****, 112*, 5360.
[1054] Mukaiyama, T.; Arai, H.; Shiina, I. *Chem. Lett.* ***2000***, 580.

ketone lithium enolate anions.[1055] A computational study gave the gas-phase activation energies for lithium enolate anions in an aldol-type reaction.[1056] There is a computational study of the mechanism for an aldol reaction in pure water.[1057]

The reactions with pre-formed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.[1058] As with the *Michael reaction* (**15-24**), the aldol reaction creates two new stereogenic centers. In the most general case, there are four stereoisomers of the aldol product (two racemic diastereomers), which can be represented as the syn and anti diastereomers shown. The reaction may be diastereoselective, however, if one is preferred over the other.



Syn (here erythro) (±) pair Anti (here threo) (±) pair

Among the preformed enol, derivatives used for diastereoselective aldol condensations have been enolates of Li,[1059] Mg, Ti,[1060] and Sn,[1061] silyl enol ethers,[1062] enol borinates,[1063] and enol borates [$R'CH{=}CR^2OB(OR)_2$].[1064] The nucleophilicity of silyl enol ethers has been examined[1065] and reactions of these compounds are discussed in Reaction **16-35**.

Base-induced formation of the enolate anion generally leads to a mixture of (*E*)- and (*Z*)-isomers, and dialkyl amide bases are used in most cases. The (*E*/*Z*) stereoselectivity depends on the structure of the lithium dialkylamide base, with the highest (*E*/*Z*) ratios obtained with LiTMP–butyllithium mixed aggregates in THF.[1066] The use of LiHMDS resulted in a reversal of the (*E*/*Z*) selectivity. In general, metallic (*Z*)-enolates give the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.[1067] The (*E*) isomers generally react nonstereoselectively. However, anti-stereoselectivity has been achieved in a number of cases, with Ti enolates,[1068] with Mg

[1055] Liu, C.M.; Smith, III, W.J.; Gustin, D.J.; Roush, W.R. *J. Am. Chem. Soc.* ***2005****, 127,* 5770.
[1056] Pratt, L.M.; Nguên, NV.; Ramachandran, B. *J. Org. Chem.* ***2005****, 70,* 4279.
[1057] Zhang, X.; Houk, K.N. *J. Org. Chem.* ***2005****, 70,* 9712.
[1058] Heathcock, C.H. *Aldrichimica Acta* ***1990****, 23,* 99; *Science* ***1981****, 214,* 395; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 193–220; Heathcock, C.H. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Acaademic Press, NY, ***1984***, pp. 111–212; Heathcock, C.H. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry,* pt. B, Elsevier, NY, ***1984***, pp. 177–237; Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* ***1982****, 13*, 1; Evans, D.A. *Aldrichimica Acta* ***1982****, 15,* 23; Braun, M.; Sacha, H.; Galle, D.; Baskaran, S. *Pure Appl. Chem.* ***1996****, 68*, 561; Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* ***2001****, 123*, 8939.
[1059] Ertas, M.; Seebach, D. *Helv. Chim. Acta* ***1985****, 68,* 961.
[1060] Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* ***2008****, 73,* 813; Mahrwald, R.; Schetter, B. *Org. Lett.* ***2006****, 8,* 281.
[1061] Labadie, S.S.; Stille, J.K. *Tetrahedron* ***1984****, 40,* 2329; Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1986***, 187. See also, Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1983****, 24,* 3347.
[1062] Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* ***1983****, 105*, 6963; Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* ***1983****, 56*, 3195; Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* ***1986***, 860.
[1063] Walker, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1991****, 56,* 5747. For reviews, see Paterson, I. *Chem. Ind. (London)* ***1988***, 390; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 324.
[1064] Hoffmann, R.W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* ***1987***, 977.
[1065] Patz, M.; Mayr, H. *Tetrahedron Lett.* ***1993****, 34*, 3393.
[1066] Pratt, L. M.; Newman, A.; Cyr, J. S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* ***2003****, 68,* 6387.
[1067] See Paddon-Row, M.N.; Houk, K.N. *J. Org. Chem.* ***1990****, 55,* 481; Denmark, S.E.; Henke, B.R. *J. Am. Chem. Soc.* ***1991****, 113,* 2177.
[1068] See Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* ***1991****, 56*, 2489.

enolates,[1069] with certain enol borinates,[1070] and with lithium enolates at –78 °C.[1071] Enolization accounts for syn–anti isomerization of aldols.[1072] In another variation, a β-keto *Weinreb amide* (see Reaction **16-82**) reacted with $TiCl_4$ and *Hünig's base* ($i Pr_2NEt$) and then an aldehyde to give the β-hydroxy ketone.[1073]

These reactions are enantioselective[1074] (in which case only one of the four isomers predominates)[1075] by using[1076] chiral enol derivatives,[1077] chiral aldehydes or ketones,[1078] or both.[1079] Chiral bases[1080] can be used (e.g., proline),[1081] proline derivatives,[1082] or chiral additives used in conjunction with an organobase.[1083] Indeed, chiral organocatalysts are increasingly important,[1084] including those that can be used in aqueous

[1069] Swiss, K.A.; Choi, W.; Liotta, D.; Abdel-Magid, A.F.; Maryanoff, C.A. *J. Org. Chem.* ***1991****, 56*, 5978.
[1070] Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* ***1990****, 55,* 173. See also, Corey, E.J.; Kim, S.S. *Tetrahedron Lett.* ***1990****, 31*, 3715.
[1071] Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* ***1988****, 61*, 2645; Majewski, M.; Gleave, D.M. *Tetrahedron Lett.* ***1989****, 30,* 5681.
[1072] Ward, D.E.; Sales, M.; Sasmal, P.K. *J. Org. Chem.* ***2004****, 69*, 4808.
[1073] Calter, M.A.; Guo, X.; Liao, W. *Org. Lett.* ***2001****, 3*, 1499.
[1074] Allemann, C.; Gordillo, R.; Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* ***2004****, 37*, 558; Saito, S.; Yamamoto, H. *Acc. Chem. res.* ***2004****, 37*, 570; Geary, L.M.; Hultin. P.G. *Tetrahedron Asymm.* ***2009****, 20*, 131. For a discussion of chelation versus nonchelation control, see Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* ***1993****, 115*, 2613. See Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* ***1995****, 36*, 5465; Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 861–873. For a model for acyclic stereocontrol, see Evans, D.A.; Cee, V.J.; Siska, S.J. *J. Am. Chem. Soc.* ***2006****, 128,* 9433.
[1075] For antiselective aldol reactions see Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* ***1993****, 34*, 4321. For a "non-Evans" *syn*-aldol, see Yan, T.-H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett.* ***1993****, 34*, 3559.
[1076] Klein, J. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 567–677; Braun, M. *Angew. Chem. Int. Ed.* ***1987****, 26*, 24.
[1077] Paterson, I.; Goodman, J.M. *Tetrahedron Lett.* ***1989****, 30,* 997; Siegel, C.; Thornton, E.R. *J. Am. Chem. Soc.* ***1989****, 111*, 5722; Faunce, J.A.; Grisso, B.A.; Mackenzie, P.B. *J. Am. Chem. Soc.* ***1991****, 113,* 3418.
[1078] See Reetz, M.T.; Kesseler, K.; Jung, A. *Tetrahedron* ***1984****, 40,* 4327.
[1079] See Short, R.P.; Masamune, S. *Tetrahedron Lett.* ***1987****, 28*, 2841.
[1080] Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res.* ***2004****, 37*, 580.
[1081] See Northrup, A.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2002****, 124*, 6798. See Suri, J.T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas III, C.F. *J. Org. Chem.* ***2006****, 71,* 3822; Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron Asymmetry* ***2006****, 17,* 2754. See Chimni, S.S.; Mahajan, D. *Tetrahedron* ***2005****, 61,* 5019.
[1082] Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* ***2003****, 125*, 5262; Zhong, G.; Fan, J.; Barbas, III, C.F. *Tetrahedron Lett.* ***2004****, 45,* 5681.
[1083] See Mahrwald, R. *Org. Lett.* ***2000****, 2*, 4011; Zhou, Y.; Shan, Z. *J. Org. Chem.* ***2006****, 71,* 9510.
[1084] For a review, see Guillena, G.; Nájera, C.; Ramón, D.J. *Tetrahedron Asymmetry* ***2007****, 18,* 2249. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* ***2005****, 127,* 9285; Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* ***2006****, 128,* 7442; Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.P. *J. Am. Chem. Soc.* ***2007****, 129,* 3074; Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* ***2008****, 130,* 5654; Denmark, S.E.; Bui, T. *J. Org. Chem.* ***2005****, 70,* 10393; Guillena, G.; Hita, M.d.C.; Nájera, C.; Viózquez, S.F. *J. Org. Chem.* ***2008****, 73,* 5933; Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* ***2005****, 7,* 601; Krattiger, P.; Kovasy, R.; Revell, J.D.; Ivan, S.; Wennemers, H. *Org. Lett.* ***2005****, 7,* 1101; Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* ***2005****, 7,* 5321; Revell, J.D.; Wennemers, H. *Tetrahedron* ***2007****, 63,* 8420; Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C.; Dhavale, D.D. *Tetrahedron* ***2008****, 64,* 9203; Guillena, G.; Hita, M.d.C.; Nájera, C. *Tetrahedron Asymmetry* ***2006****, 17,* 1493; Tang, X.; Liégault, B.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* ***2006****, 17,* 2187; Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chemistry: European J.* ***2007****, 13,* 4710; Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* ***2005***, 3586; Sun, G.; Fan, J.; Wang, Z.; Li, Y. *Synlett* ***2008***, 2491; Rambo, R.S.; Schneider, P.H. *Tetrahedron Asymm.* ***2010****, 21*, 2254.

media.[1085] Chiral auxiliaries[1086] have been developed that can be used in conjunction with the aldol condensation, as well as chiral transition metal complexes[1087] and chiral ligands[1088] in catalytic reactions. The enantioselective condensation of methyl vinyl ketone and an aldehyde used a chiral Zn catalyst.[1089] Structural variations in the aldehyde or ketone are compatible with many enantioselective condensation reactions. An α-hydroxy ketone was condensed with an aldehyde using a chiral Zn catalyst to give the aldol (an α,β-dihydroxy ketone) with good syn selectivity and good enantioselectivity.[1090] Chiral vinylogous aldol reactions (Sec. 6.B) have been reported.[1091] Formation of the magnesium enolate anion of a chiral amide, adds to aldehydes to give the alcohol enantioselectively.[1092] Diamine protonic acids have been used for catalytic asymmetric aldol reactions.[1093]

Silyl enol ethers react with aldehydes in the presence of chiral boranes[1094] or other additives[1095] to give aldols with good asymmetric induction (see the *Mukaiyama aldol Reaction* in **16-35**). Chiral boron enolates have been used.[1096] Since both new stereogenic centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.[1097] Where both the enolate derivative and substrate were achiral, carrying out the reaction in the presence of an optically active boron compound[1098] or a diamine coordinated with a Sn compound[1099] gave the aldol product with excellent enantioselectivity for one stereoisomer. Boron triflate (R_2BOTf) derivatives have been used for the condensation of ketals and ketone to give β-alkoxy ketones.[1100]

[1085] See Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* ***2006****, 128,* 734; Chi, Y.; Scroggins, S.T.; Boz, E.; Fréchet, J.M.J. *J. Am. Chem. Soc.* ***2008****, 130,* 17287; Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* ***2007****, 9,* 1247; Maya, V.; Raj, M.; Singh, V.K. *Org. Lett.* ***2007****, 9,* 2593; Chimni, S.S.; Mahajan, D.; Suresh Babu, V.V. *Tetrahedron Lett.* ***2005****, 46,* 5617; Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* ***2005****, 46,* 8185; Lei, L.; Shi, L.; Li, G.; Chen, S.; Weihai, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* ***2007****, 63,* 7892; Amedjkouh, M. *Tetrahedron Asymmetry* ***2005****, 16,* 1411; Chimni, S.S.; Mahajan, D. *Tetrahedron Asymmetry* ***2006****, 17,* 2108; Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2006****, 45,* 958; Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* ***2006***, 2801.

[1086] Hein, J.E.; Hultin, P.G. *Synlett* ***2003***, 635.

[1087] See Kantam, M.L.; Ramani, T.; Chakrapani, L.; Kumar, K.V. *Tetrahedron Lett.* ***2008****, 49*, 1498; Inoue, H.; Kikuchi, M.; Ito, J.-i.; Nishiyama, H. *Tetrahedron* ***2008****, 64,* 493.

[1088] Trost, B.M.; Ito, H. *J. Am. Chem. Soc.* ***2000****, 122*, 12003.

[1089] Trost, B.M.; Shin, S.; Sclafani, J.A. *J. Am. Chem. Soc.* ***2005****, 127*, 8602.

[1090] Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshma, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001****, 123*, 2466; Trost, B.M.; Ito, H.; Silcoff, E.R. *J. Am. Chem. Soc.* ***2001****, 123*, 3367.

[1091] Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* ***2004***, 732; Denmark, S.E.; Heemstra Jr., J.R. *Synlett* ***2004***, 2411.

[1092] Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2002****, 124*, 392.

[1093] Trost, B.M.; Fettes, A.; Shireman, B.T. *J. Am. Chem. Soc.* ***2004****, 126*, 2660.

[1094] Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1993****, 66*, 3483.

[1095] Corey, E.J.; Cywin, C.L.; Roper, T.D. *Tetrahedron Lett.* ***1992****, 33*, 6907.

[1096] See Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* ***2003****, 68*, 1901.

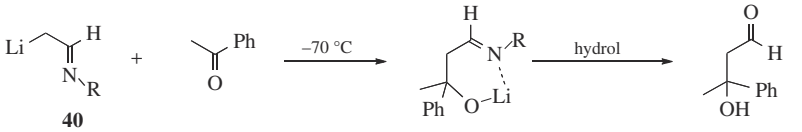
[1097] For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985****, 24*, 1.

[1098] Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* ***1991****, 113*, 1041; Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* ***1991****, 56*, 2276. For a review, see Bernardi, A.; Gennari, C.; Goodman, J.M.; Paterson, I. *Tetrahedron Asymmetry* ***1995****, 6*, 2613.

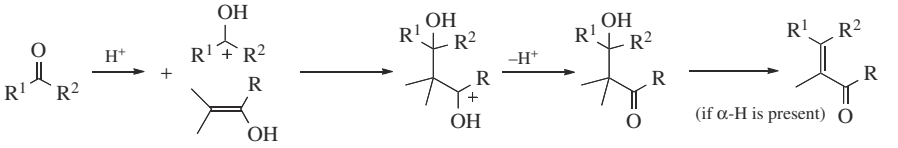
[1099] Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* ***1990***, 1147.

[1100] Li, L.-S.; Das, S.; Sinha, S.C. *Org. Lett.* ***2004****, 6*, 127.

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde, and $LiN(iPr)_2$ as the base to form the α-lithio imine (**40**).[1101] This is known as a *directed aldol reaction*. Similar reactions have been performed with α-lithiated dimethylhydrazones of aldehydes or ketones[1102] and with α-lithiated aldoximes.[1103]



The aldol reaction can also be performed with acid catalysts, as mentioned above, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group, which attacks the α carbon of the *enol* form of the other molecule[1104]:



With respect to the enol, this mechanism is similar to that of halogenation (Reaction **12-4**). A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone. The aldol condensation of aldehydes has also been done using a mixture of pyrrolidine and benzoic acid.[1105]

The intramolecular aldol condensation is well known, and aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (Sec. 6.D), such ring closures generally take place with ease[1106] when using hydroxide or alkoxide bases in protic solvents. In aprotic solvents with amide bases, formation of the enolate anion occurs by deprotonation of the more acidic site, followed by cyclization to the second carbonyl. The acid-catalyzed intramolecular aldol condensation is known, and the mechanism has been studied.[1107] Stereoselective proline-catalyzed intramolecular aldol reactions give the cyclized product with good enantioselectivity.[1108] Chiral ligands, in conjugation with transition metal compounds of Cu[1109], lead to asymmetric intramolecular aldol condensation reactions. An asymmetric intramolecular aldol reaction was catalyzed by a chiral

[1101] Wittig, G.; Frommeld, H.D.; Suchanek, P. *Angew. Chem. Int. Ed.* ***1963****, 2*, 683. For reviews, see Mukaiyama, T. *Org. React.* ***1982****, 28*, 203; Wittig, G. *Top. Curr. Chem.* ***1976****, 67,* 1; Wittig, G.; Reiff, H. *Angew. Chem. Int. Ed.* ***1968****, 7*, 7; Reiff, H. *Newer Methods Prep. Org. Chem.* ***1971****, 6*, 48.

[1102] Corey, E.J.; Enders, D. *Tetrahedron Lett.* ***1976***, 11. See also, Sugasawa, T.; Toyoda, T.; Sasakura, K. *Synth. Commun.* ***1979****, 9,* 515; Depezay, J.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* ***1981***, II-306.

[1103] Hassner, A.; Näumann, F. *Chem. Ber.* ***1988****, 121*, 1823.

[1104] See Baigrie, L.M.; Cox, R.A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985****, 107*, 3640.

[1105] Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* ***1999***, 450.

[1106] See Guthrie, J.P.; Guo, J. *J. Am. Chem. Soc.* ***1996****, 118*, 11472; Eberle, M.K. *J. Org. Chem.* ***1996****, 61*, 3844.

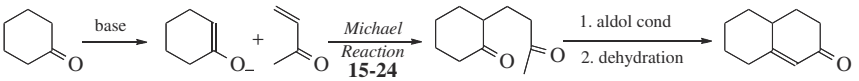
[1107] Bouillon, J.-P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* ***2000****, 65*, 5823.

[1108] Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* ***2003****, 42*, 2785.

[1109] Lipshutz, B.H.; Amorelli, B.; Unger, J.B. *J. Am. Chem. Soc.* ***2008****, 130,* 14378.

amine.[1110] The regioselectivity of an intramolecular aldol condensation of unsaturated 1,5-diketones is strongly influenced by the presence or absence of a trialkylphosphine.[1111]

An important extension of the intramolecular aldol condensation is the *Robinson annulation* reaction,[1112] which has often been used in the synthesis of steroids and terpenes. In original versions of this reaction, a cyclic ketone is converted to another cyclic ketone under equilibrium conditions using hydroxide or alkoxide bases in a protic solvent, forming one additional six-membered ring containing a double bond. The reaction can be done in a stepwise manner using amide bases in aprotic solvents. In the reaction with hydroxide or alkoxide bases in alcohol or water solvents, the substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[1113] The enolate ion of the substrate adds to the methyl vinyl ketone in a *Michael reaction* (**15-24**) to give a diketone that undergoes or is made to undergo an internal aldol reaction and subsequent dehydration to give the product.[1114] The *Robinson annulation* can be combined with alkylation.[1115] Enantioselective *Robinson annulation* techniques have been developed, including a proline-catalyzed reaction.[1116] The *Robinson annulation* has been done in ionic liquids[1117] and a solvent-free version of the reaction is known.[1118]



Because methyl vinyl ketone has a tendency to polymerize, surrogates are often used instead (i.e., compounds that will give methyl vinyl ketone when treated with a base). One common example, $MeCOCH_2CH_2NEt_2Me^+\ I^-$ (see Reaction **17-9**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared by a *Mannich Reaction* (**16-19**) involving acetone, formaldehyde, and diethylamine. α-Silylated vinyl ketones [$RCOC(SiMe_3)=CH_2$] have also been used successfully in annulation reactions[1119] because the $SiMe_3$ group is easily removed. When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high ee.[1120] *Stryker's reagent,*[1121] $[(Ph_3P)CuH]_6$, has been used for an intramolecular addition where a ketone enolate anion adds to a conjugated ketone, giving cyclic alcohol with a pendant ketone unit.[1122]

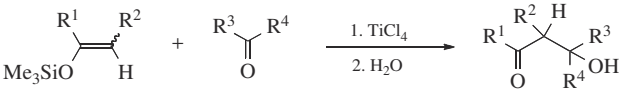
[1110] Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* ***2008****, 47*, 7656.
[1111] Thalji, R.K.; Roush, W.R. *J. Am. Chem. Soc.* ***2005****, 127,* 16778.
[1112] Gawley, R.E. *Synthesis* ***1976***, 777; Jung, M.E. *Tetrahedron* ***1976****, 32,* 1; Mundy, B.P. *J. Chem. Educ.* ***1973****, 50,* 110. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1356–1358.
[1113] See Heathcock, C.H.; Ellis, J.E.; McMurry, J.E.; Coppolino, A. *Tetrahedron Lett.* ***1971***, 4995.
[1114] For improved procedures, see Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1990****, 31*, 1581, and references cited therein.
[1115] Tai, C.-L.; Ly, T.W.; Wu, J.-D.; Shia, K.-S.; Liu, H.-J. *Synlett* ***2001***, 214.
[1116] Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* ***2001****, 42*, 4887.
[1117] Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001****, 42*, 6053.
[1118] Miyamoto, H.; Kanetaka, S.; Tanaka, K.; Yoshizawa, K.; Toyota, S.; Toda, F. *Chem. Lett.* ***2000***, 888.
[1119] Stork, G.; Singh, J. *J. Am. Chem. Soc.* ***1974****, 96*, 6181; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1974****, 96,* 6179.
[1120] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* ***1971****, 10*, 496; Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974****, 39*, 1615. See Agami, C. *Bull. Soc. Chim. Fr.* ***1988***, 499.
[1121] Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* ***1988****, 110,* 291; Brestensky, D.M.; Stryker, J.M. *Tetrahedron Lett.* ***1989****, 30,* 5677.
[1122] Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* ***2001****, 3*, 1901.

OS **I**, 77, 78, 81, 199, 283, 341; **II**, 167, 214; **III**, 317, 353, 367, 747, 806, 829; **V**, 486, 869; **VI**, 496, 666, 692, 781, 901; **VII**, 185, 190, 332, 363, 368, 473; **VIII**, 87, 208, 241, 323, 339, 620; **IX**, 432, 610; **X**, 339.

16-35 Mukaiyama Aldol and Related Reactions[1123]

O-Hydro-*C*-(α-acylalkyl)-addition

An important variation of the aldol condensation involves treatment of an aldehyde or ketone with a silyl ketene acetal [$R_2C{=}C(OSiMe_3)OR'$][1124] or a silyl enol ether, in the presence of $TiCl_4$[1125], to give **41**. This variation is known as the *Mukaiyama aldol reaction*, or simply the *Mukaiyama reaction*. The silyl ketene acetal can be considered a pre-formed enolate that gives aldol product with $TiCl_4$ in aqueous solution, or with no



41

catalyst at all.[1126] A combination of $TiCl_4$ and *N*-tosyl imine has also been used to facilitate the Mukaiyama aldol reaction.[1127] Reaction at the carbonyl of saturated carbonyl compounds is significantly faster than 1,2-addition to unsaturated carbonyl compounds.[1128] The mechanism of this reaction has been explored.[1129] Other catalysts have been used for this reaction, including $InCl_3$,[1130] SmI_2,[1131] HgI_2,[1132] $Yb(OTf)_3$,[1133] $Cu(OTf)_2$,[1134] $LiClO_4$,[1135] $VOCl_3$,[1136] an Fe catalyst,[1137] and $Bi(OTf)_3$.[1138] Lithium perchlorate in acetonitrile (5 M) can be used for the reaction of an aldehyde and a silyl enol ether.[1139]

[1123] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 837–841.

[1124] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1745–1752. Also see Revis, A.; Hilty, T.K. *Tetrahedron Lett.* ***1987***, *28*, 4809, and references cited therein.

[1125] Mukaiyama, T. *Pure Appl. Chem.* ***1983***, *55*, 1749; Kohler, B.A.B. *Synth. Commun.* ***1985***, *15*, 39; Mukaiyama, T.; Narasaka, K. *Org. Synth.*, *65*, 6. See Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* ***1987***, *52*, 2754; Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1977***, *16*, 817. See also, Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Spinger, NY, ***1986***.

[1126] Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1998***, *39*, 2585. For a high pressure, uncatalyzed reaction, see Bellassoued, M.; Reboul, E.; Dumas, F. *Tetrahedron Lett.* ***1997***, *38*, 5631.

[1127] Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* ***2002***, *124*, 536.

[1128] Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* ***2002***, *43*, 1469.

[1129] Hollis, T.K.; Bosnich, B. *J. Am. Chem. Soc.* ***1995***, *117*, 4570. For the transition state geometry, see Denmark, S.E.; Lee, W. *J. Org. Chem.* ***1994***, *59*, 707.

[1130] Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 1622.

[1131] Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1993***, *34*, 3881.

[1132] Dicker, I.B. *J. Org. Chem.* ***1993***, *58*, 2324.

[1133] This catalyst is tolerated in water. See Kobayashi, S.; Hachiya, I. *J. Org. Chem.* ***1994***, *59*, 3590.

[1134] Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1997***, 959.

[1135] Reetz, M.T.; Fox, D.N.A. *Tetrahedron Lett.* ***1993***, *34*, 1119.

[1136] Kurihara, M.; Hayshi, T.; Miyata, N. *Chem. Lett.* ***2001***, 1324.

[1137] Bach, T.; Fox, D.N.A.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* ***1992***, 1634.

[1138] Ollevier, T.; Desyroy, V.; Debailleul, B.; Vaur, S. *Eur. J. Org. Chem.* ***2005***, 4971; ***2006***, 1061; Ollevier, T.; Li, Z. *Eur. J. Org. Chem.* ***2007***, 5665.

[1139] Sudha, R.; Sankararaman, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 383.

The reaction can be done in water using a Sc catalyst[1140] or on a Montmorillonite K-10 clay.[1141] Silyl enol ethers react with aq formaldehyde in the presence of TBAF to give the aldol product.[1142] A catalytic amount of Me_3SiCl facilitates the Ti mediated reaction.[1143] Sulfonamides (e.g., $HNTf_2$) have been used as a catalyst[1144] as has pyridine *N*-oxide[1145] and *N*-methylimidazole.[1146] An *ab initio* study of the uncatalyzed Mukaiyama aldol reaction showed that the nucleophilicity of silyl enol ether and the electrophilicity of the aldehyde are important in promoting the reactivity.[1147] This reaction can also be run with the aldehyde or ketone in the form of its acetal [$R^3R^4C(OR')_2$], in which case the product is the ether $R^1COCHR_2CR^3R^4OR'$ instead of **41**.[1148] Vinylogous (Sec. 6.B) silyl ketene acetals with Ti,[1149] Cu,[1150] In,[1151] Fe,[1152] or Zn[1153] catalysts or an organocatalyst,[1154] give the product with good enantioselectivity.

Silyl enol ethers[1155] derived from esters (silyl ketene acetals) react with aldehydes in the presence of various catalysts to give β-hydroxy esters. Water accelerates the reaction of an aldehyde and a ketene silyl acetal with no other additives.[1156] The reaction is catalyzed by triphenylphosphine[1157] and also by $SiCl_4$ with a chiral bis(phosphoramide) catalyst.[1158] The reaction was done without a catalyst in an ionic liquid.[1159] A vinylogous reaction (Sec. 6.B) is known that gives δ-hydroxy-α,β-unsaturated esters.[1160] An interesting variation in this reaction combined an intermolecular *Mukaiyama aldol* followed by an intramolecular reaction (a "domino" *Mukaiyama aldol*) that gave cyclic conjugated ketone products.[1161] Under different conditions, silyl ketene acetals of conjugated esters react with aldehydes to give conjugated lactones.[1162] Imines react with silyl ketene acetals in the presence of SmI_3

[1140] Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* ***1999****, 40*, 3773. See Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Bu, Y.-P.; Li, C.-J. *Tetrahedron Lett.* ***2001****, 42*, 1803; Komoto, I.; Kobayashi, S. *J. Org. Chem.* ***2004****, 69,* 680

[1141] Loh, T.-P.; Li, X.-R. *Tetrahedron* ***1999****, 55*, 10789.

[1142] Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* ***2003***, 2219.

[1143] Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett* ***1999****, 40*, 4227.

[1144] Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2001***, 1851.

[1145] Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* ***2002****, 124*, 4233.

[1146] Hagiwara, H.; Inoguchi, H.; Fukushima, M.; Hoshi, T.; Suzuki, T. *Tetrahedron Lett.* ***2006****, 47*, 5371.

[1147] Wong, C.T.; Wong, M.W. *J. Org. Chem.* ***2005****, 70,* 124.

[1148] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* ***1988****, 44,* 4259. For a review of cross-coupling reactions of acetals, see Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043.

[1149] Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004****, 126*, 13604.

[1150] Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* ***2005****, 127*, 7288; Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2006****, 128,* 7164.

[1151] Fu, F.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* ***2006****, 47,* 4267.

[1152] Jankowska, J.; Paradowska, J.; Mlynarski, J. *Tetrahedron Lett.* ***2006****, 47,* 5281.

[1153] Jankowska, J.; Mlynarski, J. *J. Org. Chem.* ***2006****, 71*, 1317.

[1154] Denmark, S.E.; Heemstra, Jr., J.R. *J. Am. Chem. Soc.* ***2006****, 128,* 1038; Jang, H.-Y.; Hong, J.-B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2007****, 129,* 7004.

[1155] See Carswell, E.L.; Hayes, D.; Henderson, K.W.; Kerr, W.J.; Russell, C.J. *Synlett* ***2003***, 1017.

[1156] Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2000****, 56*, 7309.

[1157] Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* ***2000****, 41*, 103.

[1158] Denmark, S.E.; Heemstra, Jr., J.R. *Org. Lett.* ***2003****, 5*, 2303; Denmark, S.E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* ***2002****, 124,* 13405.

[1159] Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2004****, 45,* 375.

[1160] Bluet, G.; Campagne, J.-M. *J. Org. Chem.* ***2001****, 66*, 4293; Christmann, M.; Kalesse, M. *Tetrahedron Lett.* ***2001****, 42,* 1269.

[1161] Langer, P.; Köhler, V. *Org. Lett.* ***2000****, 2*, 1597.

[1162] Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* ***2001****, 3*, 3807.

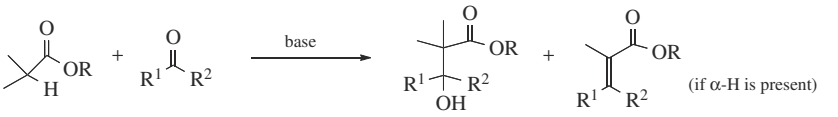
to give β-amino esters.[1163] Imines react with silyl enol ethers in the presence of BF_3•OEt_2 to give β-amino ketones.[1164] Silyl ketene acetals also undergo conjugate addition in reactions with conjugated ketones.[1165] Propargylic acetals react with silyl enol ethers and a Sc catalyst to give β-alkoxy ketones.[1166] α-Silyl silyl enol ethers [RCH=CH(OTMS)$SiMe_3$] react with acetals in the presence of $SnCl_4$ to give β-alkoxy silyl ketones.[1167] Borane derivatives [e.g., C=C—$OB(NMe_2)_2$] react with aldehydes to give β-amino ketones.[1168]

Asymmetric *Mukaiyama aldol reactions* and reactions of silyl ketene acetals have been reported,[1169] usually using chiral additives[1170] although chiral auxiliaries have also been used.[1171] Chiral catalysts, usually transition metal complexes using chiral ligands, are quite effective[1172] but chiral organocatalysts[1173] are increasingly important.

Enol acetates and enol ethers also give this product when treated with acetals and $TiCl_4$ or a similar catalyst.[1174] A variation of this condensation uses an enol acetate with an aldehyde in the presence of Et_2AlOEt to give the aldol product.[1175]

16-36 Aldol-Type Reactions between Carboxylic Acid Derivatives and Aldehydes or Ketones

O-Hydro-*C*-(α-alkoxycarbonylalkyl)-addition; α-Alkoxycarbonylalkylidene-de-oxo-bisubstitution



In the presence of a strong base, removal of a proton from the α carbon of a carboxylic ester or other acid derivative generates an enolate anion that can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[1176] amide, and so on. These products may or may not be dehydrated to the α,β-unsaturated derivative. This

[1163] Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***1999***, 591.
[1164] Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* ***1999***, 947.
[1165] Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubu, M.; Oku, A. *Org. Lett.* ***2001****, 3*, 2101.
[1166] Yoshimatsu, M.; Kuribayashi, M.; Koike, T. *Synlett* ***2001***, 1799.
[1167] Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* ***2002****, 58*, 6815.
[1168] Suginome, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* ***2004****, 6*, 1167.
[1169] Bach, T. *Angew. Chem. Int. Ed.* ***1994****, 33*, 417. For a discussion of stereocontrol, see Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *J. Org. Chem.* ***1992****, 57*, 456.
[1170] See Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* ***1994****, 116*, 4077; Kaneko, Y.; Matsuo, T.; Kiyooka, S. *Tetrahedron Lett.* ***1994****, 35*, 4107; Kiyooka, S.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett.* ***1994****, 35*, 5243.
[1171] See Vasconcellos, M.L.; Desmaële, D.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron Lett.* ***1992****, 33*, 4921.
[1172] **Ag**: Wadamoto, M.; Ozasa, N.; Yanigisawa, A.; Yamamoto, H. *J. Org. Chem.* ***2003****, 68*, 5593. **Ce:** Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* ***2001****, 3*, 165. **Cu**: Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* ***1999****, 55*, 8739. **Pb**: Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc* ***2000****, 122*, 11531. **Sc**: Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004****, 126*, 12236. **Ti**: Imashiro, R.; Kuroda, T. *J. Org. Chem.* ***2003****, 68*, 974. **Zr**: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* ***2001****, 57*, 861.
[1173] Denmark, S.E.; Beutner, G.L.; Wynn, T.; Eastgate, M.D. *J. Am. Chem. Soc.* ***2005****, 127,* 3774; Denmark, S.E.; Bui, T. *J. Org. Chem.* ***2005****, 70,* 10190; Adachi, S.; Harada, T. *Org. Lett.* ***2008****, 10,* 4999; Senapati, B.K.; Gao, L.; Lee, S.I.; Hwang, G.-S.; Ryu, D.H. *Org. Lett.* ***2010****, 12*, 5088.
[1174] Kitazawa, E.; Imamura, T.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* ***1975***, 569.
[1175] Mukaiyama, T.; Shibata, J.; Shimamura, T.; Shiina, I. *Chem. Lett.* ***1999***, 951.
[1176] See Solladié, G. *Chimia* ***1984****, 38*, 233.

reaction is sometimes called the *Claisen reaction*,[1177] an unfortunate usage since that name is more firmly connected to Reaction **16-85**. *Claisen condensation* is a better descriptor. Early reactions used hydroxide or an alkoxide base in water or alcohol solvents, where self-condensation was the major process. Under such conditions, the aldehyde or ketone was usually chosen for its lack of an α-proton. Much better control of the reaction was achieved when dialkylamide bases in aprotic solvents (e.g., ether or THF) were used. The reaction of *tert*-butyl acetate and LDA[1178] in hexane or more commonly THF at –78 °C gives the enolate anion of *tert*-butyl acetate,[1179] (Reaction **12-23**, e.g., although self-condensation is occasionally a problem even here). Additives play an important role in the LDA mediated enolization of esters[1180]. Subsequent reaction of a ketone provides a simple rapid alternative to the *Reformatsky Reaction* (**16-28**) as a means of preparing β-hydroxy *tert*-butyl esters. It is also possible for the α carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this is a different reaction (**16-86**) involving nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Transition metal mediated condensation of esters with aldehydes is known. The reaction of a thioester and an aryl aldehyde with $TiCl_4$—NBu_3, for example, gave a β-hydroxy thioester with good syn selectivity.[1181] Selenoamides [$RCH_2C(=Se)NR'_2$] react with LDA and then an aldehyde to give β-hydroxy selenoamides.[1182] The reaction of an α,β-unsaturated ester and benzaldehyde with a chiral Rh catalyst gave a β-hydroxy ester with good diastereoselectivity and good enantioselectivity.[1183]

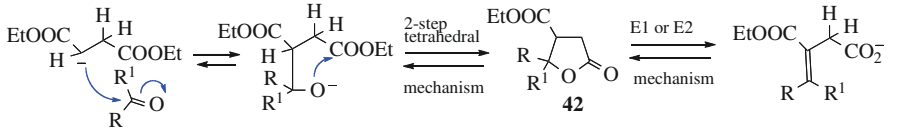
Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in Reaction **16-34**, with the γ position of α,β-unsaturated esters (vinylogy; Sec. 6.B). The enolate anion of an amide can be condensed with an aldehyde.[1184] Thioesters undergo aldol-type condensations.[1185]

For most esters, a much stronger base is needed than for aldol reactions; $(i\text{Pr})_2\text{NLi}$ (LDA, Sec. 8.F, category 7), Ph_3CNa and $LiNH_2$ are among those employed. However, esters of malonic and succinic acid react more easily, and such strong bases are not needed. For example, diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases (e.g., NaOEt, NaH, or $KOCMe_3$). This reaction is called the *Stobbe condensation*.[1186] One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (1) the fact the succinic esters react so much better than others; (2) one ester group is always cleaved; and (3) the alcohol is not the product but the alkene. In addition, intermediate lactones (**42**) have been isolated from the mixture.[1187] The *Stobbe condensation* has been extended to di-*tert*-butyl esters of glutaric acid.[1188] The boron-mediated reaction is known.[1189]

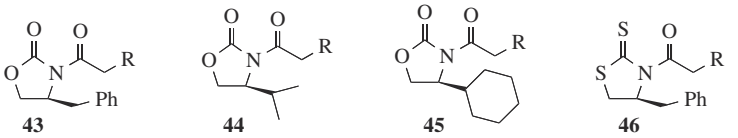
[1177] Because it was discovered by Claisen, L. *Ber.* ***1890****, 23,* 977.
[1178] Huerta, F.F.; Bäckvall, J.-E. *Org. Lett.* ***2001****, 3*, 1209.
[1179] Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973****, 95,* 3050.
[1180] Ramirez, A.; Sun, X.; Collum, D.B. *J. Am. Chem. Soc.* ***2006****, 128,* 10326.
[1181] Tanabe, Y.; Matsumoto, N.; Funakoshi, S.; Manta, N. *Synlett* ***2001***, 1959.
[1182] Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2711.
[1183] Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* ***2005****, 127,* 6972.
[1184] See Shang, X.; Liu, H-J. *Synth. Commun.* ***1994****, 24*, 2485.
[1185] Yost, J.M.; Zhou, G.; Coltart, D.M. *Org. Lett.* ***2006****, 8,* 1503.
[1186] See Johnson, W.S.; Daub, G.H. *Org. React.* ***1951****, 6,* 1.
[1187] Robinson, R.; Seijo, E. *J. Chem. Soc.* ***1941***, 582.
[1188] Puterbaugh, W.H. *J. Org. Chem.* ***1962****, 27*, 4010. See also, El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiouny, F.A. *J. Prakt. Chem.* ***1982****, 324,* 379.
[1189] See Abiko, A. *Acc. Chem. Res.* ***2004****, 37*, 387.

The intramolecular reaction of an aldehyde–carboxylic acid in the presence of triethylamine and a pyridinium salt led to the ring-forming condensation reaction, followed by formation of a β-lactone.[1190]

Amides participate in this condensation reaction, reacting with aldehydes in the presence of a Ba catalyst to give a β-hydroxy amide derivative.[1191] The reaction of an amide with LDA in the presence of an acyl silane, followed by reaction with an alkyl halide, leads to the β-hydroxy amide with the additional alkyl group at the β-carbon.[1192]



Chiral additives (e.g., diazaborolidines) can be added to an ester, and subsequent treatment with a base, and then an aldehyde leads to a chiral β-hydroxy ester.[1193] A variety of chiral amide or oxazolidinone derivatives have been used to form amide linkages to carboxylic acid derivatives. These chiral auxiliaries lead to chirality transfer from the enolate anion of such derivatives, in both alkylation reactions and acyl substitution reactions with aldehydes and ketones. The so-called *Evans auxiliaries* (**43**–**45**) are commonly used and give good enantioselectivity.[1194] A variation is the magnesium halide-catalyzed anti-aldol reaction of chiral *N*-acylthiazolidinethiones (see **46**).[1195] The use of chiral *N*-acyloxazolidinthiones with $TiCl_4$ and sparteine also gave good selectivity in the acyl addition.[1196] Chiral diazaboron derivatives have also been used to facilitate the condensation of a α-phenylthio ester with an aldehyde.[1197]



The condensation of an ester enolate and a ketone[1198] can be used as part of a *Robinson annulation*-like sequence (see Reaction **16-34**).

OS **I**, 252; **III**, 132; **V**, 80, 564; **70**, 256; **X**, 437; **81**, 157. Also see, OS **IV**, 278, 478; **V**, 251.

[1190] Oh, S.H.; Cortez, G.S.; Romo, D. *J. Org. Chem.* ***2005****, 70,* 2835.
[1191] Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2006****, 128*, 8704.
[1192] Lettan, II, R.B.; Reynolds, T.E.; Galliford, C.V.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2006****, 128,* 15566.
[1193] Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000****, 41*, 2769.
[1194] See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984****, 25*, 4071.
[1195] Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* ***2002****, 4,* 1127.
[1196] Crimmins, M.T.; McDougall, P.J. *Org. Lett.* ***2003****, 5*, 591.
[1197] Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000****, 41*, 2769.
[1198] Posner, G.H.; Lu, S.; Asirvatham, E.; Silversmith, E.F.; Shulman, E.M. *J. Am. Chem. Soc.* ***1986****, 108,* 511; Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* ***1988****, 110,* 4754.

16-37 The Henry Reaction[1199]

$$CH_3NO_2 + HCHO \xrightarrow{^-OH} HOCH_2CH_2NO_2$$

The classical condensation of an aliphatic nitro compound with an aldehyde or ketone is usually called the *Henry reaction*[1200] or the *Kamlet reaction*, and is essentially a nitro aldol reaction. A variety of conditions have been reported, including the use of a recoverable polymer catalyst,[1201] a silica catalyst,[1202] a tetraalkylammonium hydroxide,[1203] proazaphosphatranes,[1204] and it has been done in an aqueous media[1205] or an ionic liquid.[1206] A solvent-free *Henry reaction* was reported in which a nitroalkane and an aldehyde were reacted on KOH powder.[1207] A solvent-free microwave assisted reaction was reported.[1208] Potassium phosphate has been used with nitromethane and aryl aldehydes.[1209] The *Henry reaction* has been done using $ZnEt_2$ and 20% ethanolamine.[1210] A gel-entrapped base has been used to catalyze this reaction.[1211] Biocatalysts have been used.[1212]

Catalytic enantioselective *Henry reactions* are known,[1213] including the use of a chiral Cu,[1214] Zn,[1215] Nd,[1216] or Ti catalyst.[1217] The *Henry reaction* of nitromethane and a chiral aldehyde under high pressure gives the β-nitro alcohol with excellent

[1199] Baer, H.H.; Urbas, L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 76–117. See also, Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* ***1983***, 1014; Matsumoto, K. *Angew. Chem. Int. Ed.* ***1984***, *23*, 617; Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* ***1985***, *107,* 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* ***1986***, *86*, 751; Kabalka, G.W.; Varma, R.S. *Org. Prep. Proced. Int.* ***1987***, *19,* 283.

[1200] Henry, L. *Compt. Rend.* ***1895***, *120,* 1265; Kamlet, J. *U.S. Patent* 2,151,171 ***1939*** [*Chem. Abstr., 33*: 5003[9] ***1939***]; Hass, H.B.; Riley, E.F. *Chem. Rev.* ***1943***, *32,* 373 (see p. 406); Lichtenthaler, F.W. *Angew. Chem. Int. Ed.* ***1964***, *3,* 211. For a review, see Luzzio, F.A. *Tetrahedron* ***2001***, *57*, 915.

[1201] Yan, S.; Gao, Y.; Xing, R.; Shen, Y.; Liu, Y.; Wu, P.; Wu, H. *Tetrahedron* ***2008***, *64*, 6294.

[1202] Demicheli, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G.; Bigi, F. *Tetrahedron Lett.* ***2001***, *42*, 2401; Hagiwara, H.; Sekifuji, M.; Tsubokawa, N.; Hoshi, T.; Suzuki, T. *Chem. Lett.* ***2009***, *38*, 790.

[1203] Bulbule, V.J.; Jnaneshwara, G.K.; Deshmukh, R.R.; Borate, H.B.; Deshpande, V.H. *Synth. Commun.* ***2001***, *31*, 3623.

[1204] Kisanga, P.B.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 4298.

[1205] Phukan, M.; Borah, K.J.; Borah, R. *Synth. Commun.* ***2008***, *38,* 3068.

[1206] Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* ***2004***, *45*, 2699.

[1207] Ballini, R.; Bosica, G.; Parrini, M. *Chem. Lett.* ***1999***, 1105.

[1208] Gan, C.; Chen, X.; Lai, G.; Wang, Z. *Synlett* ***2006***, 387.

[1209] Desai, U.V.; Pore, D.M.; Mane, R.B.; Solabannavar, S.B.; Wadgaonkar, P.P. *Synth. Commun.* ***2004***, *34*, 19.

[1210] Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* ***2002***, *43*, 7503.

[1211] Bandgar, B.P.; Uppalla, L.S. *Synth. Commun.* ***2000***, *30*, 2071.

[1212] Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skranc, W.; Mink, D.; Griengl, H *Angew. Chem. Int. Ed.* ***2006***, *45,* 3454.

[1213] Christensen, C.; Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 4875. For reviews, see Boruwa, J.; Gogoi, N.; Saikia, P.P.; Barua, N.C. *Tetrahedron Asymmetry* ***2006***, *17,* 3315; Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* ***2007***, 2561.

[1214] Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* ***2008***, *64,* 11724.

[1215] Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* ***2008***, *73,* 7373.

[1216] Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* ***2008***, *49,* 272.

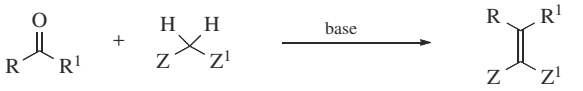
[1217] Tur, F.; Saá, J.M. *Org. Lett.* ***2007***, *9*, 5079.

enantioselectivity.[1218] Enantioselective nitro–aldol reactions are catalyzed by organocatalysts (e.g., Cinchona alkaloids[1219] or other organocatalysts).[1220]

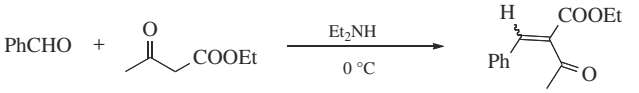
A variation of this reaction converts nitro compounds to nitronates [$RCH{=}N^{+}(OTMS){-}O^{-}$], which subsequently react with aldehydes in the presence of a Cu catalyst to give the β-nitro alcohol.[1221] aza-*Henry reactions* condense nitroalkanes with imine derivatives, and the resulting amino nitro compounds are formed with good enantioselectivity in the presence of organocatalysts[1222] or Brønsted acid catalysts.[1223] Aza-*Henry products* are also formed by the reaction of amines with activated unsaturated compounds.[1224]

16-38 The Knoevenagel Reaction

Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, and so on



The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form $Z{-}CH_2{-}Z'$ or $Z{-}CHR{-}Z'$ is called the *Knoevenagel reaction*.[1225] Both Z and Z' may be CHO, COR, CO_2H, CO_2R, CN, NO_2, SOR, SO_2R, SO_2OR, or similar groups. The presence of two electron-withdrawing groups makes the α-proton much more acidic (Table 8.1 in Sec. 8.A.i), and such compounds have a significantly higher enol content.[1226] When $Z = CO_2H$, decarboxylation of the product often takes place *in situ*.[1227] As shown in the example, the reaction of β-keto esters and aldehydes to give **47** is promoted by diethylamine at 0 °C. Nitroalkanes,[1199] as well as β-keto sulfoxides,[1228] undergo the reaction.



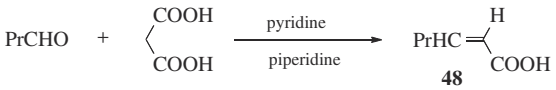
47

As with Reaction **16-34**, these reactions have sometimes been mediated by an acid catalyst.[1229] Ionic liquid solvents have been used,[1230] and heating on quaternary

[1218] Misumi, Y.; Matsumoto, K. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1031.
[1219] Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* ***2006****, 128*, 732.
[1220] Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* ***2007****, 129*, 12392; Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* ***2007****, 9,* 943; Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* ***2007****, 9,* 3595; Liu, S.; Wolf, C. *Org. Lett.* ***2008****, 10,* 1831; Marcelli, T.; van der Haas, R.N.S.; van Maarseveen, J.H.; Hiemstra, H. *Angew. Chem. Int. Ed.* ***2006****, 45,* 929; Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* ***2008***, 4591.
[1221] Risgaard, T.; Gothelf, K.V.; Jørgensen, K.A. *Org. Biomol. Chem.* ***2003****, 1*, 153.
[1222] Robak, M.T.; Trincado, M.; Ellman, J.A. *J. Am. Chem. Soc.* ***2007****, 129,* 15110; Singh, A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2008****, 130,* 5866.
[1223] Rueping, M.; Antonchick, A.P. *Org. Lett.* ***2008****, 10,* 1731.
[1224] Ziyaei-Halimehjani, A.; Saidi, M.R. *Tetrahedron Lett.* ***2008****, 49,* 1244.
[1225] For reviews, see Jones, G. *Org. React.* ***1967****, 15*, 204; Wilk, B.K. *Tetrahedron* ***1997****, 53*, 7097.
[1226] Rochlin, E.; Rappoport, Z. *J. Org. Chem.* ***2003****, 68*, 1715.
[1227] See Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* ***1988****, 61*, 2473.
[1228] Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107. See also, Huckin, S.N.; Weiler, L. *Can. J. Chem.* ***1974****, 52*, 2157.
[1229] See Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* ***2006****, 47,* 6501.
[1230] Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2002****, 43*, 1127. See Su, C.; Chen, Z.-C.; Zheng, Q.G. *Synthesis* ***2003***, 555.

ammonium salts without solvent leads to a *Knoevenagel reaction*.[1231] Other solvent-free reactions are known.[1232] Ultrasound has been used to promote the reaction,[1233] and it has also been done using microwave irradiation[1234] or on silica,[1235] with microwave irradiation. Another solid-state variation is done on moist LiBr,[1236] heating with sodium carbonate and molecular sieves 4 Å promotes the reaction,[1237] as do zeolites.[1238] High-pressure conditions have been used.[1239] Transition metal compounds of Pd,[1240] Sm[1241] Ce,[1242] Ti,[1243] or Bi[1244] have been used to promote the *Knoevenagel reaction*.

With most of these reagents the alcohol is not isolated (only the alkene) *if* the alcohol has a hydrogen in the proper position,[1245] but with a careful workup the alcohol may be the major product. With suitable reactants, the *Knoevenagel reaction*, like the aldol condensation (**16-34**), has been carried out diastereoselectively[1246] and enantioselectively.[1247] When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of the alkene from the condensation of diethyl malonate [$CH_2(CO_2Et)_2$] with ketones, as well as with aldehydes, if the reaction is run with $TiCl_4$ and pyridine in THF.[1248] In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperidine is the most common, but see formation of **47**), but many other catalysts have been used. Alkoxides are also common catalysts. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the *Knoevenagel reaction* and the product is usually the conjugated acid (**48**). Microwave-induced *Doebner condensation* reactions are known.[1249]

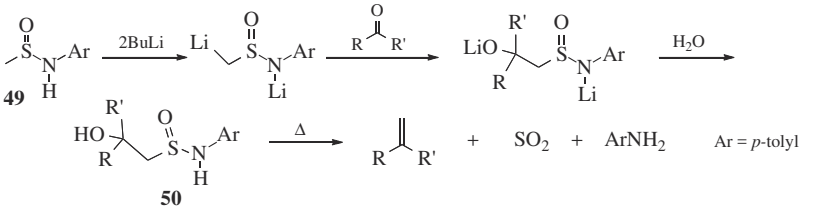


48

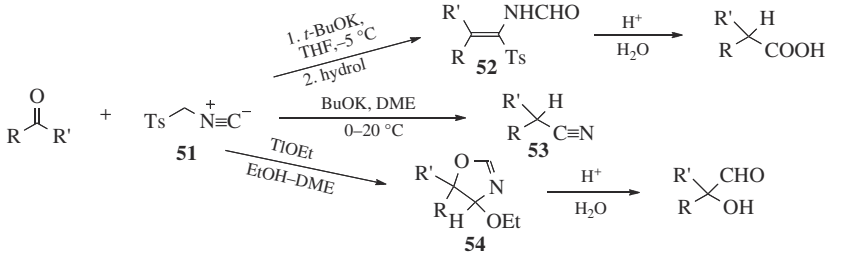
[1231] Bose, D.S.; Narsaiah, A.V. *J. Chem. Res. (S)* ***2001***, 36.
[1232] See Pillai, M.K.; Singh, S.; Jonnalagadda, S.B. *Synth. Commun.* ***2010****, 40,* 3710.
[1233] Li, J.-T.; Zang, H.-J.; Feng, Y.-Y.; Li, L.-J.; Li, T.-S. *Synth. Commun.* ***2001****, 31,* 653.
[1234] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Visali, B.; Narsaiah, A.V.; Nagaiah, K. *Eur. J. Org. Chem.* ***2004***, 546.
[1235] Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Srinivas, D.; Yadav, J.S. *Org. Prep. Proceed. Int.* ***2000****, 32*, 81; Peng, Y.; Song, G.; Qian, X. *J. Chem. Res. (S)* ***2001***, 188.
[1236] Prajapati, D.; Lekhok, K.C.; Sandhu, J.S.; Ghosh, A.C. *J. Chem. Soc. Perkin Trans. 1* ***1996***, 959.
[1237] Siebenhaar, B.; Casagrande, B.; Studer, M.; Blaser, H.-U. *Can. J. Chem.* ***2001***, *79*, 566.
[1238] Reddy, T.I.; Varma, R.S. *Tetrahedron Lett.* ***1997****, 38*, 1721.
[1239] Jenner, G. *Tetrahedron Lett.* ***2001****, 42,* 243.
[1240] You, J.; Verkade, J.G. *J. Org. Chem.* ***2003****, 68*, 8003.
[1241] Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C. *Tetrahedron Lett.* ***1994****, 35*, 5441.
[1242] Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* ***2006****, 47,* 6501.
[1243] Yamashita, K.; Tanaka, T.; Haya, M. *Tetrahedron* ***2005****, 61,* 7981.
[1244] A solvent free reaction. See Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1992***, 1945.
[1245] For lists of reagents (with references) see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 317–325, 341–350. For those that give the alcohol product, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 1178–1179, 1540–1541, 1717–1724, 1727, 1732–1736, 1778–1780, 1801–1805.
[1246] See Barrett, A.G.M.; Robyr, C.; Spilling, C.D. *J. Org. Chem.* ***1989****, 54,* 1233; Pyne, S.G.; Boche, G. *J. Org. Chem.* ***1989****, 54,* 2663.
[1247] See Togni, A.; Pastor, S.D. *J. Org. Chem.* ***1990****, 55,* 1649; Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* ***1990****, 31*, 5349; Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 937.
[1248] Lehnert, W. *Tetrahedron* ***1973****, 29*, 635; *Synthesis* ***1974***, 667 and references cited therein.
[1249] Pellón, R.F.; Mamposo, T.; González, E.; Calderón, O. *Synth. Commun.* ***2000****, 30*, 3769.

A number of special applications of the *Knoevenagel reaction* follow:

1. The dilithio derivative of *N*-methanesulfinyl-*p*-toluidine[1250] (**49**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides (**50**). Subsequent heating leads to a stereospecific syn eliminations to give an alkene.[1251] The reaction is thus a method for achieving the conversion $RR'CO \rightarrow RR'C{=}CH_2$ and represents an alternative to the *Wittig reaction*.[1252] Note that sulfones with an amide group at the α-position, $[ArSO_2CH(R)N(R)C{=}O]$ react with ketones via acyl addition in the presence of SmI_2.[1253]

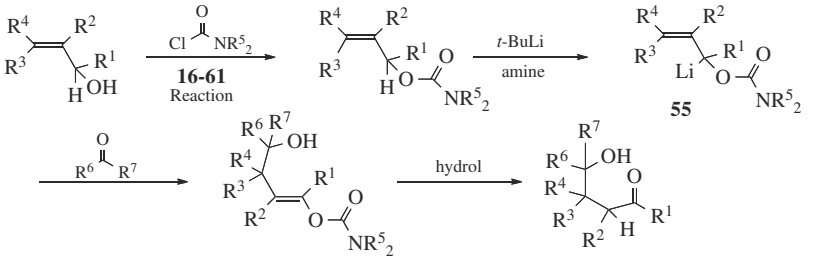


2. The reaction of ketones with tosylmethylisocyanide (**51**) gives different products,[1254] depending on the reaction conditions. When the reaction is run with potassium *tert*-butoxide in THF at –5 °C, one obtains (after hydrolysis) the normal *Knoevenagel* product (**52**), except that the isocyano group has been hydrated (Reaction **16-97**).[1255] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile (**53**).[1256] When the ketone is treated with **51** and thallium(I) ethoxide in a 4: 1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline (**54**).[1257] Since **53** can be hydrolyzed to a carboxylic acid[1198] and **54** to an α-hydroxy aldehyde,[1257] this versatile reaction provides a means for achieving the conversion of RCOR′ to $RCHR'CO_2H$, RCHR′CN, or RCR′(OH)CHO. The conversions to RCHR′COOH and to RCHR′CN[1258] have also been carried out with certain aldehydes (R′ = H).

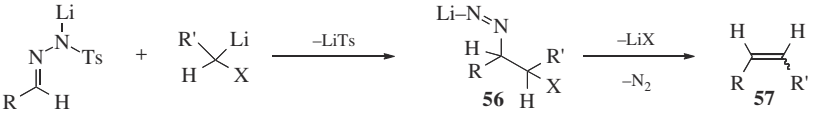


[1250] For a method of preparing **49**, see Bowlus, S.B.; Katzenellenbogen, J.A. *Synth. Commun.* ***1974****, 4,* 137.
[1251] Corey, E.J.; Durst, T. *J. Am. Chem. Soc.* ***1968****, 90,* 5548, 5553.
[1252] See Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* ***1980****, 21*, 2861; Martin, S.F.; Phillips, G.W.; Puckette, T.A.; Colapret, J.A. *J. Am. Chem. Soc.* ***1980****, 102,* 5866; Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* ***1991***, 23.
[1253] Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* ***2001****, 42*, 9225.
[1254] See Schöllkopf, U. *Pure Appl. Chem.* ***1979****, 51*, 1347; *Angew. Chem. Int. Ed.* ***1977****, 16*, 339; Hoppe, D. *Angew. Chem. Int. Ed.* ***1974****, 13,* 789.
[1255] Schöllkopf, U.; Schröder, U.; Blume, E. *Liebigs Ann. Chem.* ***1972****, 766,* 130; Schöllkopf, U.; Schröder, U. *Angew. Chem. Int. Ed.* ***1972****, 11*, 311.
[1256] Oldenziel, O.H.; van Leusen, D.; van Leusen, A.M. *J. Org. Chem.* ***1977****, 42,* 3114.
[1257] Oldenziel, O.H.; van Leusen, A.M. *Tetrahedron Lett.* ***1974***, 163, 167. See, Moskal, J.; van Leusen, A.M. *Tetrahedron Lett.* ***1984****, 25,* 2585; van Leusen, A.M.; Oosterwijk, R.; van Echten, E.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* ***1985****, 104,* 50.
[1258] van Leusen, A.M.; Oomkes, P.G. *Synth. Commun.* ***1980****, 10,* 399.

3. Aldehydes and ketones (RCOR′) react with α-methoxyvinyllithium [CH_2=C(Li)OMe] to give hydroxy enol ethers [RR′C(OH)C(OMe)=CH_2], which are easily hydrolyzed to acyloins [RR′C(OH)COMe].[1259] In this reaction, the CH_2=C(Li)OMe is a synthon for the unavailable H_3C—C=O,[1260] and is termed an *acyl anion equivalent*. The reagent also reacts with esters (RCOOR′) to give RC(OH)(COMe=CH_2)$_2$. A synthon for the Ph—C=O ion is PhC(CN)OSiMe_3, which adds to aldehydes and ketones (RCOR′) to give, after hydrolysis, the α-hydroxy ketones [RR′C(OH)COPh].[1261]
4. Lithiated allylic carbamates (**55**) (prepared as shown) react with aldehydes or ketones (R^6COR^7), in a reaction accompanied by an allylic rearrangement, to give (after hydrolysis) γ-hydroxy aldehydes or ketones.[1262] The reaction is called *the homoaldol reaction*, since the product is a homologue of the product of Reaction **16-34**. The reaction has been performed enantioselectively.[1263]



5. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **56**. If X = CN, SPh, or SO_2R, **56** spontaneously loses N_2 and LiX to give the alkene **57**. The entire process is done in one reaction vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with (*i*Pr)$_2$NLi to form both salts at once.[1264] This process is another alternative to the *Wittig reaction* for forming double bonds.

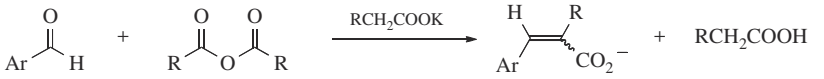


OS **I**, 181, 290, 413; **II**, 202; **III**, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV**, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V**, 130, 381, 572, 585, 627, 833, 1088, 1128; **VI**, 41, 95, 442, 598, 683; **VII**, 50, 108, 142, 276, 381, 386, 456; **VIII**, 258, 265, 309, 353, 391, 420; **X**, 271. Also see, OS **III**, 395; **V**, 450.

[1259] Baldwin, J.E.; Höfle, G.A.; Lever, Jr., O.W. *J. Am. Chem. Soc.* ***1974****, 96*, 7125. For a similar reaction, see Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* ***1978***, 4809.
[1260] Also see Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* ***1984****, 25*, 511.
[1261] Hünig, S.; Wehner, G. *Synthesis* ***1975***, 391.
[1262] For a review, see Hoppe, D. *Angew. Chem. Int. Ed.* ***1984****, 23,* 932.
[1263] Krämer, T.; Hoppe, D. *Tetrahedron Lett.* ***1987****, 28*, 5149.
[1264] Vedejs, E.; Dolphin, J.M.; Stolle, W.T. *J. Am. Chem. Soc.* ***1979****, 101,* 249.

16-39 The Perkin Reaction

α-Carboxyalkylidene-de-oxo-bisubstitution

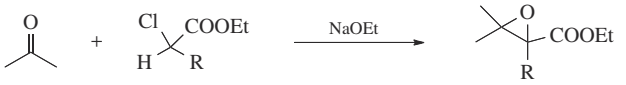


The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.[1265] When the anhydride has two α hydrogen atoms (as shown), dehydration almost always occurs; the β-hydroxy acid salt is rarely isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the *Perkin reaction* is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.[1266] Besides aromatic aldehydes, their vinylogs (ArCH=CHCHO) also give the reaction (see Sec. 6.B). Otherwise, the reaction is not suitable for aliphatic aldehydes.[1267]

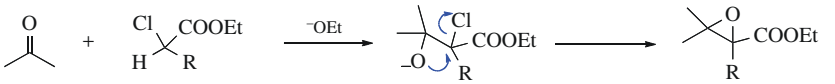
OS **I**, 398; **II**, 61, 229; **III**, 426.

16-40 Darzens Glycidic Ester Condensation

(2+1) *OC,CC-cyclo*-α-Alkoxycarbonylmethylene-addition



Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters*. This is called *the Darzens condensation*.[1268] The reaction consists of an initial *Knoevenagel-type* Reaction (**16-38**), followed by an internal S_N2 Reaction (**10-9**)[1269]:



Although the intermediate halo alkoxide is generally not isolated,[1270] it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions), but also with α-chloro esters.[1271] This is only one of several types of evidence that rule out a carbene intermediate.[1272] Sodium ethoxide is often used as the base, but other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields. The reaction can be made to give good yields (~ 80%) with simple aliphatic aldehydes, as well as with aromatic aldehydes and ketones, by treatment of the α-halo ester with the base lithium bis(trimethylsilyl)amide [$LiN(SiMe_3)_2$] in THF at

[1265] See Johnson, J.R. *Org. React.* ***1942****, 1,* 210.
[1266] Koepp, E.; Vögtle, F. *Synthesis* ***1987***, 177.
[1267] Crawford, M.; Little, W.T. *J. Chem. Soc.* ***1959***, 722.
[1268] See Berti, G. *Top. Stereochem.* ***1973****, 7*, 93, pp. 210–218. Also see, Bakó, P.; Szöllõsy, Á; Bombicz, P.; Töke, L. *Synlett* ***1997***, 291.
[1269] See Bansal, R.K.; Sethi, K. *Bull. Chem. Soc. Jpn.* ***1980****, 53,* 1197.
[1270] See Yliniemelä, A.; Brunow, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* ***1996****, 61*, 6723.
[1271] Ballester, M.; Pérez-Blanco, D. *J. Org. Chem.* ***1958****, 23,* 652; Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* ***1973***, 1277, 1281.
[1272] See also, Zimmerman, H.E.; Ahramjian, L. *J. Am. Chem. Soc.* ***1960****, 82,* 5459.

–78 °C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.[1273] If a preformed dianion of an α-halo carboxylic acid ($Cl^-CRCO_2^-$) is used instead, α,β-epoxy acids are produced directly.[1274] The *Darzens reaction* has also been carried out on α-halo ketones, α-halo nitriles,[1275] α-halo sulfoxides[1276] and sulfones,[1277] α-halo N,N-disubstituted amides,[1278] α-halo ketimines,[1279] and even on allylic[1280] and benzylic halides. Phase-transfer catalysis has been used.[1281] Note that the reaction of a β-bromo-α-oxo ester and a *Grignard reagent* leads to the glycidic ester.[1282] Acid-catalyzed *Darzens reactions* have also been reported.[1283] (see also, Reaction **16-46**).

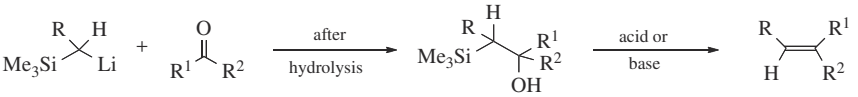
Diastereoselective *Darzens condensations* are possible.[1284] The *Darzens reaction* has been performed with good enantioselectivity,[1285] and chiral additives have proven to be effective.[1286] Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity.[1287]

Glycidic esters can easily be converted to aldehydes (Reaction **12-40**). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo N,N-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.[1288] However, yields were not high.

OS **III**, 727; **IV**, 459, 649.

16-41 The Peterson Alkenylation Reaction

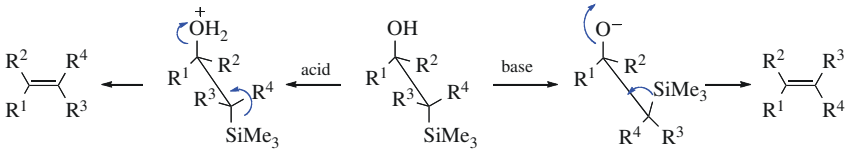
Alkylidene-de-oxo-bisubstitution



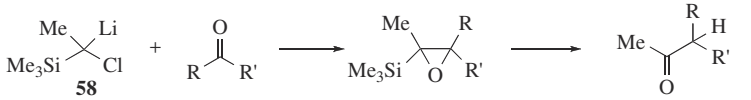
In the *Peterson alkenylation reaction*[1289], the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β-hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an alkene. This reaction is still another alternative to the *Wittig reaction* (**16-44**), and is sometimes

[1273] Borch, R.F. *Tetrahedron Lett.* ***1972***, 3761.
[1274] Johnson, C.R.; Bade, T.R. *J. Org. Chem.* ***1982****, 47,* 1205.
[1275] See White, D.R.; Wu, D.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 988.
[1276] Satoh, T.; Sugimoto, A.; Itoh, M.; Yamakawa, K. *Tetrahedron Lett.* ***1989****, 30*, 1083.
[1277] Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* ***1998****, 39*, 8299.
[1278] Tung, C.C.; Speziale, A.J.; Frazier, H.W. *J. Org. Chem.* ***1963****, 28,* 1514.
[1279] Mauzé, B. *J. Organomet. Chem.* ***1979****, 170,* 265.
[1280] Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J.; Tinant, B. *J. Org. Chem.* ***1988****, 53,* 4457.
[1281] See Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* ***2002****, 43*, 833. See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis* Academic Press, NY, ***1978***, pp. 197–198.
[1282] Jung, M.E.; Mengel, W.; Newton, T.W. *Synth. Commun.* ***1999****, 29*, 3659.
[1283] Sipos, G.; Schöbel, G.; Sirokmán, F. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 805.
[1284] Achard, T.J.R.; Belokon', Y.N.; Hunt, J.; North, M.; Pizzato, F. *Tetrahedron Lett.* ***2007****, 48,* 2961.
[1285] Achard, T.J.R.; Belokon', Y.N.; Ilyin, M.; Moskalenko, M.; North, M.; Pizzato, F. *Tetrahedron Lett.* ***2007****, 48,* 2965. For a review, see Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* ***1996***, 2411.
[1286] Aggarwal, V.K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* ***2002****, 124*, 9964.
[1287] Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999****, 55*, 6375.
[1288] Deyrup, J.A. *J. Org. Chem.* ***1969****, 34*, 2724.
[1289] Peterson, D.J. *J. Org. Chem.* ***1968***, *33*, 780. See Ager, D.J. *Org. React*. ***1990***, *38*, 1; *Synthesis* ***1984***, 384; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 63–75; Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer, NY, ***1983***, pp. 58–78; Magnus, P. *Aldrichimica Acta* ***1980***, *13*, 43; Chan, *T. Acc. Chem. Res*. ***1977***, *10*, 442. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 337–341.

called the *silyl–Wittig reaction*.[1290] The R group can also be a COOR group, in which case the product is an α,β-unsaturated ester,[1291] or an SO_2Ph group, in which case the product is a vinylic sulfone.[1292] The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. The role of Si—O interactions has also been examined.[1293] Use of a base generally gives syn elimination (Ei mechanism, see Sec. 17.C.i), while an acid usually results in anti elimination (E2 mechanism, see Sec. 17.A.i).[1294] Samarium(II) iodide in HMPA has also been used for elimination of the hydroxy sulfone.[1295]



When aldehydes or ketones are treated with reagents of the form **58**, the product is an epoxy silane (Reaction **16-46**), which can be hydrolyzed to a methyl ketone.[1296] For aldehydes, this is a method for converting RCHO to a methyl ketone (RCH_2COMe).



58

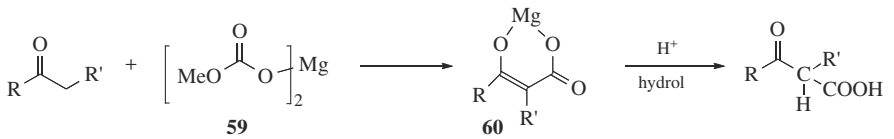
The reagents $Me_3SiCHRM$ (M = Li or Mg) are often prepared from $Me_3SiCHRCl$[1297] (by Reaction **12-38** or **12-39**), but they have also been made by Reaction **12-22** and other procedures.[1298] Lithio alkenylsilanes have been used for this reaction.[1299]

A new version of the reaction has been developed, reacting $Me_3SiCH_2CO_2Et$ with an aldehyde and a catalytic amount of CsF in DMSO.[1300] A seleno-amide derivative has been used in a similar manner.[1301]

There are no references in *Organic Syntheses*, but see OS **VIII**, 602, for a related reaction.

16-42 The Addition of Active Hydrogen Compounds to CO_2 and CS_2

α-Acylalkyl-de-methoxy-substitution (Overall reaction)



59 **60**

[1290] See Hudrlik, P.F.; Agwaramgbo, E.L.O.; Hudrlik, A.M. *J. Org. Chem.* ***1989****, 54*, 5613.
[1291] See Strekowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* ***1984****, 25,* 5603.
[1292] Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1949.
[1293] Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *J. Chem. Res. (S)* ***1996***, 34.
[1294] See Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 65–69.
[1295] Markò, I.E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* ***2001****, 57*, 2609.
[1296] Cooke, F.; Roy, G.; Magnus, P. *Organometallics* ***1982****, 1,* 893.
[1297] For a review of these reagents, see Anderson, R. *Synthesis* ***1985***, 717.
[1298] See Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.* ***1991****, 56*, 638.
[1299] Tsubouchi, A.; Kira, T.; Takeda, T. *Synlett* ***2006***, 2577.
[1300] Bellassoued, M.; Ozanne, N. *J. Org. Chem.* ***1995****, 60*, 6582.
[1301] Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* ***2003****, 68*, 7979.

Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate (**59**).[1302] Because formation of the chelate (**60**) provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2, on compounds of the form RCH_2NO_2[1303] and on certain lactones.[1304] Direct carboxylation has been reported in a number of instances. Ketones have been carboxylated in the α position to give β-keto acids.[1305] The base here was lithium 4-methyl-2,6-di-*tert*-butylphenoxide.

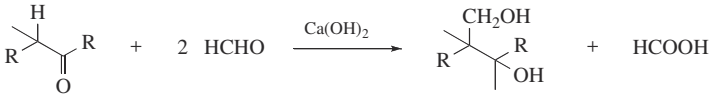
Ketones ($RCOCH_2R'$), as well as other active hydrogen compounds, undergo base-catalyzed addition to CS_2[1306] to give a dianion intermediate ($RCOC^-R'CSS^{2-}$), which can be dialkylated with a halide (R^2X) to produce α-dithiomethylene ketones [$RCOCR'{=}C(SR^2)_2$].[1307] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give analogous dianions.[1308]

Although reactions with N=O derivatives do not formally fall into this category of reactions, it is somewhat related. Nitroso compounds react with activated nitriles in the presence of LiBr and microwave irradiation to give a cyano imine [$ArN{=}C(CN)Ar$].[1309] This transformation has been called the *Ehrlich–Sachs reaction*.[1310]

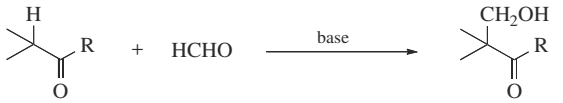
OS **VII**, 476. See also, OS **VIII**, 578.

16-43 Tollens' Reaction

O-Hydro-*C* (β-hydroxyalkyl)-addition



In the *Tollens' reaction*, an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is a mixed-aldol reaction (**16-34**).



The reaction can be stopped at this point, but more often a second equivalent of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a *crossed-Cannizzaro Reaction* (**19-81**). If the aldehyde or ketone has several α hydrogen atoms, they can all be replaced. An

[1302] Stiles, M. *J. Am. Chem. Soc.* ***1959****, 81*, 2598; *Ann. N.Y. Acad. Sci.* ***1960****, 88,* 332; Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* ***1968***, 3021.
[1303] Finkbeiner, H.L.; Stiles, M. *J. Am. Chem. Soc.* ***1963****, 85,* 616; Finkbeiner, H.L.; Wagner, G.W. *J. Org. Chem.* ***1963****, 28,* 215.
[1304] Martin, J.; Watts, P.C.; Johnson, F. *Chem. Commun.* ***1970***, 27.
[1305] Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* ***1985****, 50,* 4877. For an enantioselective version, see Hogeveen, H.; Menge, W.M.P.B. *Tetrahedron Lett.* ***1986****, 27*, 2767.
[1306] See Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 120–225; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, pp. 797–804.
[1307] See Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* ***1973***, 3817.
[1308] See Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron* ***1976****, 32,* 2507, and references cited therein.
[1309] Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2001****, 31*, 1427.
[1310] Ehrlich, P.; Sachs, F. *Chem. Ber.* ***1899****, 32,* 2341

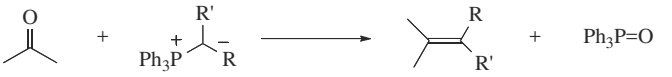
important use of the reaction is to prepare pentaerythritol from acetaldehyde:

$$CH_3CHO + 4HCHO \longrightarrow C(CH_2OH)_4 + HCOOH$$

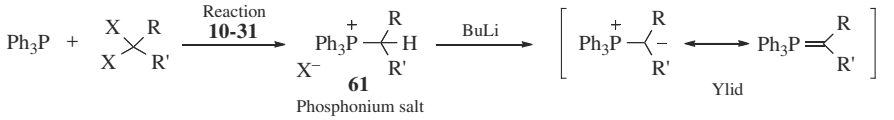
OS **I**, 425; **IV**, 907; **V**, 833.

16-44 The Wittig Reaction

Alkylidene-de-oxo-bisubstitution



In the *Wittig reaction*, an aldehyde or ketone is treated with a *phosphorus ylid* (a *phosphorane*; also spelled ylide) to give an alkene.[1311] The conversion of a carbonyl compound to an alkene with a phosphorus ylid is called the *Wittig reaction*. Phosphorus ylids are usually prepared by treatment of a phosphonium salt with a base,[1312] and phosphonium salts (**61**) are usually prepared from a triaryl phosphine and an alkyl halide (Reaction **10-31**):



The reaction of triphenylphosphine and an alkyl halides is facilitated by the use of microwave irradiation.[1313] Indeed, the *Wittig reaction* itself is assisted by microwave irradiation.[1314] Phosphonium salts are also prepared by addition of phosphines to *Michael alkenes* (like Reaction **15-8**) and in other ways.

The phosphonium salts are most often converted to the ylids by treatment with a strong base (e.g., butyllithium, sodium amide,[1315] sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. In some cases, and excess of fluoride ion is sufficient.[1316] For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[1317] When the base used does not contain lithium, the ylid is said to be prepared under "salt-free" conditions[1318] because the lithium halide (where the halide counterion comes from

[1311] See Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***; Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***. For reviews, see Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989,*** *89*, 863; Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983,*** *109*, 85; Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* ***1983,*** *109*, 165; Pommer, H. *Angew. Chem. Int. Ed.* ***1977,*** *16*, 423; Maercker, A. *Org. React.* ***1965,*** *14*, 270; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 682–709. For related reviews, see Zbiral, E. *Synthesis* ***1974***, 775; Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965,*** *4*, 583, 645–660, 830–838; *Newer Methods Prep. Org. Chem.* ***1968,*** *5,* 1; Horner, L. *Fortschr. Chem. Forsch.,* ***1966,*** *7,* 1. For a historical background, see Wittig, G. *Pure Appl. Chem.* ***1964,*** *9*, 245. For a list of reagents and references for the Wittig and related reactions, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 327–337.

[1312] When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the alkene: Schiemenz, G.P.; Becker, J.; Stöckigt, J. *Chem. Ber.* ***1970,*** *103*, 2077.

[1313] Kiddle, J.J. *Tetrahedron Lett.* ***2000,*** *41*, 1339.

[1314] Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* ***2004,*** *45*, 4401.

[1315] See Schlosser, M.; Schaub, B. *Chimia* ***1982,*** *36*, 396.

[1316] Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* ***2002,*** *67*, 3156.

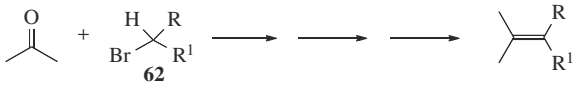
[1317] Ramirez, F.; Pilot, J.F.; Desai, N.B.; Smith, C.P.; Hansen, B.; McKelvie, N. *J. Am. Chem. Soc.* ***1967,*** *89*, 6273.

[1318] Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965,*** *4,* 586.

the phosphonium salt) is absent. *Wittig reactions* can be done in aqueous media in the presence of surfactants.[1319]

When the phosphorus ylid reacts with the aldehyde or ketone to form an alkene, a phosphine oxide is also formed. When triphenylphosphine is used to give $Ph_3P{=}CRR'$, for example, the byproduct is triphenylphosphine oxide (Ph_3PO), which is sometimes difficult to separate from the other reaction products. Other triarylphosphines[1320] and trialkylphosphines[1321] have been used. Phosphines that have an α-hydrogen should be avoided, so that reaction with the chosen alkyl halide will lead to a phosphonium salt (**61**) with the α-proton at the desired position. This limitation is essential if a specific ylid is to be formed from the alkyl halide precursor. The *Wittig reaction* has been carried out with polymer-supported ylids.[1322] It has also been done on silica gel.[1323] Polymer-bound aryldiphenylphosphino compounds[1324] have been used in reactions with alkyl halides to complete a *Wittig reaction.*

If an alkyl halide is viewed as the starting material (alkyl halide phosphonium salt → phosphorus ylid → alkene), the halogen-bearing carbon of an alkyl halide must contain at least one hydrogen, as in **62** (for deprotonation at the phosphonium salt stage).



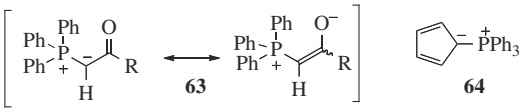
62

The reaction is very general.[1325] The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones). *Wittig reactions* are known in which the ylid and/or the carbonyl substrate contain double or triple bonds; various functional groups may be present (e.g., OH, OR, NR_2, aromatic nitro or halo, acetal, amide,[1326] or even ester groups).[1327] Note, however, that a *Wittig reaction* has been reported in which the carbonyl group of an ester was converted to a vinyl ether.[1328] An important advantage of the *Wittig reaction* is that the *position* of the new double bond is always certain, in contrast to the result in most of the base-catalyzed condensations (Reactions **16-34**–**16-43**). Ylids have been shown to react with lactones, however, to form ω-alkenyl alcohols.[1329] β-Lactams have also been converted to alkenyl-azetidine derivatives using phosphorus ylids.[1330] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon. The carbonyl partner can be generated *in situ*, in the presence of an ylid; the reaction of an alcohol with a mixture of an oxidizing agent and an ylid generates an alkene. Oxidizing agents used in this manner include $BaMnO_4$,[1331] MnO_2,[1332] and $PhI(OAc)_2$.[1333]

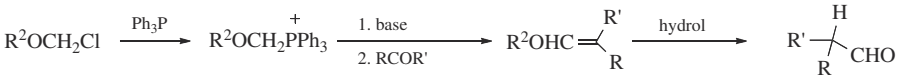
[1319] Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* ***2006***, 1717.
[1320] Schiemenz, G.P.; Thobe, J. *Chem. Ber.* ***1966****, 99,* 2663.
[1321] See Bestmann, H.J.; Kratzer, O. *Chem. Ber.* ***1962****, 95,* 1894.
[1322] Bernard, M.; Ford, W.T.; Nelson, E.C. *J. Org. Chem.* ***1983****, 48*, 3164.
[1323] Patil, V.J.; Mävers, U. *Tetrahedron Lett.* ***1996****, 37*, 1281.
[1324] Betancort, J.M.; Barbas, III, C.F. *Org. Lett.* ***2001****, 3*, 3737.
[1325] See Dunne, E.C.; Coyne, É.J.; Crowley, P.B.; Gilheany, D.G. *Tetrahedron Lett.* ***2002****, 43*, 2449.
[1326] Smith, M.B.; Kwon, T.W. *Synth. Commun.* ***1992****, 22*, 2865. Also see Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004****, 126*, 7559.
[1327] See Harcken, C.; Martin, S.F. *Org. Lett.* ***2001****, 3*, 3591; Yu, X.; Huang, X. *Synlett* ***2002***, 1895. Also see Greenwald, R.; Chaykovsky, M.; Corey, E.J. *J. Org. Chem.* ***1963****, 28*, 1128.
[1328] Tsunoda, T.; Takagi, H.; Takaba, D.; Kaku, H.; Itô, S. *Tetrahedron Lett.* ***2000****, 41*, 235.
[1329] Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* ***1996****, 37*, 3853.
[1330] Baldwin, J.E.; Edwards, A.J.; Farthing, C.N.; Russell, A.T. *Synlett* ***1993***, 49.
[1331] Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* ***1998****, 63*, 4489.
[1332] Reid, M.; Roman, E.; Taylor, R.J.K. *Synlett* ***2004***, 819.
[1333] Zhang, P.-F.; Chen, Z.-C. *Synth. Commun.* ***2001****, 31,* 1619.

Weinreb amides (Reaction **16-82**) can be converted to the corresponding aldehyde via the *Wittig reaction.*[1334]

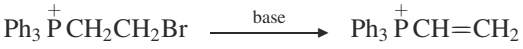
As noted above, the phosphorus ylid may also contain double or triple bonds and certain functional groups. Simple ylids (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group (e.g., COR, CN, CO_2R, CHO) is present in the α position, the ylids are much more stable, because the charge on the carbon is delocalized by



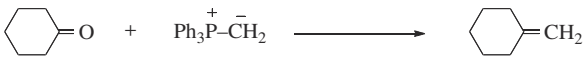
resonance as in **63**. Such ylids react readily with aldehydes, but slowly or not at all with ketones.[1335] In extreme cases (e.g., **64** where the carbanion unit is part of the aromatic cyclopentadienyl anion), the ylid does not react with ketones *or* aldehydes. Besides these groups, the ylid may contain one or two α halogens[1336] or



an α OR or OAr group. In the latter case, the product is an enol ether, which can be hydrolyzed (Reaction **10-6**) to an aldehyde,[1337] so that this reaction is a means of achieving the conversion RCOR′ → RR′CHCHO.[1338] However, the ylid may not contain an α nitro group. If the phosphonium salt contains a potential leaving group (e.g., Br or OMe) in the β position, treatment with a base gives elimination, instead of the ylid:



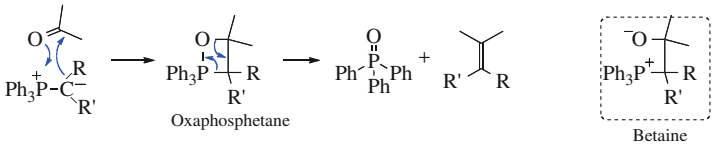
However, a β COO^- group may be present, and the product is a β,γ-unsaturated acid:[1339] This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the *Wittig* method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to alkenes containing exocyclic double bonds, for example:[1340]



[1334] Hisler, K.; Tripoli, R.; Murphy, J.A. *Tetrahedron Lett.* ***2006****, 47,* 6293.
[1335] See Isaacs, N.S.; El-Din, G.N. *Tetrahedron Lett.* ***1987****, 28,* 2191. See also, Dauben, W.G.; Takasugi, J.J. *Tetrahedron Lett.* ***1987***, *28,* 4377.
[1336] Smithers, R.H. *J. Org. Chem.* ***1978****, 43,* 2833; Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1979****, 52*, 1197; Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989****, 30*, 2173.
[1337] See Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1441–1444, 1457–1458.
[1338] See Ceruti, M.; Degani, I.; Fochi, R. *Synthesis* ***1987***, 79; Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas* ***1987****, 106,* 137; Doad, G.J.S. *J. Chem. Res. (S)* ***1987***, 370.
[1339] Corey, E.J.; McCormick, J.R.D.; Swensen, W.E. *J. Am. Chem. Soc.* ***1964****, 86*, 1884.
[1340] Wittig, G.; Schöllkopf, U. *Chem. Ber.* ***1954****, 87,* 1318.

Still another example is the formation of *anti-Bredt* bicycloalkenones[1341] (see Sec. 4.Q.iii). As indicated above, α,α'-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare haloalkenes[1342] is to treat the carbonyl compound with a mixture of CX_4 (X = Cl, Br, or I) and triphenylphosphine, either with or without the addition of zinc dust, which allows less Ph_3P to be used.[1343] Aryl aldehydes react with these dihalophosphoranes to give aryl alkynes after treatment of the initially formed vinyl halide with potassium *tert*-butoxide.[1344]

The mechanism[1345] of the key step of the *Wittig reaction* is as follows:[1346]

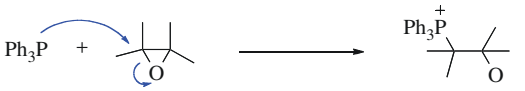


The energetics of ylid formation and their reaction in solution has been studied.[1347] For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds to the oxaphosphetane, but it has been argued that there is little evidence for it.[1348] However, "betaine" precipitates have been isolated in certain *Wittig reactions*,[1349] although these are betaine–lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.[1350] There is one report of an observed betaine lithium salt during the course of a *Wittig reaction*.[1351] An X-ray structure was determined for a *gauche* betaine from a thio-*Wittig reaction*.[1352] In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylids. For example, ^{31}P NMR spectra taken of the reaction mixtures at low temperatures[1353] are compatible with an oxaphosphetane structure that persists for some time but not with a tetra-coordinated phosphorus species. Since a betaine, an ylid, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases, oxaphosphetanes have been isolated.[1354] It has even been

[1341] Bestmann, H.J.; Schade, G. *Tetrahedron Lett.* ***1982****, 23*, 3543.
[1342] For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 725–727.
[1343] See Li, P.; Alper, H. *J. Org. Chem.* ***1986****, 51,* 4354.
[1344] Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* ***1999****, 40*, 8575. See Michael, P.; Rassat, A. *Tetrahedron Lett.* ***1999****, 40*, 8579.
[1345] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 232–240; Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1988****, 110*, 3948.
[1346] It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah, G.A.; Krishnamurthy, V.V. *J. Am. Chem. Soc.* ***1982****, 104*, 3987; Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* ***1989****, 30*, 7187. A diradical mechanism has also been proposed for certain cases: Ward, Jr., W.J.; McEwen, W.E. *J. Org. Chem.* ***1990****, 55,* 493.
[1347] Arnett, E.M.; Wernett, P.C. *J. Org. Chem.* ***1993****, 58*, 301.
[1348] See Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1990****, 112,* 3905.
[1349] See Schlosser, M.; Christmann, K.F. *Liebigs Ann. Chem.* ***1967****, 708,* 1.
[1350] Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989****, 89*, 863, see p. 865.
[1351] Neumann, R.A.; Berger, S. *Eur. J. Org. Chem.* ***1998***, 1085.
[1352] Puke, C.; Erker, G.; Wibbeling, B.; Fröhlich, R. *Eur. J. Org. Chem.* ***1999***, 1831.
[1353] Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* ***1981****, 103,* 2823. See also, Nesmayanov, N.A.; Binshtok, E.V.; Reutov, O.A. *Doklad. Chem.* ***1973****, 210*, 499.
[1354] Mazhar-Ul-Haque; Caughlan, C.N.; Ramirez, F.; Pilot, J.F.; Smith, C.P. *J. Am. Chem. Soc.* ***1971****, 93,* 5229.

possible to detect cis and trans isomers of the intermediate oxaphosphetanes by NMR spectroscopy.[1355] According to this mechanism, an optically active phosphonium salt ($RR^1R^2P^+CHR^2$) should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide (RR^1R^2PO). This has been shown to be the case.[1356]

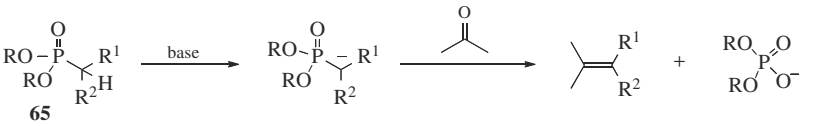
Note that the proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**10-35**):



Betaines formed in this way can then be converted to the alkene. This is one reason why betaine intermediates were long accepted in the *Wittig reaction*. It is also noteworthy that stable phosphonium enolate zwitterions have been formed by the reaction of an aryl aldehyde, a phosphine, and a propargylic ester.[1357]

Phosphorus is not the only key element used to produce useful ylids. Triphenylarsine[1358] has been used. Tellurium ylids have been prepared *in situ* from α-halo esters and $BrTeBu_2OTeBu_2Br$ and react with aldehydes to give conjugated esters.[1359]

The *Wittig reaction* has been carried out with phosphorus ylids other than phosphoranes, the most important being prepared from phosphonate esters (e.g., **65**).[1360]



65

This method, sometimes called the *Horner–Emmons*, *Wadsworth–Emmons*, *Wittig–Horner, or Horner–Wadsworth–Emmons reaction*,[1361] has several advantages over the use of phosphoranes, including selectivity.[1362] These ylids are more reactive than the corresponding phosphoranes, and when R^1 or R^2 is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. High pressure has been used to facilitate this reaction.[1363] In addition, the phosphorus product is a phosphate ester, and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the

[1355] Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond Jr., H.R.; Whittle, R.R.; Olofson, R.A. *J. Am. Chem. Soc.* ***1986****, 108,* 7664. See also, Pískala, A.; Rehan, A.H.; Schlosser, M. *Coll. Czech. Chem. Commun.* ***1983****, 48,* 3539.

[1356] McEwen, W.E.; Kumli, K.F.; Bladé-Font, A.; Zanger, M.; VanderWerf, C.A. *J. Am. Chem. Soc.* ***1964****, 86*, 2378.

[1357] Zhu, X.-F.; Henry, C.E.; Kwon, O. J. *Am. Chem. Soc.* ***2007****, 129,* 6722.

[1358] For a catalytic version, see Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* ***1989****, 54,* 2027; Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* ***1995****, 36*, 425.

[1359] Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* ***2002****, 67*, 5320.

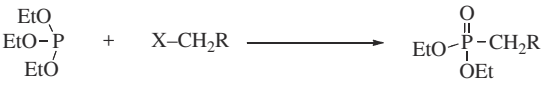
[1360] Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* ***1959****, 92,* 2499; Wadsworth, Jr., W.S.; Emmons, W.D. *J. Am. Chem. Soc.* ***1961****, 83,* 1733.

[1361] Wadsworth, Jr., W.S. *Org. React.* ***1977****, 25,* 73; Stec, W.J. *Acc. Chem. Res.* ***1983****, 16,* 411; Walker, B.J. in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 156–205; Boutagy, J.; Thomas, R. *Chem. Rev.* ***1974****, 74,* 87; Seguineau, P.; Villieras, J. *Tetrahedron Lett.* ***1988****, 29,* 477, and other papers in this series.

[1362] Motoyoshiya, J.; Kasaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* ***2001****, 57*, 1715.

[1363] Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* ***2001***, 1395.

alkene product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*:[1364]



Phosphonates have also been prepared from alcohols and $(ArO)_2P(=O)Cl$, NEt_3, and a $TiCl_4$ catalyst.[1365] The reaction of $(RO)_2P(=O)H$ and aryl iodides with a CuI catalyst leads to aryl phosphonates.[1366] Polymer-bound phosphonate esters have been used for olefination.[1367] Dienes are produced when allylic phosphonate esters react with aldehydes.[1368] Nucleophilicity parameters have been determined for phosphoryl-stabilized carbanions.[1369] A Zn promoted reaction is known using diprotic phosphonates.[1370] *Wittig reactions* of stabilized phosphorus ylids have also been done in water.[1371]

Stereoselective alkenylation reactions have been achieved using chiral additives[1372] or auxiliaries.[1373] Ylids formed from phosphine oxides $[Ar_2P(=O)CHRR']$, phosphonic acid bis(amides), $(R_2{}^2N)_2POCHRR^1]$,[1374] and alkyl phosphonothionates $[(MeO)_2PSCHRR^1]$,[1375] share some of these advantages. Reagents (e.g., $Ph_2POCH_2NR_2$') react with aldehydes or ketones (R^2COR^3) to give good yields of enamines ($R^2R^3C{=}CHNR$).[1376] (*Z*)-Selective reagents are also known,[1377] including the use of a di(2,2,2-trifluoroethoxy)phosphonate with KHMDS and 18-crown-6.[1378] An interesting intramolecular version of the *Horner–Emmons reaction* leads to alkynes.[1379] The reaction of a functionalized aldehyde (R—CHO) with $(MeO)_2POCHN_2$, leads to an alkyne (R—C≡CH).[1380]

[1364] Also known as the *Michaelis–Arbuzov rearrangement*. For reviews, see Petrov, A.A.; Dogadina, A.V.; Ionin, B.I.; Garibina, V.A.; Leonov, A.A. *Russ. Chem. Rev.* ***1983****, 52,* 1030; Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* ***1981****, 81,* 415. See also Shokol, V.A.; Kozhushko, B.N. *Russ. Chem. Rev.* ***1985****, 53*, 98; Brill, T.B.; Landon, S.J. *Chem. Rev.* ***1984****, 84,* 577; Lherbet, C.; Castonguay, R.; Keillor, J.W. *Tetrahedron Lett.* ***2005****, 46,* 3565; Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* ***2006****, 71,* 5020.

[1365] Jones, S.; Selitsianos, D. *Org. Lett.* ***2002****, 4*, 3671.

[1366] Gelman, D.; Jiang, L.; Buchwald, S.L. *Org. Lett.* ***2003****, 5*, 2315.

[1367] Barrett, A.G.M.; Cramp, S.M.; Roberts, R.S.; Zecri, F.J. *Org. Lett.* ***1999****, 1*, 579.

[1368] Wang, Y.; West, F.G. *Synthesis* ***2002***, 99.

[1369] Appel, R.; Loos, R.; Mayr, H. *J. Am. Chem. Soc.* ***2009****, 131*, 704.

[1370] Schauer, D.J.; Helquist, P. *Synthesis* ***2006***, 3654.

[1371] Wu, J.; Zhang, D.; Wei. S. *Synth. Commun.* ***2005****, 35,* 1213; Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* ***2005****, 35*, 2543. See also McNulty, J.; Das, P. *Tetrahedron Lett.* ***2009****, 50*, 5737; McNulty, J.; Das, P.; McLeod, D. *Chemistry: Eur. J.* ***2010****, 16*, 6756.

[1372] Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem. Int. Ed.* ***1998****, 37*, 515. Also see, Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* ***1998****, 39*, 2997. For a review of asymmetric Wittig-type reactions see Rein, T.; Pedersen, T.M. *Synthesis* ***2002***, 579.

[1373] Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1996****, 37*, 1077.

[1374] Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1969****, 34*, 3053. For a chiral derivative, see Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* ***1992****, 33*, 7655, 7659.

[1375] Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* ***1966****, 88,* 5654.

[1376] Broekhof, N.L.J.M.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984****, 103*, 305; Broekhof, N.L.J.M.; van Elburg, P.; Hoff, D.J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984****, 103*, 317.

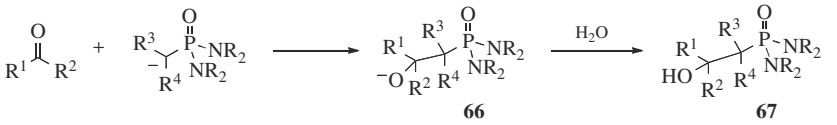
[1377] Ando, K. *Tetrahedron Lett.* ***1995****, 36*, 4105.

[1378] Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* ***1999****, 40*, 6725.

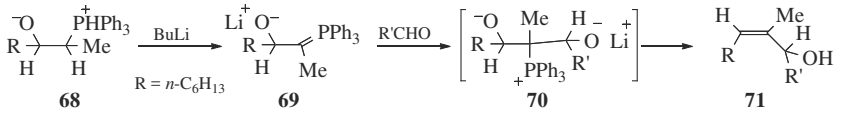
[1379] Nangia, A.; Prasuna, G.; Rao, P.B. *Tetrahedron Lett.* ***1994****, 35*, 3755; Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 2463.

[1380] Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* ***1992****, 33*, 3715.

Some *Wittig reactions* give the (*Z*)-alkene; some the (*E*), and others give mixtures. The question of which factors determine the stereoselectivity has been much studied.[1381] It is generally found that ylids containing stabilizing groups or formed from trialkylphosphines give (*E*)-alkenes. The origin of the (*E*) selectivity in salt-free stabilized ylids may be related to dipole–dipole interactions.[1382] The energy of the elimination transition state must also be taken into account.[1383] It has been shown that ylids formed from triarylphosphines and not containing stabilizing groups often give (*Z*) or a mixture of (*Z*)- and (*E*)-alkenes.[1384] One explanation for this[1356] is that the reaction of the ylid with the carbonyl compound is a [2+2]-cycloaddition, which in order to be concerted must adopt the $[\pi 2_s + \pi 2_a]$-pathway. As discussed in Reaction **15-63**, this pathway leads to the formation of the more sterically crowded product, in this case the (*Z*)-alkene. If this explanation is correct, it is not easy to explain the predominant formation of (*E*) *p*roducts from stable ylids, but (*E*) compounds are of course generally thermodynamically more stable than the (*Z*) isomers, and the stereochemistry seems to depend on many factors.



The (*E*/*Z*) ratio of the product can often be changed by a change in solvent or by the addition of salts.[1385] Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bis(amides). In this case, the betaine (**66**) does form and when treated with water gives the β-hydroxyphosphonic acid bis(amides) (**67**), which can be crystallized and then cleaved to $R^1R^2C{=}CR^3R^4$ by refluxing in benzene or toluene in the presence of silica gel.[1374] β-Hydroxy products (**67**) are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Each diastereomer will give one of the two isomeric alkenes. Optically active phosphonic acid bis(amides) have been used to give optically active alkenes.[1386] Another method of controlling the stereochemistry of the alkene [to obtain either the (*Z*)- or (*E*)-isomer] starting with a phosphine oxide (Ph_2POCH_2R) has been reported.[1387]



[1381] See Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989****, 89*, 863; Gosney, I.; Rowley, A.G. in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 17–153; Reucroft, J.; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1971****, 25,* 135, see pp. 137–148, 169; Schlosser, M. *Top. Stereochem.* ***1970****, 5,* 1. Also see, Takeuchi, K.; Paschal, J.W.; Loncharich, R.J. *J. Org. Chem.* ***1995****, 60*, 156.

[1382] Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* ***2005****, 127,* 13468.

[1383] Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* ***2006****, 128,* 2394.

[1384] See Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. *J. Am. Chem. Soc.* ***1985****, 107*, 217; Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* ***1986****, 42*, 3813. Also see Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* ***1986****, 40*, 244.

[1385] See Reitz, A.B.; Nortey, S.O.; Jordan, Jr., A.D.; Mutter, M.S.; Maryanoff, B.E. *J. Org. Chem.* ***1986****, 51*, 3302.

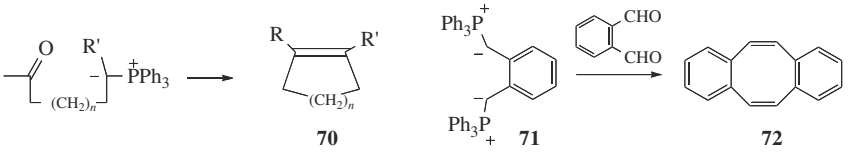
[1386] See Rein, T.; Reiser, O. *Acta Chem. Scand. B,* ***1996****, 50*, 369. For a review of asymmetric ylid reactions, see Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. *Chem. Rev.* ***1997****, 97*, 2341.

[1387] Ayrey, P.M.; Warren, S. *Tetrahedron Lett.* ***1989****, 30*, 4581.

In reactions where the betaine–lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylidenetriphenylphosphorane with heptanal at −78 °C gave **68**, and subsequent treatment with butyllithium gave the ylid, (**69**). Treatment of **69** with an aldehyde (R′CHO) gave the intermediate (**70**) that gave, after workup, **71**[1388] stereoselectively. Alkoxide **69** also reacts with other electrophiles. For example, treatment of **69** with NCS or $PhICl_2$ gave the vinylic chloride (RCH=CMeCl) stereoselectively: NCS gave the cis and $PhICl_2$ the trans-isomer.[1389] The use of Br_2 and $FClO_3$ (several explosions[1390] have been observed with this reagent) gives the corresponding bromide or fluoride, respectively.[1391] Reactions of **69** with electrophiles have been called *scoopy reactions* (α *s*ubstitution plus *c*arbonyl alkenylation via β-*o*xido *p*hosphorus *ylid*s).[1392]

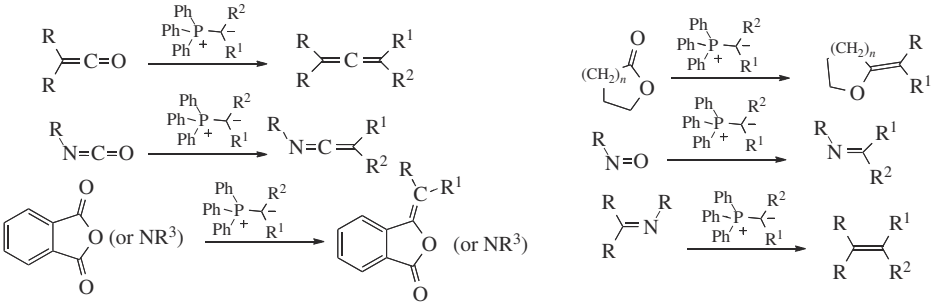
The reaction of a phosphonate ester, DBU, NaI, and HMPA with an aldehyde leads to a conjugated ester with excellent (*Z*)-selectivity.[1393] A (*Z*)-selective reaction was reported using a trifluoroethyl phosphonate in a reaction with an aldehyde and potassium *tert*-butoxide.[1394]

The *Wittig reaction* has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[1395] both by single-ring closure to give alkenes (e.g., **70**), or by double-ring closure, as in the conversion of **71** to **72**).[1396]



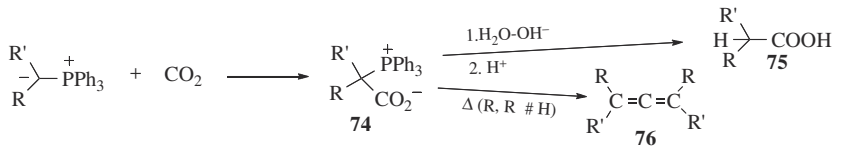
70 **71** **72**

The *Wittig reaction* has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.[1397]



[1388] See Schlosser, M.; Tuong, H.B.; Respondek, J.; Schaub, B. *Chimia* ***1983****, 37*, 10.
[1389] See Corey, E.J.; Shulman, J.I.; Yamamoto, H. *Tetrahedron Lett.* ***1970***, 447.
[1390] Peet, J.H.J.; Rockett, B.W. *J. Organomet. Chem.* ***1974****, 82*, C57; Adcock, W.; Khor, T. *J. Organomet. Chem.* ***1975****, 91*, C20.
[1391] Schlosser, M.; Christmann, K.-F. *Synthesis* ***1969***, 38.
[1392] Schlosser, M. *Top. Stereochem.* ***1970****, 5*, 1, p. 22.
[1393] Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* ***2000****, 65*, 4745.
[1394] Touchard, F.P. *Tetrahedron Lett.* ***2004****, 45*, 5519.
[1395] For a review, see Becker, K.B. *Tetrahedron* ***1980****, 36,* 1717.
[1396] For a review of these double ring closures, see Vollhardt, K.P.C. *Synthesis* ***1975***, 765.
[1397] See Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983****, 109*, 85.

Phosphorus ylids also react in a similar manner with the C=O bonds of ketenes,[1398] isocyanates,[1399] certain anhydrides[1400] lactones,[1401] and imides,[1402] the N=O of nitroso groups, and the C=N of imines,[1403] as shown in the composite reaction. Phosphorus ylids react with carbon dioxide to give the isolable salts (**74**),[1404] which can be hydrolyzed to the carboxylic acids (**75**) (thus achieving the conversion RR′CHX → RR′CHCOOH) or (if neither R nor R′ is hydrogen) dimerized to allenes (**76**).



Although phosphorus ylids are most commonly used for alkenylation reactions, nitrogen ylids can occasionally be used. However, nitrogen ylids are often difficult to form, are unstable and highly reactive. The reaction of *N*-benzyl-*N*-phenylpiperidinium bromide with base to give an N-ylid is one example, and it reacted with benzaldehyde to form styrene.[1405] The structure has been determined for an intermediate in an *aza*-Wittig reaction.[1406] An *aza-Wittig reaction*[1407] has been used to prepare pyrrolines and tetrahydropyridines.[1408]

OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **VI**, 358; **VII**, 164, 232; **VIII**, 265, 451; **75**, 139, **OS IX**, 39, 230.

16-45 Tebbe, Petasis, and Alternative Alkenylations

Methylene-de-oxo-bisubstitution



A useful alternative to phosphorus ylids are Ti reagents (e.g., **77**) prepared from dicyclopentadienyltitanium dichloride and trimethylaluminum.[1409] Treatment of a carbonyl compound with **77** (*Tebbe reagent*) in toluene–THF containing a small amount of

[1398] See Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* ***1968****, 22,* 2347.
[1399] See Frøyen, P. *Acta Chem. Scand. Ser. B* ***1974****, 28*, 586.
[1400] See Kayser, M.M.; Breau, L. *Can. J. Chem.* ***1989****, 67,* 1401. For a study of the mechanism, see Abell, A.D.; Clark, B.M.; Robinson, W.T. *Aust. J. Chem.* ***1988****, 41*, 1243.
[1401] With microwave irradiation, see Sabitha, G.; Reddy, M.M.; Srinivas, D.; Yadov, J.S. *Tetrahedron Lett.* ***1999****, 40*, 165.
[1402] Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* ***1988****, 17*, 1; Flitsch, W.; Schindler, S.R. *Synthesis* ***1975***, 685.
[1403] Bestmann, H.J.; Seng, F. *Tetrahedron* ***1965****, 21*, 1373.
[1404] Bestmann, H.J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* ***1974***, 1275.
[1405] Lawrence, N.J.; Beynek, H. *Synlett* ***1998***, 497.
[1406] Kano, N.; Hua, X.J.; Kawa, S.; Kawashima, T. *Tetrahedron Lett.* ***2000****, 41*, 5237.
[1407] For a review, see Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J.M. *Tetrahedron* ***2007****, 63,* 523.
[1408] Singh, P.N.D.; Klima, R.F.; Muthukrishnan, S.; Murthy, R.S.; Sankaranarayanan, J.; Stahlecker, H.M.; Patel, B.; Gudmundsdóttir, A.D. *Tetrahedron Lett.* ***2005****, 46,* 4213.
[1409] For *in situ* generation of this reagent, see Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* ***1985****, 50*, 2386.

pyridine[1410] leads to the alkene. Dimethyltitanocene (Me_2TiCp_2), called the *Petasis reagent*, is a convenient and highly useful alternative to **77**.[1411] The mechanism of *Petasis olefination* has been examined.[1412] Both the *Tebbe* and the *Petasis reagent* give good results with ketones.[1413] An important feature of these new reagents is that carboxylic esters and lactones[1414] can be converted to the corresponding enol ethers in good yields. The enol ether can be hydrolyzed to a ketone (Reaction **10-6**), so this is also an indirect method for making the conversion $RCO_2R' \rightarrow RCOCH_3$ (see also, Reaction **16-82**). Conjugated esters are converted to alkoxy-dienes with this reagent.[1415] Lactams, including β-lactams, are converted with alkylidene cycloamines (alkylidene azetidines from β-lactams, which are easily hydrolyzed to β-amino ketones).[1416]

Besides stability and ease of preparation, another advantage of the Petasis reagent is that structural analogues can be prepared, including $Cp_2Ti(C_3H_5)_2$[1417] (C_3H_5 = cyclopropyl), $CpTi(CH_2SiMe_3)_3$,[1418] and $Cp_2TiMe(CH{=}CH_2)$.[1419] In another variation, 2 molar equivalents of $Cp_2Ti[P(OEt)_3]_2$ reacted with a ketone in the presence of 1,1-diphenylthiocyclobutane to give the alkenylcyclobutane derivative.[1420] An alternative Ti reagent was prepared using $TiCl_4$, Mg metal and dichloromethane, reacting with both ketones[1421] and esters[1422] to give alkenes or vinyl ethers, respectively. Alkenes are generated form ketones and alkyl iodides in the presence of a catalytic amount of $Cp_2Ti[POEt)_3]_2$.[1423]

Carboxylic esters undergo the conversion $C{=}O \rightarrow C{=}CHR$ (R = primary or secondary alkyl) when treated with $RCHBr_2$, Zn,[1424] and $TiCl_4$ in the presence of *N,N,N',N'*-tetramethylethylenediamine.[1425] Metal carbene complexes[1426] $R_2C{=}ML_n$ (L = ligand), where M is a transition metal (e.g., Zr, W, or Ta) have also been used to convert the C=O of carboxylic esters and lactones to CR_2.[1427] It is likely that the complex $Cp_2Ti{=}CH_2$ is an

[1410] Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* ***1978****, 100,* 3611; Pine, S.H.; Pettit, R.J.; Geib, G. D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* ***1985****, 50,* 1212. See also, Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* ***1984****, 25,* 5733; Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* ***1984****, 106,* 8300.

[1411] Petasis, N.A.; Bzowej, E.I. *J. Am. Chem. Soc.* ***1990****, 112,* 6392.

[1412] Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. *Org. Lett.* ***2003****, 5*, 1391.

[1413] Pine, S.H.; Shen, G.S.; Hoang, H. *Synthesis* ***1991***, 165.

[1414] Martínez, I.; Andrews, A.E.; Emch, J.D.; Ndakala, A.J.; Wang, J.; Howell, A.R. *Org. Lett.* ***2003****, 5*, 399.

[1415] Petasis, N.A.; Lu, S.-P. *Tetrahedron Lett.* ***1995****, 36*, 2393.

[1416] Tehrani, K.A.; De Kimpe, N. *Tetrahedron Lett.* ***2000****, 41*, 1975. See Martínez, I.; Howell, A.R. *Tetrahedron Lett.* ***2000****, 41*, 5607.

[1417] Petasis, N.A.; Browej, E.I. *Tetrahedron Lett.* ***1993****, 34*, 943.

[1418] Petasis, N.A.; Akritopoulou, I. *Synlett* ***1992***, 665.

[1419] Petasis, N.A.; Hu, Y.-H. *J. Org. Chem,.* ***1997****, 62*, 782. Also see, Petasis, N.A.; Browej, E.I. *J. Org. Chem.* ***1992****, 57*, 1327.

[1420] Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* ***1998***, 741. For an example using a *gem*-dichloride, see Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* ***1998****, 63*, 7286.

[1421] Yan, T.H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* ***2004****, 6*, 4961.

[1422] Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* ***2004****, 6*, 4965.

[1423] Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Communn.* ***2002***, 1974.

[1424] Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* ***1998****, 71*, 2669.

[1425] Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* ***1987****, 52,* 4410; Matsubra, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* ***1999***, 825; Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* ***1988****, 29,* 1065.

[1426] For a review, see Aguero, A.; Osborn, J.A. *New J. Chem.* ***1988****, 12,* 111.

[1427] See Hartner Jr., F.W.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* ***1990****, 105,* 640.

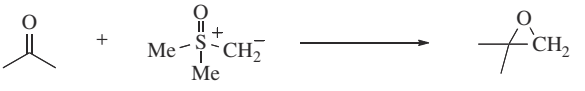
intermediate in the reaction with the *Tebbe reagent*. Indeed, Ti carbenoids have been used to convert carbonyl groups to the corresponding alkene.[1428]

There are a few other methods for converting ketones or aldehydes to alkenes.[1429] Carbonyl compounds react with bis(iodozincio)methane to give alkenes.[1430] When a ketone is treated with CH_3CHBr_2/Sm/SmI_2, with a catalytic amount of $CrCl_3$, the alkene is formed.[1431] α-Halo esters also react with $CrCl_2$ in the presence of a ketone to give vinyl halides.[1432] Organozinc reagents have been used to convert carbonyl compounds to alkenes in the presence of Lewis acids.[1433] α-Diazo esters react with ketones in the presence of an iron catalyst to give the corresponding alkene.[1434] α-Diazo silylalkanes react similarly in the presence of a Rh catalyst.[1435] Ketone olefination has been accomplished using methyltrioxorhenium.[1436] α-Halosulfones react with aldehydes in the presence of LiHMDS and $MgBr_2{}^{\bullet}OEt_2$ to give a vinyl chloride.[1437]

OS **VIII**, 512, **IX**, 404; **X**, 355.

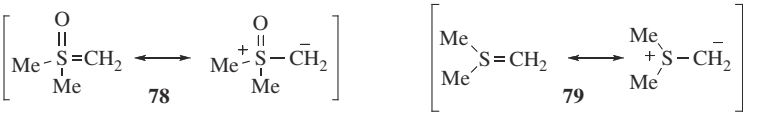
16-46 The Formation of Epoxides from Aldehydes and Ketones

(1+2)*OC*,*CC-cyclo*-Methylene-addition



78

Aldehydes and ketones can be converted to epoxides[1438] in good yields with the sulfur ylids[1439] dimethyloxosulfonium methylid (**78**)[1440] and dimethylsulfonium methylid (**79**).[1441] Ylid **79** is much less stable



78 **79**

[1428] Hartley, R.C.; Li, J.; Main, C.A.; McKiernan, G.J. *Tetrahedron* ***2007****, 63,* 4825.

[1429] See List, B.; Doehring, A.; Fonseca, M.T.H.; Job, A.; Torres, R.R. *Tetrahedron* ***2006****, 62,* 476.

[1430] Sada, M.; Komagawa, S.; Uchiyama, M.; Kobata, M.; Mizuno, T.; Utimoto, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* ***2010****, 132,* 17452.

[1431] Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* ***1995***, 259. See also, Concellón, J.M.; Concellón, C. *J. Org. Chem.* ***2006****, 71,* 1728.

[1432] Barma, D.K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J.R. *J. Am. Chem. Soc.* ***2003****, 125*, 3218.

[1433] Peng, Z.-Y.; Ma, F.-F.; Zhu, L.-F.; Xie, X.-M.; Zhang, Z. *J. Org. Chem.* ***2009****, 74,* 6855.

[1434] Chen, Y.; Huang, L.; Zhang, X.P. *Org. Lett.* ***2003****, 5*, 2493; Aggarwal, V.K.; Fulton, J.R.; Sheldon, C.G.; de Vincente, J. *J. Am. Chem. Soc.* ***2003****, 125*, 6034.

[1435] Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* ***2004****, 6*, 3047. For a synthesis of dienes from conjugated aldehydes, see Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004****, 126*, 320.

[1436] Pedro, F.M.; Hirner, S.; Kühn, F.E. *Tetrahedron Lett.* ***2005****, 46,* 7777.

[1437] Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* ***2006****, 71,* 2009.

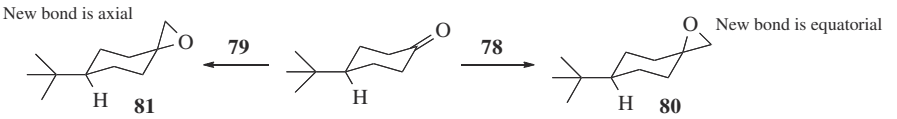
[1438] See Block, E. *Reactions of Organosulfur Compounds* Academic Press, NY, ***1978***, pp. 101–105; Berti, G. *Top. Stereochem.* ***1973****, 7,* 93, pp. 218–232. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 944–951.

[1439] The bond enthalpies for S and Se ylids has been determined. See Stoffregen, S.A.; McCulla, R.D.; Wilson, R.; Cercone, S.; Miller, J.; Jenks, W.S. *J. Org. Chem.* ***2007****, 72*, 8235.

[1440] See Paxton, R.J.; Taylor, R.J.K. *Synlett* ***2007***, 633.

[1441] See Kavanagh, S.A.; Piccinini, A.; Fleming, E.M.; Connon, S.J. *Org. Biomol. Chem.* ***2008****, 6*, 1339. For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, , pp. 709–733; Durst, T. *Adv. Org. Chem.* ***1969****, 6*, 285, see pp. 321–330. For a monograph on sulfur ylids, see Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***.

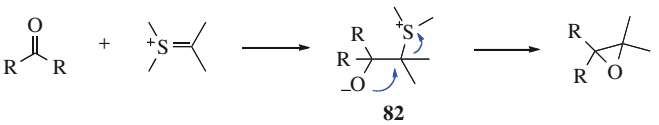
and ordinarily must be used as soon as it is formed, while **78** can be stored several days at room temperature. When diastereomeric epoxides can be formed, **79** usually attacks from the more hindered and **78** from the less-hindered side. Thus, 4-*tert*-butylcyclohexanone, treated with **78** gave exclusively **80** while **79** gave mostly **81**.[1442] Another difference in behavior between the two reagents is that with α,β-unsaturated ketones, **78** gives



only cyclopropanes (Reaction **15-64**), while **79** gives oxirane formation. Other sulfur ylids have been used in an analogous manner, to transfer CHR or CR_2.[1443] Other sulfur ylids convert aldehydes to epoxides.[1444] High yields have been achieved by the use of sulfonium ylids anchored to insoluble polymers under phase-transfer conditions.[1445] A solvent-free version of this reaction has been developed using powdered K *tert*-butoxide and $Me_3S^+I^-$.[1446] Note that treatment of epoxides with 2 equiv of $Me_2S{=}CH_2$ leads to allylic alcohols.[1447]

Chiral sulfur ylids[1448] have been prepared, giving the epoxide with good asymmetric induction,[1449] and chiral additives have also been used.[1450] Chiral Se ylids have been used in a similar manner.[1451]

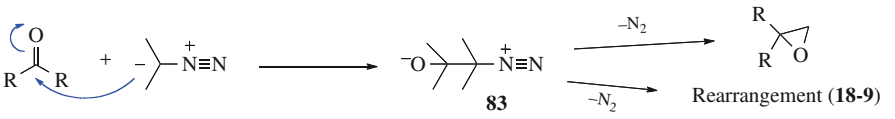
The generally accepted mechanism for the reaction between sulfur ylids and aldehydes or ketone is formation of **82**, with displacement of the Me_2S leaving group by the alkoxide.[1452] This mechanism is similar to that of the reaction of sulfur ylids with C=C double bonds (Reaction **15-64**).[1453] The stereochemical difference in the behavior of **78** and **79** has been attributed to formation of the betaine (**82**) being reversible for **78**, but not for the less stable **79**, so that the more-hindered product is the result of kinetic control and the less hindered of thermodynamic control.[1454]



[1442] Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965****, 87,* 1353.
[1443] Adams, J.; Hoffman, Jr., L.; Trost, B.M. *J. Org. Chem.* ***1970****, 35,* 1600; Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* ***1973***, 4033; Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* ***1967***, 2325.
[1444] See Forbes, D.C.; Amin, S.R.; Bean, C.J.; Standen, M.C. *J. Org. Chem.* ***2006****, 71*, 8287.
[1445] Farrall, M.J.; Durst, T.; Fréchet, J.M.J. *Tetrahedron Lett.* ***1979***, 203.
[1446] Toda, F.; Kanemoto, K. *Heterocycles* ***1997****, 46*, 185.
[1447] Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994****, 35*, 5449. Also see, Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994****, 35*, 5453.
[1448] See Aggarwal, V.K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonguerna, S.J.; Ford, G.D.; Hynd, G.; Jones, E.; Jones, R.V.H.; Jubault, P.; Palmer, M.J.; Ratcliffe, P.D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2604.
[1449] See Sone, T.; Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2008****, 130,* 10078.
[1450] Hansch, M.; Illa, O.; McGarrigle, E.M.; Aggarwal, V.K. *Chemistry: Asian J.* ***2008****, 3,* 1657.
[1451] See Takada, H.; Metzner, P.; Philouze, C. *Chem. Commun.* ***2001***, 2350.
[1452] See Aggarwal, V.K.; Harvey, J.N.; Richardson, J. *J. Am. Chem. Soc.* ***2002****, 124*, 5747.
[1453] See Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973****, 95*, 7424.
[1454] Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973****, 95*, 7424.

Phosphorus ylids do not give this reaction, but give **16-44** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane.[1455] Most commonly it is diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (Reaction **18-9**). The reaction can be carried out with many aldehydes, ketones, and quinones, usually with a Rh catalyst.[1456] A mechanism that accounts for both products follows:



Compound **83** or nitrogen-containing derivatives of it have sometimes been isolated.

An alternative route to epoxides from ketones uses α-chloro sulfones and potassium *tert*-butoxide to give α,β-epoxy sulfones.[1457] A similar reaction was reported using KOH and 10% of a chiral phase-transfer agent, giving moderate enantioselectivity in the epoxy sulfone product.[1458]

Dihalocarbenes and carbenoids, which readily add to C=C bonds (Reaction **15-64**), do not generally add to the C=O bonds of ordinary aldehydes and ketones.[1459] See also, Reaction **16-91**.

There is a report of a strained azetidinium ylid that has been used for epoxidation.[1460]

OS **V**, 358, 755.

16-47 The Formation of Aziridines from Imines

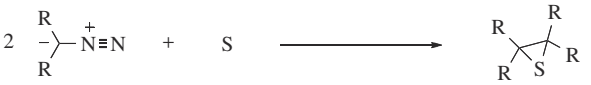
(1+2)*NC*,*CC-cyclo*-Methylene-addition



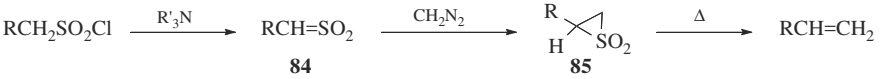
Just as sulfur ylids (e.g., **78**) react with the carbonyl of an aldehyde or ketone to give an epoxide, Te ylids react with imines to give an aziridine. The reaction of an allylic Te salt ($RCH{=}CHCH_2Te^+Bu_2\ Br^-$), with lithium hexamethyldisilazide in HMPA/toluene leads to the tellurium ylid via deprotonation. In the presence of an imine, the ylid add to the imine and subsequent displacement of Bu_2Te generates an aziridine with a pendant vinyl group.[1461] Catalytic aziridination of tosylimines was reported and mediated by arsonium ylids.[1462]

[1455] See Gutsche, C.D. *Org. React.* ***1954****, 8,* 364.
[1456] See Davies, H.M.L.; De Meese, J. *Tetrahedron Lett.* ***2001****, 42*, 6803.
[1457] Mąkosza, M.; Urbańska, N.; Chesnokov, A.A. *Tetrahedron Lett.* ***2003****, 44*, 1473.
[1458] Arai, S.; Shioiri, T. *Tetrahedron* ***2002****, 58*, 1407.
[1459] For exceptions, see Sadhu, K.M.; Matteson, D.S. *Tetrahedron Lett.* ***1986****, 27,* 795; Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 1286.
[1460] Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* ***2007***, 2500.
[1461] Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* ***2004***, 1516.
[1462] Zhu, S.; Liao, Y.; Zhu, S. *Synlett* ***2005***, 1429.

16-48 The Formation of Episulfides and Episulfones[1463]



Epoxides can be converted directly to episulfides by treatment with NH_4SCN and ceric ammonium nitrate.[1464] Diazoalkanes, treated with sulfur, give episulfides.[1465] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in Reaction **16-46**. Thioketones *do* react with diazoalkanes to give episulfides,[1466] and have also been converted to episulfides with sulfur ylids.[1442] Carbenes (e.g., the dichlorocarbene from $CHCl_3$) and base react with thioketones to give an α,α-dichloro episufide.[1467]



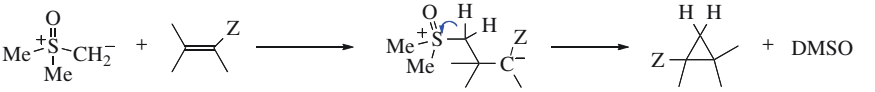
84 **85**

Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (**85**).[1468] The base removes HCl from the sulfonyl halide to produce the highly reactive sulfene (**84**) (see Reaction **17-14**), which then adds CH_2. The episulfone can then be heated to give off SO_2 (see Reaction **17-20**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[1469]

OS **V**, 231, 877.

16-49 Cyclopropanation of Conjugated Carbonyl Compounds

Double-bond compounds that undergo the *Michael reaction* (**15-24**) can be converted to cyclopropane derivatives with sulfur ylids.[1470] Among the most common of these is dimethyloxosulfonium methylid (**78**),[1471]

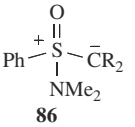


78

which is widely used to transfer CH_2 to activated double bonds, but other sulfur ylids have also been used. A combination of DMSO and KOH in an ionic liquid converts conjugated

[1463] For a review, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 57–86.
[1464] Iranpoor, N.; Kazemi, F. *Synthesis* ***1996***, 821.
[1465] Schönberg, A.; Frese, E. *Chem. Ber.* ***1962****, 95,* 2810.
[1466] For example, see Beiner, J.M.; Lecadet, D.; Paquer, D.; Thuillier, A. *Bull. Soc. Chim. Fr.* ***1973***, 1983.
[1467] Mlostoń, G.; Romański, J.; Swiatek, A.; Heimgartner, H. *Helv. Chim. Acta* ***1999****, 82*, 946.
[1468] Opitz, G.; Fischer, K. *Angew. Chem. Int. Ed.* ***1965****, 4,* 70.
[1469] For a review of this process, see Fischer, N.S. *Synthesis* **1970**, 393.
[1470] Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***. For reviews, see Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981****, 50,* 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, part 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 91–127.
[1471] See Gololobov, Yu.G.; Nesmeyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. *Tetrahedron* ***1987****, 43*, 2609.

ketones to α,β-cyclopropyl ketones.[1472] Both CHR and CR_2 can be added in a similar manner with certain nitrogen-containing compounds. For example, ylids[1473] (e.g., **86**), add various groups to activated double bonds.[1474] Sulfur ylids react with allylic alcohols in the presence of MnO_2 and molecular sieve 4 Å to give the cyclopropyl aldehyde.[1475] Similar reactions have been performed with phosphorus ylids,[1476] with pyridinium ylids,[1477] and with the compounds $(PhS)_3CLi$ and $Me_3Si(PhS)_2CLi$.[1478] The reactions with ylids such as these of course involve nucleophilic acyl addition. Enantioselective cyclopropanation occurs in the presence of certain organocatalysts[1479] or chiral metal catalysts.[1480]

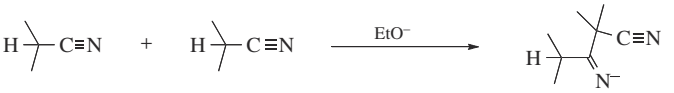


86

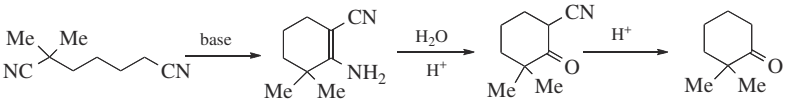
Other reagents can be used to convert an aldehyde or ketone to a cyclopropane derivative. Tellurium ylids react with conjugated imines to the cyclopropyl aldehyde after hydrolysis of the imine.[1481] Conjugated ketones react with $Cp_2Zr(CH_2{=}CH_2)$ and PMe_3 to give a vinyl cyclopropane derivative after treatment with aq H_2SO_4.[1482]

16-50 The Thorpe Reaction

N-Hydro-*C*-(α-cyanoalkyl)-addition



In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction has analogies with the aldol reaction (**16-34**). The C=NH bond is, of course, hydrolyzable (Reaction **16-2**), so β-keto nitriles can be prepared in this manner. The *Thorpe reaction* can be done intramolecularly, in which case it



87

is called the *Thorpe–Ziegler reaction*.[1483] As with other cyclization methods, yields are high for 5–8-membered rings, fall off to about zero for rings of 9–13 members, but are high

[1472] Chandrasekhar, S.; Jagadeshwar, N.V.; Reddy, K.V. *Tetrahedron Lett.* ***2003****, 44*, 3629.
[1473] See Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1980****, 9,* 477.
[1474] Johnson, C.R. *Aldrichimica Acta* ***1985****, 18,* 1; *Acc. Chem. Res.* ***1973****, 6*, 341; Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1975****, 4*, 189; Trost, B.M. *Acc. Chem. Res.* ***1974****, 7,* 85.
[1475] Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* ***2004****, 6*, 3997.
[1476] Bestmann, H.J.; Seng, F. *Angew. Chem. Int. Ed.* ***1962****, 1*, 116; Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett.* ***1972***, 3781.
[1477] Shestopalov, A.M.; Sharanin, Yu.A.; Litvinov, V.P.; Nefedov, O.M. *J. Org. Chem. USSR* ***1989****, 25,* 1000.
[1478] Cohen, T.; Myers, M. *J. Org. Chem.* ***1988****, 53,* 457.
[1479] Kunz, R.K.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2005****, 127,* 3240.
[1480] Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007****, 129,* 13410.
[1481] Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Daim L.-X.*J. Am. Chem. Soc.* ***2005****, 127,* 12222.
[1482] Bertus, P.; Gandon, V.; Szymoniak, J. *Chem. Commun.* ***2000***, 171.
[1483] Taylor, E.C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*, Wiley, NY, ***1970***; Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967****, 15,* 1.

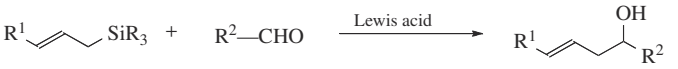
again for 14-membered and larger rings, if high-dilution techniques are employed. The product in the *Thorpe–Ziegler reaction* is not the imine, but the tautomeric enamine (e.g., **87**); if desired this can be hydrolyzed to an α-cyano ketone (Reaction **16-2**), which can in turn be hydrolyzed and decarboxylated (Reactions **16-4** and **12-40**). Other active-hydrogen compounds can also be added to nitriles.[1484]

OS **VI**, 932.

H. Other Carbon or Silicon Nucleophiles

16-51 Addition of Silanes

***O*-Hydro-*C*-alkyl-addition**

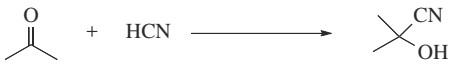


Allylic silanes react with aldehydes, in the presence of Lewis acids, to give a homoallylic alcohol.[1485] In the case of benzylic silanes, this addition reaction has been induced with Mg $(ClO_4)_2$ under photochemical conditions.[1486] Cyclopropylcarbinyl silanes add to acetals in the presence of TMSOTf to give a homoallylic alcohol.[1487] Allyltrichlorosilane adds an allyl group to an aldehyde in the presence of a cyclic urea and AgOTf.[1488] In a related reaction, allylic silanes react with acyl halides to produce the corresponding carbonyl derivative. The reaction of phenyl chloroformate, allyltrimethylsilane, and $AlCl_3$, for example, gave phenyl but-3-enoate.[1489] The use of chiral additives leads to the alcohol with good asymmetric induction.[1490]

Allylic silanes also add to imines, in the presence of $TiCl_4$, to give amines.[1491] Silanes also add to iminium salts, mediated by alkyltin compounds.[1492]

16-52 The Formation of Cyanohydrins

***O*-Hydro-*C*-cyano-addition**

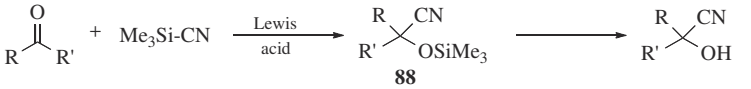


The addition of HCN to aldehydes or ketones produces cyanohydrins.[1493] This is an equilibrium reaction, and for aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones (e.g., diisopropyl ketone). However, ketones (ArCOR) give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic

[1484] See Page, P.C.B.; van Niel, M.B.; Westwood, D. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 269.
[1485] Panek, J.S.; Liu, P. *Tetrahedron Lett.* ***1997****, 38*, 5127.
[1486] Fukuzumi, S.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* ***1994****, 116*, 5503.
[1487] Braddock, D.C.; Badine, D.M.; Gottschalk, T. *Synlett* ***2001***, 1909.
[1488] Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* ***1999****, 40*, 3633.
[1489] Mayr, H.; Gabriel, A.O.; Schumacher, R. *Liebigs Ann. Chem.* ***1995***, 1583.
[1490] Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993****, 115*, 11490. See Malkov, A.V.; Liddon, A.J.P.S.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem. Int. Ed.* ***2006****, 45,* 1432.
[1491] Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* ***1996****, 118*, 4200.
[1492] Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* ***2007****, 129,* 1902.
[1493] Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 72–77.

aldehydes the *benzoin condensation* (Reaction **16-55**) competes. With α,β-unsaturated aldehydes and ketones, 1,4-addition competes (Reaction **15-38**).

Ketones of low reactivity (e.g., ArCOR) can be converted to cyanohydrins by treatment with diethylaluminum cyanide (Et_2AlCN) (see OS **VI**, 307) or, indirectly, with cyanotrimethylsilane (Me_3SiCN)[1494] in the presence of a Lewis acid or base,[1495] followed by hydrolysis of the resulting *O*-trimethylsilyl cyanohydrin (**88**). Both direct formation of the cyanohydrin (hydrocyanation) and formation of the cyano-*O*-silyl ether have been carried out enantioselectively using chiral catalysts,[1496] including chiral organocatalysts,[1497] or chiral additives.[1498] Biocatalysts have been used.[1499] Hydrogen cyanide adds to aldehydes in the presence of a lyase to give the cyanohydrin with good enantioselectivity.[1500] Cyanohydrins have been formed using a lyase in an ionic liquid.[1501]



88

Solvent-free conditions have been reported using TMSCN, an aldehyde, and potassium carbonate.[1502] Amine *N*-oxides catalyze the reaction,[1503] as does tetrabutylammonium cyanide.[1504] Lithium perchlorate in ether facilitates this reaction,[1505] and LiCl catalyzes the reaction with Me_3SiCN.[1506] *N*-Heterocyclic carbenes catalyze the reaction,[1507] as do certain ionic liquids.[1508] With $MgBr_2$ as a catalyst, the reaction proceeds with good syn selectivity.[1509] Other useful catalysts include Pt[1510] Au,[1511] or Ti[1512] compounds, and $InBr_3$.[1513] The use of chiral additives leads to cyanohydrins with good asymmetric

[1494] Rasmussen, J.K.; Heilmann, S.M.; Krepski, L. *Adv. Silicon Chem.* ***1991****, 1,* 65; Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synthesis* ***1986***, 1054; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987****, 60*, 3820.

[1495] See Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* ***2000****, 41*, 2405. The reaction works in some cases without a Lewis acid, see Manju, K.; Trehan, S. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2383.

[1496] See Gröger, H.; Capan, E.; Barthuber, A.; Vorlop, K.-D. *Org. Lett.* ***2001****, 3*, 1969, and references cited therein; Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* ***2005****, 127,* 11592; Kim, S.S.; Kwak, J.M. *Tetrahedron* ***2006****, 62,* 48; Shen, K.; Liu, X.; Li, Q.; Feng, X. *Tetrahedron* ***2008****, 64,* 147; Kim, S.S.; Song. D. H. *Eur. J. Org. Chem.* ***2005***, 1777. See also, North, M.; Omedes-Pujol, M.; Williamson, C. *Chemistry: Eur. J.* ***2010****, 16*, 11367. See Bruneh, J.-M.; Holmes, I.P. *Angew. Chem. Int. Ed.* ***2004****, 43*, 2752.

[1497] Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* ***2005****, 127,* 5384; Douglas E.; Fuerst, D.E.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2005****, 127,* 8964; Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* ***2005****, 127,* 12224; Wen, Y.; Huang, X.; Huang, J.; Xiong, Y.; Qin, B.; Feng, X. *Synlett* ***2005***, 2445.

[1498] Lv, C.; Wu, M.; Wang, S.; Xia, C.; Sun, W. *Tetrahedron Asymm.* ***2010****, 21*, 1869.

[1499] van Langen, L.M.; Selassa, R.P.; van Rantwijk, F.; Sheldon, R.A. *Org. Lett.* ***2005****, 7,* 327.

[1500] Gerrits, P.J.; Marcus, J.; Birikaki, L.; van der Gen, A. *Tetrahedron Asymmetry* ***2001****, 12*, 971.

[1501] Gaisberger, R.P.; Fechter, M.H.; Griengl, H. *Tetrahedron Asymmetry* ***2004****, 15*, 2959.

[1502] He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* ***2004***, 1776.

[1503] Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2003****, 59*, 5667. See Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* ***2004***, 129.

[1504] Amurrio, I.; Córdoba, R.; Csákÿ, A.G.; Plumet, J. *Tetrahedron* ***2004****, 60*, 10521.

[1505] Jenner, G. *Tetrahedron Lett.* ***1999****, 40*, 491.

[1506] Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* ***2005****, 70,* 6530.

[1507] Song, J.J.; Gallou, F.; Reeves, J.T.; Tan, Z.; Yee, N.K.; Senanayake, C.H. *J. Org. Chem.* ***2006****, 71,* 1273; Suzuki, Y.; Abu Bakar M.D.; Muramatsu, K.; Sato, M. *Tetrahedron* ***2006****, 62,* 4227.

[1508] Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2005****, 46,* 3137.

[1509] Ward, D.E.; Hrapchak, M.J.; Sales, M. *Org. Lett.* ***2000****, 2*, 57.

[1510] Fossey, J.S.; Richards, C.J. *Tetrahedron Lett.* ***2003****, 44*, 8773.

[1511] Cho, W.K.; Kang, S.M.; Medda, A.K.; Lee, J.K.; Choi, I.S.; Lee, H.-S. *Synthesis* ***2008***, 50.

[1512] Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* ***2004****, 45*, 4763; He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Tetrahedron Lett.* ***2004****, 45*, 5465.

[1513] Bandini, M.; Cozzi, P.G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett* ***2001****, 42*, 3041.

induction.[1514] Chiral transition metal catalysts have been used to give *O*-trialkylsilyl cyanohydrins with good enantioselectivity.[1515] A venedium catalyst has been used in an ionic liquid.[1516] Note that the reaction of an aldehyde and TMSCN in the presence of aniline and a $BiCl_3$ catalyst leads to an α-cyano amine.[1517] Potassium cyanide and acetic anhydride react with an aldehyde in the presence of a chiral Ti catalyst to give an α-acetoxy nitrile.[1518]

Rather than direct reaction with an aldehyde or ketone, the bisulfite addition product is often treated with cyanide. The addition is nucleophilic and the actual nucleophile is ^{-}CN, so the reaction rate is increased by the addition of base.[1519] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[1520] This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ* to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani–Fischer* method of extending the carbon chain of a sugar.

A particularly useful variation of this reaction uses cyanide rather than HCN. α-Amino nitriles[1521] can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis*;[1522] and it is a special case of the *Mannich reaction* (**16-19**). Since the CN group is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with $NH_3 + HCN$ and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain *N*-substituted and *N,N*-disubstituted α-amino nitriles. Brønsted acids can also be used.[1523] Unlike Reaction **16-52**, the *Strecker synthesis* is useful for aromatic as well as aliphatic ketones. As in Reaction **16-52**, the Me_3SiCN method has been used; **76** is converted to the product with ammonia or an amine.[1524] The effect of pressure on the *Strecker synthesis* has been studied.[1525] A catalyst-free multi-component *Strecker reaction* is known.[1526] There is also an In mediated *Strecker reaction* in aq media.[1527] Enantioselective *Strecker syntheses* are possible using chiral ammonium salts[1528] and

[1514] See Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* ***2004****, 126*, 8106.

[1515] See He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* ***2004****, 69*, 7910; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2004****, 60*, 10449; Uang, B.-J.; Fu, I.-P.; Hwang, C.-D.; Chang, C.-W.; Yang, C.-T.; Hwang, D.-R. *Tetrahedron* ***2004****, 60*, 10479. Also see Aspinall, H.C.; Greeves, N.; Smith, P.M. *Tetrahedron Lett.* ***1999****, 40*, 1763; Deng, H.; Isler, M.P.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1009; Karimi, B.; Ma'Mani, L. *Org. Lett.* ***2004****, 6*, 4813.

[1516] Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* ***2003****, 44*, 6813.

[1517] De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004****, 45*, 7407.

[1518] Belokon, Y.N.; Gutnov, A.V.; Moskalenko, M.A.; Yashkina, L.V.; Lesovoy, D.E.; Ikonnikov, N.S.; Larichev, V.S.; North, M. *Chem. Commun.* ***2002***, 244; Kawasaki, Y.; Fujii, A.; Nakano, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***1999****, 64*, 4214.

[1519] Ogata, Y.; Kawasaki, A. in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 21–32. See also, Ching, W.; Kallen, R.G. *J. Am. Chem. Soc.* ***1978****, 100*, 6119.

[1520] Lapworth, A. *J. Chem. Soc.* ***1903****, 83,* 998.

[1521] See Shafran, Yu.M.; Bakulev, V.A.; Mokrushin, V.S. *Russ. Chem. Rev.* ***1989****, 58,* 148.

[1522] See Williams, R.M. *Synthesis of Optically Active α-Amino Acids* Pergamon, Elmsford, NY, ***1989***, pp. 208–229; Yet, L. *Angew. Chem. Int. Ed.* ***2001****, 40*, 875; Gröger, H. *Chem. Rev.* ***2003****, 103*, 2795.

[1523] See Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* ***2010****, 8,* 1399. See also, Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* ***2010****, 132*, 5522.

[1524] See Mai, K.; Patil, G. *Tetrahedron Lett.* ***1984****, 25,* 4583; *Synth. Commun.* ***1985****, 15,* 157.

[1525] Jenner, G.; Salem, R.B.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett.* ***2003****, 44*, 447.

[1526] Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron Lett.* ***2005****, 46,* 8471.

[1527] Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron* ***2008****, 64,* 8159.

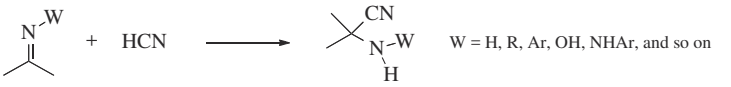
[1528] Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* ***2006****, 128,* 2548.

other organocatalysts,[1529] chiral acids,[1530] or chiral metal complexes.[1531] There is a radical version of the *Strecker synthesis*.[1532]

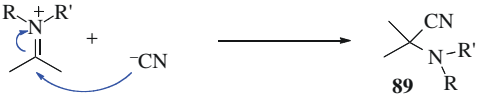
OS **I**, 336; **II**, 7, 29, 387; **III**, 436; **IV**, 58, 506; **VI**, 307; **VII**, 20, 381, 517, 521. For the reverse reaction, see OS **III**, 101. For the Strecker synthesis, see OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437; **VI**, 334.

16-53 The Addition of HCN to C=N and C≡N Bonds

***N*-Hydro-*C*-cyano-addition**



Hydrogen cyanide adds to imines, *Schiff bases*, hydrazones, oximes, and similar compounds. Cyanide can be added to iminium ions to give α-cyano amines (**89**). As in Reaction **16-50**, the addition to imines has been carried out enantioselectively.[1533] Chiral ammonium salts have been used with HCN.[1534] Trimethylsilyl cyanide (TMSCN) reacts with *N*-tosyl



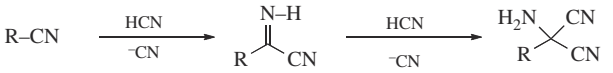
imines in the presence of $BF_3{\cdot}OEt_2$ to give the α-cyano *N*-tosyl amine.[1535] In the presence of a chiral Zr[1536] or Al[1537] catalyst, Bu_3SnCN reacts with imines to give α-cyanoamines enantioselectively. The imine can be formed *in situ b*y reaction of an aldehyde or ketone with an amine, in the present of TMSCN and a suitable promoter.[1538] The reaction of an imine and TMSCN gives the cyano amine with good enantioselectivity using a chiral Sc catalyst.[1539] Titanium catalysts have been used in the presence of a chiral *Schiff base*.[1540]

The addition of KCN to triisopropylbenzenesulfonyl hydrazones (**90**) provides an indirect method for achieving the conversion $RR'CO \rightarrow RR'CHCN$.[1541] The reaction is successful for hydrazones of aliphatic aldehydes and ketones.

$$\underset{\mathbf{90}}{RR'C{=}NN}HSO_2Ar + KCN \xrightarrow{MeOH} RR'CHCN \qquad Ar = 2,4,6(i\text{Pr})_3C_6H_2$$

[1529] Hou, Z.; Wang, J.; Liu, X.; Feng, X. C*hemistry: European J.* ***2008****, 14,* 4484.
[1530] Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem. Int. Ed.* ***2006****, 45,* 2617.
[1531] Blacker, J.; Clutterbuck, L.A.; Crampton, M.R.; Grosjean, C.; North, M. *Tetrahedron Asymmetry* ***2006****, 17,* 1449.
[1532] Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* ***2006****, 128,* 5358.
[1533] Saito, K.; Harada, K. *Tetrahedron Lett.* ***1989****, 30*, 4535.
[1534] Huang, J.; Corey, E.J. *Org. Lett.* ***2004****, 6*, 5027.
[1535] Prasad, B.A.B.; Bisai, A.; Singh, V.K. *Tetrahedron Lett.* ***2004****, 45*, 9565.
[1536] Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000****, 122*, 762.
[1537] Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron Asymmetry* ***2004****, 15*, 1513.
[1538] Royer, L.; De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2005****, 46,* 4595.
[1539] Chavarot, M.; Byrne, J.J.; Chavant, P.Y.; Vallée, Y. *Tetrahedron Asymmetry* ***2001****, 12*, 1147.
[1540] Krueger, C.A.; Kuntz, K.W.; Dzierba, C.D.; Wirschun, W.G.; Gleason, J.D.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999****, 121*, 4284.
[1541] Jiricny, J.; Orere, D.M.; Reese, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1487. Also see Okimoto, M.; Chiba, T. *J. Org. Chem.* ***1990****, 55,* 1070.

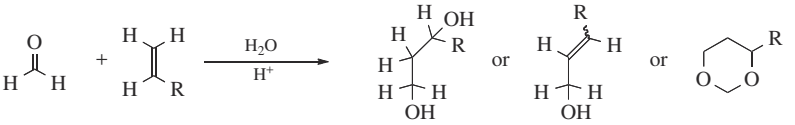
Hydrogen cyanide can also be added to the C≡N bond to give iminonitriles or α-amino-malononitriles.[1542]



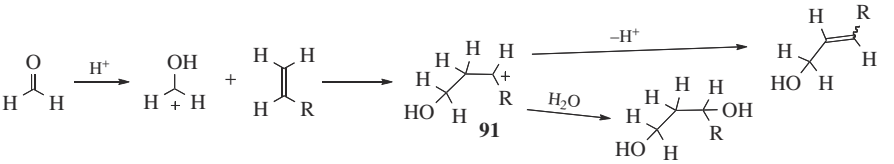
The acylcyanation of imines is known, and enantioselectivity is achieved with a suitable catalyst.[1543]

OS **V**, 344. See also, OS **V**, 269.

16-54 The Prins Reaction



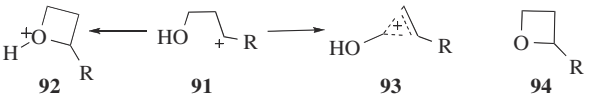
The addition of an alkene to formaldehyde in the presence of an acid[1544] catalyst is called the *Prins reaction*.[1545] Three main products are possible; which one predominates depends on the alkene and the conditions. When the product is the 1,3-diol or the dioxane,[1546] the reaction involves addition to the C=C as well as to the C=O. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the C=O, and the resulting carbocation is attacked by the C=C to give **91**. The cation product **91** can



undergo loss of H^+ to give the alkene or add water to give the diol.[1547] It has been proposed that **91** is stabilized by neighboring-group attraction, with either the oxygen[1548] or a carbon[1549] stabilizing the charge (**92** and **94**, respectively). This stabilization is postulated to explain the fact that with 2-butenes[1550] and with cyclohexenes the addition is anti. A backside attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **92** or **93**.[1548,1549]

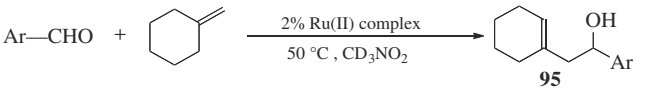
[1542] See Ferris, J.P.; Sanchez, R.A. *Org. Synth.* ***V***, 344.
[1543] Pan, S.C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* ***2007****, 46,* 612.
[1544] With basic catalysts: Griengl, H.; Sieber, W. *Monatsh. Chem.* ***1973****, 104,* 1008, 1027.
[1545] See Adams, D.R.; Bhatnagar, S.P. *Synthesis* ***1977***, 661; Isagulyants, V.I.; Khaimova, T.G.; Melikyan, V.R.; Pokrovskaya, S.V. *Russ. Chem. Rev.* ***1968****, 37,* 17. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 248.
[1546] See Safarov, M.G.; Nigmatullin, N.G.; Ibatullin, U.G.; Rafikov, S.R. *Doklad. Chem.* ***1977****, 236,* 507.
[1547] Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217.
[1548] Blomquist, A.T.; Wolinsky, J. *J. Am. Chem. Soc.* ***1957****, 79,* 6025; Schowen, K.B.; Smissman, E.E.; Schowen, R.L. *J. Org. Chem.* ***1968****, 33,* 1873.
[1549] See Safarov, M.G.; Isagulyants, V.I.; Nigmatullin, N.G. *J. Org. Chem. USSR* ***1974****, 10*, 1378.
[1550] Fremaux, B.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1967***, 4250.

Additional evidence for the intermediacy of **92** is the finding that oxetanes (**94**) subjected to the reaction conditions, which would protonate **94** to give **92**, give essentially the same product ratios as the corresponding alkenes.[1551] An argument against the intermediacy of **92** and **93** is that not all alkenes show the anti-stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.[1552] Since addition to the C=C bond is electrophilic, the reactivity of the alkene increases with alkyl substitution and *Markovnikov's rule* is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde[1553] (**16-5**) or between **92** and formaldehyde. Racemization may occur in the *Prins cyclization* reaction by 2-oxonia-*Cope rearrangements* (see **18-32**) by way of a (*Z*)-oxocarbenium ion intermediate.[1554]



92 **91** **93** **94**

Iodine can promote the *Prins reaction*.[1555] Lewis acids (e.g., $SnCl_4$) also catalyze the reaction, in which case the species that adds to the alkenes is H_2C^+–O–$SnCl_4$.[1556] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free radical one. Other transition metal complexes can be used to form homoallylic alcohols. A typical example is the reaction of methylenecyclohexane with an aryl aldehyde to give **95**.[1557]



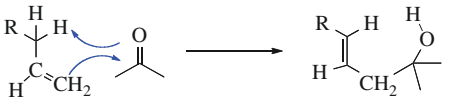
95

Samarium iodide promotes this addition reaction.[1558] In a related reaction, simple alkene units add to esters in the presence of sodium and liquid ammonia to give an alcohol.[1559] Dienes react with alcohols in the presence of a transition metal compound, to give alkenyl alcohols.[1560] Allenes also add to aldehydes.[1561] Enynes undergo *Prins cyclization* with Au catalysts.[1562]

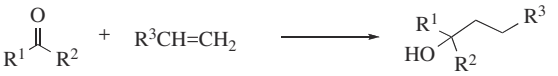
[1551] Meresz, O.; Leung, K.P.; Denes, A.S. *Tetrahedron Lett.* ***1972***, 2797.
[1552] See Wilkins, C.L.; Marianelli, R.S. *Tetrahedron* ***1970***, *26*, 4131; Karpaty, M.; Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1971***, 1736; Coryn, M.; Anteunis, M. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 83.
[1553] See Isagulyants, V.I.; Isagulyants, G.V.; Khairudinov, I.R.; Rakhmankulov, D.L. *Bull. Acad. Sci. USSR. Div. Chem. Sci.,* ***1973***, *22*, 1810; Sharf, V.Z.; Kheifets, V.I.; Freidlin, V.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.,* ***1974***, *23,* 1681.
[1554] Jasti, R.; Rychnovsky, S.D. *J. Am. Chem. Soc.* ***2006***, *128,* 13640.
[1555] Yadav, J.S.; Subba Reddy, B.V.; Hara Gopal, A.V.; Narayana Kumar, G.G.K.S.; Madavi, C.; Kunwar, A.C. T*etrahedron Lett.* ***2008***, *49,* 4420; Reddy, S.; Krishna, V.H.; Swamy, T.; Narayana Kumar, G.G.K.S. *Can. J. Chem.* ***2007***, *85*, 412.
[1556] Yang, D.H.; Yang, N.C.; Ross, C.B. *J. Am. Chem. Soc.* ***1959***, *81,* 133.
[1557] Ellis, W.W.; Odenkirk, W.; Bosnich, B. *Chem. Commun.* ***1998***, 1311.
[1558] Sarkar, T.K.; Nandy, S.K. *Tetrahedron Lett.* ***1996***, *37*, 5195.
[1559] Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* ***1998***, *63*, 3141.
[1560] Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* ***2006***, *128*, 8559; Cho, H.Y.; Morken, J.P. *J. Am. Chem. Soc.* ***2008***, *130,* 16140. See Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007***, *129,* 2248.
[1561] Song, M.; Montgomery, J. *Tetrahedron* ***2005***, *61,* 11440.
[1562] Jiménez-Núñez, E.; Claverie, C.K.; Nieto-Oberhuber, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2006***, *45,* 5452.

Structural variations in the alkene lead to different products. Homoallylic alcohols react with aldehydes in the presence of Montmorillonite-KSF clay to give 4-hydroxytetrahydropyrans.[1563] A variation of this reaction converts an aryl aldehyde and a homoallylic alcohol to a 4-chlorotetrahydropyran in the presence of $InCl_3$.[1564] Homoallylic alcohols, protected as —O(CHMeOAc) react with BF_3•OEt_2 and acetic acid to give 4-acetoxytetrahydropyrans or with $SnBr_4$ to give 4-bromotetrahydropyrans.[1565] Homoallylic alcohols with a vinyl silane moiety react with $InCl_3$ and an aldehyde to give a dihydropyran.[1566]

A closely related reaction has been performed with activated aldehydes or ketones; without a catalyst (e.g., chloral and acetoacetic ester), but with heat.[1567] The product in these cases is a β-hydroxy alkene, and the mechanism is pericyclic:[1568]



This reaction is reversible and suitable β-hydroxy alkenes can be cleaved by heat (**17-32**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (see **17-32**), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.[1569] Note that this reaction is an oxygen analogue of the ene synthesis (**15-23**). This reaction can also be done with unactivated aldehydes[1570] and ketones[1571] if Lewis acid catalysts [e.g., dimethylaluminum chloride (Me_2AlCl) or ethylaluminum dichloride ($EtAlCl_2$)] are used.[1572] Lewis acid catalysts also increase rates with activated aldehydes.[1573] The use of optically active catalysts has given optically active products with a high % ee.[1574]



96

In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols (**96**). This has been accomplished by several methods,[1575] including treatment

[1563] Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Tetrahedron Lett.* ***2001****, 42*, 89.
[1564] Yang, J.; Viswanathan, G.S.; Li, C.-J. *Tetrahedron Lett.* ***1999****, 40*, 1627.
[1565] Jaber, J.J.; Mitsui, K.; Rychnovsky, S.D. *J. Org. Chem.* ***2001****, 66*, 4679.
[1566] Dobbs, A.P.; Martinović, S. *Tetrahedron Lett.* ***2002****, 43*, 7055.
[1567] Arnold, R.T.; Veeravagu, P. *J. Am. Chem. Soc.* ***1960****, 82*, 5411; Klimova, E.I.; Abramov, A.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969****, 5*, 1308; Klimova, E.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969****, 5,* 1312, 1315.
[1568] See Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986****, 27,* 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982****, 47*, 3353.
[1569] Also see Achmatowicz, Jr., O.; Szymoniak, J. *J. Org. Chem.* ***1980****, 45,* 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986****, 27,* 1575; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1981****, 22*, 2773.
[1570] See Cartaya-Marin, C.P.; Jackson, A.C.; Snider, B.B. *J. Org. Chem.* ***1984****, 49,* 2443.
[1571] Jackson, A.C.; Goldman, B.E.; Snider, B.B. *J. Org. Chem.* ***1984****, 49*, 3988.
[1572] See Song, Z.; Beak, P. *J. Org. Chem.* ***1990****, 112,* 8126.
[1573] Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 291, 315, 331.
[1574] Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* ***1990****, 112*, 3949.
[1575] See Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1178–1179.

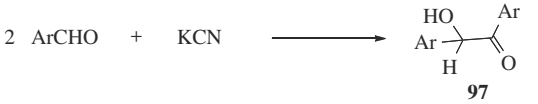
with SmI_2[1576] or Zn and Me_3SiCl,[1577] and by electrochemical[1578] and photochemical[1579] methods. Most of these methods have been used for intramolecular addition and most or all involve free radical intermediates.

There is an *aza-Prins reaction*, promoted by TiI_4 and I_2.[1580]

OS **IV**, 786. See also, OS **VII**, 102.

16-55 The Benzoin Condensation

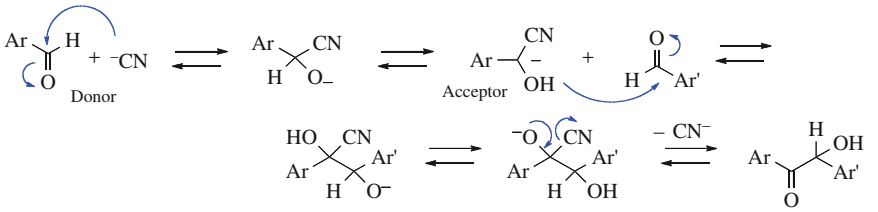
Benzoin aldehyde condensation



97

When certain aldehydes are treated with cyanide ion, *benzoins* (**97**) are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction only occurs with aromatic aldehydes, but not all of them,[1581] and for glyoxals (RCOCHO). The two molecules of aldehyde obviously perform different functions. The one that no longer has a C—H bond in the product is called the *donor*, because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions, and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor, but only a donor. Thus it cannot condense with itself. It can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor. *N*-alkyl-3-methylimidazolium salts catalyze the reaction,[1582] as does an imidazole-based solid supported catalyst.[1583]

The following is the accepted mechanism[1584] for this reversible reaction, which was originally proposed by Lapworth in 1903:[1585]



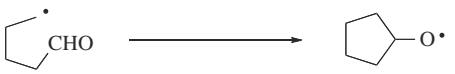
[1576] Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837.
[1577] Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* ***1983***, *24,* 2821.
[1578] See Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* ***1989***, *54,* 6001.
[1579] See Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* ***1986***, *51,* 4196.
[1580] Shimizu, M.; Baba, T.; Toudou, S.; Hachiya, I. *Chem. Lett.* ***2007***, *36*, 12.
[1581] For a review, see Ide, W.S.; Buck, J.S. *Org. React.* ***1948***, *4,* 269.
[1582] Xu, L.-W.; Gao, Y.; Yin, J.-J.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* ***2005***, *46*, 5317. See also, Iwamoto, K.; Kimura, H.; Oike, M.; Sato, M. *Org. Biomol. Chem.* ***2008***, *6*, 912; Iwamoto, K.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* ***2006***, *47,* 7175;
[1583] Storey, J.M.D.; Williamson, C. *Tetrahedron Lett.* ***2005***, *46*, 7337.
[1584] See Kuebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E. *J. Am. Chem. Soc.* ***1971***, *93,* 1214.
[1585] Lapworth, A. *J. Chem. Soc.* ***1903***, *83,* 995; ***1904***, *85*, 1206.

The key step, the loss of the aldehyde proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (1) It acts as a nucleophile; (2) its electron-withdrawing ability permits loss of the aldehyde proton; and (3) having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze the reaction.[1586] In this case, aliphatic aldehydes can also be used[1587] (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.[1588] The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.[1589] The condensation has also been done with excellent enantioselectivity using benzoyl formate decarboxylase.[1590] Enantiopure triazolium salts have been evaluated as catalysts in the enantioselective benzoin condensation.[1591] *N*-Heterocyclic carbene catalysts have been used for asymmetric induction.[1592]

A "mixed"-benzoin condensation has been accomplished by using aryl silyl ketones [$ArC(=O)SiMe_2Ph$] and aldehydes with a La catalyst.[1593] The reaction of acylsilanes and aldehydes, catalyzed by metal cyanides, is known as the silyl-benzoin reaction.[1594]

OS **I**, 94; **VII**, 95.

16-56 Addition of Radicals to C=O, C=S, C=N Compounds



Radical cyclization is not limited to reaction with a C=C unit (see **15-29** and **15-30**), and reactions with both C=N and C=O moieties are known. Reaction of $MeON{=}CH(CH_2)_3CHO$ with Bu_3SnH and AIBN, for example, led to *trans*-2-(methoxyamino)cyclopentanol in good yield.[1595] Conjugated ketones add to aldehyde via the β carbon under radical conditions (2 molar equivalents of Bu_3SnH and 0.1 equiv of CuCl) to give a β-hydroxy ketone.[1596]

In a related reaction, diazo compounds add to ketenes to give allenes.[1597]

Addition of radical to the C=N unit of R–C=N–SPh[1598] or R–C=N–OBz[1599] led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.[1600] Radicals

[1586] See Diederich, F.; Lutter, H. *J. Am. Chem. Soc.* ***1989****, 111,* 8438. Also see Lappert, M.F.; Maskell, R.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 580.
[1587] Kuhlmann, H. *Org. Synth.* ***VII***, 95; Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* ***1985****, 50*, 603.
[1588] Stetter, H.; Dämbkes, G. *Synthesis* ***1977***, 403.
[1589] Rozwadowska, M.D. *Tetrahedron* ***1985****, 41*, 3135.
[1590] Demir, A.S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron Asymmetry* ***1999****, 10*, 4769.
[1591] Enders, D.; Han, J. *Tetrahedron Asymmetry* ***2008****, 19,* 1367; O'Toole, S.E.; Connon, S.J. *Org. Biomol. Chem.* ***2009****, 7*, 3584; Baragwanath, L.; Rose, C.A.; Zeitler, K.; Connon, S.J. *J. Org. Chem.* ***2009****, 74*, 9214.
[1592] Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* ***2006****, 45,* 1463. See also, Mavis, M.E.; Yolacan, C.; Aydoga, F. *Tetrahedron Lett.* ***2010****, 51*, 4509.
[1593] Bausch, C.C.; Johnson, J.S. *J. Org. Chem.* ***2004****, 69*, 4283.
[1594] Linghu, X.; Bausch, C.C.; Jeffrey S.; Johnson, J.S. *J. Am. Chem. Soc.* ***2005****, 127,* 1833.
[1595] Tormo, J.; Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998****, 63*, 201.
[1596] Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* ***1999****, 40*, 2133.
[1597] Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* ***2007****, 129,* 1494.
[1598] Boivin, J.; Fouquet, E.; Zard, S.Z. *Tetrahedron* ***1994****, 50*, 1745.
[1599] Boivin, J.; Schiano, A.-M.; Zard, S.Z. *Tetrahedron Lett.* ***1994****, 35*, 249.
[1600] Bowman, W.R.; Stephenson, P.T.; Terrett, N.K.; Young, A.R. *Tetrahedron Lett.* ***1994****, 35*, 6369.

also add to the carbonyl unit of phenylthio esters to give cyclic ketones.[1601] Carbon-centered radicals add to imines.[1602] The reaction of an alkyl halide with BEt_3 in aq methanol, for example, gives the imine addition product, an alkylated amine.[1603]

Secondary alkyl iodides add to *O*-alkyl oximes in the presence of BEt_3 and AIBN. This methodology was used to convert MeO_2C-CH=NOBn to MeO_2C—CH(R)NOBn.[1604] Benzylic halides add to imines under photochemical conditions, and in the presence of 1-benzyl-1,4-dihydronicotinamide[1605] or with BEt_3 in aq methanol.[1606] Tertiary alkyl iodides add to oxime ethers using BF_3•OEt_2 in the presence of BEt_3/O_2.[1607] *O*-Trityl oximes of 5- and 6-iodoaldehydes undergo radical cyclization to give oximes[1608] (also see Reaction **15-30**). Enantioselective radical addition reactions to *N*-benzoyl hydrazones used chiral ammonium salts.[1609] The Mn mediated reaction of allyl iodides with chiral *N*-acylhydrazones leads to chiral hydrazine derivatives.[1610]

N,N-Dimethylaniline reacts with aldehydes under photochemical conditions to give acyl addition via the carbon atom of one of the methyl groups.[1611] The reaction of $PhNMe_2$ and benzaldehyde, for example, gave $PhN(Me)CH_2CH(OH)Ph$ upon photolysis.

16.B.ii. Acyl Substitution Reactions

A. O,N, and S Nucleophiles

16-57 Hydrolysis of Acyl Halides

Hydroxy-de-halogenation

$$RCOCl + H_2O \longrightarrow RCOOH$$

Acyl halides are so reactive that hydrolysis is easily carried out.[1612] In fact, most simple acyl halides must be stored under anhydrous conditions or they may react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, but in unreactive systems hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is F < Cl < Br < I.[1613] If a carboxylic acid is used as the nucleophile, an exchange may take place (see Reaction **16-79**). The mechanism[1613] of hydrolysis can be either S_N1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[1614] There is also evidence for the S_N2 mechanism in some cases.[1615]

[1601] Kim, S.; Jon, S.Y. *Chem. Commun.* ***1996***, 1335.
[1602] For a review, see Friestad, G.K. *Tetrahedron* ***2001****, 57*, 5461.
[1603] Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* ***2000****, 65*, 5043.
[1604] Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* ***2000****, 56*, 2413.
[1605] Jin, M.; Zhang, D.; Yang, L.; Liu, Y.; Liu, Z. *Tetrahedron Lett.* ***2000****, 41*, 7357.
[1606] McNabb, S.B.; Ueda, M.; Naito, T. *Org. Lett.* ***2004****, 6*, 1911.
[1607] Halland, N.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1290.
[1608] Clive, D.L.J.; Pham, M.P.; Subedi, R. *J. Am. Chem. Soc.* ***2007****, 129,* 2713.
[1609] Jang, D.O.; Kim, S.Y. *J. Am. Chem. Soc.* ***2008****, 130,* 16152.
[1610] Friestad, G.K.; Marié, J.-C.; Suh, Y.S.; Qin, J. *J. Org. Chem.* ***2006****, 71,* 7016.
[1611] Kim, S.S.; Mah, Y.J.; Kim, A.R. *Tetrahedron Lett.* ***2001****, 42*, 8315.
[1612] See Bentley, T.W.; Shim, C.S. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1659.
[1613] Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10; Elsevier, NY, ***1972***, pp. 226–257. See Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 177–230.
[1614] Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 30. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8470; Bentley, T.W.; Koo, I.S.; Norman, S.J. *J. Org. Chem.* ***1991***, *56*, 1604.
[1615] Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987****, 65*, 1951. See also, Lee, I.; Sung, D.D.; Uhm, T.S.; Ryu, Z.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1697.

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[1616] There are several methods available for the hydrolysis of acyl fluorides.[1617]

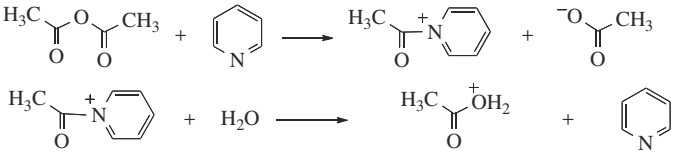
OS **II**, 74.

16-58 Hydrolysis of Anhydrides

Hydroxy-de-acyloxy-substitution



Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral.[1618] The S_N1 mechanism only occurs with acid catalysis and seldom even then.[1619] Anhydride hydrolysis can also be catalyzed by bases. Of course, hydroxide ion attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (Sec. 16.A.i, category 4), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[1620]

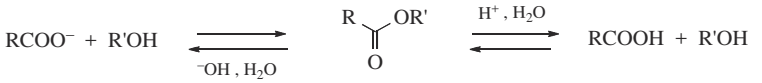


Many other nucleophiles similarly catalyze the reaction.

OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

16-59 Hydrolysis of Carboxylic Esters

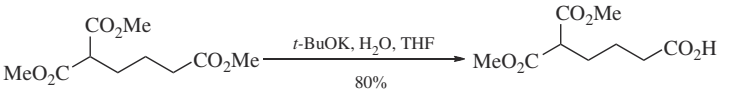
Hydroxy-de-alkoxylation



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile $^-$OH. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive, and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so there must be a way to shift the equilibrium to the right for this to be useful. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution,

[1616] Bevan, C.W.L.; Hudson, R.F. *J. Chem. Soc.* ***1953***, 2187; Satchell, D.P.N. *J. Chem. Soc.* ***1963***, 555.
[1617] Motie, R.E.; Satchell, D.P.N.; Wassef, W.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 859; ***1993***, 1087.
[1618] See Satchell, D.P.N.; Wassef, W.N.; Bhatti, Z.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 2373.
[1619] Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, see pp. 172–173. See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 10, Elsevier, NY, ***1972***, pp. 280–287.
[1620] See Deady, L.W.; Finlayson, W.L. *Aust. J. Chem.* ***1983***, *36*, 1951.

unless the compound is base sensitive. Even in the case of **98**, however, selective base hydrolysis of the ethyl ester gave an 80% yield of the acid–dimethyl ester (**99**).[1621]



98 **99**

Ester hydrolysis can also be catalyzed[1622] by metal ions, by cyclodextrins,[1623] by enzymes,[1624] and by nucleophiles.[1621] Other reagents used to cleave carboxylic esters include Dowex-50,[1625] Me_3SiI,[1626] and $InCl_3$ on moist silica gel using microwave irradiation.[1627] Cleavage of phenolic esters is usually faster than carboxylic esters derived from aliphatic acids. The reagent Sm/I_2 at -78 °C has been used,[1628] ammonium acetate in aq methanol,[1629] Amberlyst 15 in methanol,[1630] and phenolic esters have been selectively hydrolyzed in the presence of alkyl esters on alumina with microwave irradiation.[1631] Allylic esters were cleaved with DMSO—I_2.[1632] Thiophenol with K_2CO_3 in NMP quantitatively converted methyl benzoate to benzoic acid.[1633] Allylic esters were cleaved with 2% Me_3SiOTf in dichloromethane,[1634] with $CeCl_3$•7 H_2O—NaI,[1635] and with $NaHSO_4$•silica gel.[1636] Lactones also undergo the reaction[1637] (but if the lactone is five- or six-membered, the hydroxy acid often spontaneously re-forms the lactone) and thiol esters (RCOSR′) give thiols R′SH. Typical reagents for this latter transformation include NaSMe in methanol,[1638] borohydride exchange resin–$Pd(OAc)_2$ for reductive cleavage of thiol esters to thiols,[1639] and $TiCl_4/Zn$ for the conversion of phenylthioacetates to thiophenols.[1640] Sterically hindered esters are hydrolyzed with difficulty (Sec. 10.G.i), but reaction of 2 equiv of *t*-BuOK with 1 equiv of water is effective.[1641] Hindered esters can also be cleaved by sequential treatment with zinc bromide and then water,[1642] with

[1621] Wilk, B.K. *Synth. Commun.* ***1996***, *26*, 3859.
[1622] For a list of catalysts and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1959–1968
[1623] See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer, NY, ***1978***, pp. 34–41. The mechanism is shown in Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.
[1624] For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu, L.; Tedford, M.C. *Tetrahedron* ***1990***, *46*, 6587; Ohno, M.; Otsuka, M. *Org. React.* ***1989***, *37*, 1. See Wong, C. *Science* ***1989***, *244*, 1145; Whitesides, G.M.; Wong, C. *Angew. Chem. Int. Ed.* ***1985***, *24*, 617; Barbayianni, E.; Fotakopoulou, I.; Schmidt, M.; Constantinou-Kokotou, V.; Bornscheuer, U.T.; Kokotos, G. *J. Org. Chem.* ***2005***, *70,* 8730; Fotakopoulou, I.; Barbayianni, E.; Constantinou-Kokotou, V.; Bornscheuer, U.T.; Kokotos, G. *J. Org. Chem.* ***2007***, *72,* 782.
[1625] Basu, M.K.; Sarkar, D.C.; Ranu, B.C. *Synth. Commun.* ***1989***, *19*, 627.
[1626] See Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667.
[1627] Ranu, B.C.; Dutta, P.; Sarkar, A. *Synth. Commun.* ***2000***, *30* , 4167.
[1628] Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* ***1995***, 1261.
[1629] Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* ***2003***, *59*, 1049.
[1630] Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* ***2003***, *44*, 5465.
[1631] Varma, R.S.; Varma, M.; Chatterjee, A.K. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 999.
[1632] Taksande, K.N.; Sakate, S.S.; Lokhande, P.D. *Tetrahedron Lett.* ***2006***, *47*, 643.
[1633] Sharma, L.; Nayak, M.K.; Chakraborti, A.K. *Tetrahedron* ***1999***, *55*, 9595.
[1634] Nishizawa, M.; Yamamoto, H.; Seo, K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2002***, *4,* 1947.
[1635] Yadav, J.S.; Reddy, B.V.S.; Rao, C.V.; Chand, P.K.; Prasad, A.R. *Synlett* ***2002***, 137.
[1636] Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* ***2003***, *44,* 1465.
[1637] See Kaiser, E.T.; Kézdy, F.J. *Prog. Bioorg. Chem.* ***1976***, *4*, 239, pp. 254–265.
[1638] Wallace, O.B.; Springer, D.M. *Tetrahedron Lett.* ***1998***, *39*, 2693.
[1639] Choi, J.; Yoon, N.M. *Synth. Commun.* ***1995***, *25*, 2655.
[1640] Jin, C.K.; Jeong, H.J.; Kim, M.K.; Kim, J.Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* ***2001***, 1956,
[1641] Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* ***1977***, *42*, 918.
[1642] Wu, Y.-g.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. *Tetrahedron Lett.* ***2000***, *41,* 2847.

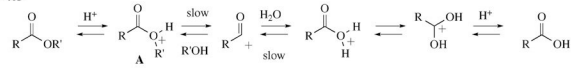
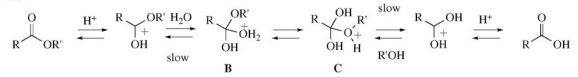
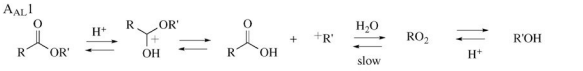
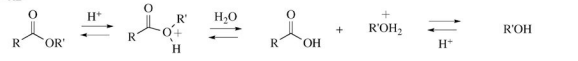
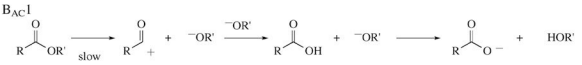
silica gel in refluxing toluene,[1643] and on alumina when irradiated with microwaves.[1644] For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound,[1645] and phase-transfer techniques have been applied.[1646]

Enzymatic hydrolysis of diesters with esterase has been shown to give the hydroxy-ester,[1647] and selective hydrolysis of dimethyl succinate to monomethyl succinic acid was accomplished with aq NaOH in THF.[1648] Hydrolysis of vinyl esters leads to ketones, and the reaction of *C*-substituted vinyl acetates with an esterase derived from *Marchantia polymorpha* gave substituted ketones with high enantioselectivity.[1649] Scandium triflate was shown to hydrolyze α-acetoxy ketones to α-hydroxy ketones.[1650]

Ingold[1651] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 16.3),[1651,1652] depending on the following criteria: (1) acid- or base catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage.[1653] All eight of these are S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible, but also symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chap 8, Ref. 17). Nevertheless the $A_{AC}1$ mechanism is shown as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations $A_{AC}1$, and so on, are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called A2 and A1, respectively. Note that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that $A_{AL}2$ is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms. Molecular dynamics has shown that "the rate of hydrolysis of methyl formate in pure water is consistent with mechanisms involving cooperative catalysis by autoionization-generated hydroxide and hydronium, a process known to have an activation free energy of 23.8 kcal mol^{-1} (99.6 kJ mol^{-1})."[1654]

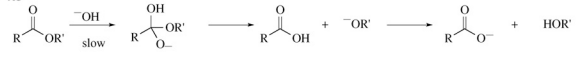
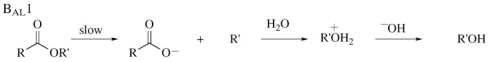
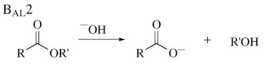
[1643] Jackson, R.W. *Tetrahedron Lett.* ***2001****, 42*, 5163.
[1644] Ley, S.V.; Mynett, D.M. *Synlett* ***1993***, 793.
[1645] Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917.
[1646] Loupy, A.; Pedoussaut, M.; Sansoulet, J. *J. Org. Chem.* ***1986***, *51*, 740.
[1647] See Nair, R.V.; Shukla, M.R.; Patil, P.N.; Salunkhe, M.M. *Synth. Commun.* ***1999****, 29,* 1671.
[1648] Niwayama, S. *J. Org. Chem.* ***2000****, 65*, 5834.
[1649] Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron Asymmetry* ***2000****, 11*, 1063.
[1650] Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999****, 72*, 1553.
[1651] Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1129–1131.
[1652] As given here, the IUPAC designations for $B_{AC}1$ and $B_{AL}1$ are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su—AL for $B_{AL}1$ and Su-AC for $B_{AC}1$. See the IUPAC rules: Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23, see p. 49.
[1653] Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, ***1972***, pp. 57–207; Euranto, E.K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 505–588.
[1654] Gunaydin, H.; Houk, K.N. *J. Am. Chem. Soc.* ***2008****, 130,* 15232.

TABLE 16.3 Classification of the Eight Mechanisms for Ester Hydrolysis and Formation

Name			
Ingold		IUPAC[a]	Type
$A_{AC}1$		$A_h+D_N+A_N+D_h$	S_N1
$A_{AC}2$		$A_h+A_N+A_hD_h+D_h$	Tetrahedral
$A_{AL}1$		$A_h+D_N+A_N+D_h$	S_N1
$A_{AL}2$		$A_h+A_ND_N+D_h$	S_N2
$B_{AC}1$		$D_N+A_N+A_{xh}D_h$	S_N1

(*continued*)

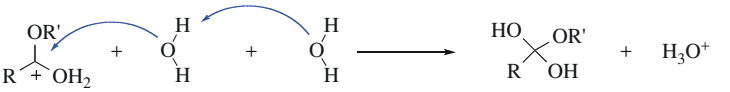
TABLE 16.3 (***Continued***)

Name			
Ingold		IUPAC[a]	Type
$B_{AC}2$		$A_N+D_N+A_{xh}D_h$	Tetrahedral
$B_{AL}1$		$D_N+A_N+A_{xh}D_h$	S_N1
$B_{AL}2$		A_ND_N	S_N2

Adapted material from *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1129–1131, edited by Ingold, C.K. Copyright © 1969 by Cornell University. Used by permission of the publisher, Cornell University Press.

[a]See Ref. 1652

Of the eight mechanisms, seven have actually been observed in the hydrolysis of carboxylic esters. The one that has not been observed is the $B_{AC}1$ mechanism.[1655] The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$[1656] for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl–oxygen cleavage. The evidence is (1) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[1657] (2) esters with chiral R′ groups give alcohols with *retention* of configuration;[1658] (3) allylic R′ gives no allylic rearrangement;[1659] (4) neopentyl R′ gives no rearrangement[1660]; all these facts indicate that the O—R′ bond is not broken. It has been concluded that two molecules of water are required in the $A_{AC}2$ mechanism, as shown:



If this were so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of *w* (see Sec. 8.C) of ~ 5, indicating that water acts as a proton donor here as well as a nucleophile.[1661] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called $B_{AC}3$, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.[1662] Such esters are mostly those containing halogen atoms in the R group.)

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$\mathrm{ArCOOH} + 2\mathrm{H_2SO_4} \rightleftharpoons \mathrm{Ar\overset{+}{C}O} + \mathrm{H_3O^+} + 2\mathrm{HSO_4^-}$$

In a comparable solution of benzoic acid, the freezing point is depressed only twice the predicted amount, indicating only a normal acid–base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[1663] The $A_{AC}1$ mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated (>90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal $A_{AC}2$).[1664]

The mechanisms involving alkyl–oxygen cleavage are ordinary S_N1 and S_N2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R′ comes off as a stable carbocation (i.e., when R′ is tertiary alkyl, allylic, benzylic, etc.). For acid

[1655] This is an S_N1 mechanism with OR' as leaving group, which does not happen.
[1656] See Zimmermann, H.; Rudolph, J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 40.
[1657] See Polanyi, M.; Szabo, A.L. *Trans. Faraday Soc.* ***1934***, *30*, 508.
[1658] Holmberg, B. *Ber.* ***1912***, *45*, 2997.
[1659] Ingold, C.K.; Ingold, E.H. *J. Chem. Soc.* ***1932***, 758.
[1660] Norton, H.M.; Quayle, O.R. *J. Am. Chem. Soc.* ***1940***, *62*, 1170.
[1661] Martin, R.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4130. See also Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Huskey, W. P.; Warren, C.T.; Hogg, J.L. *J. Org. Chem.* ***1981***, *46*, 59.
[1662] See Euranto, E.K.; Kanerva, L.T. *Acta Chem. Scand. Ser. B* ***1988***, *42* 717.
[1663] Treffers, H.P.; Hammett, L.P. *J. Am. Chem. Soc.* ***1937***, *59*, 1708. For other evidence for this mechanism, see Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 37.
[1664] Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Al-Shalchi, W.; Selwood, T.; Tillett J.G. *J. Chem. Res. (S)* ***1985***, 10.

catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the $B_{AL}1$ mechanism occurs only in neutral or weakly basic solution, where the rate of attack by hydroxide is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R′.[1665] Secondary and benzylic acetates hydrolyze by the $A_{AC}2$ mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to $A_{AL}1$.[1665] Despite its designation, the $B_{AL}1$ mechanism is actually uncatalyzed (as is the unknown $B_{AC}1$ mechanism).

The two remaining mechanisms, $B_{AL}2$ and $A_{AL}2$, are very rare. The $B_{AL}2$ mechanism because it requires hydroxide ion to attack an alkyl carbon when an acyl carbon is also available,[1666] and the $A_{AL}2$ because it requires water to be a nucleophile in an S_N2 process. Both have been observed, however. The $B_{AL}2$ has been seen in the hydrolysis of β-lactones under neutral conditions[1667] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butyl benzoate,[1668] and in the unusual reaction:[1669]

$$\mathrm{ArCOOMe} + \mathrm{RO^-} \longrightarrow \mathrm{ArCOO^-} + \mathrm{ROMe}$$

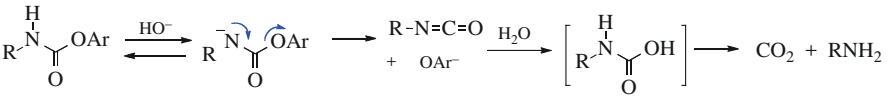
When it does occur, the $B_{AL}2$ mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R′. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The $A_{AL}2$ mechanism has been reported in the acid cleavage of γ-lactones.[1670]

To sum up the acid-catalysis mechanisms, $A_{AC}2$ and $A_{AL}1$ are the common mechanisms, the latter for R′ that give stable carbocations, the former for practically all the rest. The $A_{AC}1$ mechanism is rare, being found mostly with strong acids and sterically hindered R. The $A_{AL}2$ mechanism is even rarer. For basic catalysis, $B_{AC}2$ is almost universal; $B_{AL}1$ occurs only with R′ that give stable carbocations and then only in weakly basic or neutral solutions; $B_{AL}2$ is very rare; and $B_{AC}1$ has never been observed.

The above results pertain to reactions in solution. In the gas phase,[1671] reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO^-, which in the gas phase was shown to take place only by the $B_{AL}2$ mechanism,[1672] even with aryl esters,[1673] where this means that an S_N2 mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO^- ions, each of which was solvated with a single molecule of MeOH or H_2O, the $B_{AC}2$ mechanism was observed.[1672]

In the special case of alkaline hydrolysis of *N*-substituted aryl carbamates, there is another mechanism[1674] involving elimination–addition:[1675]

[1665] For discussions, see Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 9, Elsevier, NY, ***1973***, pp. 86–101; Ingold, C.K. *Structure and Mechanism in Organic Chemistry,* 2nd ed., Cornell University Press, Ithica, NY, ***1969***, pp. 1137–1142, 1157–1163.
[1666] Douglas, J.E.; Campbell, G.; Wigfield, D.C. *Can. J. Chem.* ***1993***, *71*, 1841.
[1667] Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1264; Long, F. A.; Purchase, M. *J. Am. Chem. Soc.* ***1950***, *73*, 3267.
[1668] Barclay, L.R.C.; Hall, N.D.; Cooke, G.A. *Can. J. Chem.* ***1962***, *40*, 1981.
[1669] Sneen, R.A.; Rosenberg, A.M. *J. Org. Chem.* ***1961***, *26*, 2099. See also, Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.
[1670] Moore, J.A.; Schwab, J.W. *Tetrahedron Lett.* ***1991***, *32*, 2331.
[1671] Takashima, K.; José, S.M.; do Amaral, A.T.; Riveros, J.M. *J. Chem. Soc., Chem. Commun.* ***1983***, 1255.
[1672] Comisarow, M. *Can. J. Chem.* ***1977***, *55*, 171.
[1673] Fukuda, E.K.; McIver, Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 2498.
[1674] See Williams, A.; Douglas, K.T. *Chem. Rev.* ***1975***, *75*, 627.
[1675] See Broxton, T.J.; Chung, R.P. *J. Org. Chem.* ***1986***, *51*, 3112.



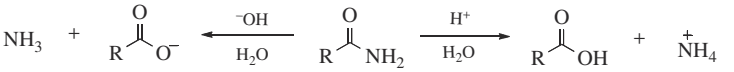
This mechanism does not apply to unsubstituted or *N,N*-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or CO_2Et) can also hydrolyze by a similar mechanism involving a ketene intermediate.[1676] These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (Sec. 17.A.iii).

The acid-catalyzed hydrolysis of enol esters ($RCOOCR'=CR$) can take place either by the normal $A_{AC}2$ mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in Reaction **10-6**,[1677] depending on reaction conditions.[1678] In either case, the products are the carboxylic acid (RCO_2H) and the aldehyde or ketone ($R—CHCOR'$).

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **VI**, 75, 121, 560, 690, 824, 913, 1024; **VII**, 4, 190, 210, 297, 319, 323, 356, 411; **VIII**, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527. Ester hydrolyses with concomitant decarboxylation are listed at Reaction **12-40**.

16-60 Hydrolysis of Amides

Hydroxy-de-amination



Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, and the products are, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. *N*-Substituted ($RCONHR'$) and *N,N*-disubstituted ($RCONR_2'$) amides can be hydrolyzed analogously, and the product is the primary or secondary amine, respectively (or their salts), rather than ammonia. Twisting of the amide bond leads to an acceleration of water-promoted hydrolysis reactions.[1679] Lactams, imides, cyclic imides, hydrazides, and so on, also undergo the reaction.

Water alone is not sufficient to hydrolyze most amides,[1680] since NH_2 is even a poorer leaving group than OR.[1681] Prolonged heating is often required, even with acidic or basic catalysts.[1682] Treatment of primary amides with phthalic anhydride at 250 °C and 4 atm

[1676] Inoue, T.C.; Bruice, T.C. *J. Org. Chem.* ***1986***, *51*, 959; Isaacs, N.S.; Najem, T.S. *Can. J. Chem.* ***1986***, *64*, 1140; *J. Chem. Soc. Perkin Trans. 2* ***1988***, 557.

[1677] Allen, A.D.; Kitamura, T.; Roberts, K.A.; Stang, P.J.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1988***, *110*, 622.

[1678] See Euranto, E.K. *Pure Appl. Chem.* ***1977***, *49*, 1009.

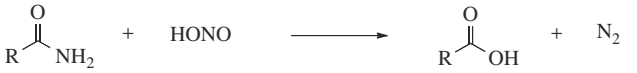
[1679] Mujika, J.I.; Mercero, J.M.; Lopez, X. *J. Am. Chem. Soc.* ***2005***, *127*, 4445.

[1680] See Zahn, D. *Eur. J. Org. Chem.* ***2004***, 4020.

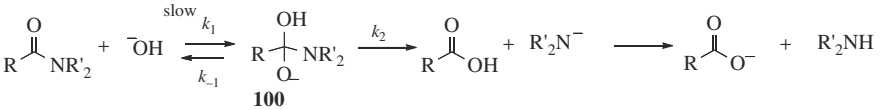
[1681] See Kahne, D.; Still, W.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7529.

[1682] For a list of catalysts and, with references, see Larock, R.C. *Comprehensive Organic Transformatinos*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1976–1977. Also see, Bagno, A.; Lovato, G.; Scorrano, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1091.

gives the carboxylic acid and phthalimide.[1683] Hydrolysis of carbamates ($RNHCO_2R$) to the corresponding amine can be categorized in this section. Although the product is an amine and the carboxyl unit fragments, this reaction is simply a variation of amide hydrolysis. Strong acids [e.g., trifluoroacetic acid (in dichloromethane)] are usually employed.[1684] Treatment of *N*-Boc derivatives ($RNHCO_2t$-Bu) with $AlCl_3$[1685] or with aq sodium *tert*-butoxide[1686] gave the amine. The byproducts of this reaction are typically carbon dioxide and isobutylene.



In difficult cases, nitrous acid, NOCl, N_2O_4,[1687] or a similar compound can be used (unsubstituted amides only[1688]). These reactions involve a diazonium ion (see Reaction **13-19**) and are much faster than ordinary hydrolysis. The benzamide–nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis, for example.[1689] Another procedure for difficult cases involves treatment with aq sodium peroxide.[1690] In still another method, the amide is treated with water and *t*-BuOK at room temperature.[1691] A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.[1692] Amide hydrolysis can also be catalyzed by nucleophiles (see Sec. 16.A.i, category 4).

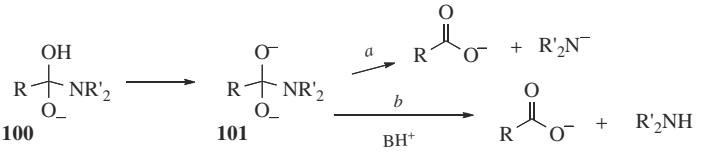


100

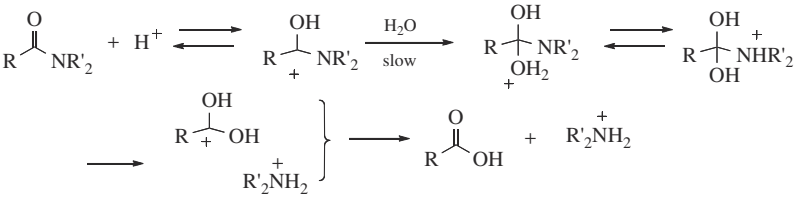
The same framework of eight possible mechanisms discussed for ester hydrolysis in Reaction **16-59** can also be applied to amide hydrolysis.[1693] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both cases. For basic catalysis[1694] the mechanism is $B_{AC}2$. There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. Molecular orbital studies on the mechanism of amide hydrolysis suggest a highly tetrahedral transition state.[1695] In certain cases, kinetic studies have shown that the reaction is second order in $^-$OH indicating that **100** can lose a proton to give **101**.[1696] Depending on the nature of R′, **101** can cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage

[1683] Chemat, F. *Tetrahedron Lett.* ***2000****, 41*, 3855.
[1684] Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta* ***1963****, 46*, 870.
[1685] Bose, D.S.; Lakshminarayana, V. *Synthesis* ***1999***, 66.
[1686] Tom, N.J.; Simon, W.M.; Frost, H.N.; Ewing, M. *Tetrahedron Lett.* ***2004****, 45*, 905.
[1687] Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* ***1990***, *31*, 3893.
[1688] See Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* ***1983***, *48*, 2424.
[1689] Ladenheim, H.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1895.
[1690] Vaughan, H.L.; Robbins, M.D. *J. Org. Chem.* ***1975***, *40*, 1187.
[1691] Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* ***1976***, *98*, 1275.
[1692] Hibbert, F.; Malana, M.A. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 755.
[1693] O'Connor, C. *Q. Rev. Chem. Soc.* ***1970***, *24*, 553; Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 9, Elsevier, NY, ***1973***, pp. 257–280; Challis, B.C.; Challis, J.C. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 731–857.
[1694] See DeWolfe, R.H.; Newcomb, R.C. *J. Org. Chem.* ***1971***, *36*, 3870.
[1695] Hori, K.; Kamimura, A.; Ando, K.; Mizumura, M.; Ihara, Y. *Tetrahedron* ***1997***, *53*, 4317. See Marlier, J.F.; Campbell, E.; Lai, C.; Weber, M.; Reinhardt, L.A.; Cleland, W.W. *J. Org. Chem.* ***2006****, 71,* 3829.
[1696] Khan, M.N.; Olagbemiro, T.O. *J. Org. Chem.* ***1982***, *47*, 3695.

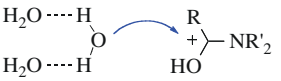
(path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.[1697] Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2, of substituents on the aromatic rings in a series of amides ($CH_3CONHAr$) led to the conclusion that path *a* is taken when Ar contains



electron-withdrawing substituents and path *b* when electron-donating groups are present.[1698] The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that $NR_2'^-$ can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not $NR_2'^-$ but the conjugate NHR_2' (path *b*). It is known that formation of **100** is the rate-determining step in the $B_{AC}2$ mechanism, but only at high-base concentrations. At lower concentrations of base, the cleavage of **100** or **101** becomes rate determining.[1699]

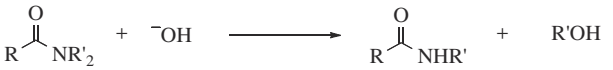


For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen. Because of these facts, it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the $A_{AC}2$ mechanism. Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see Sec. 16.A.i, category 3) has been found in the acid-catalyzed hydrolysis of benzamide[1700] (^{18}O exchange has also been detected for the base-catalyzed process,[1701] in accord with the $B_{AC}2$ mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,[1702] suggesting that, as in the $A_{AL}2$ mechanism for ester hydrolysis (Reaction **16-59**), additional water molecules take part in a process, such as:



[1697] Eriksson, S.O. *Acta Chem. Scand.* ***1968***, *22*, 892; *Acta Pharm. Suec.*, ***1969***, *6*, 139.
[1698] Menger, F.M.; Donohue, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 432; Pollack, R.M.; Dumsha, T.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4463; Kijima, A.; Sekiguchi, S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1203.
[1699] Schowen, R.L.; Jayaraman, H.; Kershner, L. *J. Am. Chem. Soc.* ***1966***, *88*, 3373. See also, Bowden, K.; Bromley, K. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2103.
[1700] Bennet, A.J.; Slebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.
[1701] See Slebocka-Tilk, H.; Bennet, A.J.; Hogg, H.J.; Brown, R.S. *J. Am. Chem. Soc.* ***1991***, *113*, 1288; Bennet, A. J.; Slebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.
[1702] See Yates, K.; Stevens, J.B. *Can. J. Chem.* ***1965***, *43*, 529; Yates, K.; Riordan, J.C. *Can. J. Chem.* ***1965***, *43*, 2328.

The four mechanisms involving alkyl–N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for *N*-substituted and *N,N*-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.



The reaction shown involves attack by the base on an *N*-alkyl group to give an alcohol. While rare, it has been observed for various *N-tert*-butylamides in 98% sulfuric acid, where the mechanism was $A_{AL}1$,[1703] and for certain amides containing an azo group, where a $B_{AL}1$ mechanism was postulated.[1704] Of the two first-order acyl cleavage mechanisms, only the $A_{AC}1$ has been observed, in concentrated sulfuric acid solutions.[1705] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[1689]

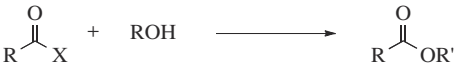
OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **VIII**, 26, 204, 241, 339, 451.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Reaction **19-23**. Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Reactions **12-43** and **12-44**.

B. Attack by OR at an Acyl Carbon

16-61 Alcoholysis of Acyl Halides

Alkoxy-de-halogenation



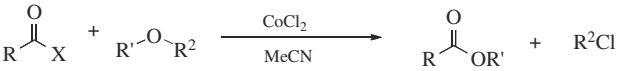
The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.[1706] As with Reaction **16-57**, however, the mechanism can be S_N1 or tetrahedral.[1613] Lewis acids (e.g., lithium perchlorate) can be used.[1707] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aq alkali is used, this is called the *Schotten–Baumann procedure*, but pyridine is also frequently used. Indeed, pyridine catalyzes the reaction by the nucleophilic catalysis route (see Reaction **16-58**). Both R and R′ may be primary, secondary, or tertiary alkyl or aryl. Enol esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R′, the alkoxide can be used instead of the alcohol.[1708] Activated alumina has also been used as a catalyst,

[1703] Lacey, R.N. *J. Chem. Soc.* ***1960***, 1633; Druet, L.M.; Yates, K. *Can. J. Chem.* ***1984***, *62*, 2401.
[1704] Stodola, F.H. *J. Org. Chem.* ***1972***, *37*, 178.
[1705] See Barnett, J.W.; O'Connor, C.J. *J. Chem. Soc., Chem. Commun.* ***1972***, 525; *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2378.
[1706] Bentley, T.W.; Llewellyn, G.; McAlister, J.A. *J. Org. Chem.* ***1996***, *61*, 7927.
[1707] Bandgar, B.P.; Kamble, V.T.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2002***, 735.
[1708] See Kaiser, E.M.; Woodruff, R.A. *J. Org. Chem.* ***1970***, *35*, 1198.

for tertiary R′.[1709] Thallium salts of phenols give very high yields of phenolic esters,[1710] and BiOCl is very effective for the preparation of phenolic acetates.[1711] Phase-transfer catalysis has been used for hindered phenols.[1712] Zinc has been used to couple alcohols and acyl chlorides,[1713] Zr compounds were used,[1714] and catalytic $Cu(acac)_2$ and benzoyl chloride was used to prepare the monobenzoate of ethylene glycol.[1715] Selective acylation is possible in some cases.[1716]

Acyl halides react with thiols, in the presence of Zn, to give the corresponding thio-ester.[1717] The reaction of acid chlorides or anhydrides (see **16-62**) with diphenyldiselenide, in the presence of $Sm/CoCl_2$[1718] or $Sm/CrCl_3$[1719] gave the corresponding seleno ester (PhSeCOMe).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, as shown, in MeCN in the presence of certain catalysts [e.g., cobalt(II) chloride].[1720] A variation of this reaction has been reported that uses acetic anhydride (also see **16-62**).[1721]

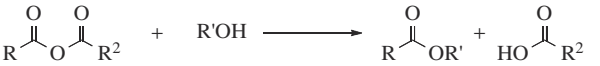


This is a method for the cleavage of ethers (see also, Reaction **10-49**).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824; **VII**, 190; **VIII**, 257, 516.

16-62 Alcoholysis of Anhydrides

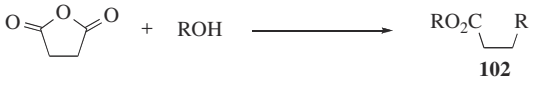
Alkoxy-de-acyloxy-substitution



The scope of this reaction is similar to that of **16-61**. Anhydrides are somewhat less reactive than acyl halides, but they are often used to prepare carboxylic esters. Acids,[1722] Lewis acids,[1723] and bases (e.g., pyridine) are often used as catalysts.[1724] Acetic anhydride

[1709] Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* ***1990***, *20*, 2033.
[1710] Taylor, E.C.; McLay, G.W.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2422.
[1711] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[1712] Illi, V.O. *Tetrahedron Lett.* ***1979***, 2431. For another method, see Nekhoroshev, M.V.; Ivakhnenko, E.P.; Okhlobystin, O.Yu. *J. Org. Chem. USSR* ***1977***, *13*, 608.
[1713] Yadav, J.S.; Reddy, G.S.; Svinivas, D.; Himabindu, K. *Synth. Commun.* ***1998***, *28*, 2337.
[1714] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2005***, *46*, 147.
[1715] Sirkecioglu, O.; Karliga, B.; Talinli, N. *Tetrahedron Lett.* ***2003***, *44*, 8483.
[1716] Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* ***1992***, *22*, 2703.
[1717] Meshram, H.M.; Reddy, G.S.; Bindu, K.H.; Yadav, J.S. *Synlett* ***1998***, 877.
[1718] Chen, R.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 1331.
[1719] Liu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29*, 4043.
[1720] See Ahmad, S.; Iqbal, J. *Chem. Lett.* ***1987***, 953, and references cited therein.
[1721] Lakouraj, M.; Movassagh, B.; Fasihi, J. *J. Chem. Res. (S)* ***2001***, 378.
[1722] Nafion-H has been used: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y.D. *Synlett* ***2000***, 1652.
[1723] **Ce**: Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* ***2003***, *44*, 5621. **Cu**: Saravanan, P.; Singh, V.K. *Tetrahedron Lett.* ***1999***, *40*, 2611. **In**: Chakraborti, A.K.; Gulhane, R. *Tetrahedron Lett.* ***2003***, *44*, 6749. **Li:** Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* ***2001***, 1584. **Mg**: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* ***2003***, 4611. **Ru**: De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 2919. **Ti**: Chandrasekhar, S.; Ramachandar, T.; Reddy, M.V.; Takhi, M. *J. Org. Chem.* ***2000***, *65*, 4729. **Yb**: Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* ***2004***, *45*, 825.
[1724] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1955–1957.

and $NiCl_2$ with microwave irradiation converts benzylic alcohols to the corresponding acetate.[1725] The monoacetates of 1,2-diols have been prepared using $CeCl_3$ as a catalyst.[1726] Pyridine is a nucleophilic-type catalyst (see Reaction **16-58**), but DMAP is superior and can be used in cases where pyridine fails.[1727] Nonaromatic amidine derivatives have been used to catalyze the reaction with acetic anhydride.[1728] Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols[1729] or phenols[1730] with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids (e.g., **102**).[1731] The asymmetric alcoholysis of cyclic anhydrides has been reviewed.[1732]



102

Alcohols can also be acylated by mixed organic–inorganic anhydrides [e.g., acetic-phosphoric anhydride, $MeCOOPO(OH)_2$,[1733] see Reaction **16-68**]. Thioesters of the type ArS(C=O)Me have been prepared by simple reaction of thiols and anhydrides in the presence of potassium carbonate,[1734] and from diphenyl disulfide and PBu_3, followed by treatment with acetic anhydride.[1735]

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; 486; **VIII**, 141, 258.

16-63 Esterification of Carboxylic Acids

Alkoxy-de-hydroxylation

$$RCOOH + R'OH \underset{}{\overset{H^+}{\rightleftharpoons}} RCOOR' + H_2O$$

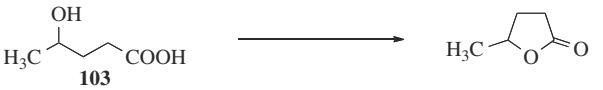
The acid-catalyzed esterification of carboxylic acids with alcohols[1736] is the reverse of Reaction **16-60** and can be accomplished only if a means is available to drive the equilibrium to the right.[1737] There are many ways of doing this, among which are (1) addition of an excess of one of the reactants, usually the alcohol; (2) removal of the ester or the water by distillation; (3) removal of water by azeotropic distillation; and (4) removal of water by use of a dehydrating agent, silica gel,[1738] or a molecular sieve. When R′ is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R′ is

[1725] Constantinou-Kokotou, V.; Peristeraki, A. *Synth. Commun.* ***2004****, 34*, 4227. Also see Bandgar, B.P.; Kasture, S.P.; Kamble, V.T. *Synth. Commun.* ***2001***, *31,* 2255.
[1726] Clarke, P.A.; Kayaleh, N.E.; Smith, M.A.; Baker, J.R.; Bird, S.J.; Chan, C. *J. Org. Chem.* ***2002****, 67*, 5226; Clarke, P.A. *Tetrahedron Lett.* ***2002****, 43*, 4761.
[1727] Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* ***2007****, 129,* 14775. See Scriven, E.F.V. *Chem. Soc. Rev.* ***1983***, *12*, 129; Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 569.
[1728] Birman, V.B.; Li, X.; Han, Z. *Org. Lett.* ***2007****, 9*, 37.
[1729] See van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 704.
[1730] See Sofuku, S.; Muramatsu, I.; Hagitani, A. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2942.
[1731] See Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2000****, 122,* 9542.
[1732] Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* ***2003****, 103*, 2965.
[1733] Fatiadi, A.J. *Carbohydr. Res.* ***1968***, *6*, 237.
[1734] Temperini, A.; Annesi, D.; Testaferri, L.; Tiecco, M. *Tetrahedron Lett.* ***2010****, 51*, 5368.
[1735] Ayers, J.T.; Anderson, S.R. *Synth. Commun* ***1999****, 29*, 351. See Movassagh, B.; Lakouraj, M.M.; Fadaei, Z. *J. Chem. Res. (S)* ***2001***, 22.
[1736] For a review of some methods, see Haslam, E. *Tetrahedron* ***1980***, *36*, 2409.
[1737] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1932–1941.
[1738] Nascimento, M.de G.; Zanotto, S.P.; Scremin, M.; Rezende, M.C. *Synth. Commun.* ***1996***, *26*, 2715.

ethyl or larger, it is preferable to remove water by azeotropic distillation.[1739] The most common catalysts are H_2SO_4 and TsOH, but some reactive carboxylic acids (e.g., formic,[1740] trifluoroacetic[1741]) do not require a catalyst. Ammonium salts have been used to initiate esterification,[1742] and boric acid has been used to esterify α-hydroxy acids.[1743] The R′ group may be primary or secondary alkyl groups other than methyl or ethyl, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low. Selective esterification of an aliphatic carboxylic acid in the presence of an aromatic acid was accomplished with $NaHSO_4$•SiO_2 and methanol.[1744] Diphenylammonium triflate was useful for direct esterification of carboxylic acids with longer chain aliphatic alcohols.[1745] Photoirradiation of carboxylic acid with CBr_4[1746] or CCl_4[1747] in methanol was shown to give the methyl ester, with high selectivity for nonconjugated acids in the case of CBr_4. Esterification has been accomplished in ionic liquids.[1748] A solid-state esterification was reported on P_2O_5/SiO_2.[1749] Diols are converted to the monoacetate by heating with acetic acid on a zeolite.[1750] Vinyl acetate and iodine has been used for the acetylation of alcohols.[1751]

O-Alkylisoureas react with conjugated carboxylic acids to give the corresponding ester with microwave irradiation,[1752] and a polymer-bound *O*-alkylurea has been used as well.[1753] Transition metal compounds of Ti,[1754] or Co[1755] catalyze esterification. Allylic sulfonium salts react with carboxylic acids to give allylic esters in the presence of CuBr.[1756] Triphenylphosphine dibromide is a useful esterification reagent.[1757] Phenols can be esterified using amide acetals.[1758]

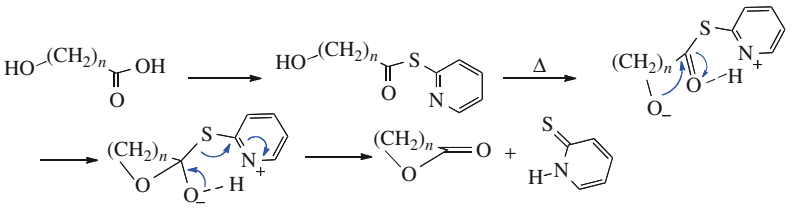
The reaction of a carboxylic acid with an alcohol, in the presence of triphenylphosphine and DEAD gives the corresponding ester. This reaction is known as the *Mitsunobu reaction* (see **10-17**). A variation of this esterification reaction used azopyridines to mediate formation of the ester.[1759]



103

[1739] Newman, M.S. *An Advanced Organic Laboratory Course*, Macmillan, NY, ***1972***, pp. 8–10.
[1740] See Werner, W. *J. Chem. Res. (S)* ***1980***, 196; Hill, D.R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S.J. *Org. Lett.* ***2002****, 4*, 111.
[1741] Johnston, B.H.; Knipe, A.C.; Watts, W.E. *Tetrahedron Lett.* ***1979***, 4225.
[1742] See Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* ***2005****, 127*, 4168.
[1743] Houston, T.A.; Wilkinson, B.L.; Blanchfield, J.T. *Org. Lett.* ***2004***, *6*, 679.
[1744] Das, B.; Venkataiah, B.; Madhsudhan, P. *Synlett* ***2000***, 59.
[1745] Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* ***2000****, 41*, 5249.
[1746] Lee, A.S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* ***2001*** *42*, 301.
[1747] Hwu, J.R.; Hsu, C.-Y.; Jain, M.L. *Tetrahedron Lett.* ***2004*** *45*, 5151.
[1748] McNulty, J.; Cheekoori, S.; Nair, J.J.; Larichev, V.; Capretta, A.; Robertson, A.J. *Tetrahedron Lett.* ***2005****, 46,* 3641; Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron* ***2006****, 62,* 1309.
[1749] Eshghi, H.; Rafei, M.; Karimi, M.H. *Synth. Commun.* ***2001****, 31,* 771.
[1750] Srinivas, K.V.N.S.; Mahender, I.; Das, B. *Synlett* ***2003***, 2419.
[1751] Bosco, J.W.J.; Agrahari, A.; Saikia, A.K. *Tetrahedron Lett.* ***2006****, 47,* 4065.
[1752] Crosignani, S.; White, P.D.; Linclau, B. *Org. Lett.* ***2002****, 4,* 2961.
[1753] See Crosignani, S.; White, P.D.; Linclau, B. *J. Org. Chem.* ***2004****, 69*, 5897.
[1754] Chen, C.-T.; Munot, Y.S. *J. Org. Chem.* ***2005****, 70*, 8625.
[1755] Velusamy, S.; Borpuzari, S.; Punniyamurthy, T. *Tetrahedron* ***2005****, 61*, 2011.
[1756] Sedighi, M.; Çalimsiz, S.; Lipton, M.A. *J. Org. Chem.* ***2006****, 71*, 9517.
[1757] Salomé, C.; Kohn, H. *Tetrahedron* ***2009****, 65*, 456.
[1758] Vorbrüggen, H. *Synlett* ***2008***, 1603.
[1759] Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* ***2008****, 73,* 4882.

Both γ- and δ-hydroxy acids (e.g., **103**) are easily converted to a lactone by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because polyester formation occurs more readily.[1760] Often the conversion of one group to a hydroxyl group, gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. Such groups include keto or halogen that are γ or δ to a carbotyl group. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0–5 °C.[1761] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[1762] Macrocyclic lactones[1763] can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.[1764]



A closely related method, which often gives higher yields of a macrocyclic lactone, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[1765] A macrocyclization technique has been developed based on formation of a mixed anhydride. The *Yamaguchi protocol*[1766] reacts a seco acid (the hydroxy acid precursor of a macrocyclic lactone) with 2,4,6-trichlorobenzoyl chloride. The resulting mixed anhydride is heated with DMAP in toluene.

Esterification is catalyzed by acids (not bases) in ways that were presented in Table 16.3 in Reaction **16-59**.[1653] The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.[1767] Certain acids (e.g., 2,6-di-ortho-substituted benzoic acids), cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (Sec. 10.G.i, category 1). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The

[1760] Wolfe, J.F.; Ogliaruso, M.A. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 2, Wiley, NY, ***1979***, pp. 1062–1330. For a list of methods for converting hydroxy acids to lactones, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1989***, pp. 1861–1867.

[1761] Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2000. Also see Merger, F. *Chem. Ber.* ***1968***, *101*, 2413; Blume, R.C. *Tetrahedron Lett.* ***1969***, 1047.

[1762] Lardelli, G.; Lamberti,V.; Weller, W.T.; de Jonge, A.P. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 481.

[1763] See Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* ***2006***, *106,* 911.

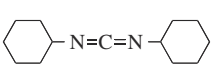
[1764] Wollenberg, R.H.; Nimitz, J.S.; Gokcek, D.Y. *Tetrahedron Lett.* ***1980***, *21*, 2791; Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* ***VII***, 470. See also, Schmidt, U.; Heermann, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 308; Trost, B.M.; Chisholm, J.D. *Org. Lett.* ***2002***, *4*, 3743.

[1765] See Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 707; Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett*. ***2004***, *45*, 3401. For a microwave-assisted reaction, see Donati, D.; Morelli, C.; Taddei, M. *Tetrahedron Lett.* ***2005***, *46,* 2817.

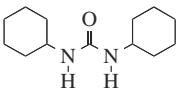
[1766] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1989; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd e*d., Wiley–Interscience, New Jersey, ***2005***, pp. 710–711. For a discussion of the mechanism, see Dhimitruka, I.; SantaLucia, Jr., J. *Org. Lett.* ***2006***, *8,* 47.

[1767] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group,* pt. 1, Wiley, NY, ***1971***, pp. 466–481.

reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two CO_2H groups, only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.

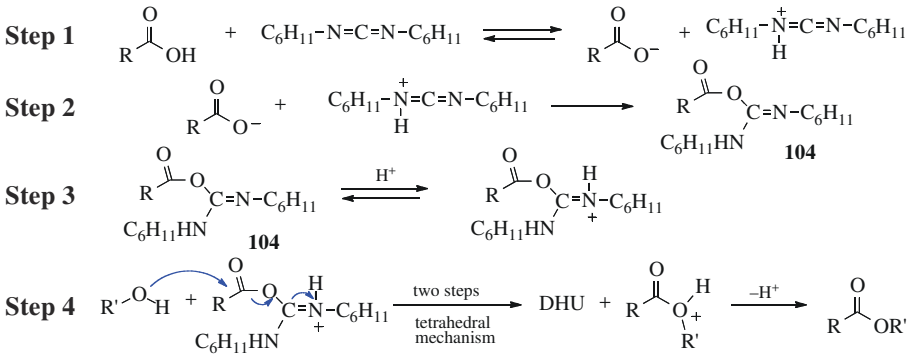


DCC



DHU

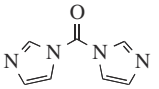
Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.[1738] One of these is dicyclohexylcarbodiimide (DCC), which is converted in the process to dicyclohexylurea (DHU). The mechanism[1768] has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group, but the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:

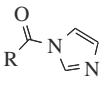


Evidence for this mechanism was the preparation of *O*-acylureas similar to **104** and the finding that when catalyzed by acids they react with alcohols to give esters.[1769] Hindered tertiary alcohols can be coupled via DCC to give the hindered ester.[1770] A polymer-bound carbodiimide has been used to prepare macrocyclic lactones.[1771] In at least one case, the reaction of $HOOCCH_2CN$ with DCC and *tert*-butanol gave the *tert*-butyl ester via a ketene intermediate.[1772]

There are limitations to the use of DCC; yields are variable and *N*-acylureas are side products. Many other dehydrating agents[1773] have been used, including DCC and an aminopyridine,[1774] chlorosilanes,[1775] and *N,N'*-carbonyldiimidazole (**105**).[1776] In the latter case, imidazolides (**106**) are intermediates that react with alcohols.

[1768] Balcom, B.J.; Petersen, N.O. *J. Org. Chem.* ***1989***, *54*, 1922.
[1769] Doleschall, G.; Lempert, K. *Tetrahedron Lett.* ***1963***, 1195.
[1770] Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* ***2001***, 1027.
[1771] Keck, G.E.; Sanchez, C.; Wager, C.A. *Tetrahedron Lett.* ***2000***, *41*, 8673.
[1772] Nahmany, M.; Melman, A. *Org. Lett.* ***2001***, *3*, 3733.
[1773] See Arrieta, A.; García, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 471.
[1774] Boden, E.P.; Keck, G.E. *J. Org. Chem.* ***1985***, *50*, 2394.
[1775] Brook, M.A.; Chan, T.H. *Synthesis* ***1983***, 201.
[1776] See Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61. See also, Morton, R.C.; Mangroo, D.; Gerber, G.E. *Can. J. Chem.* ***1988***, *66*, 1701.


105


106

It is known that the Lewis acid BF_3 promotes the esterification by converting the acid to $RCO^{+-}BF_3^{-}OH$, so the reaction proceeds by an $A_{AC}1$ type of mechanism. The use of BF_3–etherate is simple and gives high yields.[1777] Other Lewis acids can be used.[1778]

Carboxylic esters can also be prepared by treating carboxylic acids with *tert*-butyl ethers and acid catalysts:[1779]

$$RCOOH + t\text{-}Bu{-}OR' \longrightarrow RCOOR' + H_2C{=}CMe_2 + H_2O$$

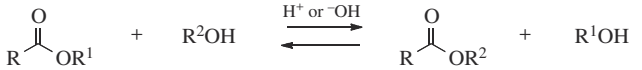
Carboxylic esters can be formed from the carboxylate anion and a suitable alkylating agent (Reaction **10-26**).

Thioesters of the type RSC(=S)R′ (a dithiocarboxylic ester) and RSC(C=O)R′ (a thiocarboxylic ester) can be generated by reaction of carboxylic acids with thiols. In one example, phosphorous pentasulfide was used in conjunction with a thiol to make dithiocarboxylic esters[1780] or thiocarboxylic esters.[1781] Thiocarboxylic esters were prepared from thiols and triflic acid.[1782]

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **VIII**, 141, 251, 597; **IX**, 24, 58; **75**, 116; **75**, 129. Also see, OS **III**, 536, 742.

16-64 Transesterification

Alkoxy-de-alkoxylation



Transesterification[1783] is catalyzed[1784] by acids[1785] or bases,[1786] or done under neutral conditions.[1787] It is an equilibrium reaction that must be shifted in the desired direction.[1788] In many cases, low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as fast as it is formed. Reagents used to catalyze[1789]

[1777] See Kadaba, P.K. *Synth. Commun.* ***1974***, *4*, 167.

[1778] **Bi**: Carrigan, D.; Freiberg, D.A.; Smith, R.C.; Zerth, H.M.; Mohan, R.S. *Synthesis* ***2001***, 2091; Mohammadpoor-Baltork, I.; Khosropour, A.R.; Aliyan, H. *J. Chem. Res.* ***2001***, 280. **Ce**: Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.J.; Wu, Y.-C. *Tetrahedron Lett.* ***2003***, *44*, 331. **Fe**: Sharma, G.V.M.; Mahalingam, A.K.; Nagarajan, M.; Ilangovan, P.; Radhakrishna, P. *Synlett* ***1999***, 1200; Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 607.. **Hf:** Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* ***2002***, *58*, 8179;

[1779] Derevitskaya, V.A.; Klimov, E.M.; Kochetkov, N.K. *Tetrahedron Lett.* ***1970***, 4269. See also, Mohacsi, E. *Synth. Commun.* ***1982***, *12*, 453.

[1780] Sudalai, A.; Kanagasabapathy, S.; Benicewicz, B.C. *Org. Lett.* ***2000***, *2*, 3213.

[1781] Curphey, T.J. *Tetrahedron Lett.* ***2002***, *43*, 371.

[1782] Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2002***, 94.

[1783] Otera, J. *Chem. Rev.* ***1993***, *93*, 1449.

[1784] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1969–1973.

[1785] See Chavan, S.P.; Subbarao, Y.T.; Dantale, S.W.; Sivappa, R. *Synth. Commun.* ***2001***, *31,* 289.

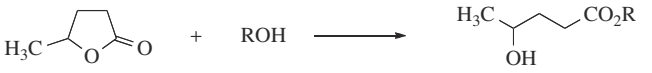
[1786] Stanton, M.G.; Gagné, M.R. *J. Org. Chem.* ***1997***, *62*, 8240; Vasin, V.A.; Razin, V.V. *Synlett* ***2001***, 658.

[1787] See Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.*, *65*, 230; Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. *Synlett* ***2001***, 1715.

[1788] See Bose, D.S.; Satyender, A.; Rudra Das, A.P.; Mereyala, H.B. *Synthesis* ***2006***, 2392.

[1789] For a review see Grasa, G.A.; Singh, R.; Nolan, S.P. *Synthesis* ***2004***, 971.

transesterification include various Lewis acids.[1790] Zwitterionic salts have been used as organocatalysts for this reaction.[1791] A polymer-bound siloxane has been used to induce transesterification.[1792] Vinyl acetate has been used for transesterification, usually with a coreagent or metal mediator.[1793] This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH.[1794] Regioselectivity has also been accomplished by using enzymes (lipases) as catalysts.[1795] Lactones, (e.g., **107**) are easily opened by treatment with alcohols[1796] to give open-chain hydroxy esters.



107

Transesterification has been carried out with phase-transfer catalysts, without an added solvent.[1797] Nonionic superbases (see Sec. 8.A.i) of the type $P(RNCH_2CH_2)_3N$ catalyze the transesterification of carboxylic acid esters at 25 °C.[1798] Silyl esters ($R'CO_2SiR_3$) have been converted to alkyl esters ($R'CO_2R$) via reaction with alkyl halides and tetrabutylammonium fluoride.[1799] Thioesters are converted to phenolic esters by treatment with triphosgene–pyridine and then phenol.[1800]

Transesterification occurs by mechanisms[1801] that are identical with those of ester hydrolysis, except that ROH replaces HOH (by the acyl–oxygen fission mechanisms). When alkyl fission takes place, the products are the *acid* and the *ether*:



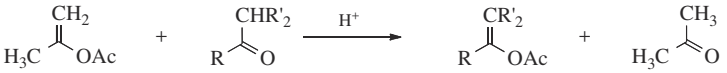
Therefore, transesterification reactions frequently fail when R′ is tertiary, since this type of substrate most often reacts by alkyl–oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see Reaction **10-10**).



108

[1790] Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2001***, 1338; Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synth. Commun.* ***2001****, 31,* 2063; Štefane, B.; Kočevar, M.; Polanc, S. *Synth. Commun.* ***2002****, 32*, 1703.
[1791] Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* ***2008****, 10,* 2187.
[1792] Hagiwara, H.; Koseki, A.; Isobe, K.; Shimizu, K.-i.; Hoshi, T.; Suzuki, T. *Synlett* ***2004***, 2188.
[1793] See Shirae, Y.; Mino, T.; Hasegawa, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* ***2005****, 46,* 5877.
[1794] Yamada, S. *Tetrahedron Lett.* ***1992***, *33*, 2171. See also, Costa, A.; Riego, J.M. *Can. J. Chem.* ***1987***, *65*, 2327.
[1795] Wong, C.H.; Whitesides, G. M. in Baldwin, J.E. *Enzymes in Synthetic Organic Chemistry, Tetrahedron Organic Chemistry Series* Vol. 12, Pergamon Press, NY, ***1994***; Faber, K. *Biotransformations in Organic Chemistry. A Textbook*, 2nd ed, Springer–Verlag, NY, ***1995***; Córdova, A.; Janda, K.D. *J. Org. Chem.* ***2001***, *66*, 1906; Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett*. ***2003***, *44*, 3663.
[1796] Anand, R.C.; Sevlapalam, N. *Synth. Commun.* ***1994***, *24*, 2743.
[1797] Barry, J.; Bram, G.; Petit, A. *Tetrahedron Lett.* ***1988***, *29*, 4567. See also, Nishiguchi, T.; Taya, H. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 172.
[1798] Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999****, 64*, 3086.
[1799] Ooi, T.; Sugimoto, H.; Maruoka, K. *Heterocycles* ***2001****, 54,* 593.
[1800] Joshi, U.M.; Patkar, L.N.; Rajappa, S. *Synth. Commun.* ***2004****, 34*, 33.
[1801] See Koskikallio, E.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 103–136.

With enol esters (e.g., **108**), reaction with an alcohol gives an ester and the enol of a ketone, which readily tautomerizes to the ketone as shown. Hence, enol esters are good acylating agents for alcohols.[1802] This transformation has been accomplished in ionic liquid media,[1803] and there is a $PdCl_2/CuCl_2$ mediated version.[1804] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:[1805]



Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate[1806] or Pd(II) chloride,[1807] for example,

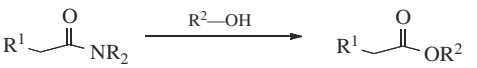
$$\mathrm{RCOOH + R'COOCH{=}CH_2 \underset{H_2SO_4}{\overset{Hg(OAc)_2}{\rightleftharpoons}} RCOOCH{=}CH_2 + R'COOH}$$

A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters: The reaction of a carboxylic acid with ethyl acetate, in the presence of $NaHSO_4{\cdot}SiO_2$, was shown to give the corresponding ethyl ester.[1808] Iodine catalyzes the transesterification of β-keto esters.[1809]

OS **II**, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630, 977; **V**, 155, 545, 863; **VI**, 278; **VII**, 4, 164, 411; **VIII**, 155, 201, 235, 263, 350, 444, 528. See also, OS **VII**, 87; **VIII**, 71.

16-65 Alcoholysis of Amides

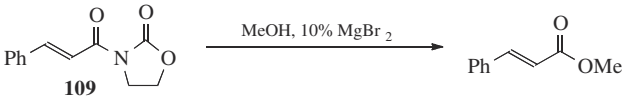
Alkoxy-de-amidation



Alcoholysis of amides is possible,[1810] although it is usually difficult. It has been most common with the imidazolide type of amides (e.g., **100**). For other amides, an activating agent is usually necessary before the alcohol will replace the NR_2 unit. *N*, *N*-Dimethylformamide, however, reacted with primary alcohols in the presence of 2,4,6-trichloro-1,3,5-pyrazine (cyanuric acid) to give the corresponding formate ester.[1811] Treatment of an amide with triflic anhydride ($CF_3SO_2OSO_2CF_3$) in the presence of pyridine, and then with an excess of alcohol, leads to the ester,[1812] as does treatment with $Me_2NCH(OMe)_2$ followed by

[1802] Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999****, 64*, 9063.
[1803] Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* ***2002****, 4*, 3583.
[1804] Bosco, J.W.J.; Saikia, A.K. *Chem. Commun.* ***2004***, 1116.
[1805] See House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 2502.
[1806] See Mondal, M.A.S.; van der Meer, R.; German, A.L.; Heikens, D. *Tetrahedron* ***1974***, *30*, 4205.
[1807] Henry, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 3853; *Acc. Chem. Res.* ***1973***, *6*, 16.
[1808] Das, B.; Venkataiah, B. *Synthesis* ***2000***, 1671.
[1809] Chavan, S.P.; Kale, R.R.; Shivasankar, K.; Chandake, S.I.; Benjamin, S.B. *Synthesis* ***2003***, 2695.
[1810] For example, see Czarnik, A.W. *Tetrahedron Lett.* ***1984***, *25*, 4875. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 197–1978.
[1811] DeLuca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* ***2002****, 67,* 5152.
[1812] Charette, A.B.; Chua, P. *Synlett* ***1998***, 163.

the alcohol.[1813] Trimethyloxonium tetrafluoroborate converted primary amides to methyl esters.[1814] The reaction of acetanilide derivatives with sodium nitrite in the presence of acetic anhydride–acetic acid leads to phenolic acetates.[1815] Acyl hydrazides ($RCONHNH_2$) were converted to esters by reaction with alcohols and various reagents,[1816] and methoxyamides (RCONHOMe) were converted to esters with $TiCl_4$/ROH.[1817] The reaction of an oxazolidinone amide (**109**) with methanol and 10% $MgBr_2$ gave the corresponding methyl ester.[1818]



109

C. Attack by OCOR at an Acyl Carbon

16-66 Acylation of Carboxylic Acids with Acyl Halides

Acyloxy-de-halogenation

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical, as well as symmetrical, anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. If a metallic salt is used, Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid. The resulting salt is subsequently treated with the acyl halide. Zinc–DMF has been used to mediate the synthesis of symmetrical anhydrides from acid chlorides.[1819] Cobalt(II) chloride ($CoCl_2$) has been used as a catalyst.[1820] Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.[1821] Symmetrical anhydrides can be prepared by reaction of the acyl halide with aq NaOH or $NaHCO_3$ under phase-transfer conditions,[1822] or with sodium bicarbonate with ultrasound.[1823]

OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **VIII**, 132. See also, OS **VI**, 418.

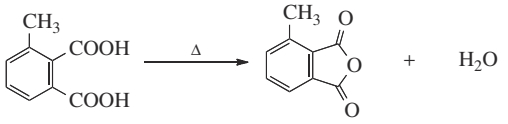
16-67 Acylation of Carboxylic Acids with Carboxylic Acids

Acyloxy-de-hydroxylation

$$2RCOOH \overset{P_2O_5}{\rightleftharpoons} (RCO)_2O + H_2O$$

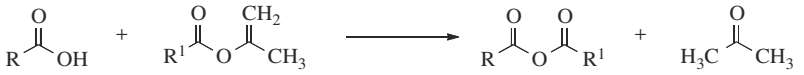
[1813] Anelli, P.L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* ***1997***, *38*, 2367.
[1814] Kiessling, A.J.; McClure, C.K. *Synth. Commun.* ***1997***, *27*, 923.
[1815] Glatzhofer, D.T.; Roy, R.R.; Cossey, K.N. *Org. Lett.* ***2002***, *4*, 2349. See Naik, R.; Pasha, M.A. *Synth. Commun.* ***2005***, *35,* 2823.
[1816] See Yamaguchi, J.-i.; Aoyagi, T.; Fujikura, R.; Suyama, T. *Chem. Lett.* ***2001***, 466.
[1817] Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* ***1994***, *72*, 142.
[1818] Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* ***2001***, 637.
[1819] Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A. *Tetrahedron Lett.* ***2008***, *49,* 5322.
[1820] Srivastava, R.R.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 593.
[1821] Fife, W.K.; Zhang, Z. *J. Org. Chem.* ***1986***, *51*, 3744. For a review of acetic formic anhydride see Strazzolini, P.; Giumanini, A.G.; Cauci, S. *Tetrahedron* ***1990***, *46* 1081.
[1822] Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* ***1988***, *44*, 2471; Wang, J.; Hu, Y.; Cui, W. *J. Chem. Res. (S)* ***1990***, 84.
[1823] Hu, Y.; Wang, J.-X.; Li, S. *Synth. Commun.* ***1997***, *27*, 243.

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents[1824] are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[1825] and P_2O_5. Triphenylphosphine/CCl_3CN with triethylamine has also been used with benzoic acid derivatives.[1826] The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, for example:



Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated, but undergo decarboxylation (**12-40**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted. Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.



The combination of KF with 2-acetoxypropene under microwave conditions was effective.[1827] Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts (e.g., by treatment of trimethylammonium carboxylates with phosgene):[1828]



or of thallium(I) carboxylates with thionyl chloride,[1710] or of sodium carboxylates with CCl_4 and a catalyst (e.g., CuCl or $FeCl_2$).[1829]

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822; **IX**, 151. Also see, OS **VI**, 757; **VII**, 506.

[1824] For lists of other dehydrating agents with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1930–1932; Ogliaruso, M.A.; Wolfe, J.F. in Patai, S. *The Chemistry of Acid Derivatives,* pt.1, Wiley, NY, ***1979***, pp. 437–438.

[1825] See Rammler, D.H.; Khorana, H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1997. See also, Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2746.

[1826] Kim, J.; Jang, D.O. *Synth. Commun.* ***2001***, *31*, 395.

[1827] Villemin, D.; Labiad, B.; Loupy, A. *Synth. Commun.* ***1993***, *23*, 419.

[1828] Rinderknecht, H.; Ma, V. *Helv. Chim. Acta* ***1964***, *47*, 152. See also, Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* ***1984***, 100.

[1829] Weiss, J.; Havelka, F.; Nefedov, B.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1978***, *27*, 193.

16-68 Preparation of Mixed Organic–Inorganic Anhydrides

Nitrooxy-de-acyloxy-substitution

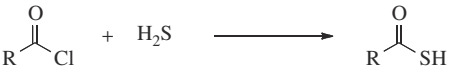
$$(RCO)_2O + HONO_2 \longrightarrow RCOONO_2$$

Mixed organic–inorganic anhydrides are seldom isolated, although they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, $RCOOPO(OH)_2$ can be prepared in the form of its salts.[1830] Mixed anhydrides of carboxylic and sulfonic acids ($RCOOSO_2R'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.[1831]

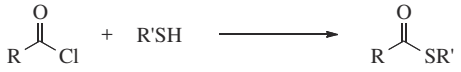
OS **I**, 495; **VI**, 207; **VII**, 81.

16-69 Attack by SH or SR at an Acyl Carbon[1832]

Mercapto-de-halogenation



Alkylthio-de-halogenation



Thiol acids and thiol esters[1833] can be prepared in this manner, which is analogous to Reaction **16-57** and **16-64**. Anhydrides[1834] and aryl esters ($RCOOAr$)[1835] are also used as substrates, but the reagents in these cases are usually HS^- and RS^-. Thiol esters can also be prepared by treatment of carboxylic acids with P_4S_{10}—Ph_3SbO,[1836] or with a thiol (RSH) and either polyphosphate ester or phenyl dichlorophosphate ($PhOPOCl_2$).[1837] Carboxylic acids are converted to thioacids with *Lawesson's reagent* (structure **18** in Reaction 16-**11**).[1838] Esters $RCOOR'$ can be converted to thiol esters ($RCOSR^2$) by treatment with trimethylsilyl sulfides (Me_3SiSR^2) and $AlCl_3$.[1839]

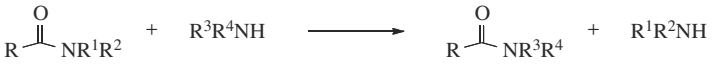
Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters ($R'COSR$)[1840]

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **VIII**, 71.

[1830] Avison, A.W.D. *J. Chem. Soc.* ***1955***, 732.
[1831] Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 528.
[1832] See Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, pp. 182–184.
[1833] See Scheithauer, S.; Mayer, R. *Top. Sulfur Chem.* ***1979***, *4*, 1.
[1834] Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* ***1986***, *27*, 3791.
[1835] Hirabayashi, Y.; Mizuta, M.; Mazume, T. *Bull. Chem. Soc. Jpn.* ***1965***, *38*, 320.
[1836] Nomura, R.; Miyazaki, S.; Nakano, T.; Matsuda, H. *Chem. Ber.* ***1990***, *123*, 2081.
[1837] Imamoto, T.; Kodera, M.; Yokoyama, M. *Synthesis* ***1982***, 134. See also, Dellaria, Jr., F.F.; Nordeen, C.; Swett, L.R. *Synth. Commun.* ***1986***, *16*, 1043.
[1838] Rao, Y.; Li, X.; Nagorny, P.; Hayashida, J.; Danishefsky, S.J. *Tetrahedron Lett.* ***2009***, *50*, 6684.
[1839] Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* ***1974***, 187. See also, Hatch, R.P.; Weinreb, S.M. *J. Org. Chem.* ***1977***, *42*, 3960; Cohen, T.; Gapinski, R.E. *Tetrahedron Lett.* ***1978***, 4319.
[1840] Gauthier, J.Y.; Bourdon, F.; Young, R.N. *Tetrahedron Lett.* ***1986***, *27*, 15.

16-70 Transamidation

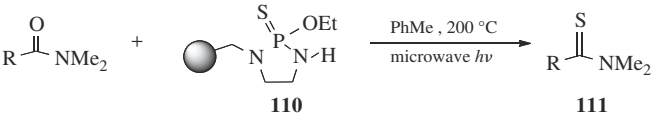
Alkylamino-de-amidation



It is sometimes necessary to replace one amide group with another, particularly when the group attached to nitrogen functions as a protecting group[1841] *N*-Benzyl amides can be converted to the corresponding *N*-allyl amide with allylamine and Ti catalysts.[1842] Reaction of *N*-Boc 2-phenylethylamine with Ti(O*i*Pr)$_4$ and benzyl alcohol, for example, gives the *N*-Cbz derivative.[1843] *N*-Carbamoyl amines were converted to *N*-acetyl amines with acetic anhydride, Bu_3SnH, and a Pd catalyst[1844] Triethylaluminum converts methyl carbamates ($ArNHCO_2Me$) to the corresponding propanamide.[1845]

A related process reacts acetamide with amines and aluminum chloride to give the *N*-acetyl amine.[1846] Another related process converted imides to *O*-benzyloxy amides by the Sm catalyzed reaction with *O*-benzylhydroxylamine.[1847]

Thioamides can be prepared from amide by reaction with an appropriate sulfur reagent. The reaction of *N,N*-dimethylacetamide under microwave irradiation, with the polymer-bound reagent **110** (where ● = polymeric backbone) gave **111**.[1848] Reaction of the thioamide with $Bi(NO_3)_3 \cdot 5H_2O$ regenerates the amide.[1849] Other methods are known to convert a thioamide to an amide.[1850] Selenoamides [$RC(=Se)NR'_2$] have also been prepared from amides.[1851]

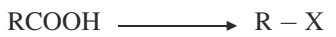


110 **111**

D. Attack by Halogen

16-71 The Conversion of Carboxylic Acids to Halides

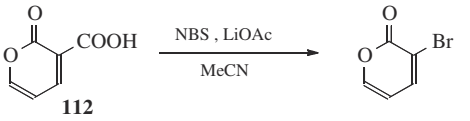
Halo-de-oxido,oxo-tersubstitution



In certain cases, carboxyl groups can be replaced by halide. Acrylic acid derivatives ($ArCH{=}CHCOOH$), for example, react with 3 molar equivalents of Oxone in the presence of NaBr to give a vinyl bromide ($ArCH{=}CHBr$).[1852] Diphosphorus tetraiodide/tetraethylammonium bromide (TEAB) readily converts conjugated acids to vinyl

[1841] See Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.
[1842] Eldred, S.E.; Stone, D.A.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2003****, 125,* 3422.
[1843] Shapiro, G.; Marzi, M. *J. Org. Chem.* ***1997***, *62*, 7096.
[1844] Roos, E.C.; Bernabé, P.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Boesten, W.H.J. *J. Org. Chem.* ***1995***, *60*, 1733.
[1845] El Kaim, L.; Grimaud, L.; Lee, A.; Perroux, Y.; Tiria, C. *Org. Lett.* ***2004****, 6,* 381.
[1846] Bon, E.; Bigg, D.C.H.; Bertrand, G. *J. Org. Chem.* ***1994***, *59*, 4035.
[1847] Sibi, M.P.; Hasegawa, H.; Ghorpade, S.R. *Org. Lett.* ***2002****, 4,* 3343.
[1848] Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 358.
[1849] Mohammadpoor-Baltork, I.; Khodaei, M.M.; Nikoofar, K. *Tetrahedron Lett.* ***2003****, 44*, 591.
[1850] Inamoto, K.; Shiraishi, M.; Hiroya, K.; Doi, T. *Synthesis* ***2010***, 3087.
[1851] Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***2004****, 45*, 681.
[1852] You, H.-W.; Lee, K.-J. *Synlett* ***2001***, 105.

bromides.[1853] In other cases, conjugated acids, (e.g., **112**), have been converted to the bromide by reaction with (NBS, Reaction **14-3**) and LiOAc.[1854]



112

E. Attack by Nitrogen at an Acyl Carbon[1855]

16-72 Acylation of Amines by Acyl Halides

Amino-de-halogenation

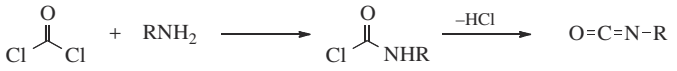
$$RCOX + NH_3 \longrightarrow RCONH_2 + HX$$

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[1856] The reaction is exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give *N*-substituted amides,[1857] and secondary amines give *N,N*-disubstituted amides. Arylamines can be similarly acylated. Hydroxamic acids have been prepared by this route.[1858] In some cases, aq alkali is added to combine with the liberated HCl. This is called the *Schotten–Baumann procedure*, as in Reaction **16-61**. Activated Zn can be used to increase the rate of amide formation when hindered amines and/or acid chlorides are used.[1859] A solvent-free reaction was reported using DABCO and methanol.[1860] Metal-mediated reactions using In,[1861] Sm,[1862] or a BiOCl mediated reaction[1863] have been reported. A variation of this basic reaction uses DMF with acyl halides to give *N,N*-dimethylamides.[1864] Formic acid and iodine react with amines to give the formamide.[1865]

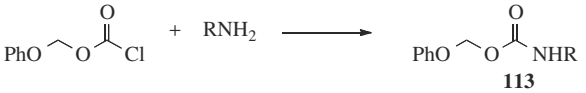
Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides ($RCONHNH_2$)[1866] and hydroxamic acids (RCONHOH).[1867] When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides

[1853] Telvekar, V.N.; Chettiar, S.N. *Tetrahedron Lett.* ***2007****, 48,* 4529.
[1854] Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* ***2001****, 42*, 1065.
[1855] See Challis, M.S.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 279–290.
[1856] See Beckwith, A.L.J. in Zabicky, J.*The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 73–185; Jedrzejczak, M.; Motie, R.E.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 599.
[1857] See Bhattacharyya, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003****, 44*, 6099.
[1858] Reddy, A.S.; Kumar, M.S.; Reddy, G.R. *Tetrahedron Lett.* ***2000****, 41*, 6285.
[1859] Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 4103.
[1860] Hajipour, A.R.; Mazloumi, Gh. *Synth. Commun.* ***2002****, 32,* 23.
[1861] Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004****, 45*, 2285.
[1862] Shi, F.; Li, J.; Li, C.; Jia, X. *Tetrahedron Lett.* ***2010****, 51*, 6049.
[1863] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004****, 45*, 6775.
[1864] Lee, W.S.; Park, K.H.; Yoon, Y.-J. *Synth. Commun.* ***2000****, 30,* 4241.
[1865] Kim, J.-G.; Jang, D.O. *Synlett* ***2010***, 2093. For other formylation reactions, see Shekhar, A.C.; Kumar, A.R.; Sathaiah, G.; Paul, V.L.; Sridhar, M.; Rao, P.S. *Tetrahedron Lett.* ***2009****, 50*, 7099; Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* ***2010****, 51*, 2319; Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* ***2010****, 51*, 2896; Deutsch, J.; Eckelt, R.; Köckritz, A.; Martin, A. *Tetrahedron* ***2009****, 65*, 10365.
[1866] See Paulsen, H.; Stoye, D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 515–600.
[1867] For an improved method, see Ando, W.; Tsumaki, H. *Synth. Commun.* ***1983***, *13*, 1053.

(ClCONHR) that lose HCl to give isocyanates (RNCO).[1868] This is one of the most common methods for the preparation of isocyanates.[1869] Similar



treatment with thiophosgene[1870] gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate (CCl_3OCOCl).[1871] When chloroformates (ROCOCl) are treated with primary amines, carbamates (ROCONHR′) are obtained.[1872] An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides.



113

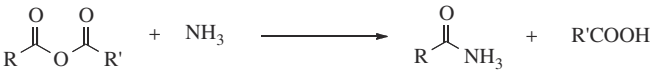
The $PhCH_2OCO$ group in **113** has been called the carbobenzoxy group,[1873] and is often abbreviated Cbz or Z, but it is really a benzyl carbamate. Another important group similarly used is Boc, which is a *tert*-butyl carbamate. In this case, the chloride ($Me_3COCOCl$) is unstable, so the anhydride [$(Me_3COCO)_2O$] is used instead, in an example of Reaction **16-73**. Amino groups in general are often protected by conversion to amides.[1874] The reactions proceed by the tetrahedral mechanism.[1875]

An interesting variation of this transformation reacts carbamoyl chlorides with organocuprates to give the corresponding amide.[1876]

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **VIII**, 16, 339; **IX**, 559; **81**, 254. See also, OS **VII**, 302.

16-73 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution



[1868] Richter, R.; Ulrich, H. pp. 619–818, and Drobnica, L.; Kristián, P.; Augustín, J. pp. 1003–1221, in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, ***1977***.

[1869] See Ozaki, S. *Chem. Rev.* ***1972***, *72*, 457, see pp. 457–460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, H.J. *Chem. Soc. Rev.* ***1974***, *3*, 209.

[1870] For a review of thiophosgene, see Sharma, S. *Sulfur Rep.* ***1986***, *5*, 1.

[1871] Kurita, K.; Iwakura, Y. *Org. Synth.* ***VI***, 715.

[1872] Heydari, A.; Shiroodi, R.K.; Hamadi, H.; Esfandyari, M.; Pourayoubi, M. *Tetrahedron Lett.* ***2007***, *48,* 5865; Upadhyaya, D.J.; Barge, A.; Stefania, R.; Cravotto, G. *Tetrahedron Lett.* ***2007***, *48,* 8318; Shrikhande, J.J.; Gawande, M.B.; Jayaram, R.V. *Tetrahedron Lett.* ***2008***, *49,* 4799. See Vilaivan, T. *Tetrahedron Lett.* ***2006***, *47,* 6739.

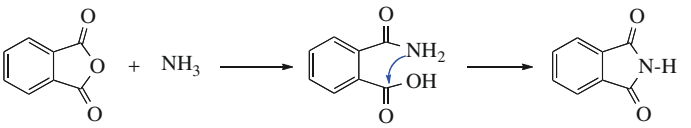
[1873] See Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2233.

[1874] Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, NY, ***1980***, pp 222–248, 324–326; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis,* 2nd ed., Wiley, NY, ***1991***, pp 327–330; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, NY, ***1999***, pp 518–525; 737–739.

[1875] Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***; Bender, M.L.; Jones, M.J. *J. Org. Chem.* ***1962***, *27*, 3771. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8479.

[1876] Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* ***2004***, *6,* 3703.

This reaction, similar in scope and mechanism[1877] to Reaction **16-72**, can be carried out with ammonia or primary or secondary amines.[1878] Note that there is a report where a tertiary amine (an *N*-alkylpyrrolidine) reacted with acetic anhydride at 120 °C, in the presence of a BF_3•etherate catalyst, to give *N*-acetylpyrrolidine (an acylative dealkylation).[1879] Amino acids can be N-acylated using acetic anhydride and ultrasound.[1880] However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. The conversion of cyclic anhydrides to cyclic imides is generally facile,[1881] although elevated temperatures are occasionally required to generate the imide.[1882] Microwave irradiation of formamide and a cyclic anhydride generates the cyclic imide.[1883] Cyclic imides have also been formed in ionic liquids.[1884] Cyclic imides were also formed by microwave irradiation of a polymer-bound phthalate after initial reaction with an amine.[1885]



The second step for imide formation, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and *N*-substituted amides have been used instead of ammonia. Since the other product of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.[1886]

Even though formic anhydride is not a stable compound (see Reaction **11-17**), amines can be formylated with the mixed anhydride of acetic and formic acids (HCOOCOMe)[1887] or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.[1888] The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated. Dimethyl carbonate can be used to prepare methyl carbamates in a related procedure.[1889] *N*-Acetylsulfonamides were prepared from acetic anhydride and a primary sulfonamide, catalyzed by Montmorillonite K10–FeO[1890] or sulfuric acid.[1891]

[1877] For a discussion of the mechanism, see Kluger, R.; Hunt, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 3325.
[1878] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 86–96. See also, Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B.K. *Eur. J. Org. Chem.* ***2004***, 1254.
[1879] Dave, P.R.; Kumar, K.A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K.K.; Guan, X.-P.; Sun, J.; Trivedi, N.J.; Gilardi, R.D. *J. Org. Chem.* ***2000***, *65*, 1207.
[1880] Anuradha, M.V.; Ravindranath, B. *Tetrahedron* ***1997***, *53*, 1123.
[1881] See Wheeler, O.H.; Rosado, O. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 335–381; Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* ***1970***, *70*, 439 (cyclic imides).
[1882] Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* ***1994***, 63.
[1883] Kacprzak, K. *Synth. Commun.* ***2003***, *33*, 1499.
[1884] Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 995.
[1885] Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* ***2003***, *5*, 1851.
[1886] Eaton, J.T.; Rounds, W.D.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6553.
[1887] Vlietstra, E.J.; Zwikker, J.W.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 460.
[1888] Barrett, A.G.M.; Lana, J.C.A. *J. Chem. Soc., Chem. Commun.* ***1978***, 471.
[1889] Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* ***2000***, *41*, 6347.
[1890] Singh, D.U.; Singh, P.R.; Samant, S.D. *Tetahedron Lett.* ***2004***, *45*, 4805.
[1891] Martin, M.T.; Roschangar, F.; Eaddy, J.F. *Tetrahedron Lett.* ***2003***, *44*, 5461.

There are acylating reagents other than anhydrides of course. The reaction with acyl halides is discussed in Reaction **16-72**. There are a few specialized reagents. Kinetic resolution of racemic amines was accomplished using (1*S*,2*S*)-*N*-acetyl-1,2- bis(trifluoromethanesulfonamido)cyclohexane.[1892]

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **VIII**, 132; **76**, 123.

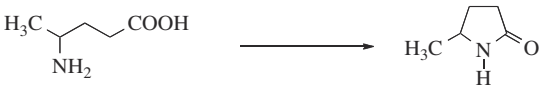
16-74 Acylation of Amines by Carboxylic Acids

Amino-de-hydroxylation

$$RCOOH + NH_3 \longrightarrow RCOO^-NH_4^+ \xrightarrow{\text{pyrolysis}} RCONH_2$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,[1893] but the method is less convenient than Reaction **16-72**, **16-73**, and **16-75** and is seldom of preparative value.[1894] Heating in the presence of a base (e.g., hexamethyldisilazide) makes the amide-forming process more efficient.[1895] Boronic acids catalyze the direct conversion of carboxylic acid and amine to amides.[1896] Polymer-bound reagents have also been used.[1897] Triphenylphosphine/-trichloroisocyanuric acid converts acids and amides to the amide.[1898] The *Burgess reagent* ($Et_3N^+{}^-SO_2N{-}CO_2Me$; see Reaction **17-29**) activates carboxylic acids for amide formation.[1899] The reaction of a carboxylic acid and imidazole under microwave irradiation gives the amide.[1900] Microwave irradiation of a secondary amine, formic acid, 2-chloro-4,6-dimethoxy [1,3,5]triazine, and a catalytic amount of DMAP leads to the formamide.[1901] Ammonium bicarbonate and formamide converts acids to amides with microwave irradiation.[1902] Formamides are produced from formic acid and anion nitriles in the presence of ZnO.[1903]

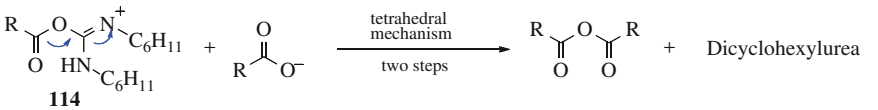
Lactams are readily produced from γ- or δ-amino acids,[1904] for example,



[1892] Arseniyadis, S.; Subhash, P.V.; Valleix, A.; Mathew, S.P.; Blackmond, D.G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* ***2005****, 127,* 6138.
[1893] See Gooßen, L.J.; Ohlmann, D.M.; Lange, P.P. *Synthesis* ***2009***, 160.
[1894] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 105–109.
[1895] Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett.* ***1999****, 40*, 3419. Also see White, J.M.; Tunoori, A.R.; Turunen, B.J.; Georg, G.I *J. Org. Chem.* ***2004****, 69*, 2573.
[1896] Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* ***2001***, 1371.
[1897] Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* ***2004****, 6*, 4579; Chichilla, R.; Dodsworth, D.J.; Nájera, C.; Soriano, J.M. *Tetrahedron Lett.* ***2003****, 44,* 463.
[1898] da C. Rodrigues, R.; Barros, I.M.A.; Lima, E.L.S. *Tetrahedron Lett.* ***2005****, 46*, 5945.
[1899] Wodka, D.; Robbins, M.; Lan, P.; Martinez, R.L.; Athanasopoulos, J.; Makara, G.M. *Tetrahedron Lett.* ***2006****, 47,* 1825.
[1900] Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. *Tetrahedron Lett.* ***2003****, 44,* 7325; Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* ***2002****, 58*, 2155. See also, Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Guha, A.; Pombo-Villars, E. *Tetrahedron Lett.* ***2006****, 47,* 4605.
[1901] De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* ***2004***, 2570.
[1902] Peng, Y.; Song, G. *Org. Prep. Proceed. Int.* ***2002****, 34*, 95.
[1903] Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* ***2006****, 71*, 6652.
[1904] See Bladé-Font, A. *Tetrahedron Lett.* ***1980***, *21*, 2443. Also see Wei, Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* ***1993***, *34*, 4439 for a variation of this reaction.

This lactonization process can be promoted by enzymes (e.g., pancreatic porcine lipase).[1905] Reduction of ω-azide carboxylic acids leads to macrocyclic lactams.[1906]

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,[1907] the most important of which is dicyclohexylcarbodiimide. This reagent is very convenient and is used[1908] a great deal in peptide synthesis.[1909] A polymer-supported carbodiimide has been used.[1910] The mechanism is probably the same as in Reaction **16-63** up to the formation of **114**. This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species that reacts with the amine:



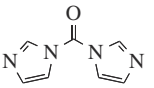
114

The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[1911]

The synthetically important *Weinreb amides* [RCON(Me)OMe, see Reaction **16-82**] can be prepared from the carboxylic acid and MeO(Me)NH•HCl in the presence of tributylphosphine and 2-pyridine-*N*-oxide disulfide.[1912] Di(2-pyridyl)carbonate has been used in a related reaction that generates amides directly.[1913] Other promoting agents[1914] are $ArB(OH)_2$ reagents,[1915] *N,N'*-carbonyldiimidazole (**115**, in Reaction **16-63**),[1916] $POCl_3$,[1917] $TiCl_4$,[1918] molecular sieves,[1919] *Lawesson's reagent* (Reaction **16-11**),[1920] and $(MeO)_2POCl$.[1921] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases, the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[1922] Carboxylic acids can also be

[1905] Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* ***1992***, *33*, 3943.
[1906] Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1993***, *34*, 4671. See Bai, D.; Shi, Y. *Tetrahedron Lett.* ***1992***, *33*, 943 for the preparation of lactam units in *p*-cyclophanes.
[1907] See Klausner, Y.S.; Bodansky, M. *Synthesis* ***1972***, 453.
[1908] It was first used this way by Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* ***1955***, *77*, 1067.
[1909] See Gross, E.; Meienhofer, J. *The Peptides*, 3 Vols., Academic Press, NY, ***1979–1981***. See Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, Springer, NY, ***1984***.
[1910] Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 6667.
[1911] See Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1974***, *96*, 1606. Also see Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1973***, *95*, 4052.
[1912] Banwell, M.; Smith, J. *Synth. Commun.* ***2001***, *31*, 2011. For another procedure, see Kim, M.; Lee, H.; Han, K.-J.; Kay, K.-Y. *Synth. Commun.* ***2003***, *33*, 4013.
[1913] Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2811.
[1914] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1941–1949.
[1915] Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* ***1996***, *61*, 4196.
[1916] See Vaidyanathan, R.; Kalthod, V.G.; Ngo, D.; Manley, J.M.; Lapekas, S.P. *J. Org. Chem.* ***2004***, *69*, 2565. Also see Grzyb, J.A.; Batey, R.A. *Tetrahedron Lett.* ***2003***, *44*, 7485.
[1917] Klosa, J. *J. Prakt. Chem.* ***1963***, *[4] 19*, 45.
[1918] Wilson, J.D.; Weingarten, H. *Can. J. Chem.* ***1970***, *48*, 983.
[1919] Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* ***1989***, *30*, 2771.
[1920] Thorsen, M.; Andersen, T.P.; Pedersen, U.; Yde, B.; Lawesson, S. *Tetrahedron* ***1985***, *41*, 5633.
[1921] Jászay, Z.M.; Petneházy, I.; Töke, L. *Synth. Commun.* ***1998***, *28*, 2761.
[1922] Higuchi, T.; Miki, T.; Shah, A.C.; Herd, A.K. *J. Am. Chem. Soc.* ***1963***, *85*, 3655.

converted to amides by heating with amides of carboxylic acids (exchange),[1923] sulfonic acids, or phosphoric acids, for example,[1924]



115

$$RCOOH + Ph_2PONH_2 \longrightarrow RCONH_2 + Ph_2POOH$$

or by treatment with trisalkylaminoboranes [$B(NHR')_3$], with trisdialkylaminoboranes [$B(NR_2')_3$],[1925]

$$RCOOH + B(NR_2')_3 \longrightarrow RCONR_2'$$

or with bis(diorganoamino)magnesium reagents [$(R_2N)_2Mg$].[1926] The reaction of thiocarboxylic acids and azides, in the presence of triphenylphosphine, gives the corresponding amide.[1927]

An important technique, discovered by R.B. Merrifield[1928] and since used for the synthesis of many peptides,[1929] is called *solid-phase synthesis* or *polymer-supported synthesis*.[1930] The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains. One of the amino acids, protected by (Boc), would then be coupled to the side chains. It is not necessary that all the side chains be converted, but a random selection will be converted. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 and the second amino acid is coupled to the first, using DCC or some other coupling agent. The second Boc group is removed, resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the

[1923] For example, see Schindbauer, H. *Monatsh. Chem.* ***1968***, *99*, 1799.

[1924] Zhmurova, I.N.; Voitsekhovskaya, I.Yu.; Kirsanov, A.V. *J. Gen. Chem. USSR* ***1959***, *29*, 2052. See also, Liu, H.; Chan, W.H.; Lee, S.P. *Synth. Commun.* ***1979***, *9*, 31.

[1925] Pelter, A.; Levitt, T.E.; Nelson, P. *Tetrahedron* ***1970***, *26*, 1539; Pelter, A.; Levitt, T.E. *Tetrahedron* ***1970***, *26*, 1545, 1899.

[1926] Sanchez, R.; Vest, G.; Despres, L. *Synth. Commun.* ***1989***, *19*, 2909.

[1927] Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* ***2002***, *43*, 6309.

[1928] Merrifield, R.B. *J. Am. Chem. Soc.* ***1963***, *85*, 2149.

[1929] Birr, C. *Aspects of the Merrifield Peptide Synthesis*, Springer, NY, ***1978***. For reviews, see Bayer, E. *Angew. Chem. Int. Ed.* ***1991***, *30*, 113; Kaiser, E.T. *Acc. Chem. Res.* ***1989***, *22*, 47; Jacquier, R. *Bull. Soc. Chim. Fr.* ***1989***, 220; Barany, G.; Kneib-Cordonier, N.; Mullen, D.G. *Int. J. Pept. Protein Res.* ***1987***, *30*, 705; Andreev, S.M.; Samoilova, N.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1987***, *56*, 366; Gross, E.; Meienhofer, J. *The Peptides,* Vol. 2, Academic Press, NY, ***1980***, the articles by Barany, G.; Merrifield, R.B. pp. 1–184; Fridkin, M. pp. 333–363; Erickson, B.W.; Merrifield, R.B. in Neurath, H.; Hill, R.L.; Boeder, C.-L. *The Proteins*, 3rd ed., Vol. 2, Academic Press, NY, ***1976***, pp. 255–527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield, R.B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 799.

[1930] Laszlo, P. *Preparative Organic Chemistry Using Supported Reagents*, Academic Press, NY, ***1987***; Mathur, N.K.; Narang, C.K.; Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, NY ***1980***; Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***. For reviews, see Pillai, V.N.R.; Mutter, M. *Top. Curr. Chem.* ***1982***, *106*, 119; Akelah, A.; Sherrington, D.C. *Chem. Rev.* ***1981***, *81*, 557; Akelah, A. *Synthesis* ***1981***, 413; Rebek, J. *Tetrahedron* ***1979***, *35*, 723; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, 481; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Patchornik, A.; Kraus, M.A. *Pure Appl. Chem.* ***1975***, *43*, 503.

polymer by various methods,[1931] one of which is treatment with HF. If a longer peptide is wanted, additional amino acids can be added by repeating the requisite steps.

The basic advantage of the polymer support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (e.g., dicyclohexylurea), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species is rapid and complete. The process can even be automated,[1932] to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.[1933]

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.[1934] The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.[1935] Combinatorial chemistry in some ways can be viewed as an extension of the *Merrifield synthesis*, particularly when applied to peptide synthesis, and continues as an important part of modern organic chemistry.[1936]

OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **V**, 670, 1070; **VIII**, 241; **81**, 262. Also see, OS **III**, 360; **VI**, 263; **VIII**, 68.

16-75 Acylation of Amines by Carboxylic Esters

Amino-de-alkoxylation

$$\mathrm{RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH}$$

The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, *N*-substituted, and *N,N*-disubstituted amides can be prepared this way from the appropriate amine[1937] or ammonia.[1938] Both R and R′ can be alkyl or aryl, but *an especially good leaving group is p-nitrophenyl*. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.[1939] Many simple esters

[1931] See Whitney, D.B.; Tam, J.P.; Merrifield, R.B. *Tetrahedron* ***1984***, *40*, 4237.
[1932] Merrifield, R.B.; Stewart, J.M.; Jernberg, N. *Anal. Chem.* ***1966***, *38*, 1905.
[1933] See Schnorrenberg, G.; Gerhardt, H. *Tetrahedron* ***1989***, *45*, 7759.
[1934] For a review, see Bannwarth, W. *Chimia* ***1987***, *41*, 302.
[1935] Fréchet, J.M.J. *Tetrahedron* ***1981***, *37*, 663; Fréchet, J.M.J. in Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis,* Wiley, NY, ***1980***, pp. 293–342, Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327; *Chem. Soc. Rev.* ***1974***, *3*, 64.
[1936] Czarnik, A.W.; DeWitt, S.H. *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington, D.C., ***1997***; Chaiken, I.N.; Janda, K.D. *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, American Chemical Society, Washington, D.C; ***1996***; Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* ***1996,*** *35*, 2289; Thompson, L.A.; Ellman, J.A. *Chem. Rev.* ***1996***, 96, 555; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976,*** *9*, 135; Leznoff, C.C. *Acc. Chem. Res.* ***1978,*** *11*, 327.
[1937] Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 96–105. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1973–1976. See Sabot, C.; Kumar, K.A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* ***2007,*** *48*, 3863.
[1938] See Mizuhara, T.; Hioki, K.; Yamada, M.; Sasaki, H.; Morisaki, D.; Kunishima, M. *Chem. Lett.* ***2008,*** *37,* 1190. Magnesium nitride is a useful source of ammonia in this reaction. See Veitch, G.E.; Bridgwood, K.L.; Ley, S.V. *Org. Lett.* ***2008,*** *10,* 3623.
[1939] Xu, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***1995***, *36*, 7357.

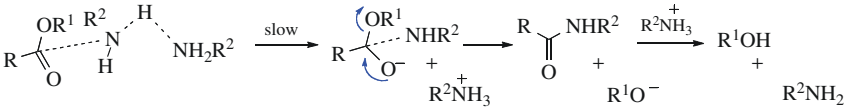
(R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used in such cases,[1940] but catalysis by cyanide ion[1941] $MgBr_2$,[1942] InI_3,[1943] and acceleration by high pressure[1944] have been reported. Methyl esters[1945] and ethyl esters[1946] have been converted to the corresponding amide under microwave irradiation. Lithium amides have been used to convert esters to amides as well.[1947] β-Keto esters undergo the reaction especially easily.[1948] Aniline was treated with *n*-butyllithium to form the lithium amide, which reacted with an ester to give the amide.[1949] An enzyme-mediated amidation is known using amino cyclase I.[1950] The reaction of dimethyl carbonate and an amine is an effective way to prepare methyl carbamates.[1951]

Lactones give lactams when treated with ammonia or primary amines. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Lactonization has been accomplished in ionic liquids.[1952]

As in Reaction **16-72**, hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine,[1953] respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, Sec. 10.G.ii). Imidates [RC(=NH)OR′] give amidines [$RC(=NH)NH_2$]. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[1954]

$$R_2NH + HCOOCMe{=}CH_2 \longrightarrow R_2NCHO + CH_2{=}CMeOH \rightleftharpoons MeCOMe$$

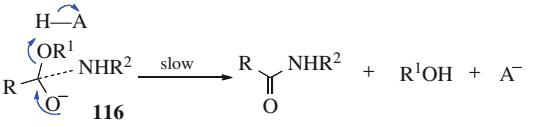
Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.[1955] In its broad outlines, the mechanism appears to be essentially $B_{AC}2$.[1956] Under normal basic conditions, the reaction is general base catalyzed,[1957] indicating that a proton is being transferred in the rate-determining step and that two molecules



116

[1940] See Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989****, 122*, 1357.
[1941] Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* ***1987***, *52*, 2033.
[1942] Guo, Z.; Dowdy, E.D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* ***2001****, 42*, 1843.
[1943] Ranu, B.C.; Dutta, P. *Synth. Commun.* ***2003****, 33*, 297.
[1944] Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.
[1945] Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1999****, 40*, 6177.
[1946] Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* ***2002****, 32*, 3525.
[1947] See Wang, J.; Rosingana, M.; Discordia, R.P.; Soundararajan, N.; Polniaszek, R. *Synlett* ***2001***, 1485.
[1948] Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* ***1985***, 105.
[1949] Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett.* ***1999***, 729.
[1950] Youshko, M.I.; van Rantwijk, F.; Sheldon, R.A. *Tetrahedron Asymmetry* ***2001****, 12*, 3267.
[1951] Distaso, M.; Quaranta, E. *Tetrahedron* ***2004****, 60*, 1531.
[1952] Orrling, K.M.; Wu, X.; Russo, F.; Larhed, M. *J. Org. Chem.* ***2008****, 73,* 8627.
[1953] Ho, C.Y.; Strobel, E.; Ralbovsky, J.; Galemmo, Jr., R.A. *J. Org. Chem.* ***2005****, 70*, 4873.
[1954] van Melick, J.E.W.; Wolters, E.T.M. *Synth. Commun.* ***1972***, *2*, 83.
[1955] Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters,* Wiley, NY, ***1969***, pp. 410–431; Ilieva, S.; Galabov, B.; Musaev, D.G.; Morokuma, K.; Schaefer, III, H.F. *J. Org. Chem.* ***2003****, 68*, 1496.
[1956] Bruice, T.C.; Donzel, A.; Huffman, R.W.; Butler, A.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2106.
[1957] Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665, Jencks, W.P.; Carriuolo, J. *J. Am. Chem. Soc.* ***1960***, *82*, 675; Bruice, T.C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1960***, *82*, 3067.

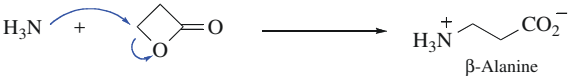
of amine are involved.[1958] Alternatively, another base (e.g., H_2O or OH^-) can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **116** can become rate determining.[1959] The reaction also takes place under acidic conditions and is general acid catalyzed, so that breakdown of **116** is rate determining and proceeds as follows:[1960]



116

Here HA may be $R^2NH_3^+$ or another acid. Intermediate **116** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[1961]

In the special case of β-lactones, where small-angle strain is an important factor, alkyl–oxygen cleavage is observed ($B_{AL}2$ mechanism, as in the similar case of hydrolysis of β-lactones, Reaction **16-59**), and the product is not an amide but a β-amino acid (β-alanine).



β-Alanine

A similar result has been found for certain sterically hindered esters.[1962] This reaction is similar to **10-31**, with OCOR as the leaving group. Other lactones have been opened to ω-hydroxy amides with Dibal-H:$BnNH_2$.[1963]

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **VIII**, 26, 204, 528. Also see, OS **I**, 5; **V**, 582; **VII**, 75.

16-76 Acylation of Amines by Amides

Alkylamino-de-amination

$$RCONH_2 + R'\overset{+}{N}H_3 \longrightarrow RCONHR' + NH_4^+$$

[1958] Bruice, T.C.; Felton, S.M. *J. Am. Chem. Soc.* ***1969***, *91*, 2799; Felton, S.M.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 6721; Nagy, O.B.; Reuliaux,V.; Bertrand, N.; Van Der Mensbrugghe, A.; Leseul, J.; Nagy, J.B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 1055.

[1959] Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 6963, 6970. See also, Um, I.-H.; Lee, J.-Y.; Lee, H.W.; Nagano, Y.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* ***2005***, *70*, 4980.

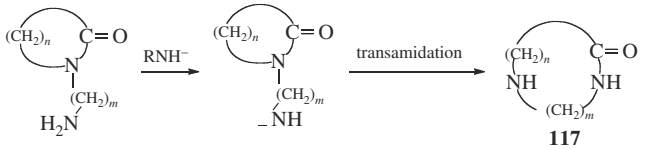
[1960] Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638.

[1961] Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665.

[1962] Zaugg, H.E.; Helgren, P.F.; Schaefer, A.D. *J. Org. Chem.* ***1963***, *28*, 2617. See also, Weintraub, L.; Terrell, R. *J. Org. Chem.* ***1965***, *30*, 2470; Harada, R.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2706.

[1963] Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* ***2001***, *42*, 9039. See also, Taylor, S.K.; Ide, N.D.; Silver, M.E.; Stephan, M. *Synth. Commun.* ***2001***, *31*, 2391.

This is an exchange reaction and is usually carried out with the salt of the amine.[1964] The leaving group is usually NH_2 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. Boron trifluoride can be added to complex with the leaving ammonia. Neutral amines also react in some cases to give the new amide.[1965] The reaction is catalyzed by Al(III).[1966] The reaction is often used to convert urea to substituted ureas: $NH_2CONH_2 + RNH_3^+ \rightarrow NH_2CONHR + NH_4^+$.[1967] An *N*-aryl group of a urea can be converted to a *N,N*-dialkyl group by heating the urea with the amine in an autoclave.[1968] *N*-alkyl substituted amides (alkyl = R) are converted to *N*-R′-substituted amides, where alkyl = R′, by treatment with N_2O_4 to give an *N*-nitroso compound, followed by treatment of this with a primary amine ($R'NH_2$).[1969] Lactams can be converted to ring-expanded lactams (e.g., **117**) if a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^-, which then acts as a nucleophile, expanding the ring by means of a transamidation.[1970] The discoverers call it the *Zip reaction*, by analogy with the action of zippers.[1971]



117

Lactams can be opened to ω-amino amides by reaction with amines at 10 kbar.[1972]

OS **I**, 302 (but see **V**, 589), 450, 453; **II**, 461; **III**, 151, 404; **IV**, 52, 361. See also, OS **VIII**, 573.

16-77 Acylation of Amines by Other Acid Derivatives

Acylamino-de-halogenation or dealkoxylation

$$RCOCl + H_2NCOR' \longrightarrow RCONHCOR'$$

Acid derivatives that can be converted to amides include thiol acids (RCOSH), thiol esters (RCOSR),[1973] acyloxyboranes [$RCOB(OR'_2)$],[1974] α-keto nitriles, acyl azides, and nonenolizable ketones (see the *Haller–Bauer Reaction* **12-34**). *N*-Acylsulfonamides react with primary amines to the amide (AcNHR).[1975] Carbonylation reactions can be used to

[1964] For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1978–1982.

[1965] Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* ***1997***, *38*, 3751.

[1966] Hoerter, J.M.; Otte, K.M.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2006****, 128,* 5177.

[1967] See Chimishkyan, A.L.; Snagovskii, Yu.S.; Gulyaev, N.D.; Leonova, T.V.; Kusakin, M.S. *J. Org. Chem. USSR* ***1985***, *21*, 1955.

[1968] Yang, Y.; Lu, S. *Org. Prep. Proceed. Int.* ***1999****, 31*, 559.

[1969] Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* ***1982***, *23*, 1127.

[1970] Askitoglu, E.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 750 and references cited therein. For a carbon analog, see Süsse, M.; Hájicek, J.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 1986.

[1971] See Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573.

[1972] Kotsuki, H.; Iwasaki, M.; Nishizawa, H. *Tetrahedron Lett.* ***1992***, *33*, 4945.

[1973] See Douglas, K.T. *Acc. Chem. Res.* ***1986***, *19*, 186.

[1974] See Collum, D.B.; Chen, S.; Ganem, B. *J. Org. Chem.* ***1978***, *43*, 4393.

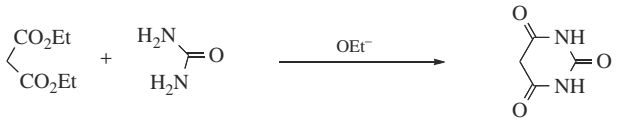
[1975] Coniglio, S.; Aramini, A.; Cesta, M.C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* ***2004****, 45*, 5375.

prepare amides and related compounds. The reaction of a primary amine, an alkyl halide with CO_2, in the presence of Cs_2CO_3/Bu_4NI, gave the corresponding carbamate.[1976]

OS **III**, 394; **IV**, 6, 569; **V**, 160, 166; **VI**, 1004.

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.[1977] A good synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100 °C catalyzed by H_2SO_4.[1978] When acyl chlorides are treated with amides in a 2: 1 molar ratio at low temperatures in the presence of pyridine, the products are *N,N*-diacylamides $[(RCO)_3N]$.[1979]

This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid (**118**).[1980]

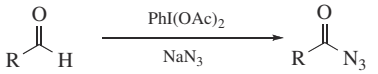


118

When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The "normal" product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl.[1981]

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

16-78 Acylation of Azides



The reaction of an aldehyde with sodium azide and $Et_4{}^+ I(OAc)_2$ or polymer-bound PhI $(OAc)_2$ leads to an acyl azide.[1982] Acyl azides are also prepared directly from aldehydes using *tert*-butyl hypochlorite.[1983]

F. Attack by Halogen at an Acyl Carbon

16-79 Formation of Acyl Halides from Carboxylic Acids

Halo-de-hydroxylation

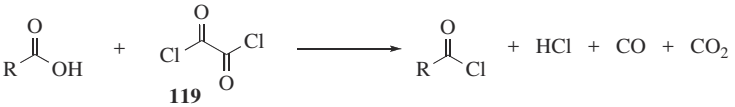
$$\text{RCOOH} + \text{halogenating } \textit{agent} \longrightarrow \text{RCOX}$$

Halogenating agent = $SOCl_2$,$SOBr_2$,PCl_3,$POCl_3$,PBr_3,and so on

[1976] Salvatore, R.N.; Shin, S.I.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2001****, 66,* 1035.
[1977] For a review, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 759–773.
[1978] Baburao, K.; Costello, A.M.; Petterson, R.C.; Sander, G.E. *J. Chem. Soc. C* ***1968***, 2779; Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* ***1958***, *80*, 376.
[1979] See LaLonde, R.T.; Davis, C.B. *J. Org. Chem.* ***1970***, *35*, 771.
[1980] See Bojarski, J.T.; Mokrosz, J.L.; Barton, H.J.; Paluchowska, M.H. *Adv. Heterocycl. Chem.* ***1985***, *38*, 229.
[1981] Speziale, A.J.; Smith, L.R.; Fedder, J.E. *J. Org. Chem.* ***1965***, *30*, 4306.
[1982] Marinescu, L.G.; Pedersen, C.M.; Bols, M. *Tetrahedron* ***2005****, 61,* 123. See Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* ***2003****, 68,* 9453; Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982****, 21*, 36.
[1983] Arote, N.D.; Akamanchi, K.G. *Tetrahedron Lett.* ***2007****, 48,* 5661.

The same inorganic acid halides that convert alcohols to alkyl halides (Reaction **10-48**) also convert carboxylic acids to acyl halides.[1984] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides[1985] are also made in this manner, but much less often. Acyl bromides can be prepared with BBr_3 on alumina,[1986] or with ethyl tribromoacetae/PPh_3.[1987] Thionyl chloride[1988] is a good reagent, since the byproducts are gases and the acyl halide is easily isolated, but PX_3 and PX_5 (X = Cl or Br) are also commonly used.[1989] Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in Reaction **10-48**, involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without obtaining any acidic compound as a byproduct.[1990]

Oxalyl chloride (**113**) and oxalyl bromide are mild and often superior reagents, since the oxalic acid byproduct decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.[1991] These reagents are commonly the reagent of choice, particularly when sensitive functionality is present elsewhere in the molecule.



119

Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[1992] *C*, *N*-Chelated di-*n*-butyltin(IV) fluoride has been used to prepare acyl fluorides.[1993] Acid salts are also sometimes used as substrates and acyl halides are used as reagents in an exchange reaction:

$$RCOOH + R'COCl \rightleftharpoons RCOCl + R'COOH$$

which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side.

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **VIII**, 441, 486, 498.

16-80 Formation of Acyl Halides from Acid Derivatives

Halo-de-acyloxy-substitution

Halo-de-halogenation

$$(RCO)_2O + HF \longrightarrow RCOF$$
$$RCOCl + HF \longrightarrow RCOF$$

[1984] See Ansell, M.F. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 35–68.
[1985] See Keinan, E.; Sahai, M. *J. Org. Chem.* ***1990***, *55*, 3922.
[1986] Bains, S.; Green, J.; Tan, L.C.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 7475.
[1987] Kang, D.H.; Joo, T.Y.; Lee, E.H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* ***2006***, *47*, 5693.
[1988] See Pizey, J.S. *Synthetic Reaagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A. R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492.
[1989] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1929–1930.
[1990] Lee, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3440. See Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1979***, 3037; Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* ***1979***, 1180.
[1991] Adams, R.; Ulich, L.H. *J. Am. Chem. Soc.* ***1920***, *42,* 599; Wood, T.R.; Jackson, F.L.; Baldwin, A.R.; Longenecker, H.E. *J. Am. Chem. Soc.* ***1944***, *66,* 287; Zhang, A.; Nie, J. *J. Agric. Food Chem.* ***2005***, *53,* 2451.
[1992] Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 487. For other methods of preparing acyl fluorides, see Mukaiyama, T.; Tanaka, T. *Chem. Lett.* ***1976***, 303; Ishikawa, N.; Sasaki, S. *Chem. Lett.* ***1976***, 1407.
[1993] Švec, P.; Eisner, A.; Kolářová, L.; Weidlich, T.; Pejchal, V.; Růžička, A. *Tetrahedron Lett.* ***2008***, *49,* 6320.

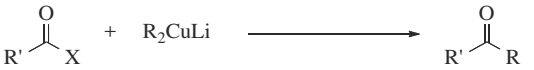
These reactions are most important for the preparation of acyl fluorides.[1994] Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution[1995] or with liquid HF at –10 °C.[1996] Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.[1997] Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid[1998] or with diethylaminosulfur trifluoride (DAST).[1999] Carboxylic esters and anhydrides can be converted to acyl halides other than fluorides by the inorganic acid halides mentioned in Reaction **16-79**, as well as with Ph_3PX_2 (X = Cl or Br),[2000] but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.[2001]

OS **II**, 528; **III**, 422; **V**, 66, 1103; **IX**, 13. See also, OS **IV**, 307.

G. Attack by Carbon at an Acyl Carbon[2002]

16-81 The Conversion of Acyl Halides to Ketones with Organometallic Compounds[2003]

Alkyl-de-halogenation



Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents (see Reaction **10-58**)[2004] to give high yields of ketones.[2005] The R′ group may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. The R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (Reaction **10-58**) instead of R_2CuLi,[2006] or by the use of either the mixed homocuprate $[(R'SO_2CH_2CuR)^- \ Li^+]$,[2007] or a magnesium dialkylcopper reagent '(RMeCuMgX).'[2008] Secondary alkyl groups can also be introduced with the copper–zinc

[1994] For lists of reagents converting acid derivatives to acyl halides, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1950–1951, 1955, 1968.
[1995] Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.
[1996] Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1961***, *26*, 237.
[1997] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.
[1998] Emsley, J.; Gold, V.; Hibbert, F.; Szeto, W.T.A. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 923.
[1999] Markovski, L.N.; Pashinnik, V.E. *Synthesis* ***1975***, 801.
[2000] Burton, D.J.; Koppes, W.M. *J. Chem. Soc., Chem. Commun.* ***1973***, 425; *J. Org. Chem.* ***1975***, *40*, 3026; Anderson Jr., A.G.; Kono, D.H. *Tetrahedron Lett.* ***1973***, 5121.
[2001] See Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* ***1981***, 216; Hoffmann, H.M.R.; Haase, K. *Synthesis* ***1981***, 715.
[2002] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 691–694, 734–765.
[2003] For a review, see Cais, M.; Mandelbaum, A. in Patai, S. *The Chemistry of the Carbonyl Group,* Vol. 1, Wiley, NY, ***1966***, Vol. 1, pp. 303–330.
[2004] See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents,* Wiley, NY, ***1980***, pp. 81–85. Ryu, I.; Ikebe, M.; Sonoda, N.; Yamamoto, S.-y.; Yamamura, G.-h.; Komatsu, M. *Tetrahedron Lett.* ***2002***, *43*, 1257.
[2005] Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5106; Luong-Thi, N.; Rivière, H. *J. Organomet. Chem.* ***1974***, *77,* C52.
[2006] See Bennett, G.B.; Nadelson, J.; Alden, L.; Jani, A. *Org. Prep. Proced. Int.* ***1976***, *8,* 13.
[2007] Johnson, C.R.; Dhanoa, D.S. *J. Org. Chem.* ***1987***, *52*, 1885.
[2008] Bergbreiter, D.E.; Killough, J.M. *J. Org. Chem.* ***1976***, *41,* 2750.

reagents [RCu(CN)ZnI].[2009] The R group may be alkynyl if a cuprous acetylide ($R^2C{\equiv}CCu$) is the reagent.[2010] Organocopper reagents generated *in situ* from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.[2011]

When the organometallic compound is a *Grignard reagent*,[2012] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (Reaction **16-82**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the *Grignard reagent* to the acyl halide rather than the other way), excess acyl halide, and so on, but the yields are usually low, although high yields have been reported in THF at –78 °C.[2013] Pretreatment with a trialkylphosphine followed by the *Grignard reagent* gave the ketone.[2014] Using CuBr[2015] or a Ni catalyst[2016] with the *Grignard reagent* can lead to the ketone. Some ketones are unreactive toward *Grignard reagents* for steric or other reasons; these can be prepared in this way.[2017] Other methods involve running the reaction in the presence of Me_3SiCl[2018], which reacts with the initial adduct in the tetrahedral mechanism (Sec. 16.A.i), and the use of a combined *Grignard*–$LiNEt_2$ reagent.[2019] Certain metallic halides, notably ferric and cuprous halides, are catalysts that improve the yields of ketone at the expense of tertiary alcohol.[2020] For this catalysis, both free radical and ionic mechanisms have been proposed.[2021]

Grignard reagents react with ethyl chloroformate to give carboxylic esters [EtOCOCl + RMgX → EtOCOR].

The Pd catalyzed reaction of an acyl chloride and an arylboronic acid[2022] or an alkenylboronic acid[2023] gives a ketone. Surfactants are known to promote arylboronic acid coupling reactions.[2024] Arylboronic esters add to carbamoyl halides, in the presence of a Pd catalyst, to give the corresponding benzamide.[2025] Arylboronic acids also react with

[2009] Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* ***1988****, 53*, 2390.
[2010] Castro, C.E.; Havlin, R.; Honwad, V.K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* ***1969****, 91,* 6464. See Verkruijsse, H.D.; Heus-Kloos, Y.A.; Brandsma, L. *J. Organomet. Chem.* ***1988****, 338,* 289.
[2011] Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1992****, 114*, 5110.
[2012] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, Englewood, NJ, ***1954***, pp. 712–724. See Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C.H. *Org. Lett.* ***2005****, 7,* 5593.
[2013] Föhlisch, B.; Flogaus, R. *Synthesis* ***1984***, 734.
[2014] Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* ***1996****, 37*, 5381.
[2015] Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* ***1996****, 52*, 13513.
[2016] Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995****, 36*, 9185. See Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* ***2000****, 41*, 9997.
[2017] See Dubois, J.E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* ***1984****, 93*, 1083.
[2018] Cooke, Jr., M.P. *J. Org. Chem.* ***1986****, 51*, 951.
[2019] Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* ***1987****, 70*, 1745.
[2020] See Fujisawa, T.; Sato, T. *Org. Synth. 66,* 116; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Organomet. Chem.* ***1991****, 405*, 53.
[2021] See MacPhee, J.A.; Boussu, M.; Dubois, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1525.
[2022] Bandgar, B.P.; Patil, A.V. *Tetrahedron Lett.* ***2005****, 46,* 7627; Ekoue-Kovi, K.; Xu, H.; Wolf, C. *Tetrahedron Lett.* ***2008****, 49,* 5773. For a Cu-mediated reaction, see Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* ***2005***, 2309.
[2023] Thimmaiah, M.; Zhang, X.; Fang, S. *Tetrahedron Lett.* ***2008****, 49*, 5605.
[2024] Xin, B.; Zhang, Y.; Cheng, K. *Synthesis* ***2007***, 1970.
[2025] Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J.L. *J. Org. Chem.* ***2005****, 70,* 5342.

anhydrides to give a ketone in the presence of a Pd catalyst.[2026] Similar reaction of acid chlorides, $NaBPh_4$, KF, and a Pd catalyst gave the aryl ketone.[2027]

Other organometallic reagents[2028] give good yields of ketones when treated with acyl halides because, as with R_2CuLi or R_2Cd, these compounds do not generally react with the ketone product. A particularly useful class of organometallic reagent are the organocadmium reagents (R_2Cd), prepared from *Grignard reagents* (Reaction **12-22**). In this case, R may be an aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[2029] An ester group may be present in either $R'COX$ or R_2Cd. Direct treatment of the acid chloride with an alkyl halide and Cd metal leads to the ketone in some cases.[2030] Organozinc compounds behave similarly to dialkylcadmium reagents, but are used less often.[2031] Organotin reagents (R_4Sn) react with acyl halides to give high yields of ketones, if a Pd complex is present.[2032] Organolead reagents (R_4Pb) behave similarly.[2033] Allylic halides and In metal react with acyl chlorides to give the ketone.[2034] Various other groups (e.g., nitrile, ester, and aldehyde) can be present in the acyl halide without interference. Other reagents include organomanganese compounds[2035] (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organozinc,[2036] organobismuth,[2037] and organothallium compounds (R can be primary alkyl or aryl).[2038] The reaction of an α-halo-ketone and an acyl chloride with SmI_2 leads to a β-diketone.[2039]

Antimony alkynes (e.g., $Ph_2Sb—C{\equiv}C—Ph$) react with acid chloride in the presence of a Pd catalyst to give the conjugated alkynyl ketone.[2040] Such conjugated ketones can also be prepared from an acyl halide, a terminal alkyne, and a CuI,[2041] Pd,[2042] or Fe catalyst,[2043]

[2026] Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* ***2006****, 71,* 5725.
[2027] Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Yang, Y. *Synth. Commun.* ***2001****, 31*, 3885.
[2028] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1389–1400.
[2029] Cason, J.; Fessenden, R. *J. Org. Chem.* ***1960****, 25*, 477.
[2030] Baruah, B.; Boruah. A.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***1996****, 37*, 9087.
[2031] See Grey, R.A. *J. Org. Chem.* ***1984****, 49*, 2288; Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth. 67,* 98.
[2032] Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* ***1983****, 105*, 669, 6129; Labadie, J.W.; Tueting, D.; Stille, J.K. *J. Org. Chem.* ***1983****, 48,* 4634. See Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* ***2001***, 1659.
[2033] Yamada, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* ***1987***, 1302.
[2034] Yadav, J.S.; Srinivas, D.; Reddy, G.S.; Bindu, K.H. *Tetrahedron Lett.* ***1997****, 38,* 8745. Also see, Bryan, V.J.; Chan, T.-H. *Tetrahedron Lett.* ***1997****, 38*, 6493 for a similar reaction with an acyl imidazole.
[2035] Kim, S.-H.; Rieke, R.D. *J. Org. Chem.* ***1998****, 63*, 6766; Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* ***1999****, 40*, 6407.
[2036] Filon, H.; Gosmini, C.; Périchon, J. *Tetrahedron* ***2003****, 59*, 8199.
[2037] Rao, M.L.N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* ***2007****, 63*, 12917.
[2038] Markó, I.E.; Southern, J.M. *J. Org. Chem.* ***1990****, 55*, 3368.
[2039] Ying, T.; Bao, W.; Zhang, Y.; Xu, W. *Tetrahedron Lett.* ***1996****, 37*, 3885.
[2040] Kakusawa, N.; Yamaguchi, K.; Kurita, J.; Tsuchiya, T. *Tetraehdron Lett.* ***2000****, 41*, 4143.
[2041] Chowdhury, C.; Kundu, N.G. *Tetrahedron* ***1999****, 55*, 7011; Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res. (S)* ***2001***, 146.
[2042] Karpov, A.S.; Müller, T.J.J. *Org. Lett.* ***2003****, 5*, 3451.
[2043] Wang, B.; Wang, S.; Li, P.; Wang, L. *Chem. Commun.* ***2010***, 5891.

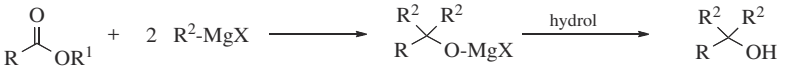
or with In metal.[2044] Terminal alkynes react with chloroformates and a Pd catalyst to give the corresponding propargyl ester.[2045] Similar reaction of an alkyne with an acid chloride and a Pd—Cu[2046] or CuI catalyst,[2047] both with microwave irradiation, gave alkynyl ketones.

Acyl halides can also be converted to ketones by treatment with $Na_2Fe(CO)_4$ followed by R′X (Reaction **10-76**).

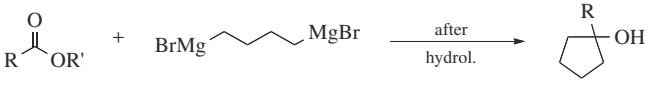
OS **II**, 198; **III**, 601; **IV**, 708; **VI**, 248, 991; **VII**, 226, 334; **VIII**, 268, 274, 371, 441, 486.

16-82 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones with Organometallic Compounds[2048]

Dialkyl,hydroxy-de-alkoxy,oxo-tersubstitution; Alkyl-de-acyloxy- or de-amido substitution

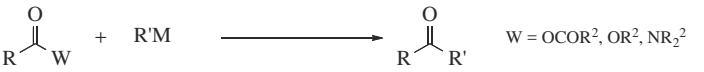


When carboxylic esters are treated with *Grignard reagents*, addition to the carbonyl (Reaction **16-24**) generates a ketone. Under the reaction conditions, the initially formed ketone usually undergoes acyl substitution of R^2 for OR′ (Reaction **16-81**), so that tertiary alcohols are formed in which two R groups are the same. Isolation of the ketone as the major product is possible in some cases, particularly when the reaction is done at low temperature[2049] and when there is steric hindrance to the carbonyl in the first-formed ketone. Esters (RCO_2Me) react with $Zn(BH_4)_2$/EtMgBr to give an alcohol [RCH(OH)Et].[2050] Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: $(EtO)_2C{=}O + RMgX \rightarrow R_3COMgX$. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.[2051] Many side reactions are possible, especially when the acid derivative or the *Grignard reagent* is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (**16-81**), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.[2052] 1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.[2053]



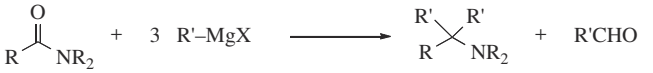
[2044] Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2009****, 131,* 6668.
[2045] Böttcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J.; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans.1* ***1999***, 3555.
[2046] Wang, J.-x.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* ***2001****, 31*, 3337.
[2047] Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* ***2001****, 31*, 3527.
[2048] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, Englewood, NJ, ***1954***, pp. 561–562, 846–908.
[2049] Deskus, J.; Fan, D.; Smith, M.B. *Synth. Commun.* ***1998****, 28*, 1649.
[2050] Hallouis, S.; Saluzzo, C.; Amouroux, R. *Synth. Commun.* ***2000****, 30*, 313.
[2051] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 549–766, 846–869.
[2052] Canonne, P.; Bernatchez, M. *J. Org. Chem.* ***1986****, 51*, 2147; ***1987****, 52,* 4025.
[2053] Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

As is the case with acyl halides (Reaction **16-81**), anhydrides and carboxylic esters give tertiary alcohols (Reaction **16-82**) when treated with *Grignard reagents*. Low temperatures,[2054] the solvent HMPA,[2055] and inverse addition have been used to increase the yields of ketone.[2056] Amides give better yields of ketone at room temperature, but still not very high.[2057] Anhydrides can react with arylmagnesium halides at low temperature, and in the presence of (−)-sparteine, to give a keto acid with good enantioselectivity.[2058] Organocadmium reagents are less successful with these substrates than with acyl halides (Reaction **16-81**). Esters of formic acid, dialkylformamides, and lithium or sodium formate[2059] give good yields of aldehydes, when treated with *Grignard reagents*.



Organolithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent (e.g., toluene), since reaction at lower temperatures gives tertiary alcohols.[2060] Organolithium reagents also give good yields of carbonyl compounds with *N,N*-disubstituted amides.[2061] Dialkylformamides react to give aldehydes, other disubstituted amides give ketones and other acid derivatives have been used.[2062]

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an organolithium reagent (Reaction **16-28**). For an indirect way to convert carboxylic esters to ketones, see Reaction **16-82**. A similar reaction with hindered aryl carboxylic acids has been reported.[2063] Carboxylic acids can be treated with 2-chloro-4,6-dimethoxy[1,3,5] triazine and the RMgX/CuI to give ketones.[2064]



Disubstituted formamides can give addition of 2 molar equivalents of *Grignard reagent*. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.[2065] The use of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. The addition of 2 molar equivalents of

[2054] See Newman, M.S.; Smith, A.S. *J. Org. Chem.* ***1948****, 13,* 592; Edwards, Jr., W.R.; Kammann, Jr., K.P. *J. Org. Chem.* ***1964****, 29*, 913; Araki, M.; Sakat, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1974***, 687.

[2055] Huet, F.; Pellet, M.; Conia, J.M. *Tetrahedron Lett.* ***1976***, 3579.

[2056] For a list of reactions with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1386–1389, 1400–1419.

[2057] See Olah, G.S.; Prakash, G.K.S.; Arvanaghi, M. *Synthesis* ***1984***, 228; Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* ***1997***, 1414. Also see Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocyclic Chem.* ***1995****, 32*, 25 for a related reaction.

[2058] Shintani, R.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002****, 41*, 1057.

[2059] Bogavac, M.; Arsenijevic, L.; Pavlov, S.; Arsenijevic, V. *Tetrahedron Lett.* ***1984****, 25*, 1843.

[2060] Petrov, A.D.; Kaplan, E.P.; Tsir, Ya. *J. Gen. Chem. USSR* ***1962****, 32*, 691.

[2061] Evans, E.A. *J. Chem. Soc.* ***1956***, 4691. See Clark, C.T.; Milgram, B.C.; Scheidt, K.A. *Org. Lett.* ***2004****, 6*, 3977. See Wakefield, B.J. *Organolithium Methods*; Academic Press, NY, ***1988***, pp. 82–88.

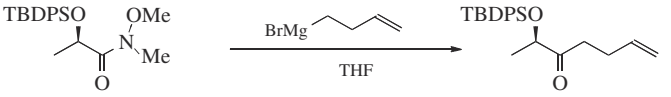
[2062] Mueller-Westerhoff, U.T.; Zhou, M. *Synlett* ***1994***, 975.

[2063] Zhang, P.; Terefenko, E.A.; Slavin, J. *Tetrahedron Lett.* ***2001****, 42*, 2097.

[2064] DeLuca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* ***2001****, 3*, 1519.

[2065] Spialtr, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 59–63.

phenyllithium to a carbamate gave good yields of the ketone, however.[2066] The reaction of *N*-(3-bromopropyl) lactams with *tert*-butyllithium gave cyclization to the bicyclic amino alcohol, and subsequent reduction with $LiAlH_4$ (Reaction **19-64**) gave the bicyclic amine.[2067] Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).[2068] Cerium reagents (e.g., $MeCeCl_2$) also add two R groups to an amide.[2069] More commonly, an organolithium reagent is treated with $CeCl_3$ to generate the organocerium reagent *in situ*.[2070] It has proven possible to add two different R groups by sequential addition of two *Grignard reagents*.[2071] Diketones have also been produced by using the bis(imidazole) derivative of oxalic acid.[2072] When an amide having a *gem*-dibromocyclopropyl unit elsewhere in the molecule was treated with methyllithium, Li—Br exchange was accompanied by intramolecular acyl addition to the amide carbonyl, giving a bicyclic amino alcohol.[2073]



121 **122**

N-Methoxy-*N*-methyl amides, (e.g., **120**) are referred to as a *Weinreb amide*.[2074] When a *Weinreb amide* reacts with a *Grignard reagent* or an organolithium reagent,[2075] the product is the ketone. The reaction of **121** (TBDPSO = tertiarybutyldiphenylsilyl) with 3-butenylmagnesium bromide to give ketone **122** is a typical example.[2076] Aryloxy carbamates with a *Weinreb amide* unit [ArO_2C-NMe(OMe)] react with RMgBr and then R′Li to give an unsymmetrical ketone [RC(=O)R′].[2077] Intramolecular displacement of a *Weinreb amide* by an organolithium reagent generated *in situ* from an iodide precursor leads to cyclic ketones.[2078] Reaction with vinylmagnesium bromide led to a β-*N*-methoxy-*N*-methylamino ketone, presumably by initial formation of the conjugated ketone followed by *Michael addition* (Reaction **15-24**) of the liberated amine.[2079] By the use of the compound *N*-methoxy-*N,N',N'*-trimethylurea, it is possible to add two R groups as RLi, the same or different, to a CO group.[2080] Another variant used organocerium reagents with (*Z*)-α,β-unsaturated *Weinreb amides* to give (*Z*)-α,β-unsaturated ketones.[2081]

[2066] Prakash, G.K.S.; York, C.; Liao, Q.; Kotian, K.; Olah, G.A. *Heterocycles* ***1995****, 40*, 79.
[2067] Jones, K.; Storey, J.M.D. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 769.
[2068] Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* ***1987****, 28*, 1529.
[2069] Calderwood, D.J.; Davies, R.V.; Rafferty, P.; Twigger, H.L.; Whelan, H.M. *Tetrahedron Lett.* ***1997****, 38*, 1241.
[2070] Ahn, Y.; Cohen, T. *Tetrahedron Lett.* ***1994****, 35*, 203.
[2071] Comins, D.L.; Dernell, W. *Tetrahedron Lett.* ***1981****, 22,* 1085.
[2072] Mitchell, R.H.; Iyer, V.S. *Tetrahedron Lett.* ***1993****, 34*, 3683. Also see, Sibi, M.P.; Sharma, R.; Paulson, K.L. *Tetrahedron Lett.* ***1992****, 33*, 1941.
[2073] Baird, M.S.; Huber, F.A.M.; Tverezovsky, V.V.; Bolesov, I.G. *Tetrahedron* ***2001****, 57*, 1593.
[2074] Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981****, 22*, 3815. For a review, see Balasubramaniam, S.; Aidhen, I.S. Sy*nthesis* ***2008***, 3707.
[2075] See Tallier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* ***2004****, 6*, 2145.
[2076] Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* ***2005****, 7*, 2775. For other exmaples see Andrés, J.M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* ***2000****, 56,* 1217.
[2077] Lee, N.R.; Lee, J.I. *Synth. Commun.* ***1999****, 29*, 1249.
[2078] Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* ***2003****, 5*, 1115.
[2079] See Hansford, K.A.; Dettwiler, J.E.; Lubell, W.D. *Org. Lett.* ***2003****, 5*, 4887.
[2080] Hlasta, D.J.; Court, J.J. *Tetrahedron Lett.* ***1989****, 30,* 1773. See also, Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981****, 22,* 3815.
[2081] Kojima, S.; Hidaka, T.; Yamakaw, A. *Chem. Lett.* ***2005****, 34,* 470.

N,N-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes: $RCONR_2^2 + (R'C{\equiv}C)_3B \rightarrow RCOC{\equiv}CR'$.[2082] Lactams react with triallylborane to give cyclic 2,2-diallyl amines after treatment with methanol and then aq hydroxide.[2083] Triallylborane reacts with the carbonyl group of lactams, and after treatment with methanol and then aq NaOH gives the *gem*-diallyl amine: 2-pyrrolidinone $\rightarrow$ 2,2-diallylpyrrolidine.[2084] *N,N*-Disubstituted carbamates ($X = OR^2$) and carbamoyl chlorides ($X = Cl$) react with 2 molar equivalents of an alkyl- or aryllithium or *Grignard reagent* to give symmetrical ketones, in which both R groups are derived from the organometallic compound: R_2'NCOX + 2 RMgX $\rightarrow R_2CO$.[2085] *N,N*-Disubstituted amides give ketones in high yields when treated with alkyllanthanum triflates [$RLa(OTf)_2$].[2086]

Other organometallic reagents give acyl substitution. Sodium naphthalenide reacts with esters to give naphthyl ketones.[2087] Trimethylaluminum, which exhaustively methylates ketones (Reaction **16-24**), also exhaustively methylates carboxylic acids to give *tert*-butyl compounds[2088] (see also, Reaction **10-63**). Trimethylaluminum reacts with esters to form ketones, in the presence of *N,N'*-dimethylethylenediamine.[2089] Trialkylboranes have been used to convert thioesters to ketones.[2090] Thioesters ($RCOSR'$) react with arylboronic acids, in the presence of a Pd catalyst, to give the corresponding ketone,[2091] and esters react similarly with arylboronic acids (a Pd catalyst)[2092] or arylboronates (a Ru catalyst).[2093] Arylboronic acids also react with dialkyl anhydrides, with a Rh[2094] or a Pd catalyst,[2095] to give the ketone. Thioesters are converted to ketones with organoindium compounds.[2096] Thioesters give good yields of ketones when treated with lithium dialkylcopper reagents (R_2^2CuLi, $R'' =$ primary or secondary alkyl or aryl).[2097] Organozinc reagents convert thioesters to ketones.[2098] Diaryl- or dialkylzinc reagents react with anhydrides and a Pd[2099] or a Ni catalyst[2100] to give the ketone. The reaction of alkylzinc halides and thioesters leads to ketones in the presence of 1.5% Pd/C,[2101] in what has been called *Fukuyama coupling*.[2102] Note that in the presence of a SmI_2 catalyst and 2 molar equivalents of

[2082] Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* ***1983***, 35.
[2083] Bubnov, Y.N.; Pastukhov, F.V.; Yampolsky, I.V.; Ignatenko, A.V. *Eur. J. Org. Chem.* ***2000***, 1503; Li, Z.; Zhang, Y. *Tetrahedron Lett.* ***2001****, 42*, 8507.
[2084] Bubnov, Yu.N.; Klimkina, E.V.; Zhun', I.V.; Pastukhov, F.V.; Yampolsky, I.V. *Pure Appl. Chem.* ***2000****, 72*, 1641.
[2085] Michael, U.; Hörnfeldt, A. *Tetrahedron Lett.* ***1970***, 5219; Scilly, N.F. *Synthesis* ***1973***, 160.
[2086] Collins, S.; Hong, Y. *Tetrahedron Lett.* ***1987****, 28*, 4391.
[2087] Periasamy, M.; Reddy, M.R.; Bharathi, P. *Synth. Commun.* ***1999****, 29*, 677.
[2088] Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974****, 27,* 1665.
[2089] Chung, E.-A.; Cho, C.-W.; Ahn, K.H. *J. Org. Chem.* ***1998****, 63*, 7590.
[2090] Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* ***2004****, 69*, 3554.
[2091] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* ***2003****, 5*, 3033.
[2092] Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* ***2004****, 6*, 3597.
[2093] Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* ***2004****, 69*, 5615.
[2094] Frost, C.G.; Wadsworth, K.J. *Chem. Commun.* ***2001***, 2316.
[2095] Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* ***2002***, 3254.
[2096] Fausett, B.W.; Liebeskind, L.S. *J. Org. Chem.* ***2005****, 70,* 4851.
[2097] Anderson, R.J.; Henrick, C.A.; Rosenblum, L.D. *J. Am. Chem. Soc.* ***1974****, 96*, 3654. See also, Kim, S.; Lee, J. I. *J. Org. Chem.* ***1983****, 48,* 2608.
[2098] Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2002****, 43*, 1039.
[2099] Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2004****, 126*, 10248.
[2100] O'Brien, E.M.; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2003****, 125*, 10498.
[2101] Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2001****, 42*, 429.
[2102] See Mori, Y.; Seki, M. *Tetrahedron Lett.* ***2004****, 45, 7*343. For a different but related cross-coupling, see Zhang, Y.; Rovis, T. *J. Am. Chem. Soc* . ***2004****, 126,* 15964.

allyl bromide, lactones were converted to the diallyl diol.[2103] Aryl iodides react with acetic anhydride, with a Pd catalyst, to give the aryl methyl ketone.[2104]

Carboxylic esters can be converted to their homologues (RCOOEt → RCH_2COOEt) by treatment with Br_2CHLi followed by BuLi at -90 °C. The ynolate (RC≡COLi) is an intermediate.[2105] If the ynolate is treated with 1,3-cyclohexadiene, followed by $NaBH_4$, the product is the alcohol RCH_2CH_2OH.[2106]

Note that acyl benzotriazoles react with β-keto esters to give diketones via acyl substitution.[2107] Acyl cyanides [RC(=O)CN] react with allylic bromides and In metal to give the corresponding ketone.[2108] Acyl benzotriazoles have been coupled with SmI_2 to give the 1,2-diketone.[2109] α-Cyanoketones (acyl nitriles) were coupled with YbI_2 in a similar manner.[2110]

Vinyl organometallic reagents can be added to acyl derivatives. Reaction of an alkyne with Cp_2ZrEt_2 generates the vinyl zirconium reagent, which react with ethyl chloroformate to give an α,β-unsaturated ester.[2111]

OS **I**, 226; **II**, 179, 602; **III**, 237, 831, 839; **IV**, 601; **VI**, 240, 278; **VIII**, 474, 505.
OS **II**, 282; **72**, 32; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451; **81**, 14.

16-83 The Coupling of Acyl Halides

De-halogen-coupling

$$2\,RCOCl \xrightarrow{\text{pyrophoric Pb}} RCOCOR$$

Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a *Wurtz-type reaction*.[2112] The reaction has been performed with R = Me and Ph. Samarium iodide[2113] gives the same reaction. The photochemical coupling of acyl iodides gives α-diketones.[2114] Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire: 2 PhCOCl + Li → PhCOCOPh.[2115]

Unsymmetrical α-diketones (RCOCOR′) have been prepared by treatment of an acyl halide (RCOCl) with an acyltin reagent $R'COSnBu_3$, with a Pd complex catalyst.[2116]

[2103] Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron Lett.* ***2002****, 43*, 8007.
[2104] Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* ***2003****, 5*, 289.
[2105] Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* ***1985****, 107*, 1429; Kowalski, C.J.; Haque, M.S. *J. Org. Chem.* ***1985****, 50,* 5140.
[2106] Kowalski, C.J.; Haque, M.S. *J. Am. Chem. Soc.* ***1986****, 108*, 1325.
[2107] Katritzky, A.R.; Wang, Z.; Wang, M.; Wilkerson, C.R.; Hall, C.D.; Akhmedov, N.G. *J. Org. Chem.* ***2004****, 69*, 6617.
[2108] Yoo, B.W.; Choi, K.H.; Lee, S.J.; Nam, G.S.; Chang, K.Y.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2002****, 32*, 839.
[2109] Wang, X.; Zhang, Y. *Tetrahedron Lett.* ***2002****, 43*, 5431.
[2110] Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Tetahedron Lett.* ***2002****, 43*, 7525.
[2111] Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* ***2000****, 122*, 3228.
[2112] Mészáros, L. *Tetrahedron Lett.* ***1967***, 4951.
[2113] Souppe, J.; Namy, J.; Kagan, H.B. *Tetrahedron Lett.* ***1984****, 25*, 2869. See also, Collin, J.; Namy, J.; Dallemer, F.; Kagan, H.B. *J. Org. Chem.* ***1991****, 56*, 3118.
[2114] Voronkov, M.G.; Belousova, L.I.; Vlasov, A.V.; Vlasova, N.N. *Russ. J. Org. Chem* ***2008****, 44,* 929.
[2115] Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.
[2116] Verlhac, J.; Chanson, E.; Jousseaume, B.; Quintard, J. *Tetrahedron Lett.* ***1985****, 26*, 6075. For another procedure, see Olah, G.A.; Wu, A. *J. Org. Chem.* ***1991****, 56,* 902.

16-84 Acylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



This reaction is similar to **10-67**, but there are fewer examples.[2117] Either Z or Z′ may be any of the electron-withdrawing groups listed in Reaction **10-67** (CO_2R, COR, CN, etc.)[2118] Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (Reactions **12-40** and **12-43**). In this way, a compound ZCH_2Z' can be converted to ZCH_2Z[2] or an acyl halide (RCOCl) to a methyl ketone ($RCOCH_3$). O-Acylation is sometimes a side reaction.[2119] When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at -78 °C gave >90% O-acylation, while acetyl fluoride at room temperature gave >95% C-acylation.[2120] The use of an alkyl chloroformate gives triesters.[2121]

The application of this reaction to simple ketones[2122] (in parallel with Reaction **10-68**) requires a strong base (e.g., $NaNH_2$ or Ph_3CNa) and is often complicated by O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of C-acylated product by employing an excess (2–3 molar equivalents) of enolate anion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (e.g., Mg^{2+}), which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,[2123] and by working at low temperatures.[2124] In cases where the use of an excess of enolate anion results in C-acylation, it is because O-acylation takes place first, and the O-acylated product (an enol ester) is then C-acylated. Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.[2125] Ketones can be acylated by anhydrides to give β-diketones, with BF_3 as catalyst.[2126] Simple esters (RCH_2CO_2Et) can be acylated at the α carbon (at –78 °C) if a strong base (e.g., lithium *N*-isopropylcyclohexylamide) is used to remove the proton.[2127]

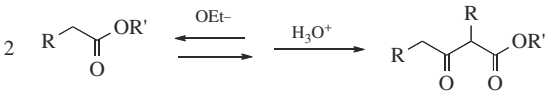
[2117] For examples of reactions in this section, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1484–1485, 1522–1527.
[2118] For an improved procedure, see Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* ***1985****, 50,* 2622.
[2119] When phase-transfer catalysts are used, O-acylation becomes the main reaction: Jones, R.A.; Nokkeo, S.; Singh, S. *Synth. Commun.* ***1977****, 7,* 195.
[2120] Taylor, E.C.; Hawks, III, G.H.; McKillop, A. *J. Am. Chem. Soc.* ***1968****, 90*, 2421.
[2121] See Skarzewski, J. *Tetrahedron* ***1989****, 45,* 4593; Newkome, G.R.; Baker, G.R. *Org. Prep. Proced. Int.* ***1986****, 19,* 117.
[2122] Hegedus, L.S.; Williams, R.E.; McGuire, M.A.; Hayashi, T. *J. Am. Chem. Soc.* ***1980****, 102*, 4973.
[2123] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 762–765; House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. *J. Org. Chem.* ***1973****, 38*, 514.
[2124] Seebach, D.; Weller, T.; Protschuk, G.; Beck, A.K.; Hoekstra, M.S. *Helv. Chim. Acta* ***1981****, 64,* 716.
[2125] Tirpak, R.E.; Rathke, M.W. *J. Org. Chem.* ***1982****, 47,* 5099.
[2126] See Hauser, C.R.; Swamer, F.W.; Adams, J.T. *Org. React.* ***1954****, 8,* 59, pp. 98–106.
[2127] See Hayden, W.; Pucher, R.; Griengl, H. *Monatsh. Chem.* ***1987****, 118*, 415.

Silyl enol esters react with acetic anhydride, in the presence of a chiral Fe complex, to give a chiral β-keto ester.[2128]

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **VIII**, 71, 326, 467. See also, OS **VI**, 620.

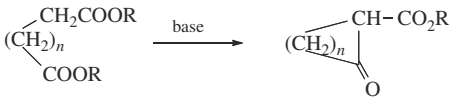
16-85 Acylation of Carboxylic Esters by Carboxylic Esters: The Claisen and Dieckmann Condensations

Alkoxycarbonylalkyl-de-alkoxy-substitution



When carboxylic esters containing an α hydrogen are treated with a strong base (e.g., sodium ethoxide), a condensation occurs to give a β-keto ester via an ester enolate anion.[2129] This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen (this reaction is called a *mixed-Claisen* or a *crossed-Claisen condensation*), a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.[2130] However, if only one of the esters has an α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking α hydrogen atoms (hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. When the ester enolate reacts with ethyl carbonate, the product is a malonic ester, and reaction with ethyl formate introduces a formyl group. *Claisen condensation* of phenyl esters with $ZrCl_4$ and diisopropylethylamine (*Hünigs base*) give the corresponding keto ester.[2131] Titanium compounds catalyze a *crossed-Claisen condensation*.[2132] Boron(III) compounds also catalyzed ester condensation reactions.[2133]

As with ketone enolate anions (see Reaction **16-34**), the use of amide bases under kinetic control conditions (strong base with a weak conjugate acid, aprotic solvents, low temperatures), allows the *mixed-Claisen condensation* to proceed. Self-condensation of the lithium enolate with the parent ester is a problem when LDA is used as a base,[2134] but this is minimized with LICA.[2135] Note that solvent-free *Claisen condensation* reactions have been reported.[2136] There is a *retro-Claisen condensation*, catalyzed by indium.[2137]



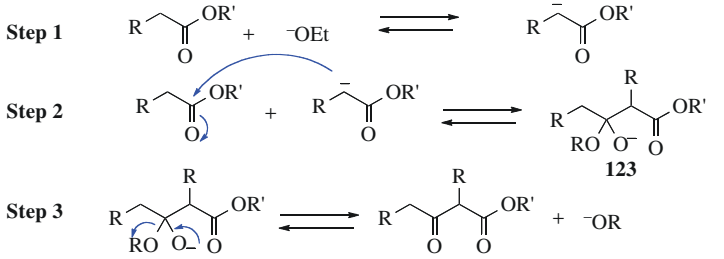
122

When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester (**122**) and the reaction is called the *Dieckmann*

[2128] Mermerian, A.H.; Fu, G.C. *J. Am. Chem. Soc.* ***2005****, 127,* 5604.
[2129] See Rablen, P.R.; Bentrup, KL.H. *J. Am. Chem. Soc.* ***2003****, 125*, 2142.
[2130] See Tanabe, Y. *Bull. Chem. Soc. Jpn.* ***1989****, 62*, 1917.
[2131] Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* ***2001***, 1674.
[2132] Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* ***2005****, 127*, 2854.
[2133] Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* ***2007****, 63*, 8645.
[2134] Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* ***1977****, 42*, 2038.
[2135] Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971****, 93*, 2318.
[2136] Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001****, 42*, 7983.
[2137] Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* ***2007****, 46*, 7793.

condensation:[2138] The *Dieckmann condensation* is most successful for the formation of 5-, 6-, and 7-membered rings, but yields for rings of 9–12 members are very low or nonexistent. Reactions that form large rings are generally assisted by high dilution. A solvent-free *Dieckmann condensation* has been reported on solid potassium *tert*-butoxide.[2139] *Dieckmann condensation* of unsymmetrical substrates can be made regioselective by the use of solid-phase supports.[2140] The *Dieckmann condensation* has also been done using $TiCl_3/NBu_3$ with a TMSOTf catalyst.[2141] A *Dieckmann-like condensation* was reported where an α,ω-dicarboxylic acid was heated to 450 °C on graphite, with microwave irradiation, to give the cyclic ketone.[2142]

The mechanism of the *Claisen* and *Dieckmann condensations* (steps 1–3) is the ordinary *tetrahedral mechanism*,[2143] with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate. This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion (e.g., an enolate anion) is added to the carbonyl group of an aldehyde or ketone (Reaction **16-38**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead, the intermediate similar to **123** adds a proton at the oxygen to give a hydroxy compound.



In contrast to Reaction **10-67**, ordinary esters react quite well; that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left, but the small amount of enolate anion formed is sufficient to attack the readily approachable ester substrate. All the steps are in equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (i.e., a β-keto ester is a stronger acid than an alcohol):



The use of a stronger base (e.g., $NaNH_2$, NaH, or KH),[2144] often increases the yield. For some esters, stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are

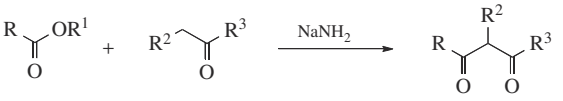
[2138] See Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967****, 15*, 1.
[2139] Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3521.
[2140] Crowley, J.I.; Rapoport, H. *J. Org. Chem.* ***1980****, 45*, 3215. For another method, see Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* ***1981****, 22,* 1353.
[2141] Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* ***1997****, 38*, 8727.
[2142] Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.
[2143] In some cases, an SET mechanism may be involved: Ashby, E.C.; Park, W. *Tetrahedron Lett.* ***1983***, 1667. See Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* ***1997****, 38*, 7063.
[2144] Brown, C.A. *Synthesis* ***1975***, 326.

esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2CO_2Et$) lack an acidic hydrogen, so that they cannot be converted to enolate anions by sodium ethoxide.[2145]

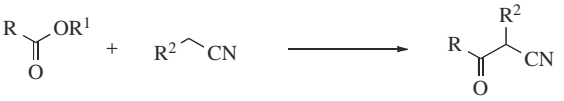
OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **VIII**, 112.

16-86 Acylation of Ketones and Nitriles by Carboxylic Esters

α-Acylalkyl-de-alkoxy-substitution



Carboxylic esters can be treated with ketones to give β-diketones. The reaction is so similar that it is sometimes also called the *Claisen reaction*, but this usage may be confusing. A strong base (e.g., sodium amide or sodium hydride) is required. Yields can be increased by the catalytic addition of crown ethers.[2146] Esters of formic acid (R = H) give β-keto aldehydes and ethyl carbonate gives β-keto esters. β-Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate (MeOCOCN,[2147] in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate [$(EtOCO)_2O$].[2148] This reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles, as shown.

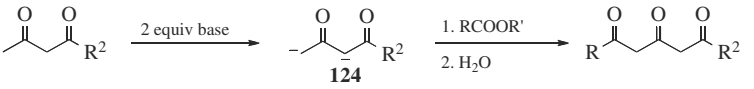


Other nucleophilic carbon reagents (e.g., acetylide ions) and ions derived from α-methylpyridines have also been used. A particularly useful nucleophile is the methylsulfinyl carbanion ($CH_3SOCH_2^-$),[2149] the conjugate base of DMSO, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (see Reaction **10-67**). The methylsulfonyl carbanion ($CH_2SO_2CH_2^-$), the conjugate base of dimethyl sulfone, behaves similarly,[2150] and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and DMF will acylate 1,3-dithianes[2151] (see Reaction **10-71**) to give, after oxidative hydrolysis with NBS or NCS, α-keto aldehydes or α-diketones.[2152]

As in Reaction **10-67**, a ketone is deprotonated at the most acidic proton first and the second most acidic position after that if 2 equivs of base are used, to give dianion **124**.

[2145] See Garst, J.F. *J. Chem. Educ.* ***1979****, 56,* 721.
[2146] Popik, V.V.; Nikolaev, V.A. *J. Org. Chem. USSR* ***1989****, 25,* 1636.
[2147] Mander, L.N.; Sethi, P. *Tetrahedron Lett.* ***1983****, 24*, 5425.
[2148] Hellou, J.; Kingston, J.F.; Fallis, A.G. *Synthesis* ***1984***, 1014.
[2149] See Durst, T. *Adv. Org. Chem.* ***1969****, 6,* 285, pp. 296–301.
[2150] Schank, K.; Hasenfratz, H.; Weber, A. *Chem. Ber.* ***1973****, 106*, 1107, House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968****, 33*, 61.
[2151] Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975****, 40*, 231
[2152] See Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971****, 36*, 3553.

Thus, β-diketones have been converted to 1,3,5-triketones.[2153]



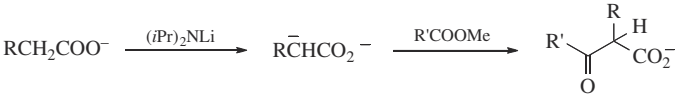
124

Side reactions are condensation of the ketone with itself (**16-34**), of the ester with itself, and of the ketone with the ester but with the ester supplying the α-position (**16-36**). The mechanism is the same as in Reaction **16-85**.[2154]

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

16-87 Acylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-alkoxy-substitution



As seen previously (Reaction **10-70**), dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester[2155] to give salts of β-keto acids. As in Reaction **10-70**, the carboxylic acid can be of the form RCH_2CO_2H or RR^2CHCO_2H. Since β-keto acids are so easily converted to ketones (Reaction **12-40**), this is also a method for the preparation of ketones ($R'COCH_2R$ and $R'COCHRR^2$), where R′ can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α-formyl carboxylate salt (R′ = H) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[2156] This method accomplishes the conversion $RCH_2CO_2H \rightarrow RCH_2CHO$, and is an alternative to the reduction methods discussed in Reaction **19-39**. When the carboxylic acid is of the form RR^2CHCO_2H, better yields are obtained by acylating with acyl halides rather than esters.[2157]

16-88 Preparation of Acyl Cyanides

Cyano-de-halogenation

$$RCOX + CuCN \longrightarrow RCOCN$$

Acyl cyanides[2158] can be prepared by treatment of acyl halides with copper cyanide. The mechanism could be free radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,[2159] with Me_3SiCN and an $SnCl_4$ catalyst,[2160] and with Bu_3SnCN,[2161] but these reagents are successful only when R = aryl or tertiary alkyl.

[2153] Miles, M.L.; Harris, T.M.; Hauser, C.R. *J. Org. Chem.* ***1965****, 30,* 1007.
[2154] Hill, D.G.; Burkus, T.; Hauser, C.R. *J. Am. Chem. Soc.* ***1959****, 81,* 602.
[2155] Kuo, Y.; Yahner, J.A.; Ainsworth, C. *J. Am. Chem. Soc.* ***1971****, 93*, 6321; Angelo, B. *C.R. Seances Acad. Sci. Ser. C* ***1973****, 276,* 293.
[2156] Koch, G.K.; Kop, J.M.M. *Tetrahedron Lett.* ***1974***, 603.
[2157] Krapcho, A.P.; Kashdan, D.S.; Jahngen, Jr., E.G.E.; Lovey, A.J. *J. Org. Chem.* ***1977****, 42*, 1189; Lion, C.; Dubois, J.E. *J. Chem. Res. (S)* ***1980***, 44.
[2158] See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982****, 21*, 36.
[2159] Taylor, E.C.; Andrade, J.G.; John, K.C.; McKillop, A. *J. Org. Chem.* ***1978****, 43*, 2280.
[2160] Olah, G.A.; Arvanaghi, M.; Prakash, G.K.S. *Synthesis* ***1983***, 636.
[2161] Tanaka, M. *Tetrahedron Lett.* ***1980****, 21*, 2959. See also, Tanaka, M.; Koyanagi, M. *Synthesis* ***1981***, 973.

Potassium cyanide has also been used, along with ultrasound,[2162] as has NaCN with phase-transfer catalysts.[2163]

OS **III**, 119.

16-89 Preparation of Diazo Ketones

Diazomethyl-de-halogenation

$$RCOX + CH_2N_2 \longrightarrow RCOCHN_2$$

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[2164] Diazomethane must be present in excess or the HX produced will react with the diazo ketone (Reaction **10-52**). This reaction is the first step of the *Arndt–Eistert synthesis* (**18-8**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of DCC.[2165]

OS **III**, 119; **VI**, 386, 613; **VIII**, 196.

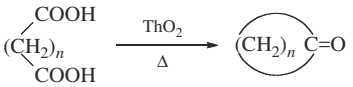
16-90 Ketonic Decarboxylation[2166]

Alkyl-de-hydroxylation

$$2 \quad RCOOH \xrightarrow[ThO_2]{400-500^\circ C} RCOR + CO_2$$

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[2167] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of C_8–C_{10} to C_{30} cyclic ketones.[2168]

Not much work has been done on the mechanism of this reaction. However, a free radical mechanism has been suggested on the basis of a thorough study of all the side products.[2169]

OS **I**, 192; **II**, 389; **IV**, 854; **V**, 589. Also see, OS **IV**, 55, 560.

[2162] Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Synthesis* ***1983***, 637.

[2163] Koenig, K.E.; Weber, W.P. *Tetrahedron Lett.* ***1974***, 2275. See also, Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60,* 1085.

[2164] See Fridman, A.L.; Ismagilova, G.S.; Zalesov, V.S.; Novikov, S.S. *Russ. Chem. Rev.* ***1972***, *41*, 371; Ried, W.; Mengler, H. *Fortshr. Chem. Forsch.,* ***1965***, *5*, 1.

[2165] Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* ***1970***, 971.

[2166] See Kwart, H.; King, K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 362–370.

[2167] Granito, C.; Schultz, H.P. *J. Org. Chem.* ***1963***, *28*, 879.

[2168] See Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* ***1926***, *9,* 249; ***1928***, *11*, 1174; Ruzicka, L.; Brugger, W.; Seidel, C.F.; Schinz, H. *Helv. Chim. Acta* ***1928***, *11,* 496.

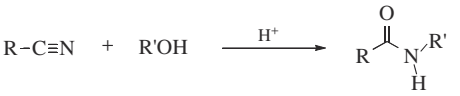
[2169] Hites, R.A.; Biemann, K. *J. Am. Chem. Soc.* ***1972***, *94,* 5772. See also, Bouchoule, C.; Blanchard, M.; Thomassin, R. *Bull. Soc. Chim. Fr.* ***1973***, 1773.

16.B.iii. Reactions in which Carbon Adds to the Heteroatom

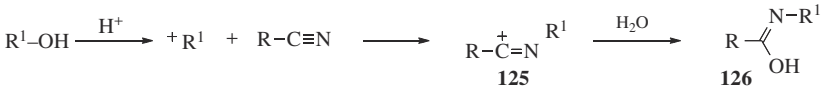
A. Oxygen Adding to the Carbon

16-91 The Ritter Reaction

***N*-Hydro,*N*-alkyl-*C*-oxo-biaddition**



Alcohols can be added to nitriles in an entirely different manner from that seen in Reaction **16-9**. In this reaction, the alcohol is converted by a strong acid to a carbocation, which is attacked by the nucleophilic nitrogen atom to give **125**. Subsequent addition of water to the electrophilic carbon atom leads to the enol form of the amide (see Reaction **126**), which tautomerizes (Sec. 2.N.i) to the *N*-alkyl amide.



Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); non-benzylic primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol, but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.[2170] Lewis acids [e.g., $Mg(HSO_4)_2$] have been used to promote the reaction.[2171] Highly sterically hindered nitriles have been converted to *N*-methyl amides by heating with methanol and sulfuric acid.[2172] Hydrogen cyanide also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.[2173]

Since the amides (especially the formamides) are easily cleaved to amines under hydrolysis conditions, the *Ritter reaction* provides a method for achieving the conversions $R'OH \rightarrow R'NH_2$ (see **10-32**) and alkene $\rightarrow R'NH_2$ (see **15-8**) in those cases, where R′ can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride[2174] or Ph_2CCl^+ $SbCl_6^-$ or a similar salt[2175] in the presence of the nitrile. A mixture of P_2O_5 and silica gel has been used to mediate the *Ritter reaction*.[2176] There is a Nafion-catalyzed,

[2170] Ritter, J.J.; Minieri, P.P. *J. Am. Chem. Soc.* ***1948****, 70,* 4045. See Krimen, L.I.; Cota, D.J. *Org. React.* ***1969****, 17,* 213; Johnson, F.; Madroñero, R. *Adv. Heterocycl. Chem.* ***1966****, 6,* 95; Tongco, E.C.; Prakash, G.K.S.; Olah, G.A. *Synlett* ***1997***, 1193.

[2171] Salehi, P.; Khodaei, M.M.; Zolfigol, M.A.; Keyvan, A. *Synth. Commun.* ***2001****, 31*, 1947.

[2172] Lebedev, M.Y.; Erman, M.B. *Tetrahedron Lett.* ***2002****, 43*, 1397.

[2173] Chen, H.G.; Goel, O.P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* ***1996****, 37*, 8129.

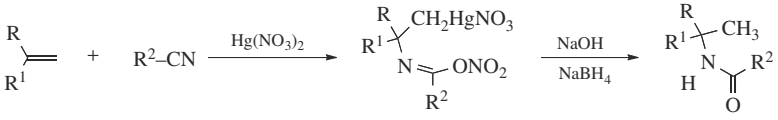
[2174] Martinez, A.G.; Alvarez, R.M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *Tetrahedron Lett.* ***1989****, 30,* 581.

[2175] Barton, D.H.R.; Magnus, P.D.; Garbarino, J.A.; Young, R.N. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 2101. See also, Top, S.; Jaouen, G. *J. Org. Chem.* ***1981****, 46,* 78.

[2176] Tamaddon, F.; Khoobi, M.; Keshavarz, E. *Tetrahedron Lett.* ***2007****, 48,* 3643.

microwave assisted variation,[2177] as well as $FeCl_3$ catalyzed[2178] and iodine-catalyzed[2179] reactions.

Alkenes of the form RCH=CHR′ and RR′C=CH_2 add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides that would be obtained by the *Ritter reaction*.[2180] This method has the advantage of avoiding strong acids.

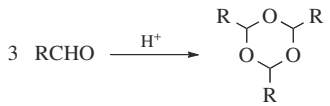


Benzylic compounds (e.g., ethylbenzene) react with alkyl nitriles, ceric ammonium nitrate, and a catalytic amount of *N*-hydroxysuccinimide to give the *Ritter* product, the amide.[2181]

The *Ritter reaction* can be applied to cyanamides RNHCN to give ureas (RNHCONHR′).[2182]

OS **V**, 73, 471.

16-92 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[2183] The cyclic trimer of formaldehyde is called *trioxane*,[2184] and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[2185] or dimers. Aldehydes can also polymerize to linear polymers, but a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases, but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

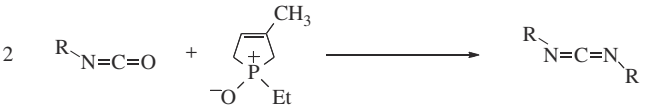
A slightly related reaction involves nitriles, which can be trimerized with various acids, bases, or other catalysts to give triazines (see OS **III**, 71).[2186] Here HCl is most often used. Most nitriles with an α hydrogen do not give the reaction.

[2177] Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* ***2008****, 49*, 2661.
[2178] Anxionnat, B.; Guérinot, A.; Reymond, S.; Cossy, J. *Tetrahedron Lett.* ***2009****, 50*, 3470.
[2179] Theerthagiri, P.; Lalitha, A.; Arunachalam, P.N. *Tetrahedron Lett.* ***2010****, 51*, 2813.
[2180] See Fry, A.J.; Simon, J.A. *J. Org. Chem.* ***1982****, 47,* 5032.
[2181] Sakaguchi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* ***2002***, 516.
[2182] Anatol, J.; Berecoechea, J. *Bull. Soc. Chim. Fr.* ***1975***, 395; *Synthesis* ***1975***, 111.
[2183] See Bevington, J.C. *Q. Rev. Chem. Soc.* ***1952****, 6,* 141.
[2184] See Camarena, R.; Cano, A.C.; Delgado, F.; Zúñiga, N.; Alvarez, C. *Tetrahedron Lett.* ***1993****, 34*, 6857.
[2185] Barón, M.; de Manderola, O.B.; Westerkamp, J.F. *Can. J. Chem.* ***1963****, 41,* 1893.
[2186] See Martin, D.; Bauer, M.; Pankratov, V.A. *Russ. Chem. Rev.* ***1978****, 47*, 975. See Pankratov, V.A.; Chesnokova, A.E. *Russ. Chem. Rev.* ***1989****, 58*, 879.

B. Nitrogen Adding to the Carbon

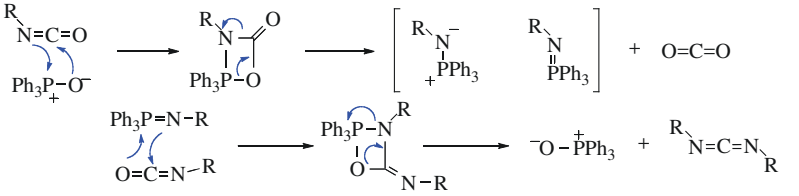
16-93 The Addition of Isocyanates to Isocyanates (Formation of Carbodiimides)

Alkylimino-de-oxo-bisubstitution



127

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**127**) is a useful method for the synthesis of carbodiimides[2187] in good yields.[2188] The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $R_3P^+—O^-$:[2189]



According to this mechanism, one molecule of isocyanate undergoes addition to C=O, and the other addition to C=N. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **127**,[2190] precisely what is predicted by this mechanism. Certain other catalysts are also effective.[2191] High load, soluble oligomeric carbodiimides have been prepared.[2192]

OS **V**, 501.

16-94 The Conversion of Carboxylic Acid Salts to Nitriles

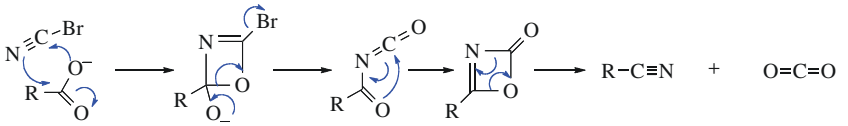
Nitrilo-de-oxido,oxo-tersubstitution

$$RCOO^- + BrCN \xrightarrow{250-300^\circ C} RCN + CO_2$$

Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Heating with acetonitrile in sulfuric acid also gave the nitrile.[2193] Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2,[2194] and optical activity in R was retained.[2195] The acyl isocyanate (RCON=C=O) could be isolated from the reaction

[2187] Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981****, 81,* 589; Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* ***1981****, 37*, 233; Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* ***1967****, 67*, 107.
[2188] Campbell, T.W.; Monagle, J.J.; Foldi, V.S. *J. Am. Chem. Soc.* ***1962****, 84*, 3673.
[2189] Monagle, J.J.; Campbell, T.W.; McShane Jr., H.F. *J. Am. Chem. Soc.* ***1962****, 84,* 4288.
[2190] Monagle, J.J.; Mengenhauser, J.V. *J. Org. Chem.* ***1966****, 31,* 2321.
[2191] See Ostrogovich, G.; Kerek, F.; Buzás, A.; Doca, N. *Tetrahedron* ***1969****, 25,* 1875.
[2192] Zhang, M.; Vedantham, P.; Flynn, D.L.; Hanson, P.R. *J. Org. Chem.* ***2004****, 69*, 8340.
[2193] Mlinarić-Majerski, K.; Margeta, R.; Veljković, J. *Synlett* ***2005***, 2089.
[2194] Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958****, 36,* 1256.
[2195] Barltrop, J.A.; Day, A.C.; Bigley, D.B. *J. Chem. Soc.* ***1961***, 3185.

mixture; hence the following mechanism was proposed:[2194]

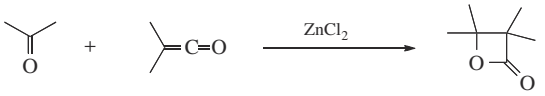


C. Carbon Adding to the Carbon

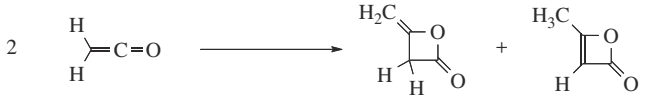
The reactions in this group are cycloadditions.

16-95 The Formation of β-Lactones and Oxetanes

(2+2)*OC*,*CC-cyclo*-[oxoethylene]-1/2/addition



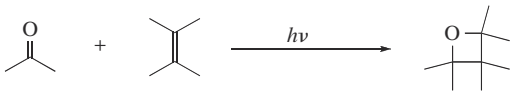
Aldehydes, ketones, and quinones react with ketenes to give β-lactones,[2196] diphenylketene being used most often.[2197] The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. When ketene was added to chloral (Cl_3CCHO) in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β-lactone was produced with excellent enantioselectivity.[2198] Enantioselective β-lactone formation was accomplished using chiral oxazaborolidines.[2199] The use of a chiral Al catalyst also led to β-lactones with good syn selectivity and good enantioselectivity.[2200] Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower enantioselectivity.[2201] Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases, the major dimerization product is not the β-lactone, but a cyclobutanedione (see Reaction **15-63**). However, the proportion of ketene that dimerizes to β-lactone can be increased by the addition of catalysts (e.g., triethylamine or triethyl phosphite).[2202] Ketene acetals [$R_2C{=}C(OR')_2$] add to aldehydes and ketones in the presence of $ZnCl_2$ to give the

[2196] See Calter, M.A.; Tretyak, O.A.; Flaschenriem, C. *Org. Lett.* ***2005****, 7,* 1809.
[2197] Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 139–168; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 39–45, 64–74.
[2198] Wynberg, H.; Staring, E.G.J. *J. Am. Chem. Soc.* ***1982****, 104,* 166; *J. Chem. Soc., Chem. Commun.* ***1984***, 1181.
[2199] Gnanadesikan, V.; Corey, E.J. *Org. Lett.* ***2006****, 8,* 4943.
[2200] Nelson, S.G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* ***2004****, 126*, 14.
[2201] Wynberg, H.; Staring, E.G.J. *J. Org. Chem.* ***1985****, 50,* 1977.
[2202] Elam, E.U. *J. Org. Chem.* ***1967****, 32*, 215.

corresponding oxetanes.[2203]



Ordinary aldehydes and ketones can add to alkenes, under the influence of UV light, to give oxetanes. Quinones also react to give spirocyclic oxetanes.[2204] This reaction, called the *Paterno–Büchi reaction*,[2205] is similar to the photochemical dimerization of alkenes discussed at Reaction **15-63**. In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the alkene. Both singlet (S_1)[2206] and $n,\pi*$ triplet[2207] states have been shown to add to alkenes to give oxetanes. A diradical intermediate $\cdot O—C—C—C\cdot$[2208] has been detected by spectroscopic methods.[2209] Yields in the *Paterno–Büchi reaction* are variable, ranging from very low to fairly high (90%). The reaction can be highly diastereoselective,[2210] and allylic alcohols were shown to react with aldehydes to give an oxetane with syn selectivity.[2211] There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet–triplet photosensitization, see Sec. 7.A.vi).[2212] In most cases, quinones react normally with alkenes, giving oxetane products, but other α,β-unsaturated ketones usually give preferential cyclobutane formation (Reaction **15-63**). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds:[2213] Aldehydes add to silyl enol ethers.[2214] An intramolecular reaction of ketones was reported to give a bicyclic oxetane via

[2203] Aben, R.W.; Hofstraat, R.; Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1981****, 100,* 355. For a discussion of oxetane cycloreversion, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *Org. Lett.* ***2001****, 3*, 1965.

[2204] Ciufolini, M.A.; Rivera-Fortin, M.A.; Byrne, N.E. *Tetrahedron Lett.* ***1993****, 34*, 3505.

[2205] Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 138–152; Carless, H.A.J. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 95–117; Carless, H.A.J. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 425–487; Jones II, M. *Org. Photochem.* ***1981****, 5,* 1; Arnold, D.R. *Adv. PhotoChem.* ***1968****, 6,* 301–423; Chapman, O.L.; Lenz, G. *Org. Photochem.* ***1967****, 1,* 283, pp. 283–294; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 111–139. Also see, Bosch, E.; Hubig, S.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998****, 120*, 386.

[2206] Turro, N.J. *Pure Appl. Chem.* ***1971****, 27,* 679; Yang, N.C.; Kimura, M.; Eisenhardt, W. *J. Am. Chem. Soc.* ***1973****, 95*, 5058; Barltrop, J.A.; Carless, H.A.J. *J. Am. Chem. Soc.* ***1972****, 94,* 1951, 8761.

[2207] Arnold, D.R.; Hinman, R.L.; Glick, A.H. *Tetrahedron Lett.* ***1964***, 1425; Yang, N.C.; Nussim, M.; Jorgenson, M.J.; Murov, S. *Tetrahedron Lett.* ***1964***, 3657.

[2208] See references cited in Griesbeck, A.G.; Stadmüller, S. *J. Am. Chem. Soc.* ***1990****, 112*, 1281. See also, Kutateladze, A.G. *J. Am. Chem. Soc.* ***2001****, 123*, 9279.

[2209] Freilich, S.C.; Peters, K.S. *J. Am. Chem. Soc.* ***1985****, 107,* 3819; Griesbeck, A.G.; Mauder, H.; Stadmüller, S. *Accts. Chem. Res.* ***1994****, 27*, 70.

[2210] Adam, W.; Stegmann, V.R. *J. Am. Chem. Soc.* ***2002****, 124*, 3600. See Ciufolini, M.A.; Rivera-Fortin, M.A.; Zuzukin, V.; Whitmire, K.H. *J. Am. Chem. Soc.* ***1994****, 116*, 1272.

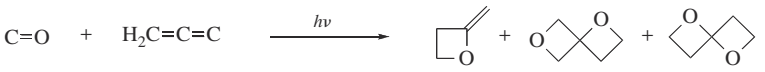
[2211] Greisbeck, A.G.; Bondock, S. *J. Am. Chem. Soc.* ***2001****, 123*, 6191. See also, Adam, W.; Stegmann, V.R. *Synthesis* ***2001***, 1203.

[2212] For a spin-directed reaction, see Griesbeck, A.G.; Fiege, M.; Bondock, S.; Gudipati, M.S. *Org. Lett.* ***2000****, 2*, 3623.

[2213] Howell, A.R.; Fan, R.; Truong, A. *Tetrahedron Lett.* ***1996****, 37*, 8651. See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 317–326.

[2214] Abe, M.; Tachibana, K.; Fujimoto, K.; Nojima, M. *Synthesis* ***2001***, 1243.

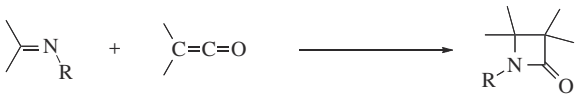
photolysis on the solid state.[2215]



OS **III**, 508; **V**, 456. For the reverse reaction, see OS **V**, 679.

16-96 The Formation of β-Lactams

(2+2)*NC*,*CC*-*cyclo*-[oxoethylene]-1/2/addition



Ketenes add to imines to give β-lactams.[2216] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to RCH=C=O, except when these are generated *in situ* by decomposition of a diazo ketone (the *Wolff rearrangement*, Reaction **18-8**) in the presence of the imine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. Thioketenes[2217] ($R_2C{=}C{=}S$) give β-thiolactams.[2218] Imines also form β-lactams when treated with (1) zinc (or another metal[2219]) and an α-bromo ester (*Reformatsky* conditions, **16-28**),[2220] or (2) the chromium carbene complexes $[(CO)_5Cr{=}C(Me)OMe]$.[2221] The latter method has been used to prepare optically active β-lactams.[2222] Ketenes have also been added to certain hydrazones (e.g., $PhCH{=}NNMe_2$) to give N-amino β-lactams.[2223] A polymer-bound pyridinium salt facilitates β-lactam formation from carboxylic acids and imines.[2224] α-Chloroimines have been used as chiral inductors in this reaction.[2225]

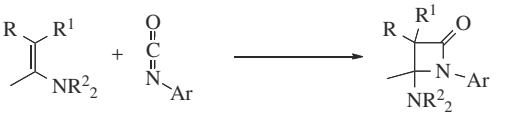
N-Tosyl imines react with ketenes, Proton Sponge (Sec. 8.A.i) and a chiral amine to give the *N*-tosyl β-lactam with good enantioselectivity.[2226] A chiral ferrocenyl catalyst also

[2215] Kang, T.; Scheffer, J.R. *Org. Lett.* ***2001****, 3*, 3361.
[2216] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley-VCH, NY, ***1999***, pp. 1919–1921. See Fu, N.; Tidwell, T.T. *Tetrahedron* ***2008****, 64,* 10465; Brown, M.J. *Heterocycles* ***1989****, 29,* 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976****, 5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327; Muller, L. L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 173–206; Anselme, J. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 305–309; Sandhu, J.S.; Sain, B. *Heterocycles* ***1987****, 26,* 777.
[2217] See Schaumann, E. *Tetrahedron* ***1988****, 44,* 1827.
[2218] Schaumann, E. *Chem. Ber.* ***1976****, 109*, 906.
[2219] With indium: Banik, B.K.; Ghatak, A.; Becker, F.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2179.
[2220] For a review, see Hart, D.J.; Ha, D. *Chem. Rev.* ***1989****, 89,* 1447.
[2221] Hegedus, L.S.; McGuire, M.A.; Schultze, L.M.; Yijun, C.; Anderson, O.P. *J. Am. Chem. Soc.* ***1984****, 106,* 2680; Hegedus, L.S.; McGuire, M.A.; Schultze, L.M. *Org. Synth. 65,* 140.
[2222] Hegedus, L.S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* ***1990****, 112*, 1109.
[2223] Sharma, S.D.; Pandhi, S.B. *J. Org. Chem.* ***1990****, 55*, 2196.
[2224] Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* ***2004****, 69*, 9316.
[2225] D'hooghe, M.; Brabandt, W.V.; Dekeukeleire, S.; Dejaegher, Y.; De Kimpe, N. *Chemistry: European J.* ***2008****, 14,* 6336.
[2226] Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2000****, 122*, 7831.

gives good enantioselectivity,[2227] and chiral ammonium salts[2228] or chiral cinchona alkaloids[2229] have been used as catalysts. A catalytic amount of benzoyl quinine gives β-lactams with good enantioselectivity.[2230]

An intramolecular version of this ketene–imine reaction is known.[2231]

Like the similar cycloaddition of ketenes to alkenes (Reaction **15-63**), most of these reactions probably take place by the diionic mechanism *c* (See **15-63**).[2232] β-Lactams have also been prepared in the opposite manner by the addition of enamines to isocyanates:[2233]



The reactive compound chlorosulfonyl isocyanate[2234] ($ClSO_2NCO$) forms β-lactams even with unactivated alkenes,[2235] as well as with imines,[2236] allenes,[2237] conjugated dienes,[2238] and cyclopropenes.[2239] With microwave irradiation, alkyl isocyanates also react.[2240]

α-Diazo ketones react with imines and microwave irradiation to give β-lactams.[2241] Allylic phosphonate esters react with imines, in the presence of a Pd catalyst, to give β-lactams.[2242] Alkynyl reagents (e.g., $BuC{\equiv}CO^-Li^+$) react with imines to form β-lactams.[2243] Imines and benzylic halides react to give β-lactams in the presence of CO and a Pd catalyst.[2244] Conjugated amides react with NBS and 20% sodium acetate to give an α-bromo β-lactam.[2245] A different approach to β-lactams heated aziridines with CO and a Co catalyst.[2246] Aziridines also react with CO and a dendrimer catalyst to such a β-lactam.[2247]

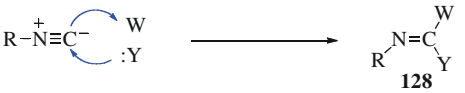
β-Thiolactams are prepared from aryl isothiocyanates.[2248]

OS **V**, 673; **VIII**, 3, 216.

[2227] Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002****, 124*, 1578.
[2228] Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* ***2002****, 124*, 6626.
[2229] France, S.; Shah, M.H.; Weatherwax, A.; Wack, H.; Roth, J.P.; Lectka, T. *J. Am. Chem. Soc.* ***2005****, 127,* 1206.
[2230] Shah, M.H.; France, S.; Lectka, T. *Synlett* ***2003***, 1937.
[2231] Clark, A.J.; Battle, G.M.; Bridge, A. *Tetrahedron Lett.* ***2001****, 42*, 4409.
[2232] See Brady, W.T.; Shieh, C.H. *J. Org. Chem.* ***1983****, 48*, 2499.
[2233] See Opitz, G.; Koch, J. *Angew. Chem. Int. Ed.* ***1963****, 2,* 152.
[2234] Kamal, A.; Sattur, P.B. *Heterocycles* ***1987****, 26*, 1051; Szabo, W.A. *Aldrichimica Acta* ***1977****, 10,* 23; Rasmussen, J.K.; Hassner, A. *Chem. Rev.* ***1976****, 76*, 389; Graf, R. *Angew. Chem. Int. Ed.* ***1968****, 7*, 172.
[2235] Bestian, H. *Pure Appl. Chem.* ***1971****, 27*, 611. See also, Barrett, A.G.M.; Betts, M.J.; Fenwick, A. *J. Org. Chem.* ***1985****, 50*, 169.
[2236] See McAllister, M.A.; Tidwell, T.T. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2239.
[2237] Moriconi, E.J.; Kelly, J.F. *J. Org. Chem.* ***1968****, 33*, 3036. See also, Martin, J.C.; Carter, P.L.; Chitwood, J.L. *J. Org. Chem.* ***1971****, 36*, 2225.
[2238] Malpass, J.R.; Tweddle, N.J. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 874.
[2239] Moriconi, E.J.; Kelly, J.F.; Salomone, R.A. *J. Org. Chem.* ***1968****, 33,* 3448.
[2240] Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn.* ***1996****, 69*, 1667.
[2241] Linder, M.R.; Podlech, J. *Org. Lett.* ***2001****, 3*, 1849.
[2242] Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A.K.M.A.; Tanaka, H. *Tetrahedron Lett.* ***1993****, 34*, 6553.
[2243] Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* ***1998****, 49,* 113.
[2244] Cho, C.S.; Jiang, L.H.; Shim, S.C. *Synth. Commun.* ***1999****, 29*, 2695.
[2245] Naskar, D.; Roy, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2435.
[2246] See Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* ***2001****, 57*, 1801.
[2247] Lu, S.-M.; Alper, H. *J. Org. Chem.* ***2004****, 69*, 3558.
[2248] Awasthi, C.; Yadav, L.D.S. *Synlett* ***2010***, 1783.

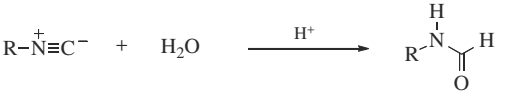
16.B.iv. Addition to Isocyanides[2249]

Addition to R–$^{+}$N≡C^{-} is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. In these additions, the electrophile and the nucleophile *both add to the carbon*. No species add to the nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons to give **128**. In most of the reactions considered below, **128** undergoes a further reaction, so the product is of the form R—$\bar{\text{N}}$H—CR_3.

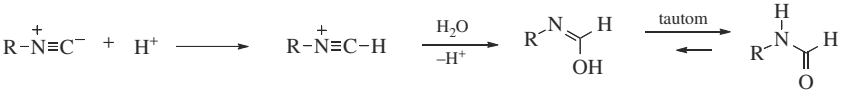


16-97 The Addition of Water to Isocyanides

1/ *N*,2/*C*-Dihydro-2/*C*-oxo-biaddition



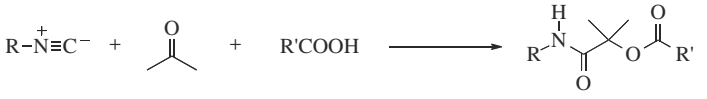
Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably[2250]



The reaction has also been carried out under alkaline conditions, with hydroxide in aq dioxane.[2251] The mechanism here involves nucleophilic attack by hydroxide at the carbon atom. An intramolecular addition of an alkyne (in an ortho alkynyl phenyl isonitrile) to the carbon of an isonitrile occurred with heating in methanol to give quinoline derivatives.[2252]

16-98 The Passerini and Ugi Reactions[2253]

1/*N*-Hydro-2/*C*-(α-acyloxyalkyl),2/*C*-oxo-biaddition



[2249] Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***; Walborsky, H.M.; Periasamy, M.P. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983,*** pp. 835–887; Hoffmann, P.; Marquarding, D.; Kliimann, H.; Ugi, I. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 853–883.

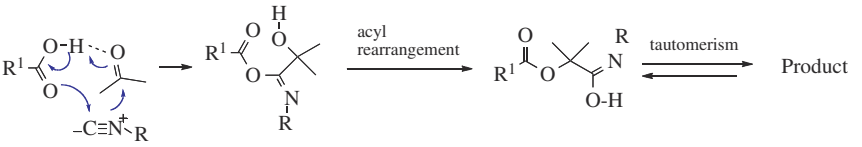
[2250] Lim, Y.Y.; Stein, A.R. *Can. J. Chem.* ***1971****, 49*, 2455.

[2251] Cunningham, I.D.; Buist, G.J.; Arkle, S.R. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 589.

[2252] Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* ***1999****, 1*, 1977.

[2253] Ugi, I. *Angew. Chem. Int. Ed.* ***1982****, 21,* 810; Marquarding, D.; Gokel, G.W.; Hoffmann, P.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 133–143, Gokel, G.W.; Lüdke, G.; Ugi, I. in Ugi, I. Ref. 936, pp. 145–199, 252–254.

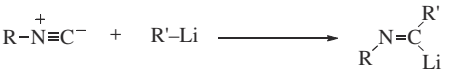
When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is the product in what is called the *Passerini reaction*. A $SiCl_4$ mediated reaction in the presence of a chiral bis(phosphoramide) gives an α-hydroxy amide with good enantioselectivity.[2254] There is a solvent-free *Passerini reaction*[2255] and ionic liquids[2256] can be used. The following mechanism has been postulated for the basic reaction:[2257]



If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*), the product is R′(C=C)NH—C—(C=O)NHR [the corresponding bis(amide) from NH_3] or R′(C=C)NR′—C—(C=O)NHR (from a primary amine R^2NH_2). There is a catalytic *three-component Ugi reaction*.[2258] Repetitive *Ugi reactions* are known.[2259] This product probably arises from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. "Isocyanide-free" *Ugi reactions* use alkyl halides/silver cyanide and KCN to generate the isocyanide *in situ*.[2260] The use of an *N*-protected amino acid[2261] or peptide as the carboxylic acid component and/or the use of an isocyanide containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.[2262] Rare earth metal triflates catalyze this reaction.[2263]

16-99 The Formation of Metalated Aldimines

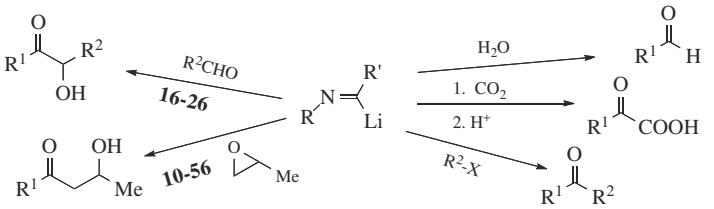
1/1/Lithio-alkyl-addition



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,[2264] as well as with *Grignard reagents*, to give lithium (or magnesium) aldimines.[2265] These

[2254] Denmark, S.E.; Fan, Y. *J. Org. Chem.* ***2005****, 70,* 9667.
[2255] Koszelewski, D.; Szymanski, W.; Krysiak, J.; Ostaszewski, R. *Synth. Commun.* ***2008****, 38,* 1120.
[2256] Fan, X.; Li, Y.; Zhang, X.; Qu, G.; Wang, J. *Can. J. Chem.* ***2006****, 84,* 794.
[2257] See Jenner, G. *Tetrahedron Lett.* ***2000****, 43*, 1235.
[2258] Pan, S.C.; List, B. *Angew. Chem. Int. Ed.* ***2008****, 47,* 3622.
[2259] Constabel, F.; Ugi, I. *Tetrahedron* ***2001****, 57*, 5785.
[2260] El Kaïm, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* ***2009****, 7,* 3024.
[2261] Godet, T.; Bovin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M.A. *Org. Lett.* ***2004****, 6*, 3281.
[2262] Ugi, I. in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, pp. 365–381, *Intra-Sci. Chem. Rep.* ***1971****, 5*, 229; Gokel, G.W.; Hoffmann, P.; Kleimann, H.; Klusacek, H.; Lüdke, G.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 201–215. See also, Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* ***1988****, 110*, 651.
[2263] Okandeji, B.O.; Gordon, J.R.; Sello, J.K. *J. Org. Chem.* ***2008****, 73,* 5595.
[2264] See Ito, Y.; Murakami, M. *Synlett* ***1990***, 245.
[2265] Walborsky, H.M. *J. Org. Chem.* ***1981****, 46*, 5405; ***1982****, 47*, 52. See also, Murakami, H.; Ito, H.; Ito, Y. *J. Org. Chem.* ***1988****, 53*, 4158.

metalated aldimines are versatile nucleophiles and react with various substrates as follows:



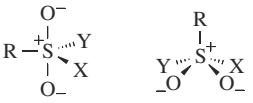
The reaction therefore constitutes a method for converting an organometallic compound (R′M) to an aldehyde (R′CHO, see also, Reaction **12-33**), an α-keto acid,[2266] a ketone R′COR (see also, Reaction **12-33**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case, the C=N bond is hydrolyzed to a C=O bond (Reaction **16-2**).

In a related reaction, isocyanides can be converted to aromatic aldimines by treatment with an iron complex followed by irradiation in benzene solution: RNC + C_6H_6 → PhCH=NR.[2267]

OS **VI**, 751.

16.B.v. Nucleophilic Substitution at a Sulfonyl Sulfur Atom[2268]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.[2269] The mechanisms[2270] are not identical, because a "tetrahedral" intermediate in this case (**129**) would have five groups on the central atom. This is possible since sulfur can accommodate up to 12 electrons in its valence shell, but it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal-bipyramidal transition state (**130**). There are two major experimental results leading to this conclusion.



129 **130**

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare. Recall (Sec. 4.C, category 2) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other is ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone by reaction with a *Grignard reagent* (**16-105**), inversion of configuration was found.[2271] This is not incompatible with an intermediate (e.g., **129**), but it is in good accord with an S_N2-like mechanism with backside attack.

[2266] See Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev.* ***1983****, 83*, 321.
[2267] Jones, W.D.; Foster, G.P.; Putinas, J.M. *J. Am. Chem. Soc.* ***1987****, 109,* 5047.
[2268] See Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* ***1968****, 6*, 81.
[2269] For a comparative reactivity study, see Hirata, R.; Kiyan, N.Z.; Miller, J. *Bull. Soc. Chim. Fr.* ***1988***, 694.
[2270] See Gordon, I.M.; Maskill, H.; Ruasse, M. *Chem. Soc. Rev.* ***1989****, 18*, 123.
[2271] Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969****, 91,* 3603. See also, Jones, M.R.; Cram, D.J. *J. Am. Chem. Soc.* ***1974****, 96,* 2183.

2. More direct evidence against **129** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **129** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[2272]

Other evidence favoring the S_N2-like mechanism comes from kinetics and substituent effects.[2273] However, evidence for the mechanism involving **129** is that the rates did not change much with changes in the leaving group[2274] and the ρ values were large, indicating that a negative charge builds up in the transition state.[2275]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[2276] that at least some of the reaction takes place by an elimination–addition mechanism (E1cB, similar to the one shown in Reaction **16-69**), going through a *sulfene* intermediate,[2277] as in the reaction between methanesulfonyl chloride and aniline.

$$CH_3—SO_2Cl \xrightarrow{\text{base}} \underset{\text{A sulfene}}{CH_2=SO_2} \xrightarrow{PhNH_2} CH_3—SO_2—NHPh$$

In the special case of nucleophilic substitution at a sulfonic ester (RSO_2OR'), where R′ is alkyl, R′–O cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (Sec. 10.G.iii).[2278] Many of these reactions have been considered previously (e.g., Reactions **10-4** and **10-10**) as nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the low tendency of aryl substrates for nucleophilic substitution.[2279]

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3 > F^- > AcO^- > Cl^- > H_2O > I^-$.[2280] This order is similar to that at a carbonyl carbon (Sec. 10.G.ii). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon that is considerably softer and has a different order of nucleophilicity (Sec. 10.G.ii).

16-100 Attack by OH: Hydrolysis of Sulfonic Acid Derivatives

***S* -Hydroxy-de-chlorination**, and so on

$$RSO_2X \xrightarrow[H_2O + H^+]{H_2O \quad \text{or}} RSO_2OH \qquad (X = Cl, OR', NR_2')$$

[2272] Kaiser, E.T.; Zaborsky, O.R. *J. Am. Chem. Soc.* ***1968****, 90,* 4626.
[2273] Lee, I.; Kang, H.K.; Lee, H.W. *J. Am. Chem. Soc.* ***1987****, 109*, 7472; Arcoria, A.; Ballistreri, F.P.; Spina, E.; Tomaselli, G.A.; Maccarone, E. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1793; Gnedin, B.G.; Ivanov, S.N.; Shchukina, M.V. *J. Org. Chem. USSR* ***1988***, *24*, 731.
[2274] Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 468.
[2275] Ciuffarin, E.; Senatore, L. *Tetrahedron Lett.* ***1974***, 1635.
[2276] Opitz, G. *Angew. Chem. Int. Ed.* ***1967****, 6*, 107. See Thea, S.; Guanti, G.; Hopkins, A.; Williams, A. *J. Org. Chem.* ***1985****, 50*, 5592; Skonieczny, S. *Tetrahedron Lett.* ***1987****, 28*, 5001; Pregel, M.J.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 307.
[2277] King, J.F. *Acc. Chem. Res.* ***1975****, 8,* 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Opitz, G. *Angew. Chem. Int. Ed.* ***1967****, 6,* 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966****, 20,* 67.
[2278] See Netscher, T.; Prinzbach, H. *Synthesis* ***1987***, 683.
[2279] See Tagaki, W.; Kurusu, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969****, 42*, 2894.
[2280] Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973****, 95*, 3912.

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can be hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **10-4**, and usually involves R′—O cleavage, except when R′ is aryl. In some cases, retention of configuration has been shown at alkyl R′, indicating S—O cleavage.[2281] Sulfonamides are generally *not* hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze sulfonamides, but less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[2282]

Magnesium in methanol has been used to convert sulfonate esters to the parent alcohol.[2283] Likewise, $CeCl_3{\bullet}7\ H_2O$—NaI in acetonitrile converted aryl tosylates to the parent phenol derivative.[2284]

OS **I**, 14; **II**, 471; **III**, 262; **IV**, 34; **V**, 406; **VI**, 652, 727. Also see, OS **V**, 673; **VI**, 1016.

16-101 Attack by OR: Formation of Sulfonic Esters

***S*-Alkoxy-de-chlorination**, and so on

$$RSO_2Cl + R'OH \xrightarrow{\text{base}} RSO_2OR'$$

$$RSO_2NR_2'' + R'OH \xrightarrow{\text{base}} RSO_2OR' + NR_2''$$

Sulfonic esters are most frequently prepared by treatment of the corresponding sulfonyl halides with alcohols in the presence of a base.[2285] This procedure is the most common method for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R′ may be alkyl or aryl. The base is often pyridine or another amine, which functions as a nucleophilic catalyst,[2286] as in the similar alcoholysis of carboxylic acyl halides (Reaction **16-61**). Primary alcohols react most rapidly, and it is often possible to sulfonate a primary OH group selectively in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to *N,N*-disubstituted sulfonamides; that is, R may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually RO^-. The R′ may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[2287] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl orthoformate [$HC(OR)_3$], without catalyst or solvent;[2288] and with a trialkyl phosphite [$P(OR)_3$].[2289]

Mono-tosylation of a 1,2-diol was achieved using tosyl chloride and triethylamine, with a tin oxide catalyst.[2290]

[2281] Chang, F.C. *Tetrahedron Lett.* ***1964***, 305.
[2282] Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* ***1974****, 64,* 315.
[2283] Sridhar, M.; Kumar, B.A.; Narender, R. *Tetrahedron Lett.* ***1998****, 39*, 2847.
[2284] Reddy, G.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000****, 30*, 3829.
[2285] See Simpson, L.S.; Widlanski, T.S. *J. Am. Chem. Soc.* ***2006****, 128*, 1605.
[2286] Rogne, O. *J. Chem. Soc. B* ***1971***, 1334. See also, Litvinenko, M.; Shatskaya, V.A.; Savelova, V.A. *Doklad. Chem.* ***1982****, 265,* 199.
[2287] Klamann, D.; Fabienke, E. *Chem. Ber.* ***1960****, 93*, 252.
[2288] Padmapriya, A.A.; Just, G.; Lewis, N.G. *Synth. Commun.* ***1985****, 15*, 1057.
[2289] Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* ***1987***, 857.
[2290] Martinelli, M.J.; Vaidyanathan, R.; Khau, V.V. *Tetrahedron Lett.* ***2000****, 41*, 3773; Bucher, B.; Curran, D.P. *Tetrahedron Lett.* ***2000****, 41,* 9617.

OS **I**, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see, OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **VIII**, 568.

16-102 Attack by Nitrogen; Formation of Sulfonamides

***S*-Amino-de-chlorination**

$$RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2$$

Microwave assisted conversion of sulfonic acids to a 2,4,6-trichloro[1,3,5]triazine derivative is followed by formation of the sulfonamide.[2291] The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides.[2292] Primary amines give *N*-alkyl sulfonamides, and secondary amines give *N,N*-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. *N*-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while *N,N*-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.[2293] (1) Many *N*-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[2294] so that a primary amine may appear to be a secondary amine. (2) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[2289]

A primary or a secondary amine can be protected by reaction with phenacylsulfonyl chloride ($PhCOCH_2SO_2Cl$) to give a sulfonamide ($RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$).[2295] The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides (RSO_2N_3).[2296] Chlorothioformates, [ROC(=S)Cl] react with triethylamine to give the *N,N*-diethylthioamide.[2297]

A quite different synthesis of sulfonamides treated allyltributyltin with PhI=NTs, in the presence of copper(II) triflate.[2298] Another alternative method treats silyl enol ethers with sulfur dioxide, and subsequent reaction with a secondary amine gave the β-sulfonamido ester.[2299]

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **VIII**, 104. See also, OS **VI**, 788.

16-103 Attack by Halogen: Formation of Sulfonyl Halides

***S*-Halo-de-hydroxylation**

$$RSO_2OH + SOCl_2 \longrightarrow RSO_2Cl$$

This reaction, parallel with **16-79**, is the standard method for the preparation of sulfonyl halides. Both PCl_3 and $SOCl_2$ have been used, and sulfonic acid salts can also serve as

[2291] De Luca, L.; Giacomelli, G. *J. Org. Chem.* ***2008****, 73,* 3967.
[2292] See Kamal, A.; Reddy, J.S.; Bharathi, E.V.; Dastagiri, D. *Tetrahedron Lett.* ***2008****, 49*, 348.
[2293] See Gambill, C.R.; Roberts, T.D.; Shechter, H. *J. Chem. Educ.* ***1972****, 49,* 287.
[2294] Fanta, P.E.; Wang, C.S. *J. Chem. Educ.* ***1964****, 41,* 280.
[2295] Hendrickson, J.B.; Bergeron, R. *Tetrahedron Lett.* ***1970***, 345.
[2296] For an example, see Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* ***V***, 179.
[2297] Milan, D.S.; Prager, R.H. *Aust. J. Chem.* ***1999****, 52*, 841.
[2298] Kim, D.Y.; Kim. H.S.; Choi, Y.J.; Mang, J.Y.; Lee, K. *Synth. Commun.* ***2001****, 31*, 2463.
[2299] Bouchez, L.C.; Dubbaka, S.R.; Urks, M.; Vogel, P. *J. Org. Chem.* ***2004****, 69,* 6413.

substrates. Cyanuric acid (2,4,6-trichloro[1,3,5]triazene) serves as a chlorinating agent.[2300] Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by Reaction **16-102**) by treatment with bromine or iodine.[2301] Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.[2302]

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also, OS **VII**, 495.

16-104 Attack by Hydrogen: Reduction of Sulfonyl Chlorides

***S*-Hydro-de-chlorination** or ***S* -Dechlorination**

$$2\ \ RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H^+} 2\ \ RSO_2H$$

Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see Reaction **19-78**.

OS **I**, 7, 492; **IV**, 674.

16-105 Attack by Carbon: Preparation of Sulfones

***S*-Aryl-de-chlorination**

$$ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'$$

Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Organolithium reagents react with sulfonyl fluorides at –78 °C to give the corresponding sulfone.[2303] Aromatic sulfonates have been converted to sulfones with organolithium compounds,[2304] with aryltin compounds,[2305] with an Fe catalyst,[2306] and with alkyl halides and Zn metal.[2307] Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a Pd complex catalyst.[2308] Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an $AlCl_3$ catalyst.[2309] Note that trifluoromethylsulfones were converted to methyl sulfones by reaction with methylmagnesium bromide.[2310]

Arylboronic acids (Reaction **12-28**) react with sulfonyl chlorides in the presence of $PdCl_2$ to give the corresponding sulfone.[2311] Arylboronic acids also react with sulfinate anions (RSO_2Na) in the presence of $Cu(OAc)_2$ to give the sulfone.[2312]

OS **VIII**, 281.

[2300] Blotny, G. *Tetrahedron Lett.* ***2003****, 44*, 1499.
[2301] Poshkus, A.C.; Herweh, J.E.; Magnotta, F.A. *J. Org. Chem.* ***1963****, 28,* 2766; Litvinenko, L.M.; Dadali, V.A.; Savelova, V.A.; Krichevtsova, T.I. *J. Gen. Chem. USSR* ***1964****, 34,* 3780.
[2302] See Bianchi, T.A.; Cate, L.A. *J. Org. Chem.* ***1977****, 42,* 2031, and references cited therein.
[2303] Frye, L.L.; Sullivan, E.L.; Cusack, K.P.; Funaro, J.M. *J. Org. Chem,* ***1992****, 57*, 697.
[2304] Baarschers, W.H. *Can. J. Chem.* ***1976****, 54*, 3056.
[2305] Neumann, W.P.; Wicenec, C. *Chem. Ber.* ***1993****, 126*, 763.
[2306] Volla, C.M.R.; Vogel, P. *Angew. Chem. Int. Ed.* ***2008****, 47,* 1305.
[2307] Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* ***1998****, 28*, 1785.
[2308] Labadie, S.S. *J. Org. Chem.* ***1989****, 54*, 2496.
[2309] See Waykole, L.; Paquette, L.A. *Org. Synth. 67*, 149.
[2310] Steensma, R.W.; Galabi, S.; Tagat, J.R.; McCombie, S.W. *Tetrahedron Lett.* ***2001****, 42*, 2281.
[2311] Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Org.Lett.* ***2004****, 6*, 2105.
[2312] Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D.A. *Tetrahedron Lett.* ***2004****, 45*, 3233.

CHAPTER 17

Eliminations



A so-called β-*elimination* reaction occurs when two groups are lost from adjacent atoms so that a new double[1] (or triple) bond is formed. In general, the atom bearing a leaving group is the α, and the other the β atom. In an α-elimination, both groups are lost from the same atom to give a carbene (or a nitrene):



In a γ-elimination, a three-membered ring is formed:



Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring (X—Y—Z → X—Z + Y). Such reactions are called *extrusion reactions*. This chapter discusses β-elimination and extrusion reactions (see Sec. 2.F.vi); however, β-elimination in which both X and W are hydrogen atoms are oxidation reactions. They are treated in Chapter 19.

17.A. MECHANISMS AND ORIENTATION

β-Elimination reactions may be divided into two types: one type taking place largely in solution, the other (pyrolytic eliminations) mostly in the gas phase. In the reactions, one group leaves with its electrons and the other without (i.e., it is pulled off), the latter most

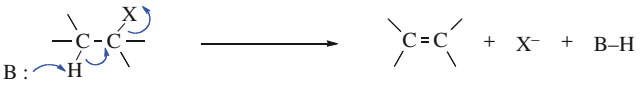
[1] See Williams, J.M.J. *Preparation of Alkenes, A Practical Approach*, Oxford Univ. Press, Oxford, ***1996***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

often being hydrogen. In these cases, the former leaves as the *leaving group or nucleofuge*. For pyrolytic eliminations, there are two principal mechanisms, one pericyclic and the other a free radical pathway. A few photochemical eliminations are also known (the most important is *Norrish-type II* cleavage of ketones, Sec. 7.A.vii), but these are not generally of synthetic importance[2] and will not be discussed further. In most β-eliminations, the new bonds are C=C or C≡C. The discussion of mechanisms is largely confined to these cases.[3] Mechanisms in solution (E2, E1)[4] and E1cB are discussed first. While standard methods are used to examine elimination reactions, new techniques (e.g., the velocity map ion imaging technique) have been used to study ultrafast elimination reactions.[5]

17.A.i. The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the proton on the β carbon is pulled off by a base, leading to near-simultaneous expulsion of the leaving group (nucleofuge):



The mechanism takes place in one step and is kinetically second order: first order in substrate and first order in base. An *ab initio* study has produced a model for the E2 transition state geometry.[6] The IUPAC designation is $A_{xH}D_HD_N$, or more generally (to include cases where the electrofuge is not hydrogen), $A_nD_ED_N$. It often competes with the S_N2 mechanism (Sec. 10.A.i). With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the S_N2 mechanism, the leaving group may be positive or neutral and the base may be negatively charged or neutral.

Evidence for the existence of the E2 mechanism includes (1) the reaction displays the proper second-order kinetics; (2) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this

[2] See Neckers, D.C.; Kellogg, R.M.; Prins, W.L.; Schoustra, B. *J. Org. Chem.* ***1971****, 36*, 1838.

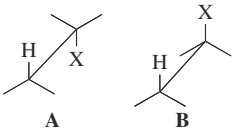
[3] Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***. For reviews, see Gandler, J.R. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 733–797; Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 153–221; More O'Ferrall, R.A. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 609–675; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, ***1973***, pp. 163–372; Saunders, Jr., W.H. *Acc. Chem. Res.* ***1976****, 9*, 19; Bordwell, F.G. *Acc. Chem. Res.* ***1972****, 5,* 374; Fry, A. *Chem. Soc. Rev.* ***1972****, 1*, 163; LeBel, N.A. *Adv. Alicyclic Chem.* ***1971****, 3,* 195; Bunnett, J.F. *Surv. Prog. Chem.* ***1969****, 5*, 53; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, the articles by Saunders, Jr., W.H. pp. 149–201 (eliminations in solution); and by Maccoll, A. pp. 203–240 (pyrolytic eliminations); Köbrich, G. *Angew. Chem. Int. Ed.* ***1965****, 4*, 49, pp. 59–63 (for the formation of triple bonds).

[4] Thibblin, A. *Chem. Soc. Rev.* ***1993****, 22*, 427.

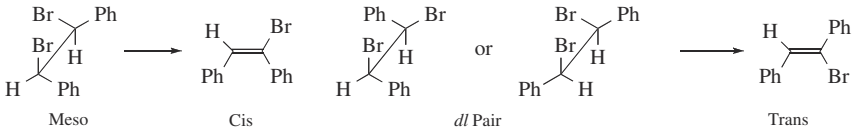
[5] Roeterdink, W.G.; Rijs, A.M.; Janssen, M.H.M. *J. Am. Chem. Soc.* ***2006****, 128*, 576.

[6] Schrøder, S.; Jensen, F. *J. Org. Chem.* ***1997****, 62*, 253. See Wu, W.; Shaik, S.; Saunders, Jr., W.H. *J. Org. Chem.* ***2010****, 75*, 3722.

bond in the rate-determining step.[7] However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB, Sec. 17.A.iii). The most compelling evidence for the E2 mechanism is found in stereochemical studies.[8]



As will be illustrated in the examples below, the E2 mechanism is stereospecific: The five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be trans to one another (**A**) with a dihedral angle of 180°, or they may be cis (**B**) with a dihedral angle of 0°.[9] Conformation **A** is called *antiperiplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti elimination*. Conformation **B** is *syn periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below), anti elimination is usually greatly favored over syn elimination, probably because **A** is a staggered conformation (Sec. 4.O.i) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. Solvent effects play an important role in the conformational preference. A few of the many known examples of predominant or exclusive anti elimination follow:



1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the *trans*-alkene. This stereospecific result, which was obtained in 1904,[10] demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds that have a meso form. Anti elimination requires that an erythro *dl* pair (or either isomer) give the cis alkene, and the threo *dl* pair (or either isomer) give the trans isomer. This result has been found many times. Anti elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide

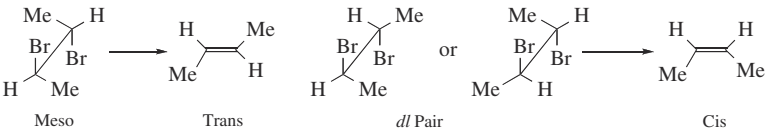
[7] See Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1961****, 83*, 593. For a review of isotope effects, see Fry, A. *Chem. Soc. Rev.* ***1972****, 1,* 163.

[8] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980****, 80,* 453; Sicher, J. *Angew. Chem. Int. Ed.* ***1972****, 11*, 200; *Pure Appl. Chem.* ***1971****, 25,* 655; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 105–163; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 217–235; More O'Ferrall, R.A. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 630–640.

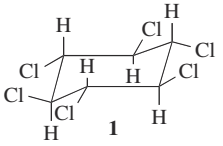
[9] DePuy, C.H.; Morris, G.F.; Smith, J.S.; Smat, R.J. *J. Am. Chem. Soc.* ***1965****, 87,* 2421.

[10] Pfeiffer, P. *Z. Phys. Chem.* ***1904****, 48*, 40.

ion, the two bromines are removed (**17-22**). Using iodide as a base in this manner is unusual nowadays, and common bases are discussed in several sections below, including Reaction **17-13**. In this case, the meso compound gave the trans alkene while the *dl* pair gave the cis:[11]



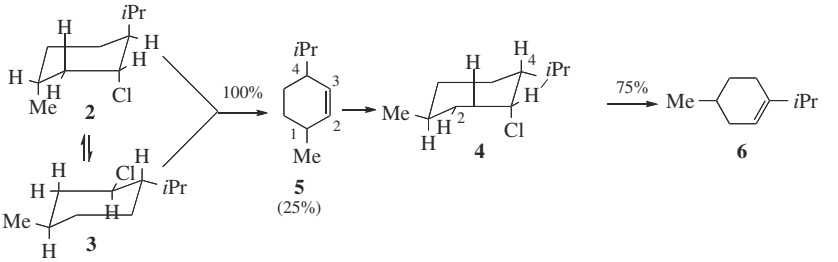
2. In open-chain compounds, rotation about C—C bonds usually lead to conformation in which H and X are antiperiplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven meso forms and a *dl* pair (see Sec. 4.G). Four of the meso compounds and the *dl* pair) were treated with base to initiate elimination. Only one of these (**1**) has no Cl that is trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[12] This result demonstrates that anti elimination is greatly favored over syn elimination, although the latter must be taking place on **1**, but very slowly, to be sure.


1

3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. Adjacent trans groups on a six-membered ring can be diaxial or diequatorial (Sec. 4.O.ii) and the molecule is generally free to adopt either conformation, although one may have a higher energy than the other. Antiperiplanarity of the leaving group and the proton on the adjacent carbon requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. Compound **3**, in which the three substituents are all equatorial, is the more stable and less reactive. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial; there are axial hydrogen atoms on both C-2 and C-4. The results are the following: neomenthyl chloride gives rapid E2 elimination and the alkene produced is predominantly **6** (**6/5** ratio is ~ 3:1) in accord with *Zaitsev's rule* (see Reaction **12-2**, Sec. 17.B). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and *Zaitsev's rule* is free to operate. However, for menthyl chloride, elimination is much slower and the product is entirely the *anti-Zaitsev* alkene **5**. It is slow because the unfavorable

[11] Winstein, S.; Pressman, D.; Young, W.G. *J. Am. Chem. Soc.* ***1939****, 61,* 1645.
[12] Cristol, S.J.; Hause, N.L.; Meek, J.S. *J. Am. Chem. Soc.* ***1951****, 73,* 674.

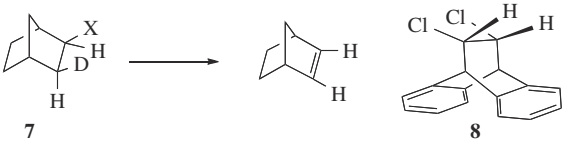
conformation (**2**) must be achieved before elimination can take place. There is an axial hydrogen only on this side as the product must be **5**.[13]



4. Anti elimination also occurs in the formation of triple bonds, as shown by elimination from *cis*- and *trans*-HO_2C-CH=C(Cl)CO_2H. In this case, the product in both cases is $HO_2CC{\equiv}CCO_2H$, but the trans isomer reacts $\sim$ 50 times faster than the cis compound.[14]

Some examples of syn elimination have been found in molecules where H and X could not achieve an antiperiplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.[15] Similar results were obtained with other leaving groups and with bicyclo [2.2.2] compounds.[16] In these cases the exo X group cannot achieve a dihedral angle of 180° with the endo β hydrogen because of the rigid structure of the molecule. The dihedral angle here is $\sim$ 120°. Syn elimination with a dihedral angle of $\sim$ 0° is clearly preferred to anti elimination where the angle is restricted to $\sim$ 120°.



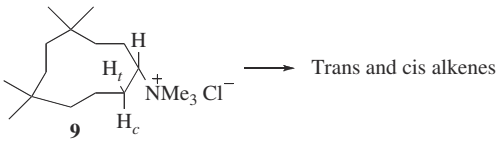
2. Molecule **8** is a particularly graphic example of the need for a planar transition state. In **8**, each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups were not required, anti elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be $\sim$ 120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.[17] Note that syn elimination from **8** is even less likely than anti elimination. Syn elimination can take place from the trans isomer of **8** (dihedral angle $\sim$ 0°); this isomer reacted about eight times faster than **8**.[17]

[13] Hughes, E.D.; Ingold, C.K.; Rose, J.B. *J. Chem. Soc.* ***1953***, 3839.
[14] Michael, A. *J. Prakt. Chem.* ***1895****, 52,* 308. See also, Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* ***1968***, 958.
[15] Kwart, H.; Takeshita, T.; Nyce, J.L. *J. Am. Chem. Soc.* ***1964****, 86,* 2606.
[16] See Sicher, J.; Pánkova, M.; Závada, J.; Kniezo, L.; Orahovats, A. *Collect. Czech. Chem. Commun.* ***1971****, 36*, 3128; Bartsch, R.A.; Lee, J.G. *J. Org. Chem.* ***1991****, 56,* 212, 2579.
[17] Cristol, S.J.; Hause, N.L. *J. Am. Chem. Soc.* ***1952****, 74,* 2193.

The examples given so far illustrate two points. (1) Anti elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, anti elimination is greatly slowed or prevented entirely. (2) For the simple systems so far discussed, syn elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

The concept of vinylogy was introduced in Section 6.B and in Reaction **10-68**, category 4. Using this concept, a 1,2-elimination can be extended to give a 1,*x*-elimination when π bonds are incorporated between the carbon bearing the acidic proton and the leaving group (e.g., X-C-C=C-C, X-C-C=C-C=C-C or X-C-C≡C-C).[18]

As noted in Section 4.Q.ii, six-membered rings are the only ones among rings of 4–13 members in which strain-free antiperiplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cycloalkyltrimethylammonium hydroxides were subjected to elimination (Reaction **17-7**) and the following percentages of syn elimination were found with each ring size: four-membered, 90%; five-membered, 46%; six-membered, 4% seven-membered, 31–37%.[19] Note that the NMe_3^+ group has a greater tendency to syn elimination than do other common leaving groups (e.g., OTs, Cl, and Br).



9

Other examples of syn elimination have been found in medium-ring compounds, where both cis and trans alkenes are possible (Sec. 4.K.i). As an illustration, elimination of 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**)[20] gave mostly *trans*- but also some *cis*-tetramethylcyclodecenes as products. Note that *trans*-cyclodecenes, although stable, are less stable than the cis isomers. In order to determine the stereochemistry of the reaction, the elimination was repeated, this time using deuterated substrates. When **9** was deuterated in the trans position ($H_t = D$), there was a substantial isotope effect in the formation of *both* cis and trans alkenes, but when **9** was deuterated in the cis position ($H_c = D$), there was *no* isotope effect in the formation of either alkene. Since an isotope effect is expected for an E2 mechanism,[21] these results indicated that *only* the trans hydrogen (H_t) was lost, whether the product was the cis or the trans isomer.[22] This in turn means that *the cis isomer must have been formed by anti elimination and the trans isomer by syn elimination*. Anti elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the C—H_t and C—NMe_3^+ bonds are syn periplanar. Other types of evidence have also demonstrated this remarkable result, called the syn–anti dichotomy.[23] The fact that syn

[18] See Werner, C.; Hopf, H.; Dix, I.; Bubenitschek, P.; Jone, P.G. *Chemistry: European J.* ***2007****, 13*, 9462.

[19] Cooke, Jr., M.P.; Coke, J.L. *J. Am. Chem. Soc.* ***1968****, 90,* 5556. See also, Coke, J.L.; Smith, G.D.; Britton, Jr., G. H. *J. Am. Chem. Soc.* ***1975****, 97*, 4323.

[20] Závada, J.; Svoboda, M.; Sicher, J. *Collect. Czech. Chem. Commun.* ***1968****, 33,* 4027.

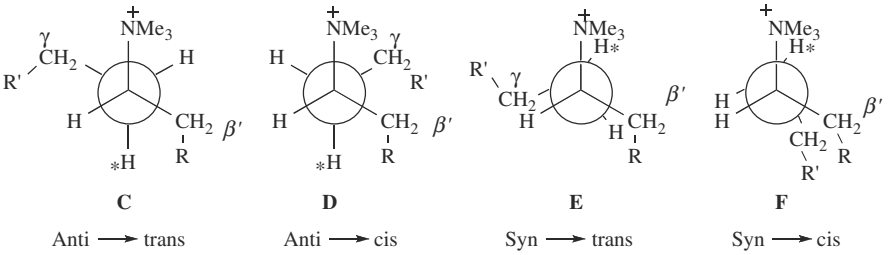
[21] Other possible mechanisms [e.g., E1cB, Sec. 17.A.iii or α′, β-elimination (Reaction **17-8**)], were ruled out in all these cases by other evidence.

[22] This conclusion has been challenged by Coke, J.L. *Sel. Org. Transform* ***1972****, 2*, 269.

[23] Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1967****, 32*, 2122; Závada, J.; Sicher, J. *Collect. Czech. Chem. Commun.* ***1967****, 32,* 3701. For a review, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980****, 80*, 453.

elimination in this case predominates over anti (as indicated by the formation of trans-isomer in greater amounts than cis) has been explained by conformational factors.[24] The syn–anti dichotomy has also been found in other medium-ring systems (8–12 membered),[25] although the effect is greatest for 10-membered rings. With leaving groups,[26] the extent of this behavior decreases in the order $^{+}NMe_3 > OTs > Br > Cl$, which parallels steric requirements. When the leaving group is uncharged, syn elimination is favored by strong bases and by weakly ionizing solvents.[27]

Syn elimination and the syn–anti dichotomy have also been found in open-chain systems, although to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, $\sim$ 67% of the reaction followed the syn-anti dichotomy.[28] In general, syn elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β' and the γ carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not completely understood, but the following conformational effects have been proposed as a partial explanation.[29] The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



In order for an E2 mechanism to take place, a base must approach the proton marked $*$. In **C**, this proton is shielded on both sides by R and R′. In **D**, the shielding is on only one side. Therefore, when anti elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti $\rightarrow$ trans route should be diminished more than the anti $\rightarrow$ cis route. When syn elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway and syn elimination should generally give the trans-isomer. In general, deviations from the synanti dichotomy are greater on the trans side than on the cis. Thus, trans-alkenes are formed partly or mainly by syn elimination, but *cis*-alkenes are formed entirely by anti elimination.

[24] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980****, 80,* 453; Coke, J.L. *Sel. Org. Transform.* ***1972****, 2*, 269; Sicher, J. *Angew. Chem. Int. Ed.* ***1972****, 11*, 200; *Pure Appl. Chem.* ***1971****, 25,* 655.

[25] See Coke, J.L.; Mourning, M.C. *J. Am. Chem. Soc.* ***1968****, 90*, 5561.

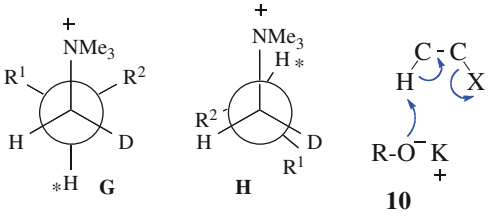
[26] See Sicher, J.; Jan, G.; Schlosser, M. *Angew. Chem. Int. Ed.* ***1971****, 10*, 926; Závada, J.; Pánková, M. *Collect. Czech. Chem. Commun.* ***1980****, 45*, 2171 and references cited therein.

[27] See Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1968****, 33*, 1278.

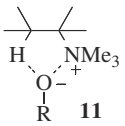
[28] Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970****, 92*, 6904. See Schlosser, M.; An, T.D. *Helv. Chim. Acta* ***1979****, 62*, 1194; Pánková, M.; Kocián, O.; Krupicka, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1983****, 48*, 2944.

[29] Chiao, W.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1977****, 99*, 6699.

Predominant syn elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.[30] In this case, the conformation leading to syn elimination (**H**) is also less strained than **G**, which gives anti elimination. The **G** compound has three bulky groups (including NMe_3^+) in the *gauche* position to each other.



It was mentioned above that weakly ionizing solvents promote syn elimination when the leaving group is uncharged. This is probably caused by ion pairing, which is greatest in nonpolar solvents.[31] Ion pairing can cause syn elimination with an uncharged leaving group by means of the transition state shown in **10**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.[32] The ratio of syn to anti elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. When the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the *t*-BuO^- K^{++} ion pair and thus leaves *t*-BuO^- as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.[33] However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti elimination.[34] In this case, a relatively free base (e.g., PhO^-) can be attracted to the leaving group (see **11**), putting it in a favorable position for attack on the syn β hydrogen, while ion pairing would reduce this attraction.

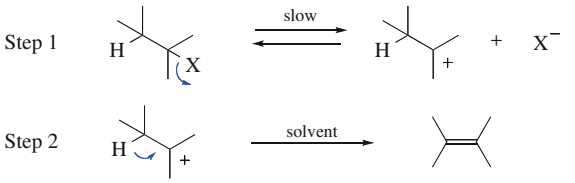


It can be concluded that anti elimination is generally favored in the E2 mechanism, but that steric (inability to form the antiperiplanar transition state), conformational, ion pairing, and other factors cause syn elimination to intervene (and even predominate) in some cases.

[30] Dohner, B.R.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1986****, 108,* 245.
[31] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980****, 80*, 453; Bartsch, R.A. *Acc. Chem. Res.* ***1975****, 8*, 239.
[32] Svoboda, M.; Hapala, J.; Závada, J. *Tetrahedron Lett.* ***1972***, 265.
[33] See Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1979****, 44,* 3718; Croft, A.P.; Bartsch, R.A. *Tetrahedron Lett.* ***1983****, 24,* 2737; Kwart, H.; Gaffney, A.H.; Wilk, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 565.
[34] Borchardt, J.K.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1974****, 96,* 3912.

17.A.ii. The E1 Mechanism

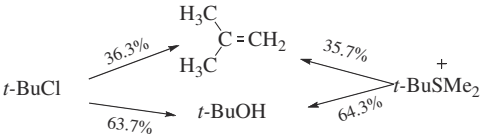
The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:



The IUPAC designation is $D_N + D_E$ (or $D_N + D_H$). This mechanism normally operates without an *added* base. Just as the E2 mechanism competes with the S_N2,[35] so the E1 mechanism competes with the S_N1. In fact, the first step of the E1 is exactly the same as that of the S_N1 mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the S_N1 process. In a pure E1 reaction (without ion pairs, etc.), the product should be completely nonstereospecific, since bond rotation is possible in the carbocation before deprotonation.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course, the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (Sec. 6.J.vi), but this point can be checked easily by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.[36]
2. If the reaction is performed on two molecules that differ only in the leaving group (e.g., *t*-BuCl and *t*-$BuSMe_2^+$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases. This means that the nature of the leaving group does not affect the second step, and *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3 °C in 80% aq ethanol with the following results:[37]



[35] See Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***2009****, 131*, 8227.
[36] Baciocchi, E.; Clementi, S.; Sebastiani, G.V.; Ruzziconi, R. *J. Org. Chem.* ***1979****, 44,* 32.
[37] Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2038.

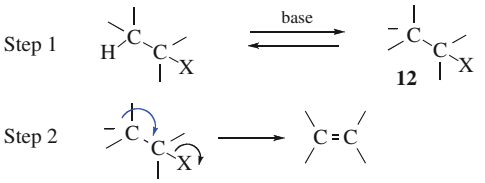
Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

3. Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give alkenes where a cis hydrogen must be removed, often in preference to the removal of a trans hydrogen. For example, menthyl chloride (**2**), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable alkene (*Zaitsev's rule*, Reaction **12-2**) is predominantly formed.
4. If carbocations are intermediates, rearrangements should occur with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for S_N1 reactions (Sec. 10A. iii).[38] This effect is naturally greatest for nondissociating solvents: It is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (Sec. 10.A.iii, category 1) extends to elimination reactions too, and that the S_N1, S_N2, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least occasionally.[39]

17.A.iii. The E1cB Mechanism[40]

In the E1 mechanism, X leaves first and then H is removed. In the E2 mechanism, H is removed, which triggers the expulsion of X. There is a third possibility: The H is removed first to form **12**, and then X leaves. This reaction is a two-step process, called the E1cB *mechanism*,[41] or the *carbanion mechanism*, since the intermediate is a carbanion, (**12**). The



name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the S_N1cB mechanism, Sec. 10.G.iii, category 1). The IUPAC designation is $A_nD_E + D_N$ or $A_{xh}D_H + D_N$ (see Sec. 9.F). Three limiting cases can be distinguished: (1) The carbanion returns to starting material faster than it forms product: step 1 is reversible; step 2 is slow. (2) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case, step 1 is essentially

[38] See Thibblin, A. *J. Am. Chem. Soc.* ***1987****, 109,* 2071; *J. Phys. Org. Chem.* ***1989****, 2*, 15.
[39] Sneen, R.A. *Acc. Chem. Res.* ***1973****, 6,* 46; Thibblin, A.; Sidhu, H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1423. See, however, McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1577.
[40] Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 9, Elsevier, NY, ***1973***, pp. 158–178; Hunter, D.H. *Intra-Sci. Chem. Rep.* ***1973****, 7(3),* 19; McLennan, D.J. *Q. Rev. Chem. Soc.* ***1967****, 21*, 490. For a general discussion, see Koch, H.F. *Acc. Chem. Res.* ***1984****, 17,* 137.
[41] See Ryberg, P.; Matsson, O. *J. Org. Chem.* ***2002****, 67*, 811.

irreversible. (3) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, step 1 is essentially irreversible. These cases have been given the designations: (1) $(E1cB)_R$, (2) $(E1cB)_I$ (or $E1cB_{irr}$), and (3) $(E1)_{anion}$. Their characteristics are listed in Table 17.1.[42] Investigations of the reaction order are generally not very useful (except for case 3, which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.[43] The greatest likelihood of finding the E1cB mechanism is expected in substrates that have (a) a poor nucleofuge and (b) an acidic hydrogen. In addition, most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism:

1. The first step of the $(E1cB)_R$ mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was* deuterium in the recovered alkene.[44] A similar result was found for pentahaloethanes.[45] These substrates are relatively acidic. In both cases, the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (Sec. 8.F, category 7). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[46] If this type of evidence is a guide, then it may be inferred that the $(E1cB)_R$ mechanism is quite rare, at least for eliminations with common leaving groups (e.g., Br, Cl, or OTs), which yield C=C double bonds.
2. When the reaction shown was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the rate leveled off at high buffer concentrations, indicating a change in rate-determining step.[47] This rules out an E2 mechanism, which has only one step.[48] When D_2O was used instead of H_2O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported).

$$p\text{-}NO_2C_6H_4{-}CH_2{-}CH_2{-}\overset{+}{N}R_4 + B^- \rightarrow p\text{-}NO_2C_6H_4{-}CH_2{=}CH_2 + BH + NR_3$$

[42] This table, which appears in Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 9, Elsevier, NY, ***1973***, p. 161, was adapted from a longer one in Bordwell, F.G. *Acc. Chem. Res.* ***1972****, 5,* 374, see p. 375.

[43] The $(E1cB)_I$ mechanism cannot be distinguished from E2 by this means, because it has the identical rate law: Rate $= k$[substrate][B^-]. The rate law for $(E1cB)_R$ is different: Rate $= k$[substrate][B^-]/[BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

[44] Houser, J.J.; Bernstein, R.B.; Miekka, R.G.; Angus, J.C. *J. Am. Chem. Soc.* ***1955****, 77*, 6201.

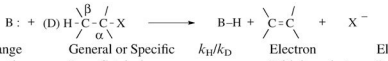
[45] Hine, J.; Wiesboeck, R.; Ghirardelli, R.G. *J. Am. Chem. Soc.* ***1961****, 83*, 1219; Hine, J.; Wiesboeck, R.; Ramsay, O.B. *J. Am. Chem. Soc.* ***1961****, 83,* 1222.

[46] Skell, P.S.; Hauser, C.R. *J. Am. Chem. Soc.* ***1945****, 67*, 1661.

[47] Keeffe, J.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1983****, 105,* 265.

[48] For a borderline E1cB–E2 mechanism, see Jia, Z.S.; Rudzinsci, J.; Paneth, P.; Thibblin, A. *J. Org. Chem.* ***2002****, 67*, 177.

TABLE 17.1 Kinetic Predictions for Base-Induced β-Eliminations[a]



Mechanism	Kinetic[b] Order	β-Hydrogen Exchange Faster Than Elimination	General or Specific Base Catalysis	k_H/k_D	Electron Withdrawal at C_β[c]	Electron Release at C_α[c]	Leaving Group Isotope Effect or Element Effect
$(E1)_{anion}$	1	Yes	General[d]	1.0	Rate decrease	Rate increase	Substantial
$(E1cB)_R$	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
$(E1cB)_{ip}$	2	No	General[f]	1.0 → 1.2	Small rate increase	Small rate increase	Substantial
$(E1cB)_I$	2	No	General	2 → 8	Rate increase	Little effect	Small to negligible
E2[e]	2	No	General	2 → 8	Rate increase	Small rate increase	Small

[a]See Ref. 42.

[b]All mechanisms exhibit first-order kinetics in substrate.

[c]Effect on rate assuming no change in mechanism is caused; steric factors upon substitution at C_α and rise to C_β have not been considered. The rate reductions are geared to substituent effects (e.g., those giving rise to Hammett reaction constants on β- and α-aryl substitution).

[d]Specific base catalysis predicted if extent of substrate ionization reduced from almost complete.

[e]Only transition states with considerable carbanion character considered in this table.

[f]Depends on whether an ion pair assists in removal of leaving group.

Reprinted with permission Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374. Copyright © 1972 American Chemical Society.

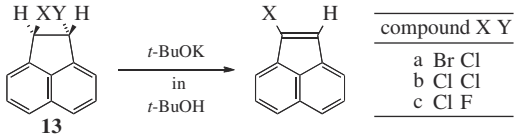
That is, the reaction took place faster in D_2O than in H_2O. This is compatible only with an E1cB mechanism in which the proton-transfer step is not entirely rate determining. The isotope effect arises from a partitioning of the carbanion intermediate (**12**). This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O, the latter process is slower (because the O—D bond of D_2O, cleaves less easily than the O—H bond of H_2O), reducing the rate at which **12** returns to starting compound. With the return reaction competing less effectively, the rate of conversion of **12** to product is increased.

3. Substrates containing acidic hydrogen atoms and poor leaving groups are most likely to proceed by the E1cB mechanism. Compounds of the type ZCH_2CH_2OPh, where Z is an electron-withdrawing group (e.g., NO_2, SMe_2^+, $ArSO_2$, CN, CO_2R), belong to this category, because OPh is a very poor leaving group (Sec. 10.A.iii, category 1). There is much evidence to show that the mechanism here is indeed E1cB.[49] Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2S^+CD_2CH_2OPh$ with NaOD in D_2O, are ~ 0.7. This is compatible with an $(E1cB)_R$ mechanism, but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^-. Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of *Michael-type addition* to C=C bonds. Such addition involves initial attack by a nucleophile Y and subsequent protonation (see Sec. 15.A.ii). Thus the initial loss of a proton from substrates of this type (i.e., an E1cB mechanism) is in accord with the principle of microscopic reversibility.[50] It may also be recalled that benzyne formation (Sec. 13.A.iii) can occur by such a process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are E1cB reactions,[51] but there is evidence that this is not the case when there is a good nucleofuge, the mechanism is E2 even when strong electron-withdrawing groups are present.[52] On the other hand, Cl^- has been found to be a leaving group in an E1cB reaction.[53]

   Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is $(E1cB)_I$. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes (**13**), where it was found that (1) the three rates were fairly similar, the largest being

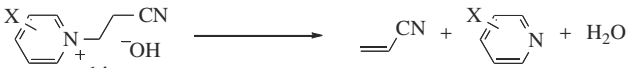
[49] Cann, P.F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 820. For other examples; see Kurzawa, J.; Leffek, K.T. *Can. J. Chem.* ***1977****, 55,* 1696.
[50] Patai, S.; Weinstein, S.; Rappoport, Z. *J. Chem. Soc.* ***1962***, 1741. See also, Hilbert, J.M.; Fedor, L.R. *J. Org. Chem.* ***1978****, 43,* 452.
[51] Bordwell, F.G. *Acc. Chem. Res.* ***1972****, 5,* 374.
[52] Banait, N.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990****, 112*, 6950.
[53] Ölwegård, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1985****, 107*, 7494.

only about four times that of the smallest, and (2) in compound c (X = Cl, Y = F), the only product contained Cl and no F (i.e., only the poorer nucleofuge F departed



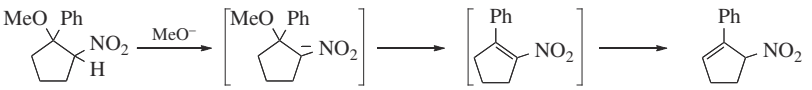
13

while Cl remained).[54] Result (1) rules out all the E1cB mechanisms except $(E1cB)_I$, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving-group effect, but an E2 mechanism with substantial carbanionic character (see Section 17.A.iv) might not. However, no E2 mechanism can explain result (2), which can be explained by the fact that an α Cl is more effective than an α F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, see Sec. 13.B.ii), when X^- leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.[55] Additional evidence for the existence of the $(E1cB)_I$ mechanism was the observation of a change in the rate-determining step in the elimination reaction of *N*-(2-cyanoethyl)pyridinium ions (**14**), treated with base, when X was changed.[56] Once again, the demonstration that two steps are involved precludes the one-step E2 mechanism. Note that pyridyl systems appear to be a borderline case, and it is not obvious if the reaction involves a carbanion intermediate (E1cb, $A_{xh}D_H + D_N$) or if the reaction proceeds by concerted loss of a proton and the halide (E2, $A_ND_ED_N$) with attack by the base.[57]



14

4. An example of an $(E1)_{anion}$ mechanism has been found with the substrate **15**, which when treated with methoxide ion undergoes elimination to **17**, which is unstable under the reaction conditions and rearranges as shown.[58] Among the evidence for the proposed mechanism in this case were kinetic and isotope-effect results, as well as the spectral detection of **16**.[59]



15 **16** **17**

[54] Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1982****, 47,* 3237.

[55] See Gula, M.J.; Vitale, D.E.; Dostal, J.M.; Trometer, J.D.; Spencer, T.A. *J. Am. Chem. Soc.* ***1988****, 110*, 4400; Garay, R.O.; Cabaleiro, M.C. *J. Chem. Res. (S)*, ***1988***, 388; Gandler, J.R.; Storer, J.W.; Ohlberg, D.A.A. *J. Am. Chem. Soc.* ***1990****, 112,* 7756.

[56] Bunting, J.W.; Toth, A.; Heo, C.K.M.; Moors, R.G. *J. Am. Chem. Soc.* ***1990****, 112,* 8878. See also, Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1991****, 113,* 6950.

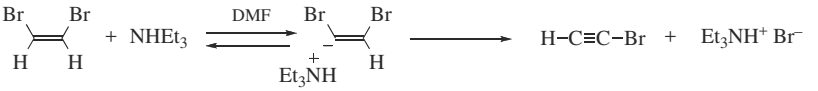
[57] Alunni, S.; De Angelis, F.; Ottavi, L.; Papavasileiou, M.; Tarantelli, F. *J. Am. Chem. Soc.* ***2005****, 127*, 15151. See also, Mosconi, E.; De Angelis, F.; Belpassi, L.; Tarantelli, F.; Alunni, S. *Eur. J. Org. Chem.* ***2009***, 5501.

[58] Bordwell, F.G.; Yee, K.C.; Knipe, A.C. *J. Am. Chem. Soc.* ***1970****, 92*, 5945.

[59] See Berndt, A. *Angew. Chem. Int. Ed.* ***1969****, 8*, 613; Albeck, M.; Hoz, S.; Rappoport, Z. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1248; ***1975***, 628.

5. In many eliminations to form C=O and C≡N bonds, the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve carbanion ion pairs, for example,[60]



This case is designated $(E1cB)_{ip}$; its characteristics are shown in Table 17.1.

17.A.iv. The E1–E2–E1cB Spectrum

In the three mechanisms so far considered, the similarities are greater than the differences. In each case, there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton is removed first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by the question: In the transition state, which bond (C—H or C—X) has undergone more cleavage?[61]

Note that in both E1 and E2 reactions, removal of the hydrogen atom is an acid–base reaction, requiring a base. A stronger base is required for the E2, and a weaker base for E1. Further, the E1 reaction requires a solvent that facilitates ionization to a carbocation (e.g., aqueous media), whereas the E2 reaction is usually done in a protic solvent (e.g., an alcohol).

One way to determine just where a given reaction stands on the E1–E2–E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.[62] For example, $CH_3CH_2NMe_3^+$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2NMe_3^+$ gave a corresponding value of 1.009.[63] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C—N bond is not as greatly broken in the

[60] Kwok, W.K.; Lee, W.G.; Miller, S.I. *J. Am. Chem. Soc.* ***1969****, 91,* 468. See also, Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C.; Mugnoli, A. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1291.

[61] See Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 9, Elsevier, NY, ***1973***, pp. 178–189; Saunders, Jr., W.H. *Acc. Chem. Res.* ***1976****, 9*, 19; Bunnett, J.F. *Surv. Prog. Chem.* ***1969****, 5*, 53; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 47–104; Bordwell, F.G. *Acc. Chem. Res.* ***1972****, 5,* 374.

[62] Fry, A. *Chem. Soc. Rev.* ***1972****, 1*, 163. See also, Hasan, T.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* ***1983****, 105*, 3967; Pulay, A.; Fry, A. *Tetrahedron Lett.* ***1986****, 27*, 5055.

[63] Ayrey, G.; Bourns, A.N.; Vyas, V.A. *Can. J. Chem.* ***1963****, 41,* 1759. Also see, Simon, H.; Müllhofer, G. *Pure Appl. Chem.* ***1964****, 8*, 379, 536; Smith, P.J.; Bourns, A.N. *Can. J. Chem.* ***1970****, 48*, 125.

transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+ leaving groups by the use of $^{32}S/^{34}S$ isotope effects[64] and with Cl ($^{35}Cl/^{37}Cl$).[65] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,[66] although interpretation of these results is clouded by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the β hydrogen from the β carbon to the base increases[67] (in Sec. 6.B, it was noted that isotope effects are greatest when the proton is half-transferred in the transition state), by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and by the possibility of tunneling.[68] Other isotope-effect studies have involved labeled α or β carbon, labeled α hydrogen, or labeled base.[58]

Another way to study the position of a given reaction on the spectrum involves the use of β aryl substitution. Since a positive *Hammet ρ value* is an indication of a negatively charged transition state, the ρ value for substituted β aryl groups should increase as a reaction moves from E1-to-E1cB-like along the spectrum. This has been shown to be the case in a number of studies;[69] for example, ρ values of $ArCH_2CH_2X$ increase as the leaving-group ability of X decreases. A typical set of ρ values was X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+, 2.75; F, 3.12.[70] As seen previously, decreasing leaving-group ability correlates with increasing E1cB character.

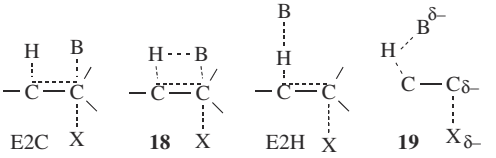
Still another method measures volumes of activation.[71] These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

17.A.v. The E2C Mechanism[72]

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases (e.g., RO^- in ROH).[73] In order to explain these results, it was proposed[74] that there is a spectrum[75] of E2 transition states in which the base can interact in the transition state with the α carbon, as well as with the β hydrogen. At one end of this spectrum is a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The

[64] Wu, S.; Hargreaves, R.T.; Saunders, Jr., W.H. *J. Org. Chem.* ***1985****, 50*, 2392 and references cited therein.
[65] Grout, A.; McLennan, D.J.; Spackman, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1758.
[66] See Thibblin, A. *J. Am. Chem. Soc.* ***1988****, 110*, 4582; Smith, P.J.; Amin, M. *Can. J. Chem.* ***1989****, 67*, 1457.
[67] However, see Blackwell, L.F. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 488.
[68] See Miller, D.J.; Saunders, Jr., W.H. *J. Org. Chem.* ***1981****, 46*, 4247 and previous papers in this series. See also, Amin, M.; Price, R.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1990****, 112,* 4467.
[69] Blackwell, L.F.; Buckley, P.D.; Jolley, K.W.; MacGibbon, A.K.H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 169; Smith, P.J.; Tsui, S.K. *J. Am. Chem. Soc.* ***1973****, 95*, 4760; *Can. J. Chem.* ***1974****, 52*, 749.
[70] DePuy, C.H.; Bishop, C.A. *J. Am. Chem. Soc.* ***1960****, 82*, 2532, 2535.
[71] Brower, K.R.; Muhsin, M.; Brower, H.E. *J. Am. Chem. Soc.* ***1976****, 98,* 779. For a review, see van Eldik, R.; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1989****, 89*, 549.
[72] McLennan, D.J. *Tetrahedron* ***1975****, 31,* 2999; Ford, W.T. *Acc. Chem. Res.* ***1973****, 6,* 410.
[73] See Hayami, J.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 1628.
[74] Parker, A.J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett.* ***1968***, 2113.
[75] This is apart from the E1-E2-E1cB spectrum.

E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. Transition state **18** represents a transition state between these extremes. Additional evidence[76] for the E2C mechanism is derived from *Brønsted equation* considerations (Sec. 8.D), from substrate effects, from isotope effects, and from the effects of solvents on rates.



However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.[77] McLennan and Lim[78] suggested that the transition state is that shown as **19**. An ion-pair mechanism has also been proposed.[79] Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.[80] These reactions also have the following general characteristics:[81] (1) they are favored by good leaving groups; (2) they are favored by polar aprotic solvents; (3) the reactivity order is tertiary > secondary > primary, the opposite of the normal E2 order (Sec. 17.D.i); (4) the elimination is always anti (syn elimination is not found), but in cyclohexyl systems, a diequatorial anti elimination is about as favorable as a diaxial anti elimination (unlike the normal E2 reaction, Sec. 17.A.i, categories 2,3); (5) they follow *Zaitsev's rule* (see below), where this does not conflict with the requirement for anti elimination.

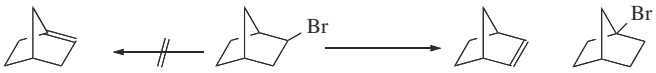
17.B. REGIOCHEMISTRY OF THE DOUBLE BOND

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three alkenyl products are possible. In the simplest such case, a *sec*-butyl compound can give either 1- or 2-butene. There are a number of rules that enable a prediction, in many instances, of which product will predominantly form.[82]

1. No matter the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (*Bredt's rule*, see Sec. 4.P.iii). This means, for

[76] See Kwart, H.; Wilk, K.A. *J. Org. Chem.* ***1985****, 50*, 3038.
[77] See Bunnett, J.F.; Migdal, C.A. *J. Org. Chem.* ***1989****, 54,* 3037, 3041 and references cited therein.
[78] McLennan, D.J.; Lim, G. *Aust. J. Chem.* ***1983****, 36*, 1821. For an opposing view, see Kwart, H.; Gaffney, A. *J. Org. Chem.* ***1983****, 48,* 4502.
[79] Ford, W.T. *Acc. Chem. Res.* ***1973****, 6*, 410.
[80] For convenience, these are called E2C reactions, although the actual mechanism is in dispute.
[81] Beltrame, P.; Biale, G.; Lloyd, D.J.; Parker, A.J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972****, 94,* 2240; Beltrame, P.; Ceccon, A.; Winstein, S. *J. Am. Chem. Soc.* ***1972****, 94,* 2315.
[82] See Hückel, W.; Hanack, M. *Angew. Chem. Int. Ed.* ***1967****, 6,* 534.

example, not only that **20** gives only **21** and not **22** (indeed **22** is not a known compound), but also that **23** does *not* undergo elimination.



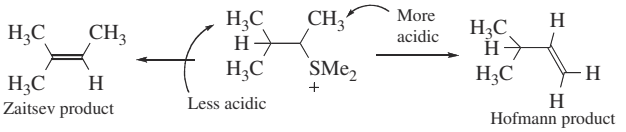
22 **20** **21** **23**

2. No matter the mechanism, if there is a double bond (C=C or C=O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see Sec. 17.C).
3. In the E1 mechanism, the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible alkenes. In such cases, *Zaitsev's rule*[83] operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, 3-bromo-2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus *Zaitsev's rule* predicts that the alkene predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat of combustion data (see Sec. 1.L), it is known that alkene stability increases with alkyl substitution, although just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations, *Zaitsev's rule* governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMeSMe_2^+$ gave 91% of the *Zaitsev* product and 9% of the other.[84] However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.[85] This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. *Zaitsev's rule* breaks down in cases where the non-*Zaitsev* product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes ($PhMeCXCH_2Ph$) were reported to give $\sim$ 50% $CH_2{=}CPhCH_2Ph$, despite the fact that the double bond of the *Zaitsev* product (PhMeC=CHPh) is conjugated with two benzene rings.[86]
4. For the anti E2 mechanism, a trans β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogen atoms are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Some compounds follow *Zaitsev's rule* and give predominant formation of the most highly substituted alkene, but others follow *Hofmann's rule: The double bond goes mainly toward the least highly substituted carbon*. Although many exceptions are known, the following general statements can be made: In most

[83] Often given the German spelling: Saytzeff, or Saytseff, or Saytzev.
[84] de la Mare, P.B.D. *Prog. StereoChem.* ***1954****, 1*, 112.
[85] See Cram, D.J.; Sahyun, M.R.V. *J. Am. Chem. Soc.* ***1963****, 85,* 1257.
[86] Ho, I.; Smith, J.G. *Tetrahedron* ***1970****, 26,* 4277.

cases, compounds containing uncharged nucleofuges (those that come off as negative ions) follow *Zaitsev's rule*, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged nucleofuges (e.g., NR_3^+, SR_2^+, those that come off as neutral molecules), follow *Hofmann's rule* if the substrate is acyclic,[87] but *Zaitsev's rule* if the leaving group is attached to a six-membered ring.[88]

Much work has been devoted to searching for reasons for the differences in orientation. Since *Zaitsev* orientation almost always gives the thermodynamically more stable isomer, are must explain why in some cases the less stable *Hofmann* product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these[89] is that *Hofmann orientation* is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $Me_2CHCHMeSMe_2^+$ gives more of the



Hofmann product; it is the more acidic hydrogen that is removed by the base. Of course, the CH_3 hydrogen atoms would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation presented was that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity greater than they are with the less electron-withdrawing neutral groups.[85,90] According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more C—H bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1-like, C—X bond breaking is more important, and alkene stability determines the direction of the new double bond.

The third explanation is completely different: Field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group and a CHR_2 group is still less easily attacked. Of course, these considerations also apply when the leaving group is neutral, but they are proposed to be much less important here because the neutral groups are smaller and do not block access to the hydrogen atoms as much. Experiments showed that *Hofmann elimination* increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $CH_3CH_2CH_2CHXCH_3$ was as follows (X listed in order of

[87] See Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970****, 92*, 5615.
[88] See Booth, H.; Franklin, N.C.; Gidley, G.C. *J. Chem. Soc. C* ***1968***, 1891; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 192–193.
[89] See Ingold, C.K. *Proc. Chem. Soc.* ***1962***, 265.
[90] Bunnett, J.F. *Surv. Prog. Chem.* ***1969****, 5*, 53.

increasing size): Br, 31%; I, 30%; OTs, 48%; SMe_2^+, 87%; SO_2Me, 89%; NMe_3^+, 98%.[91] *Hofmann elimination* was also shown to increase with increase in bulk of the substrate.[92] With large enough compounds, *Hofmann orientation* can be obtained even with halides. *tert*-Amyl bromide gave 89% of the *Hofmann* product, for example. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.[93]

There is one series of results incompatible with the steric explanation that E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.[94] The same order was found for the four 2-halohexanes.[95] Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant *Hofmann orientation*. Another result that argues against the steric explanation is the effect of changing the nature of the base. An experiment in which the effective size of the base was kept constant while its basicity was increased (by using as bases a series of $XC_6H_4O^-$ ions) showed that the percentage of *Hofmann elimination* increased with increasing base strength, although the size of the base did not change.[96] These results are in accord with the previous explanation, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free energy relationships between basicity and percentage of *Hofmann elimination*.[97] Certain very large bases (e.g., 2,6-di-*tert*-butyl-phenoxide) did not obey the relationships and steric effects are important in these cases. How large the base must be before steric effects are observed depends on the pattern of alkyl substitution in the substrate, but not on the nucleofuge.[98] One further result may be noted. In the gas phase, elimination of H and BrH^+ or H and ClH^+ using Me_3N as the base predominantly followed *Hofmann's rule*,[99] although BrH^+ and ClH^+ are not very large.

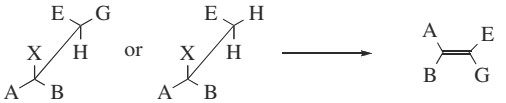
5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that *Hofmann orientation* is greatly favored over *Zaitsev*.[100]
6. In the E1cB mechanism, the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.

[91] Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956****, 78,* 2199.
[92] See Bartsch, R.A. *J. Org. Chem.* ***1970****, 35*, 1334; Charton, M. *J. Am. Chem. Soc.* ***1975****, 97,* 6159.
[93] See Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1960***, 4054.
[94] Saunders, Jr., W.H.; Fahrenholtz, S.R.; Caress, E.A.; Lowe, J.P.; Schreiber, M.R. *J. Am. Chem. Soc.* ***1965****, 87,* 3401; Brown, H.C.; Klimisch, R.L. *J. Am. Chem. Soc.* ***1966****, 88,* 1425.
[95] Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1968****, 90,* 408.
[96] Froemsdorf, D.H.; Robbins, M.D. *J. Am. Chem. Soc.* ***1967****, 89,* 1737. See also, Feit, I.N.; Breger, I.K.; Capobianco, A.M.; Cooke, T.W.; Gitlin, L.F. *J. Am. Chem. Soc.* ***1975****, 97*, 2477.
[97] Bartsch, R.A.; Roberts, D.K.; Cho, B.R. *J. Org. Chem.* ***1979****, 44,* 4105.
[98] Bartsch, R.A.; Read, R.A.; Larsen, D.T.; Roberts, D.K.; Scott, K.J.; Cho, B.R. *J. Am. Chem. Soc.* ***1979****, 101,* 1176.
[99] Angelini, G.; Lilla, G.; Speranza, M. *J. Am. Chem. Soc.* ***1989****, 111,* 7393.
[100] Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* ***1971****, 36*, 3633; Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970****, 92,* 6904.

7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.[101] In some cases, this can be put to preparative use. For example, the compound $PhCH_2CHOTsCHMe_2$ gave ~ 98% $PhCH{=}CHCHMe_2$ under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case, the double bond goes to the side with more hydrogen atoms because on that side it will be able to conjugate with the benzene ring. However, with the weak base $Bu_4N^+ Br^-$ in acetone the *Zaitsev* product ($PhCH_2CH{=}CMe_2$) was formed in 90% yield.[102]

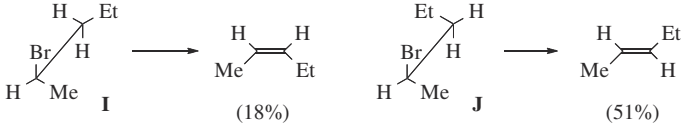
17.C. STEREOCHEMISTRY OF THE DOUBLE BOND

When elimination takes place on a compound of the form CH_3—CABX or CHAB—CGGX, the new alkene does not have cis–trans isomerism, but for compounds of the form CHEG—CABX (E and G *not* H) (**24**) and CH_2E—CABX (**25**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **24** gives the isomer



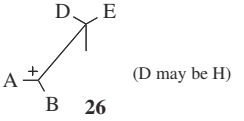
24 **25**

arising from trans orientation of X and H. As seen previously (Sec. 17.A.i), an erythro compound gives the cis alkene and a threo compound gives the trans. For **25**, two conformations are possible for the transition state; these lead to different isomers and often both are obtained. However, the one that predominates is often determined by an eclipsing effect.[103] For example, *Zaitsev elimination* from 2-bromopentane can occur as follows: In conformation **I**, the ethyl group is between Br and Me, while in **J** it is between Br and H. This means that **J** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the *Hofmann* product).[104] These effects become larger with increasing size of groups A, B, and E.



I (18%) **J** (51%)

However, eclipsing effects are not the only factors that affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all of these effects are completely understood.[105]



26

[101] Muir, D.M.; Parker, A.J. *J. Org. Chem.* ***1976****, 41*, 3201.
[102] Lloyd, D.J.; Muir, D.M.; Parker, A.J. *Tetrahedron Lett.* ***1971***, 3015.
[103] See Cram, D.J.; Greene, F.D.; DePuy, C.H. *J. Am. Chem. Soc.* ***1956****, 78*, 790; Cram, D.G. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 338–345.
[104] Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956****, 78*, 2199.
[105] Alunni, S.; Baciocchi, E. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 877; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 165–193.

For E1 eliminations, if there is a free carbocation (**26**), it is free to rotate, and no matter the geometry of the original compound, the more stable situation is the one where the larger of the D–E pair is opposite the smaller of the A—B pair and the corresponding alkene should form. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.[106]

17.D. REACTIVITY

In this section, we examine the effects of changes in the substrate, base, leaving group, and medium on (1) overall reactivity, (2) E1 versus E2 versus E1cB,[107] and (3) elimination versus substitution.

17.D.i. Effect of Substrate Structure

1. *Effect on Reactivity.* The carbon containing the nucleofuge (X) is referred to as the α carbon and the carbon that loses the positive species (usually a proton) as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:
   a. They can stabilize or destabilize the incipient double bond (both α and β groups).
   b. They can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only).
   c. They can stabilize or destabilize an incipient positive charge (α groups only).
   d. They can exert steric effects (e.g., eclipsing effects) (both α and β groups).

   Effects *a* and *d* can apply in all three mechanisms, although steric effects are greatest for the E2 mechanism. Effect *b* does not apply in the E1 mechanism, and effect *c* does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rate by any mechanism, except perhaps when formation of the C=C bond is not the rate-determining step, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the a position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, and SR in the β position all increase the rate of E2 eliminations.
2. *Effect on E1 versus E2 versus E1cB.* The α alkyl and α aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β Alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as seen in Section 17.A.iii, all electron-withdrawing groups in the β position shift the mechanism toward E1cB.[108] α alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

[106] See Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1978***, 43.
[107] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups,* Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 178–189.
[108] See Butskus, P.F.; Denis, G.I. *Russ. Chem. Rev.* ***1966****, 35,* 839.

TABLE 17.2 The Effect of α and β Branching on the Rate of E2 Elimination and the Amount of Alkene Formed[a]

Substrate	Temperature (°C)	Alkene (%)	Rate $\times 10^5$ of E2 reaction	Reference
CH_3CH_2Br	55	0.9	1.6	109
$(CH_3)_2CHBr$	24	80.3	0.237	110
$(CH_3)_3Br$	25	97	4.17	111
$CH_3CH_2CH_2Br$	55	8.9	5.3	109
$(CH_3)_2CHCH_2Br$	55	59.5	8.5	109

[a]The reactions were between the alkyl bromide and $^-$OEt. The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β hydrogen and cannot give an elimination product without rearrangement.

3. *Effect on Elimination versus Substitution.* Under second-order conditions, increased branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as seen in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with SMe_2^+ as the leaving group.[111] Two reasons can be presented for this trend. One is statistical: As α branching increases, there are usually more hydrogen atoms for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 vs S_N1), although not so much, and usually the substitution product predominates. For example, solvolysis of *tert*-butyl bromide gave only 19% elimination[112] (cf. with Table 17.2). β Branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster, but because the S_N2 mechanism is so greatly slowed (Sec. 10.G. i). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[113] However, E2 eliminations from compounds with charged leaving groups are slowed by β branching. This is related to *Hofmann's rule* (Sec. 17.B, category 4). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum, but also increase the extent of elimination as opposed to substitution.

   Another method that compares E2 and S_N2 reactions is called the *activation-strain model*. In this model, the activation energy = activation strain + transition state interaction, and corresponds directly to the strength of the Lewis acid or base. A more basic nucleophile or base, with a higher energy HOMO, and a more acidic substrate, with a lower energy LUMO, interact more strongly.[114] Activation strain is connected with the strength of the bonds broken: A strong C-leaving group bond has a higher activation strain and a higher barrier. Using this model, the E2 reaction has

[109] Hughes, E.D.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2072; Hughes, E.D.; Ingold, C.K.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2084.
[110] Brown, H.C.; Berneis, H.L. *J. Am. Chem. Soc.* ***1953****, 75,* 10.
[111] Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. *J. Chem. Soc.* ***1948***, 2055.
[112] Dhar, M.L.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1948***, 2058.
[113] Hughes, M.L.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2065.
[114] See van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.* ***2010****, 8*, 3118; de Jong, G.Th.; Bickelhaupt, F.M. *ChemPhysChem* ***2007****, 8*, 1170.

a higher activation strain than S_N2 because two bonds are broken, and with weak bases, S_N2 dominates E2 because S_N2 has less activation strain.[115] With strong bases, a favorable interaction of the more acidic transition state for the E2 reaction leads to a preference for E2.

17.D.ii. Effect of the Attacking Base

1. *Effect on E1 versus E2 versus E1cB.* In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1–E2–E1cB spectrum.[116] However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:[117] H_2O, NR_3, ^-OH, ^-OAc, ^-OR, ^-OAr, $^-NH_2$, CO_3^{2-}, $LiAlH_4$, I^-, ^-CN, and organic bases. However, the only bases of preparative importance in the normal E2 reaction are ^-OH, ^-OR, and $^-NH_2$, usually in the conjugate acid as solvent, and certain amines. Weak bases effective in the E2C reaction are Cl^-, Br^- F^-, ^-OAc, and RS^-. These bases are often used in the form of their R_4N^+ salts.
2. *Effect on Elimination versus Substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favored and E2 predominates over S_N2. At low-base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. Chapter 10 pointed out that some species are strong nucleophiles but weak bases (Sec. 10.G.ii). The use of these obviously favors substitution, except that, as seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base cyanide that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.[118]

17.D.iii. Effect of the Leaving Group

1. *Effect on Reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. The E2 eliminations have been performed with the following groups: $^+NR_3$, $^+PR_3$, $^+SR_2$, ^+OHR, SO_2R, OSO_2R, OCOR, OOH, OOR, NO_2,[119] F, Cl, Br, I, and CN (*not*$^+$ OH_2). The E1 eliminations have been

[115] See Bickelhaupt, F.M. *J. Comput. Chem.* ***1999****, 20*, 114. Prof. F.M. Bickelhaupt, Vrije Universiteit Amsterdam, personal communication.
[116] Baciocchi, E. *Acc. Chem. Res.* ***1979****, 12,* 430. See also, Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1980****, 45*, 827.
[117] This list is from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, ***1963***, p. 4.
[118] Loupy, A.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* ***1971***, 2306.
[119] See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, pp. 86–126.

carried out with: $^{+}NR_3$, $^{+}SR_2$, $^{+}OH_2$, ^{+}OHR, OSO_2R, OCOR, Cl, Br, I, and $^{+}N_2$.[120] However, the major leaving groups for preparative purposes are $^{+}OH_2$ (always by E1) and Cl, Br, I, and $^{+}NR_3$ (usually by E2).

2. *Effect on E1 versus E2 versus E1cB.* Better leaving groups shift the mechanism toward the E1 end of the spectrum, *since they make ionization easier*. This effect has been studied in various ways. One way already mentioned was a study of ρ values (Sec. 17.A.iv). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.[121] The E2C reaction is favored by good leaving groups.
3. *Effect on Elimination versus Substitution.* As seen previously (Sec. 17.A.ii), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.[122] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, although there is a slight increase in elimination in the order I > Br > Cl. When OTs is the leaving group, there is usually much more substitution. For example, *n*-$C_{18}H_{37}$Br treated with *t*-BuOK gave 85% elimination, while *n*-$C_{18}H_{37}$OTs gave, under the same conditions, 99% substitution.[123] On the other hand, positively charged leaving groups increase the amount of elimination.

17.D.iv. Effect of the Medium

1. *Effect of Solvent on E1 versus E2 versus E1cB.* With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing the polarity of the solvent and by increasing the ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).
2. *Effect of Solvent on Elimination versus Substitution.* Increasing polarity of solvent favors S_N2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aq KOH is used for substitution. Charge-dispersal discussions, similar to those in Section 10.G.iv,[124] only partially explain this. In most solvents, S_N1 reactions are favored over E1. The E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents[125] A study made in the gas phase, where there is no solvent, has shown that

[120] These lists are from Banthorpe, D.V. *Elimination Reactions,* Elsevier, NY, ***1963***, pp. 4, 7.
[121] See Stirling, C.J.M. *Acc. Chem. Res.* ***1979****, 12*, 198. See also, Varma, M.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1981***, 553.
[122] See Wright, D.G. *J. Chem. Soc., Chem. Commun.* ***1975***, 776. See, however, Cavazza, M. *Tetrahedron Lett.* ***1975***, 1031.
[123] Veeravagu, P.; Arnold, R.T.; Eigenmann, E.W. *J. Am. Chem. Soc.* ***1964****, 86,* 3072.
[124] Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2043.
[125] Aksnes, G.; Stensland, P. *Acta Chem. Scand.,* ***1989****, 43*, 893, and references cited therein.

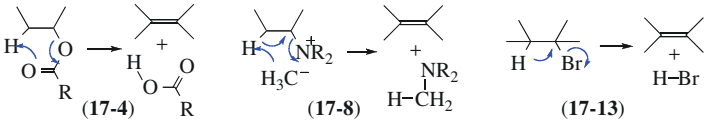
when 1-bromopropane reacts with MeO^- only elimination takes place (no substitution) even with this primary substrate.[126]

3. *Effect of Temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first or second order.[127] The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

17.E. MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

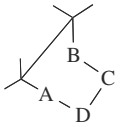
17.E.i. Mechanisms[128]

Several types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require an external base, which may be the solvent, in one of the steps, and there is no external base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four, five, or six membered. Examples of each size are



(**17-4**) (**17-8**) (**17-13**)

In this mechanism, the two groups leave at about the same time and bond to each other as they are doing so. The designation is E^i in the Ingold terminology and *cyclo*-$D_ED_NA_n$ in the IUPAC system. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.



As in the E2 mechanism, it is not necessary that the C—H and C—X bond be broken simultaneously in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C—X bond breaking is a good deal more advanced

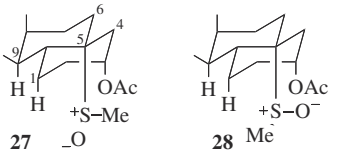
[126] Jones, M.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***1989****, 111,* 1645. For a different result with other reactants, see Lum, R.C.; Grabowski, J.J. *J. Am. Chem. Soc.* ***1988****, 110*, 8568.

[127] Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; Maw, G.A.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2049.

[128] Taylor, R. in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, ***1979***, pp. 860–914; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971****, 8,* 75, pp. 76–143, 207–234; in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, the articles by Swinbourne, E.S. pp. 149–233 (pp. 158–188), and by Richardson, W.H.; O'Neal, H.E. pp. 381–565 (pp. 381–446); Maccoll, A. *Adv. Phys. Org. Chem.* ***1965****, 3,* 91. See Egger, K.W.; Cocks, A.T. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 677–745; Maccoll, A. *Chem. Rev.* ***1969****, 69*, 33.

than C—H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E^i mechanism includes:

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (i.e., if one molecule attacked another, the kinetics would be second order in substrate).[129]
2. Free radical inhibitors do not slow the reactions, so no free radical mechanism is involved.[130]
3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.[131] The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (1) an erythro isomer gives a *trans*-alkene and a threo isomer gives a *cis*-alkene; (2) the reaction takes place only when a cis β hydrogen is available; (3) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. Another piece of evidence involves a pair of steroid molecules. In 3β-acetoxy-(*R*)-5α-methylsulfinylcholestane (**27** shows rings A and B of this compound) and in 3β-acetoxy-(*S*)-5α-methylsulfinylcholestane (**28**: rings A and B), the *only* difference is the configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **27** gave only elimination to the 4-side (86% 4-ene), while **28** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).[132] Models show that interference from the 1- and 9-hydrogen atoms causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is a stereogenic center, this means that in **27** the oxygen is near the 4-hydrogen, while in **28** it is near the 6-hydrogen. This experiment is compatible only with syn elimination.[133]



(**17-12**)

4. The ^{14}C isotope effects for the *Cope elimination* (**17-9**) show that both the C—H and C—N bonds have been extensively broken in the transition state.[134]
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C—X bond is cleaved to a much greater extent than the C—H bond; that is, there is a considerable amount of carbocation character in the transition state. This

[129] O'Connor, G.L.; Nace, H.R. *J. Am. Chem. Soc.* ***1953****, 75,* 2118.
[130] Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* ***1953***, 1715.
[131] See, however, Briggs, W.S.; Djerassi, C. *J. Org. Chem.* ***1968****, 33*, 1625; Smissman, E.E.; Li, J.P.; Creese, M.W. *J. Org. Chem.* ***1970****, 35,* 1352.
[132] Jones, D.N.; Saeed, M.A. *Proc. Chem. Soc.* ***1964***, 81. See also, Goldberg, S.I.; Sahli, M.S. *J. Org. Chem.* ***1967****, 32*, 2059.
[133] See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977****, 42*, 3895.
[134] Wright, D.R.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* ***1983****, 105,* 3714.

observation is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the *Woodward–Hoffmann rules* (see the similar case of Reaction **15-63**). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order I > Br > Cl[135] (see Sec. 10.G.iii), and that the effects of substituents on reaction rates are in accord with such a transition state.[136] Rate ratios for pyrolysis of some alkyl bromides at 320 °C were ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78,000. Also, α-phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand, β-phenylethyl bromide was only slightly faster than ethyl bromide.[137] This result indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbocation was stabilized by a alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,[138] although still in the same order, so that this reaction is closer to a pure E^i mechanism, although the transition state still has some carbocationic character. Other evidence for a greater initial C—O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbocationic character at the 1 position.[139] The extent of E1 character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.[140] Cleavage of xanthates (Reaction **17-5**), cleavage of sulfoxides (Reaction **17-12**), the *Cope Reaction* (**17-9**), and Reaction **17-8** are probably very close to straight E^i mechanisms.[141]

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown below. Free radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[142] although they also have been postulated in pyrolysis of certain carboxylic esters.[143] β-Elimination of tosyl radicals is known.[144] Much less is known about these mechanisms and we will not consider them further. Free radical eliminations in solution are also known, but are rare.[145]

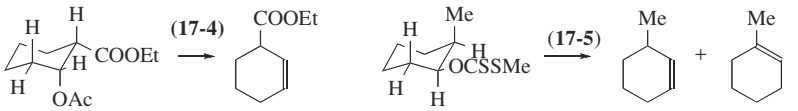
[135] Maccoll, A., in Patai, S. *The Chemistry of Alkenes,* Vol. 1, Wiley, NY, ***1964***, pp. 215–216.
[136] For reviews of such studies, see Maccoll, A. *Chem. Rev.* ***1969****, 69*, 33.
[137] See Chuchani, G.; Rotinov, A.; Dominguez, R.M.; Martin, I. *Int. J. Chem. Kinet.* ***1987****, 19,* 781.
[138] Scheer, J.C.; Kooyman, E.C.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1963****, 82,* 1123. See also, Louw, R.; Vermeeren, H.P.W.; Vogelzang, M.W. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1875.
[139] Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1255. See also, August, R.; McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1683, and other papers in this series; Al-Awadi, N.A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2187.
[140] Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1025.
[141] For a review of the mechanisms of Reaction **17-12** and **17-9**, and the pyrolysis of sulfilimines, see Oae, S.; Furukawa, N. *Tetrahedron* ***1977****, 33,* 2359.
[142] See Barton, D.H.R.; Howlett, K.E. *J. Chem. Soc.* ***1949***, 155, 165.
[143] See Louw, R.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* ***1965****, 84,* 1511.
[144] Timokhin, V.I.; Gastaldi, S.; Bertrand, M.P.; Chatgilialoglu, C. *J. Org. Chem.* ***2003****, 68*, 3532.
[145] Boothe, T.E.; Greene, Jr., J.L.; Shevlin, P.B. *J. Org. Chem.* ***1980****, 45,* 794; Stark, T.J.; Nelson, N.T.; Jensen, F.R. *J. Org. Chem.* ***1980****, 45,* 420; Kochi, J.K. *Organic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 346–349; Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* ***1988***, 1278.

Initiation	R_2CHCH_2X	$\longrightarrow R_2\dot{C}HCH_2{\cdot} + X{\cdot}$
Propagation	$R_2\dot{C}HCH_2X + X{\cdot}$	$\longrightarrow R_2\dot{C}CH_2X + HX$
	$R_2\dot{C}CH_2X$	$\longrightarrow CH_2{=}CH_2 + X{\cdot}$
Termination (disproportionation)	$2\,R_2\dot{C}CH_2X$	$\longrightarrow R_2C{=}CH_2 + R_2CXCH_2X$

17.E.ii. Orientation in Pyrolytic Eliminations

As in the E1–E2–E1cB mechanistic spectrum, *Bredt's rule* applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for E^i eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β-hydrogen atoms available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55–62% 1-butene and 38–45% 2-butene,[146] which is close to the 3:2 distribution predicted by the number of hydrogen atoms available.[147]
2. A cis β hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, cis) or equatorial (hence, trans). Thus **29**, in which the leaving group is most likely axial, does not form a double bond in the direction of the carbethoxyl group, even though that would be conjugated, because there is no equatorial hydrogen on that side. Instead, it gives 100% **30**.[148] On the other hand, **31**, with an equatorial leaving group, gives ∼ 50% of each alkene, even though, for elimination to the 1-ene, the leaving group must depart with a trans hydrogen.[149]



29 **30** **31**

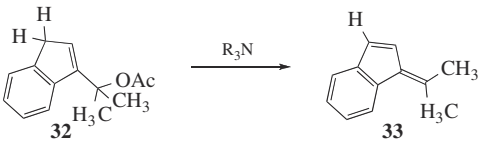
3. In some cases, especially with cyclic compounds, the more stable alkene forms and *Zaitsev's rule* applies. For example, menthyl acetate gives 35% of the *Hofmann product* and 65% of the *Zaitsev*, even though a cis β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.[150]

[146] Froemsdorf, D.H.; Collins, C.H.; Hammond, G.S.; DePuy, C.H. *J. Am. Chem. Soc.* ***1959****, 81,* 643; Haag, W.O.; Pines, H. *J. Org. Chem.* ***1959****, 24*, 877.
[147] DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960****, 60*, 431, with tables showing product distributions.
[148] Bailey, W.J.; Baylouny, R.A. *J. Am. Chem. Soc.* ***1959****, 81,* 2126.
[149] Botteron D.G.; Shulman, G.P. *J. Org. Chem.* ***1962****, 27*, 2007.
[150] See Bamkole, T.; Maccoll, A. *J. Chem. Soc. B* ***1970***, 1159.

4. There are also steric effects. In some cases the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

17.E.iii. 1,4-Conjugate Eliminations[151]

1,4-eliminations of the type H-C-C=CC-X → C=C-C=C are much rarer than conjugate additions (Chapter 15), but some examples are known.[152] One such is the conversion of **32** to **33**.[153]



17.F. REACTIONS

Reactions in which a C=C or a C≡C bond is formed will be considered first. From a synthetic point of view, the most important reactions for the formation of double bonds are **17-1** (usually by an E1 mechanism), **17-7**, **17-13**, and **17-22** (usually by an E2 mechanism), and **17-4**, **17-5**, and **17-9** (usually by an E^i mechanism). The only synthetically important method for the formation of triple bonds is **17-13**.[154] In the second section, reactions in which C≡N bonds and C=N bonds are formed will be considered, and then eliminations that give C=O bonds and diazoalkanes. Finally, extrusion reactions will be discussed.

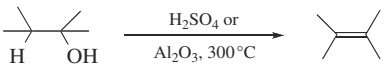
17.F.i. Reactions in which C=C and C≡C Bonds Are Formed

A. Reactions in which Hydrogen Is Removed from One Side

In Reactions **17-1**–**17-6**, the other leaving atom is oxygen. In Reactions **17-7**–**17-11**, it is nitrogen. For reactions in which hydrogen is removed from both sides, see **19-1**–**19-6**.

17-1 Dehydration of Alcohols

Hydro-hydroxy-elimination



[151] Taylor, R. in Patai, S. *The Chemistry of Functional Groups, Supplement B,* pt. 2, Wiley, NY, ***1979***, pp. 885–890; Smith, G.G.; Mutter, L.; Todd, G.P. *J. Org. Chem.* ***1977****, 42,* 44; Chuchani, G.; Dominguez, R.M. *Int. J. Chem. Kinet.* ***1981****, 13*, 577; Hernández, A.; Chuchani, G. *Int. J. Chem. Kinet.* ***1983****, 15*, 205.

[152] See Wakselman, M. *Nouv. J. Chem.* ***1983****, 7*, 439.

[153] Ölwegård, M.; Ahlberg, P. *Acta Chem. Scand.,* ***1990****, 44*, 642. See also, Ölwegård, M.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* ***1989***, 1279.

[154] Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, ***1983***; pp. 1376–1384; Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 755–790. For a comparative study of various methods, see Mesnard, D.; Bernadou, F.; Miginiac, L. *J. Chem. Res. (S)* ***1981***, 270, and referrences cited therein.

Dehydration of alcohols can be accomplished in several ways. Both H_2SO_4 and H_3PO_4 are common reagents, but formation of an intermediate carbocation can lead to rearrangement products and to ether formation (Reaction **10-12**). If the alcohol is volatile, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.[155] Other metallic oxides (e.g., Cr_2O_3, TiO_2, WO_3) have been used, as have been sulfides, other metallic salts, and zeolites. The presence of an electron-withdrawing group usually facilitates elimination of water, as in the *aldol condensation* (Reaction **16-34**). Similarly, 2-nitroalcohols (products of the *Henry reaction*, **16-37**) give conjugated nitro compounds when heated with zeolite Y—Y.[156] Treating a 4-hydroxy lactam with DMAP and Boc anhydride leads to the conjugated lactam.[157] Elimination of serine derivatives to α-alkylidene amino acid derivatives was accomplished with $(EtO)_2POCl$.[158] Another method of avoiding side reactions is the conversion of alcohols to esters, followed by pyrolysis (**17-4**–**17-6**). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens even when the investigator desires otherwise. Indeed, the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously after an acid workup (Chapter 16) because the new double bond can be in conjugation with one already there.

Many other dehydrating agents[159] have been used on occasion: P_2O_5, I_2, and PPh_3—I_2,[160] BF_3–etherate, DMSO, SiO_2—Cl/Me_3SiCl,[161] $KHSO_4$ anhydrous $CuSO_4$, and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPA.[162] With nearly all reagents, dehydration follows *Zaitsev's rule.* An exception involves the passage of hot alcohol vapors over thorium oxide at 350–450 °C, under which conditions *Hofmann's rule* is followed.[163]

Transition metals can induce the dehydration of certain alcohols. β-Hydroxy ketones are converted to conjugated ketones by treatment with $CeCl_3$ and NaI.[164] In the presence of a Pd complex, alkyl cyclopropanols undergo a dehydration reaction to give a conjugated ketone.[165] A δ-hydroxy-α,β-unsaturated aldehyde was converted to a dienyl aldehyde with a Hf catalyst.[166] β-Hydroxy esters are converted to conjugated esters when treated with 2 molar equivalents of SmI_2.[167] The reaction of a β-hydroxy nitrile

[155] Spitzin, V.I.; Michailenko, I.E.; Pirogowa, G.N. *J. Prakt. Chem.* ***1964****, [4] 25,* 160; Bertsch, H.; Greiner, A.; Kretzschmar, G.; Falk, F. *J. Prakt. Chem.* ***1964****, [4] 25,* 184.

[156] Anbazhagan, M.; Kumaran, G.; Sasidharan, M. *J. Chem. Res. (S)* ***1997***, 336.

[157] Mattern, R.-H. *Tetrahedron Lett.* ***1996****, 37*, 291.

[158] Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* ***1992****, 33*, 8145.

[159] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 291–294.

[160] Alvarez-Manzaneda, E.J.; Chahboun, R.; Torres, E.C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* ***2004****, 45*, 4453.

[161] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *Synth. Commun.* ***2003****, 33*, 3653.

[162] Monson, R.S.; Priest, D.N. *J. Org. Chem.* ***1971****, 36,* 3826; Lomas, J.S.; Sagatys, D.S.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 165.

[163] Lundeen, A.J.; Van Hoozer, R. *J. Org. Chem.* ***1967****, 32,* 3386. See also, Davis, B.H. *J. Org. Chem.* ***1982****, 47*, 900; Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* ***1991****, 32*, 1209.

[164] Bartoli, G.; Bellucci, M.C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett.* ***2000****, 2*, 1791.

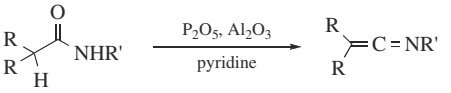
[165] Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* ***2000***, 629.

[166] Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* ***2001***, 1690.

[167] Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* ***2000****, 39*, 2773.

with MeMgCl[168] or with MgO[169] leads to a conjugated nitrile. In another variation of the dehydration reaction, vicinal bromohydrins are converted to alkenes upon treatment with In, $InCl_3$, and a Pd catalyst.[170] Chlorohydrins react similarly when treated with Sm, and then diiodomethane.[171]

Carboxylic acids can be dehydrated by pyrolysis to give a ketene: $RCH_2CO_2H \rightarrow RCH{=}C{=}O$. Ketene itself is commercially prepared in this manner. Carboxylic acids have been converted to ketenes by treatment with certain reagents, including TsCl,[172] dicyclohexylcarbodiimide,[173] and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[174] Analogously, amides can be dehydrated with P_2O_5, pyridine, and Al_2O_3 to give ketenimines:[175]



There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinylic alcohols are not normally stable compounds and *vic*-diols[176] give either conjugated dienes or lose only 1 equiv of water to give an aldehyde or ketone. Dienes can be prepared, however, by heating alkynyl alcohols with triphenylphosphine.[177]

When proton acids catalyze alcohol dehydration, the mechanism is E1.[178] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O, although with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of that ester (illustrated for H_2SO_4):

$$ROH \xrightarrow{H_2SO_4} ROSO_2OH \longrightarrow R^+ + HSO_4^-$$

Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (Reaction **15-3**), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P_2O_5, phthalic anhydride), as well as with some other reagents (e.g., HMPA),[179] it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases, the mechanism can be E1 or E2. The mechanism with Al_2O_3 and other solid catalysts has been studied extensively, but is poorly understood.[180]

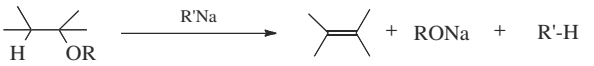
[168] Fleming, F.F.; Shook, B.C. *Tetrahedron Lett.* ***2000,*** *41*, 8847.
[169] Fleming, F.F.; Shook, B.C. *J. Org. Chem.* ***2002,*** *67*, 3668.
[170] Cho, S.; Kang, S.; Keum, G.; Kang, S.B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* ***2003,*** *68*, 180.
[171] Concellón, J.M.; Rodríguez-Solla, H.; Huerta, M..; Pérez-Andrés, J.A. *Eur. J. Org. Chem.* ***2002***, 1839.
[172] Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *Synthesis* ***1987***, 395; *J. Org. Chem.* ***1987,*** *52,* 3457.
[173] Olah, G.A.; Wu, A.; Farooq, O. *Synthesis* ***1989***, 568.
[174] Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* ***1987,*** *52*, 3457; Funk, R.L.; Abelman, M.M.; Jellison, K.M. *Synlett* ***1989***, 36.
[175] Stevens, C.L.; Singhal, G.H. *J. Org. Chem.* ***1964,*** *29*, 34.
[176] See Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups, Supplement E,* pt. 2, Wiley, NY, ***1980***, pp. 721–760.
[177] Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* ***1993***, 394.
[178] Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990,*** *59*, 63; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 221–274, 317–331; Knözinger, H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 641–718.
[179] See Kawanisi, M.; Arimatsu, S.; Yamaguchi, R.; Kimoto, K. *Chem. Lett.* ***1972***, 881.
[180] Beránek, L.; Kraus, M. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 274–295; Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971,*** *10,* 172; Berteau, P.; Ruwet, M.; Delmon, B. *Bull. Soc. Chim. Belg.* ***1985,*** *94,* 859.

Magnesium alkoxides (formed by $ROH + Me_2Mg \rightarrow ROMgMe$) have been decomposed thermally, by heating at 195–340 °C to give the alkene, CH_4, and MgO.[181] Syn elimination is found and an E^i mechanism is likely. Similar decomposition of aluminum and zinc alkoxides has also been accomplished.[182]

OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **V**, 294; **VI**, 307, 901; **VII**, 210, 241, 363, 368, 396; **VIII**, 210, 444. See also, OS **VII**, 63; **VIII**, 306, 474. No attempt has been made to list alkene-forming dehydration reactions accompanying condensations or rearrangements.

17-2 Cleavage of Ethers to Alkenes

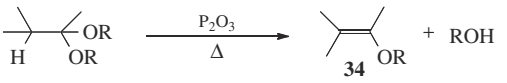
Hydro-alkoxy-elimination



Alkenes can be formed by the treatment of ethers with very strong bases (e.g., alkylsodium or alkyllithium[183] compounds, sodium amide,[184] or LDA),[185] although there are side reactions with many of these reagents. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $EtOCH_2CH(COOEt)_2$ can be converted to $CH_2{=}C(COOEt)_2$ without any base at all, but simply by heating.[186] *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases, the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,[187] since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered E^i mechanism:[188] Propargylic benzyl ethers are converted to conjugated dienes by heating with a Ru catalyst.[189] Ethers also have been converted to alkenes and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to Reaction **17-1**), but this is not a general reaction.

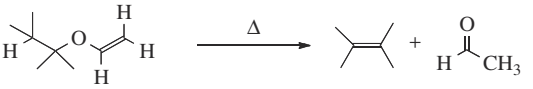
Cyclic ethers (e.g., THF) react slowly with organolithium reagents with cleavage that produces a C=C unit.[190] Fragmentation of 2,5-dihydrofuran with ethylmagnesium chloride and a chiral Zr catalyst leads to a chiral, homoallylic alcohol.[191] Acetals can be converted to enol ethers (**34**) in this manner. When ketals react with 2 molar equivalents of tri-isobutylaluminum, the product is a vinyl ether.[192] This can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine[193] or with Me_3SiI in the presence of hexamethyldisilazane.[194]

[181] Ashby, E.C.; Willard, G.F.; Goel, A.B. *J. Org. Chem.* ***1979****, 44,* 1221.
[182] Brieger, G.; Watson, S.W.; Barar, D.G.; Shene, A.L. *J. Org. Chem.* ***1979****, 44,* 1340.
[183] Tayama, E.; Sugai, S. *Synlett* ***2006***, 849.
[184] For a review, see Maercker, A. *Angew. Chem. Int. Ed.* ***1987****, 26,* 972.
[185] Fleming, F.F.; Wang, Q.; Steward, O.W. *J. Org. Chem.* ***2001****, 66*, 2171.
[186] Feely, W.; Boekelheide, V. *Org Synth.* ***IV***, 298.
[187] For a gas phase investigation, see DePuy, C.H.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1981****, 103,* 5034.
[188] Letsinger, R.L.; Pollart, D.F. *J. Am. Chem. Soc.* ***1956****, 78,* 6079.
[189] Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* ***2002****, 124,* 6510.
[190] See Cohen, T.; Stokes, S. *Tetrahedron Lett.* ***1993****, 34*, 8023.
[191] Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1993****, 115*, 6997.
[192] Cabrera, G.; Fiaschi, R.; Napolitano, E. *Tetrahedron Lett.* ***2001****, 42*, 5867.
[193] Gassman, P.G.; Burns, S.J. *J. Org. Chem.* ***1988****, 53*, 5574.
[194] Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* ***1982****, 23*, 323. For another method, see Marsi, M.; Gladysz, J.A. *Organometallics* ***1982****, 1,* 1467.



Conversion of a carbonyl compound to an enol phosphate[195] or triflate[196] allows a subsequent elimination reaction to give an alkyne. Conversion of an aldehyde to the vinyl nonaflate (nonafluorobutane-1-sulfonyl) was followed by reaction with a phosphazene base to give the alkyne.[197]

Enol ethers can be pyrolyzed to alkenes and aldehydes in a manner similar to that of Reaction **17-4**

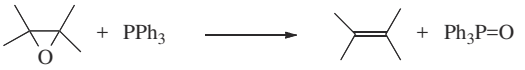


The rate of this reaction for R–O–CH=CH_2 increased in the order Et < *i*Pr < *t*-Bu.[198] The mechanism is similar to that of Reaction **17-4**.

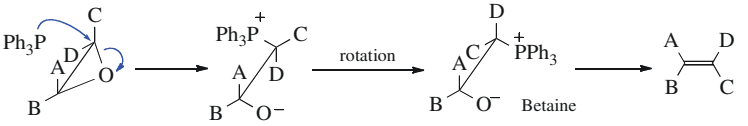
OS **IV**, 298, 404; **V**, 25, 642, 859, 1145; **VI**, 491, 564, 584, 606, 683, 948; **VIII**, 444.

17-3 The Conversion of Epoxides and Episulfides to Alkenes

epi-Oxy-elimination



Epoxides can be converted to alkenes[199] by treatment with triphenylphosphine[200] or triethylphosphite $P(OEt)_3$.[201] The first step of the mechanism is nucleophilic substitution (Reaction **10-35**), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti; that is, if two groups A and C are cis in the epoxide, they will be trans in the alkene:



Alternatively, the epoxide can be treated with lithium diphenylphosphide (Ph_2PLi), and the product quaternized with methyl iodide.[202] Alkenes have also been obtained from epoxides

[195] Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A. *J. Org. Chem.* ***1980****, 45,* 2526.
[196] Clasby, M. C.; Craig, D. *Synlett* ***1992***, 825.
[197] Lyapkalo, I.M.; Vogel, M.A.K.; Boltukhina, E.V.; Vavřík, J. *Synlett* ***2009***, 55.
[198] McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1179. See also, Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 737.
[199] For reviews, see Wong, H.N.C.; Fok, C.C.M.; Wong, T. *Heterocycles* ***1987****, 26,* 1345; Sonnet, P.E. *Tetrahedron* ***1980****, 36*, 557, p. 576.
[200] Wittig, G.; Haag, W. *Chem. Ber.* ***1955****, 88,* 1654.
[201] Scott, C.B. *J. Org. Chem.* ***1957****, 22*, 1118.
[202] Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc.* ***1971****, 93*, 4070; ***1973****, 95,* 822.

by reaction with a large number of reagents,[203] among them Li in THF,[204] trimethylsilyl iodide,[205] $F_3COOH—NaI$,[206] and compounds of Sm,[207] Mo, In,[208] and the W reagents mentioned in Reaction **17-18**. Some of these methods give syn elimination. Treatment of cyclooctane oxide with $Ph_3P—OPPh_3$ and NEt_3 gave cyclooctadiene.[209] Sodium amalgam with a Co–salen complex converted epoxides to alkenes.[210]

Epoxides can be converted to allylic alcohols[211] by treatment with several reagents, including *sec*-butyllithium,[212] and $i Pr_2NLi—t$-BuOK (the *LIDAKOR reagent*).[213] These bases remove the proton from the adjacent carbon, leading to formation of a C=C unit and opening of the epoxide to give an alkoxide. Phenyllithium reacts with epoxides in the presence of LTMP to give a *trans*-alkene.[214] Sulfur ylids (e.g., $Me_2S{=}CH_2$) also convert epoxides to allylic alcohols.[215] Bromomethyl epoxides react with $InCl_3/NaBH_4$ to give an allylic alcohol[216] or with $Me_3S^+Br^-$ and butyllithium to give a dienyl alcohol.[217] α,β-Epoxy ketones are converted to conjugated ketones by treatment with NaI in acetone in the presence of Amberlyst 15,[218] or with 2.5 molar equivalents of SmI_2.[219]

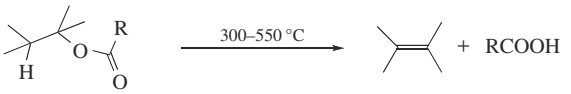
When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.[220] Sparteine and *sec*-butyllithium generate a chiral base that leads to formation of chiral allylic alcohols.[221] Chiral diamines react with organolithium reagents to produce chiral bases that convert epoxides to allylic alcohols with good enantioselectivity.[222] Chiral diamines with a mixture of LDA and DBU (Reactions **15-32** and **17-13**) give similar results.[223]

[203] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 272–277.
[204] Gurudutt, K.N.; Ravindranath, B. *Tetrahedron Lett.* ***1980****, 21*, 1173.
[205] Denis, J.N.; Magnane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim.* ***1979****, 3,* 705. See Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* ***1981****, 22,* 3551.
[206] Sarma, D.N.; Sharma, R.P. *Chem. Ind. (London)* ***1984***, 712.
[207] Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* ***1987***, 2101.
[208] Mahesh, M.; Murphy, J.A.; Wessel, H.P. *J. Org. Chem.* ***2005****, 70*, 4118.
[209] Hendrickson, J.B.; Walker, M.A.; Varvak, A.; Hussoin, Md.S. *Synlett* ***1996***, 661.
[210] Isobe, H.; Branchaud, B.P. *Tetrahedron Lett.* ***1999****, 40*, 8747.
[211] Smith, J.G. *Synthesis* ***1984***, 629, pp. 637–642; Crandall, J.K.; Apparu, M. *Org. React.* ***1983****, 29*, 345. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 231–233. See also, Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron* ***2001****, 57*, 1509.
[212] Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* ***1994****, 35*, 7943.
[213] Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* ***2001****, 57,* 8173.
[214] Hodgson, D.M.; Fleming, M.J.; Stanway, S.J. *J. Org. Chem.* ***2007****, 72,* 4763.
[215] Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* ***2001****, 3*, 4051.
[216] Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* ***2004****, 45*, 8579.
[217] Alcaraz, L.; Cox, K.; Cridland, A.P.; Kinchin, E.; Morris, J.; Thompson, S.P. *Org. Lett.* ***2005****, 7,* 1399.
[218] Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* ***2000****, 56*, 1733.
[219] Concellón, J.M.; Bardales, E. *J. Org. Chem.* ***2003****, 68*, 9492. In a similar manner, epoxy amides are converted to conjugated amides, see Concellón, J.M.; Bardales, E. *Eur. J. Org. Chem.* ***2004***, 1523.
[220] Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* ***1988****, 71,* 1073, and references cited therein. Also see, Brookes, P.C.; Milne, D.J.; Murphy, P.J.; Spolaore, B. *Tetrahedron* ***2002****, 58*, 4675.
[221] Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3354.
[222] Equey, O.; ALexakis, A. *Tetrahedron Asymmetry* ***2004****, 15*, 1069.
[223] Bertilsson, S.K.; Södergren, M.J.; Andersson, P.G. *J. Org. Chem.* ***2002****, 67*, 1567; Bertilsson, S.K.; Andersson, P.G. *Tetrahedron* ***2002****, 58,* 4665.

Episulfides[224] can be converted to alkenes.[225] However, in this case the elimination is syn, so the mechanism cannot be the same as that for conversion of epoxides. The phosphite attacks sulfur rather than carbon. Among other reagents that convert episulfides to alkenes are certain Rh complexes,[226] $LiAlH_4$[227] (this compound behaves quite differently with epoxides, see Reaction **19-35**), and MeI.[228] Episulfoxides can be converted to alkenes and sulfur monoxide simply by heating.[229]

17-4 Pyrolysis of Carboxylic Acids and Esters of Carboxylic Acids

Hydro-acyloxy-elimination



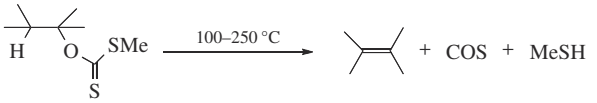
Direct elimination of a carboxylic acid (decarboxylation) to an alkene has been accomplished by heating in the presence of Pd catalysts.[230] Carboxylic esters that bear an alkyl group with a β hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an alkene.[231] No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing **17-1**. The yields are excellent and the workup is easy. Many alkenes have been prepared in this manner. For higher alkenes (above $\sim C_{10}$) a better method is to pyrolyze the alcohol in the presence of acetic anhydride.[232]

The mechanism is E^i (see Sec. 17.E.i). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for E^i reactions is available (it is not for five- and six-membered lactones, but it is for larger rings[233]). Amides give a similar reaction, but require higher temperatures.

Allylic acetates give dienes when heated with certain Pd[234] or Mo[235] compounds.

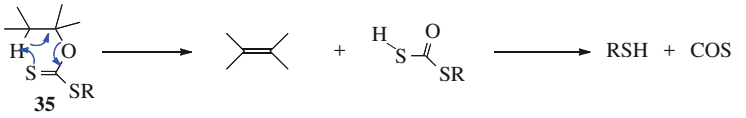
OS **III**, 30; **IV**, 746; **V**, 235; **IX**, 293.

17-5 The Chugaev Reaction



[224] See Sonnet, P.E. *Tetrahedron* ***1980****, 36*, 557, see p. 587; Goodman, L.; Reist, E.J. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 93–113.
[225] Neureiter, N.P.; Bordwell, F.G. *J. Am. Chem. Soc.* ***1959****, 81,* 578.
[226] Calet, S.; Alper, H. *Tetrahedron Lett.* ***1986****, 27,* 3573.
[227] See Latif, N.; Mishriky, N.; Zeid, I. *J. Prakt. Chem.* ***1970****, 312,* 421.
[228] See Helmkamp, G.K.; Pettitt, D.J. *J. Org. Chem.* ***1964****, 29,* 3258.
[229] Aalbersberg, W.G.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1977****, 99*, 2792.
[230] Gooßen, L.J.; Rodríguez, N. *Chem. Commun.* ***2004***, 724.
[231] See DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960****, 60*, 431, p. 432; Jenneskens, L.W.; Hoefs, C.A.M.; Wiersum, U.E. *J. Org. Chem.* ***1989****, 54,* 5811, and references cited therein.
[232] Aubrey, D.W.; Barnatt, A.; Gerrard, W. *Chem. Ind. (London)* ***1965***, 681.
[233] See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977****, 42*, 3895.
[234] Heck, R.F. *Palladium Reagents in Organic Synthesis,* Academic Press, NY, ***1985***, pp. 172–178. See Cheng, H.-Y.; Sun, C.-S.; Hou, D.-R. *J. Org. Chem.* ***2007****, 72*, 2674.
[235] Trost, B.M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* ***1983****, 24*, 4525.

Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO—C(=S)—SNa, followed by treatment of this with iodomethane.[236] Pyrolysis of the xanthate to give the alkene, COS, and the thiol is called the *Chugaev reaction*.[237] The reaction is like **17-4**; an indirect method of accomplishing **17-2**. The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting alkene is minimized. The mechanism is E^i, similar to that of Reaction **17-4**. For a time, there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ^{34}S and ^{13}C isotope effects, to show that it is the C=S sulfur (see **35**).[238] In a structural variation of this reaction, heating a propargylic xanthate with 2,4,6-trimethylpyridinium trifluoromethyl sulfonate leads to formation of an alkene.[239]

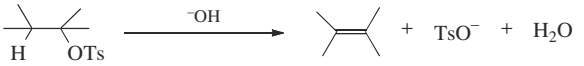


The mechanism is thus exactly analogous to that of Reaction **17-5**.

OS **VII**, 139.

17-6 Decomposition of Other Esters

Hydro-tosyloxy-elimination



Several types of inorganic ester can be cleaved to alkenes by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.[240] It has been shown that bis(tetra-*n*-butylammonium) oxalate, $(Bu_4N^+)_2\ (COO^-)_2$, is an excellent reagent for inducing tosylates to undergo elimination rather than substitution.[241] Aryl sulfonates have also been cleaved without a base. Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave alkenes in high yields simply on heating, without a solvent.[242] Phosphonate esters have been cleaved to alkenes by treatment with *Lawesson's reagent*[243] (see Reaction **16-11**).

OS, **VI**, 837; **VII**, 117.

[236] See Nagle, A.S.; Salvataore, R.N.; Cross, R.M.; Kapxhiu, E.A.; Sahab, S.; Yoon, C.H.; Jung, K.W. *Tetrahedron Lett.* ***2003****, 44*, 5695.
[237] DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960****, 60*, 431, see p. 444; Nace, H.R. *Org. React.* ***1962****, 12*, 57.
[238] Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* ***1961****, 39,* 348.
[239] Fauré-Tromeur, M.; Zard, S.Z. *Tetrahedron Lett.* ***1999****, 40,* 1305.
[240] For a list of reagents used for sulfonate cleavages, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 294–295.
[241] Corey, E.J.; Terashima, S. *Tetrahedron Lett.* ***1972***, 111.
[242] Corey, E.J.; Posner, G.H.; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org. Chem.* ***1989****, 54,* 389.
[243] Shimagaki, M.; Fujieda, Y.; Kimura, T.; Nakata, T. *Tetrahedron Lett.* ***1995****, 36*, 719.

17-7 Cleavage of Quaternary Ammonium Hydroxides

Hydro-trialkylammonio-elimination



Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation* or *Hofmann degradation* or just *Hofmann elimination*.[244] In the first step, a primary, secondary, or tertiary amine is treated with enough iodomethane to convert it to the quaternary ammonium iodide (Reaction **10-31**). In the second step, the iodide counterion is converted to the hydroxide counterion by treatment with silver oxide. In the cleavage step, an aqueous or alcoholic solution of the ammonium hydroxide is distilled, often under reduced pressure. The decomposition generally takes place between 100 and 200 °C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.[245] When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (HO^- or RO^-) is less solvated.[246] The reaction has never been an important synthetic tool, but has been used in the determination of the structure of unknown amines, especially alkaloids. In many of these compounds, the nitrogen is in a ring, or even at a ring junction, and in such cases formation of the alkene is incomplete. Repetitions of the process are required to remove the nitrogen completely, as in the conversion of 2-methylpiperidine to 1,5-hexadiene by two rounds of exhaustive methylation followed by pyrolysis.

A side reaction involving nucleophilic substitution to give an alcohol ($R_4N^+ \ ^-OH \rightarrow ROH + R_3N$) generally accompanies the normal elimination reaction,[247] but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating $Me_4N^+ \ ^-OH$ in water, methanol is obtained, although without a solvent the product is not methanol, but dimethyl ether.[248]

The mechanism of elimination is usually E2 in protic solvents. *Hofmann's rule* is generally obeyed by acyclic and *Zaitsev's rule* by cyclohexyl substrates (Sec. 17.B, category 4). In certain cases, where the molecule is highly hindered or if the ammonium hydroxide is heated without solvent (neat), a five-membered E^i mechanism, similar to that in Reaction **17-8**, has been shown to operate. That is, the hydroxide in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogen atoms (see **36**), which removes a proton from the less substituted β-carbon atom to give the less substituted alkene with loss of the amine. It is also possible that the hydroxide (rather than the *N*-ylid) removes the β-hydrogen atom via an eclipsed rotamer in which the hydroxide is tethered to the ammonium unit and a syn-transition state is lower in energy.

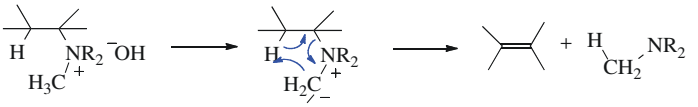
[244] Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 255–289; White, E.H.; Woodcock, D.J. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 409–416; Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960****, 11,* 317.

[245] Archer, D.A. *J. Chem. Soc. C* ***1971***, 1327.

[246] Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 4–5.

[247] Baumgarten, R.J. *J. Chem. Educ.* ***1968****, 45,* 122.

[248] See Musker, W.K.; Stevens, R.R. *J. Am. Chem. Soc.* ***1968****, 90*, 3515.

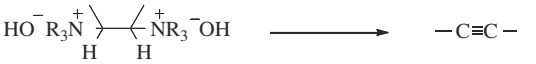


36

The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($R_2CDCH_2NMe_3^+ \ ^-OH$), the fate of the deuterium indicates the mechanism. If the E2 mechanism were in operation, the trimethylamine produced would contain no deuterium, which would be found only in the water. But if the mechanism is E^i, the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+ \ ^-OH$, the deuterium did appear in the amine, demonstrating an E^i mechanism for this case.[249] With simpler compounds, the mechanism is E2, since here the amine was deuterium-free.[250]

When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The *Hofmann rule* says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β-hydrogen atoms cleaves more readily than any longer *n*-alkyl group, all of which have two β-hydrogen atoms. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[251] In fact, the *Hofmann rule* as first stated[252] in 1851 applied only to which group cleaved, not to the orientation within a group. The latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the *Hofmann rule* (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2N^+Me_2Et \ ^-OH$ gives mostly styrene instead of ethylene.

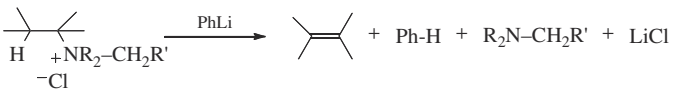
Triple bonds have been prepared by pyrolysis of 1,2-bis(ammonium) salts.[253]



OS **IV**, 980; **V**, 315, 608; **VI**, 552. Also see, OS **V**, 621, 883; **VI**, 75.

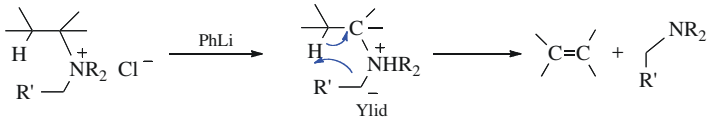
17-8 Cleavage of Quaternary Ammonium Salts with Strong Bases

Hydro-trialkylammonio-elimination



[249] Cope, A.C.; Mehta, A.S. *J. Am. Chem. Soc.* ***1963****, 85,* 1949. See also, Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. *J. Chem. Soc. B* ***1967***, 509.
[250] Cope, A.C.; LeBel, N.A.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1961****, 83*, 3861.
[251] Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960****, 11*, 317, see p. 348.
[252] Hofmann, A.W. *Liebigs Ann. Chem.* ***1851****, 78,* 253.
[253] See Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960****, 72*, 391, see pp. 397–398.

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH_2 in liquid NH_3[254]), an elimination can occur that is similar in products, although not in mechanism, to Reaction **17-7**. This is an alternative to Reaction **17-7** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is E^i:



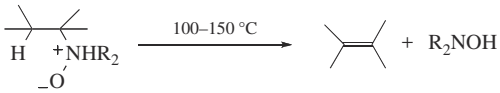
An α′ hydrogen is obviously necessary in order for the ylid to be formed. This type of mechanism is called α′,β elimination, since a β hydrogen is removed by the α′ carbon. The mechanism has been confirmed by labeling experiments similar to those described at Reaction **17-7**,[255] and by isolation of the intermediate ylids.[256] An important synthetic difference between this and most instances of Reaction **17-7** is that syn elimination is observed here and anti elimination in Reaction **17-7**, so products of opposite configuration are formed when the alkene exhibits cis–trans isomerism.

An alternative procedure that avoids the use of a very strong base is heating the salt with KOH in polyethylene glycol monomethyl ether.[257]

Benzotriazole has been shown to be a good leaving group for elimination reactions. The reaction of an allylic benzotriazole (3-benzotriazoyl-4-trimethylsilyl-1-butene) with *n*-butyllithium, and then an alkyl halide leads to an alkylated 1,3-diene upon heating.[258]

17-9 Cleavage of Amine Oxides

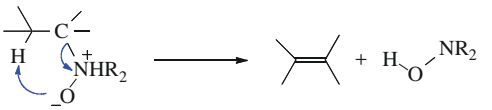
Hydro-(Dialkyloxidoammonio)-elimination



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* or *Cope elimination* (not to be confused with the Cope *rearrangement*, **18-32**). It is an alternative to Reactions **17-7** and **17-8**.[259] The reaction is usually performed with a mixture of amine and oxidizing agent (see **19-29**) without isolation of the amine oxide. Because of the mild conditions, side reactions are few, and the alkenes do not usually rearrange. The reaction is thus very useful for the preparation of many alkenes. A limitation is that it does not open six-membered rings containing nitrogen, although it does open rings of 5 and 7–10 members.[260] Rates of the reaction increase with increasing size of α- and

[254] Bach, R.D.; Bair, K.W.; Andrzejewski, D. *J. Am. Chem. Soc.* ***1972****, 94*, 8608; *J. Chem. Soc., Chem. Commun.* ***1974***, 819.
[255] Bach, R.D.; Knight, J.W. *Tetrahedron Lett.* ***1979***, 3815.
[256] Wittig, G.; Burger, T.F. *Liebigs Ann. Chem.* ***1960****, 632,* 85.
[257] Hünig, S.; Öller, M.; Wehner, G. *Liebigs Ann. Chem.* ***1979***, 1925.
[258] Katritzky, A.R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* ***1999****, 64*, 1888.
[259] See Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960****, 11*, 317, see p. 361; DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960****, 60*, 431, see pp. 448–451.
[260] Cope, A.C.; LeBel, N.A. *J. Am. Chem. Soc.* ***1960****, 82*, 4656; Cope, A.C.; Ciganek, E.; Howell, C.F.; Schweizer, E.E. *J. Am. Chem. Soc.* ***1960****, 82*, 4663.

β-substituents.[261] The reaction can be carried out at room temperature in dry Me_2SO or THF.[262] The influence of solvent effects has been examined.[263] The elimination is a stereoselective syn process,[264] and the five-membered E^i mechanism operates:

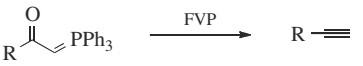


Almost all evidence indicates that the transition state must be planar. Deviations from planarity as in Reaction **17-4** (see Sec. 17.E.i) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of *trans*-cycloalkenes (eight-membered and higher). A polymer-bound *Cope elimination* reaction has been reported.[265]

OS **IV**, 612.

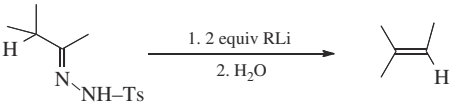
17-10 Pyrolysis of Keto-ylids

Hydro-(oxophosphoryl)-elimination



Phosphorus ylids are quite common (see Reaction **16-44**) and keto-phosphorus ylids ($RCOCH{=}PPh_3$) are also known. When these compounds are heating (flash vacuum pyrolysis, FVP) to $> 500\ ^\circ C$, alkynes are formed. Simple alkynes[266] can be formed as well as keto-alkynes[267] and en-ynes.[268] Rearrangement from ylids derived from tertiary amines and α-diazo ketones is also known.[269]

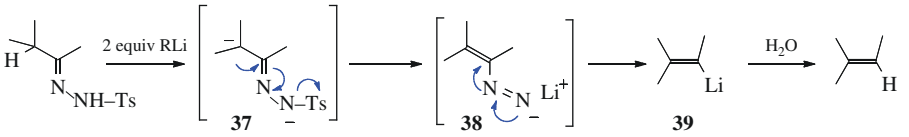
17-11 Decomposition of Toluene-p-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an alkene, the reaction being formally an elimination accompanied by a hydrogen shift.[270] The reaction (called the *Shapiro reaction*) has been applied to

[261] Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* ***1973****, 38,* 2102.
[262] Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962****, 84,* 1734.
[263] Acevedo, O.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***2006****, 128,* 6141.
[264] See, for example, Bach, R.D.; Andrzejewski, D.; Dusold, L.R. *J. Org. Chem.* ***1973****, 38,* 1742.
[265] Sammelson, R.E.; Kurth, M.J. *Tetrahedron Lett.* ***2001****, 42*, 3419.
[266] Aitken, R.A.; Atherton, J.I. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 1281.
[267] Aitken, R.A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S.V.; Seth, S.; Shannon, I.J.; Smith, F.C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2467.
[268] Aitken, R.A.; Boeters, C.; Morrison, J.J. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2473.
[269] DelZotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* ***2000***, 3731.
[270] See Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res.* ***1983****, 16*, 55; Shapiro, R.H. *Org. React.* ***1976****, 23*, 405.

tosylhydrazones[271] of many aldehydes and ketones. The most useful synthetic method involves treatment of the substrate with at least 2 molar equivalents of an organolithium compound[272] (usually MeLi) in ether, hexane, or tetramethylenediamine.[273] This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted alkene. Tosylhydrazones of α,β-unsaturated ketones give conjugated dienes.[274] The mechanism[275] has been formulated as that shown.

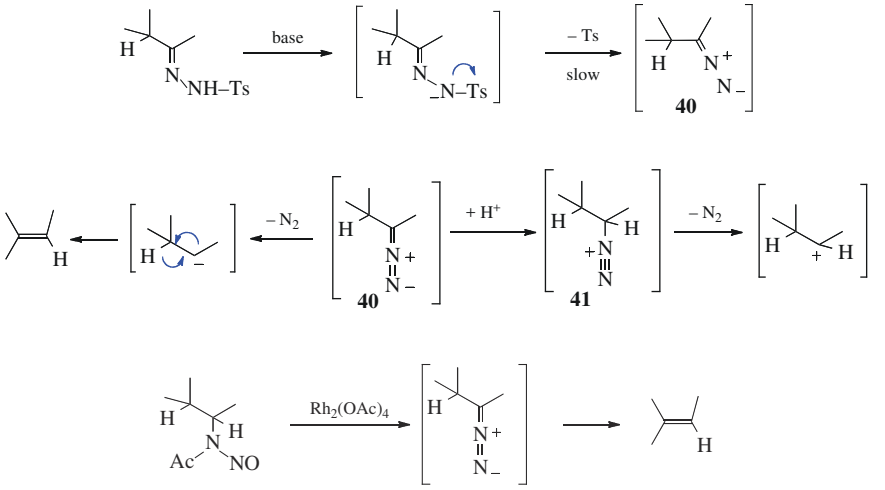


Evidence for this mechanism is (1) two molar equivalents of RLi are required; (2) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;[276] and (3) the intermediates **37–39** have been trapped.[277] This reaction, when performed in tetramethylenediamine, can be a synthetically useful method[278] of generating vinylic lithium compounds (**39**), which can be trapped by various electrophiles[279] (e.g., D_2O, to give deuterated alkenes), CO_2 (to give α,β-unsaturated carboxylic acids, Reaction **16-30**), or DMF (to give α,β-unsaturated aldehydes, Reaction **16-82**). Treatment of *N*-aziridino hydrazones with LDA leads to alkenes with high cis selectivity.[280]

The reaction also takes place with other bases (e.g., NaH, LiH,[281] Na in ethylene glycol, $NaNH_2$) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted alkene). The reaction with Na in ethylene glycol is called the *Bamford–Stevens reaction*.[282] For these reactions, two mechanisms are possible: a carbenoid and a carbocation mechanism.[283] The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**40**), which in some cases can be isolated. In fact, this reaction has been used as a synthetic method for the preparation of diazo compounds.[284] In the absence of protic solvents, **36** loses N_2, and hydrogen migrates, to give the alkene product. The migration of hydrogen may immediately follow, or be simultaneous with, the loss of N_2. In a protic

[271] See Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* ***2007****, 46,* 5587.
[272] Shapiro, R.H. *Tetrahedron Lett.* ***1968***, 345; Meinwald, J.; Uno, F. *J. Am. Chem. Soc.* ***1968****, 90*, 800.
[273] Stemke, J.E.; Bond, F.T. *Tetrahedron Lett.* ***1975***, 1815.
[274] See Dauben, W.G.; Rivers, G.T.; Zimmerman, W.T. *J. Am. Chem. Soc.* ***1977****, 99,* 3414.
[275] For a review of the mechanism, see Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 922.
[276] See Ref. 272; Shapiro, R.H.; Hornaman, E.C. *J. Org. Chem.* ***1974****, 39,* 2302.
[277] Lipton, M.F.; Shapiro, R.H. *J. Org. Chem.* ***1978****, 43,* 1409.
[278] See Traas, P.C.; Boelens, H.; Takken, H.J. *Tetrahedron Lett.* ***1976***, 2287; Stemke, J.E.; Chamberlin, A.R.; Bond, F.T. *Tetrahedron Lett.* ***1976***, 2947.
[279] For a review, see Chamberlin, A.R.; Bloom, S.H. *Org. React.* ***1990****, 39,* 1.
[280] Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***1996****, 118*, 2289.
[281] Biellmann, J.F.; Pète, J. *Bull. Soc. Chim. Fr.* ***1967***, 675.
[282] Bamford, W.R.; Stevens, R.R. *J. Chem. Soc.* ***1952***, 4735. For a tandem *Bamford–Stevens–Claisen rearrangement*, see May, J.A.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2002****, 124*, 12426.
[283] See Nickon, A.; Werstiuk, N.H. *J. Am. Chem. Soc.* ***1972****, 94,* 7081.
[284] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 257–295. For an improved procedure, see Wulfman, D.S.; Yousefian, S.; White, J.M. *Synth. Commun.* ***1988****, 18*, 2349.

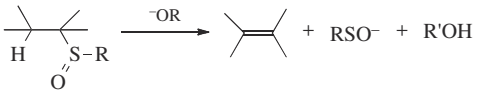
solvent, **40** becomes protonated to give the diazonium ion **41**, which loses N_2 to give the corresponding carbocation, that may then undergo elimination or give other reactions characteristic of carbocations. A diazo compound is an intermediate in the formation of alkenes by treatment of *N*-nitrosoamides with a Rh(II) catalyst.[285]



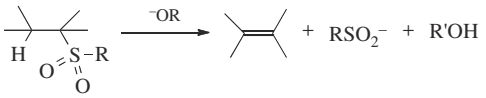
OS **VI**, 172; **VII**, 77; **IX**, 147. For the preparation of a diazo compound, see OS **VII**, 438.

17-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones

Hydro-alkylsulfinyl-elimination



Hydro-alkylsulfinyl-elimination



Sulfonium compounds (—C—$^{+}SR_2$) undergo elimination similar to that of their ammonium counterparts (Reactions **17-7** and **17-8**) in scope and mechanism, but this reaction is not of great synthetic importance. These syn-elimination reactions are related to the *Cope eln* (Reaction **17-9**) and *Hofmann elimination* (Reaction **17-7**).[286]

[285] Godfrey, A.G.; Ganem, B. *J. Am. Chem. Soc.* ***1990****, 112,* 3717.
[286] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 161–171.

Sulfones and sulfoxides[287] with a β hydrogen, on the other hand, undergo elimination on treatment with an alkoxide or, for sulfones,[288] even with hydroxide.[289] Sulfones also eliminate in the presence of an organolithium reagent and a Pd catalyst.[290] Mechanistically, these reactions belong on the E1–E2–E1cB spectrum.[291] Although the leaving groups are uncharged, the orientation follows *Hofmann's rule*, not *Zaitsev's*. Sulfoxides (but not sulfones) also undergo elimination upon pyrolysis at ∼ 80 °C in a manner analogous to Reaction **17-9**. The mechanism is also analogous, being the five-membered E^i mechanism with syn elimination.[292]

Selenoxides[293] and sulfinate esters ($R_2CH—CHR—SO—OMe$)[294] also undergo elimination by the E^i mechanism, and the selenoxide reaction takes place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.[295]

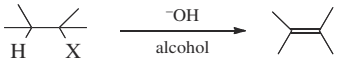
Both α-keto selenoxides[296] and sulfoxides[297] have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β-unsaturated derivatives. Allylic sulfoxides undergo 1,4-elimination to give dienes.[298]

A radical elimination reaction generates alkenes from sulfoxides. The reaction of a 2-bromophenyl alkylsulfoxide with Bu_3SnH and AIBN (see Sec. 14.A.i for a discussion of these standard radical conditions) leads to an alkene.[299]

OS **VI**, 23, 737; **VIII**, 543; **IX**, 63.

17-13 Dehydrohalogenation of Alkyl Halides

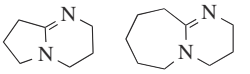
Hydro-halo-elimination



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides.[300] Hot alcoholic KOH is the

[287] See Cubbage, J.W.; Guo, Y.; McCulla, R.D.; Jenks, W.S. *J. Org. Chem.* ***2001****, 66*, 8722.
[288] See Yoshida, T.; Saito, S. *Chem. Lett.* ***1982***, 165.
[289] Hofmann, J.E.; Wallace, T.J.; Argabright, P.A.; Schriesheim, A. *Chem. Ind. (London)* ***1963***, 1234.
[290] Gai, Y.; Jin, L.; Julia, M.; Verpeaux, J.-N. *J. Chem. Soc., Chem. Commun.* ***1993***, 1625.
[291] Hofmann, J.E.; Wallace, T.L.; Schriesheim, A. *J. Am. Chem. Soc.* ***1964****, 86,* 1561.
[292] Schmitz, C.; Harvey, J.N.; Viehe, H.G. *Bull. Soc. Chim. Belg.* ***1994****, 103*, 105.
[293] Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Telurium Compounds*, Vol. 2, Wiley, NY, ***1987***, pp. 91–213, pp. 95–109; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 132–143; Reich, H.J. *Acc. Chem. Res.* ***1979****, 12*, 22, in Trahanovsky, W.S. *Oxidation in Organic Chemistry,* pt. C, Academic Press, NY, ***1978***, pp. 15–101; Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. *Chem. Scr.* ***1975****, 8A*; 9. See Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.
[294] Jones, D.N.; Higgins, W. *J. Chem. Soc. C* ***1970***, 81.
[295] Reich, H.J.; Willis Jr., W.W. *J. Am. Chem. Soc.* ***1980****, 102,* 5967.
[296] Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* ***1975****, 97,* 5434 and references cited therein; Crich, D.; Barba, G.R. *Org. Lett.* ***2000****, 2*, 989. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 287–290.
[297] Trost, B.M.; Salzmann, T.N.; Hiroi, K. *J. Am. Chem. Soc.* ***1976****, 98*, 4887. For a review of this and related methods, see Trost, B.M. *Acc. Chem. Res.* ***1978****, 11*, 453.
[298] de Groot, A.; Jansen, B.J.M.; Reuvers, J.T.A.; Tedjo, E.M. *Tetrahedron Lett.* ***1981****, 22,* 4137.
[299] Imboden, C.; Villar, F.; Renaud, P. *Org. Lett.* ***1999****, 1*, 873.
[300] See Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1173–1227.

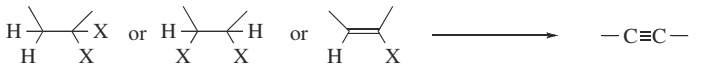
most frequently used base, although stronger bases[301] (^-OR, $^-NH_2$, etc.) or weaker ones (e.g., amines) are used where warranted.[302] The bicyclic amidines 1,5-diazabicyclo[3.4.0] non-5-ene (DBN)[303] and DBU[304] are good reagents for difficult cases.[305] Solvation by HMPA promotes LDA mediated dehydrobromination.[306]



DBN DBU

Dehydrohalogenation with the non-ionic base $(Me_2N)_3P{=}N\text{-}P(NMe_3)_2{=}NMe$ is even faster.[307] A Co catalyst with dimethylphenylsilylmethylmagnesium chloride leads to formation of terminal alkenes from 2° alkyl bromides.[308] Phase-transfer catalysis has been used with hydroxide as base.[309] As previously mentioned (Sec. 17.A.v), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr-$LiCO_3$ in DMF.[310] Dehydrohalogenation occurs by simply heating the alkyl halide in HMPA with no other reagent present.[311] As in nucleophilic substitution (Sec. 10.G.iii), the order of leaving group reactivity is $I > Br > Cl > F$.[312] Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow *Zaitsev's rule,* except for a few cases where steric effects are important (e.g., see Sec. 17.B, category 4). Eliminations of fluorides follow *Hofmann's rule* (Sec. 17.B, category 4).

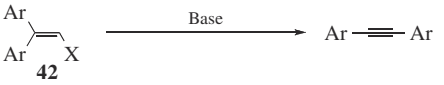
This reaction is by far the most important way of introducing a triple bond into a molecule.[313] Alkyne formation can be accomplished with substrates of the types:[314]



When the base is $NaNH_2$, 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1- and

[301] See Anton, D.R.; Crabtree, R.H. *Tetrahedron Lett.* ***1983****, 24,* 2449.
[302] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 256–258.
[303] Vogel, E.; Klärner, F. *Angew. Chem. Int. Ed.* ***1968****, 7,* 374.
[304] Oediger, H.; Möller, F. *Angew. Chem. Int. Ed.* ***1967****, 6,* 76; Wolkoff, P. *J. Org. Chem.* ***1982****, 47,* 1944.
[305] See Oediger, H.; Möller, F.; Eiter, K. *Synthesis* ***1972***, 591.
[306] Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon, New York, ***2002***.; For a mechanistic evaluation and an analysis of the influence of HMPA, see Ma, Y.; Ramirez, A.; Singh, K.J.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2006****, 128,* 15399.
[307] Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed.* ***1987****, 26,* 1167.
[308] Kobayashi, T.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2008****, 130*, 11276.
[309] Halpern, M.; Zahalka, H.A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* ***1985****, 50,* 5088. See also, Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *J. Org. Chem.* ***1984****, 49*, 1138.
[310] See Fieser, L.F.; Fieser, M. *Reagents for Organic Syntheses*, Vol. 1, Wiley, NY, ***1967***, pp. 606–609; Yakobson, G.G.; Akhmetova, N.E. *Synthesis* ***1983***, 169, see pp. 170–173.
[311] See Hoye, T.R.; van Deidhuizen, J.J.; Vos, T.J.; Zhao, P. *Synth. Commun.* ***2001****, 31*, 1367.
[312] Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* ***1988****, 44,* 2855.
[313] Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond,* pt. 2, Wiley, NY, ***1978***, p. 755; Köbrich, G.; Buck, P. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 100–134; Köbrich, G. *Angew. Chem. Int. Ed.* ***1965****, 4*, 49, see pp. 50–53.
[314] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 569–571.

2-alkynes. When the base is $^-$OH or $^-$OR, the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., —CRH—CX_2—CH_2—), allene formation can compete, although alkynes are usually more stable. Tetrabutylammonium fluoride mediates the dehydrobromination of vinyl bromide to terminal alkynes.[315] Treatment of 1,1-dibromo-1-alkenes with a Pd-catalyst, followed by reaction with tetrabutylammonium hydroxide gives an internal alkyne.[316]



42

1,1-Dibromoalkenes are converted to alkynes when treated with *n*-butyllithium.[317] This transformation is a modification of the *Fritsch–Buttenberg–Wiechell rearrangement* in which a 1,1-diaryl vinyl bromide (**42**) gives a diaryl alkyne upon treatment with base.[318] Vinyl sulfoxides that contain a leaving group (e.g., chloride) on the double bond react with *tert*-butyllithium to give a lithio alkyne, and hydrolysis leads to the final product, an alkyne.

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, although the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is E^i (Sec. 17.E.i) or, in some instances, the free radical mechanism (Sec. 17.E.i). Pyrolysis is normally performed without a catalyst at $\sim$ 400 °C. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst[319] (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.



43

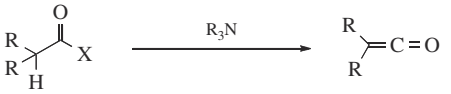
In the special case of the prochiral carboxylic acids (**43**), dehydrohalogenation with an optically active lithium amide gave an optically active product with %ee as high as 82%.[320]

OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V**, 285, 467, 514; **VI**, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; **VII**, 126, 319, 453, 491; **VIII**, 161, 173, 212, 254; **IX**, 191, 656, 662. Also see, OS **VI**, 968.

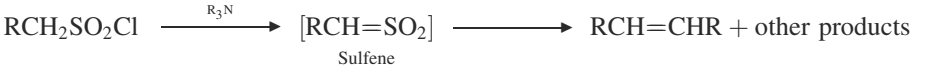
[315] Okutani, M.; Mori, Y. *Tetrahedron Lett.* ***2007****, 48*, 6856; Okutani, M.; Mori, Y. *J. Org. Chem.* ***2009****, 74*, 442.
[316] Chelucci, G.; Capitta, F.; Baldino, S. *Tetrahedron* ***2008****, 64,* 10250.
[317] Chernick, E.T.; Eisler, S.; Tykwinski, R.R. *Tetrahedron Lett.* ***2001****, 42*, 8575.
[318] Fritsch, P. *Ann.* ***1894****, 279*, 319; Buttenberg, W.P. *Ann.,* ***1894****, 279*, 324; Wiechell, H. *Ann.* ***1894****, 279*, 337. For a review, see Stang, P.J. *Chem. Rev.* ***1978****, 78*, 383. See Jahnke, E.; Tykwinski, R.R. *Chem. Commun.* ***2010***, 3235; Pratt, L.M.; Nguyen, N.V.; Kwon, O. *Chem. Lett.* ***2009****, 38*, 574.
[319] For a review, see Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971****, 10*, 172.
[320] Duhamel, L.; Ravard, A.; Plaquevent, J.C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* ***1990***, 787.

17-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides

Hydro-halo-elimination



Ketenes can be prepared by treatment of acyl halides with tertiary amines[321] or with NaH and a crown ether.[322] The scope is broad, and most acyl halides possessing an α hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if a reactive ketene must be used in a reaction with a given compound, the ketene can be generated *in situ* in the presence of the given compound.[323]



Closely related is the reaction of tertiary amines with sulfonyl halides that contain an α hydrogen. In this case, the initial product is the highly reactive sulfene, which cannot be isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.[324] Reactions of sulfenes *in situ* are also common (e.g., see **16-48**).

OS **IV**, 560; **V**, 294, 877; **VI**, 549, 1037; **VII**, 232; **VIII**, 82.

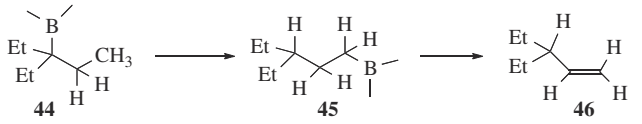
17-15 Elimination of Boranes

Hydro-boranetriyl-elimination



Trialkylboranes are formed from an alkene and BH_3 (Reaction **15-16**). When the resulting borane is treated with another alkene, an exchange reaction occurs.[325] This is an equilibrium process that can be shifted by using a large excess of alkene, by using an unusually reactive alkene, or by using an alkene with a higher boiling point than the displaced alkene and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (**12-2**). This cannot be accomplished simply by treatment of a borane with an alkene, because elimination in this reaction follows *Zaitsev's rule*: It is in the direction of the most stable alkene. However, heating borane (**44**) leads to **45** (Reaction **18-11**) and when **45** is heated with a higher-boiling alkene (e.g., 1-decene), the exchange reaction gives **46**. These isomerizations proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (Reaction **15-16**).

[321] See Tidwell, T.T. *Ketenes*, Wiley, NY, ***1995***.
[322] Taggi, A.E.; Wack, H.; Hafez, A.M.; France, S.; Lectka, T. *Org. Lett.* ***2002****, 4*, 627.
[323] See Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969****, 38,* 487.
[324] See King, J.F. Acc. Chem. Res. **1975**, 8, 10; Nagai, T.; Tokura, N. Int. J. Sulfur Chem. Part B **1972**, 207; Truce, W.E.; Liu, L.K. Mech. React. Sulfur Compd. **1969**, 4, 145; Opitz, G. Angew. Chem. Int. Ed. **1967**, 6, 107; Wallace, T.J. Q. Rev. Chem. Soc. **1966**, 20, 67.
[325] Brown, H.C.; Bhatt, M.V.; Munekata, T.; Zweifel, G. *J. Am. Chem. Soc.* ***1967****, 89,* 567; Taniguchi, H. *Bull. Chem. Soc. Jpn.* ***1979****, 52,* 2942.

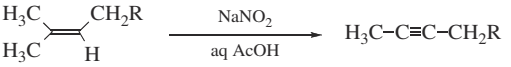


A similar reaction, but irreversible, has been demonstrated for alkynes.[326]

$$(R_2CH{-}CH_2)_3B + R'C{\equiv}CR' \longrightarrow 3\,R_2C{=}CH_2 + (R'CH{=}CR')_3B$$

17-16 Conversion of Alkenes to Alkynes

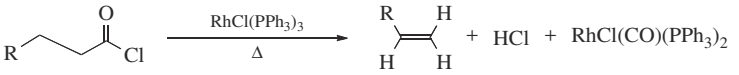
Hydro-methyl-elimination



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate-to-high yields.[327] The R may contain additional unsaturation, as well as OH, OR, OAc, C=O, and other groups, but the $Me_2C{=}CHCH_2{-}$ portion of the substrate is necessary for the reaction to take place. The mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [$Me_2C{=}CHCH_2R \rightarrow H_2C{=}CMeCH(NO_2)CH_2R$], and involving several additional intermediates.[328] The CH_3 lost from the substrate appears as CO_2, as demonstrated by the trapping of this gas.[328]

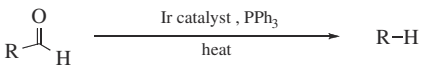
17-17 Decarbonylation of Acyl Halides or Aldehydes

Hydro-chloroformyl-elimination



Acyl chlorides containing an α hydrogen are smoothly converted to alkenes, with loss of HCl and CO, upon heating with chlorotris(triphenylphosphine)rhodium, with metallic Pt, or with certain other catalysts.[329] The mechanism probably involves conversion of RCH_2CH_2COCl to $RCH_2CH_2{-}RhCO(Ph_3P)_2Cl_2$ followed by a concerted syn elimination of Rh and H[330] (see also, Reactions **14-32** and **19-12**).

Aldehydes are decarbonylated to give the corresponding hydrocarbon in the presence of an Ir catalyst and triphenylphosphine.

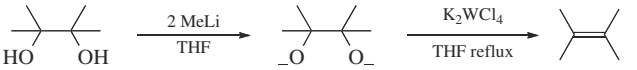


[326] Hubert, A.J. *J. Chem. Soc.* ***1965***, 6669.
[327] Abidi, S.L. *Tetrahedron Lett.* ***1986****, 27*, 267; *J. Org. Chem.* ***1986****, 51,* 2687.
[328] Corey, E.J.; Seibel, W.L.; Kappos, J.C. *Tetrahedron Lett.* ***1987****, 28*, 4921.
[329] For a review, see Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157. For extensions to certain other acid derivatives, see Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* ***1987***, 992.
[330] Lau, K.S.Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J.K. *J. Am. Chem. Soc.* ***1977****, 99*, 5664.

B. Reactions in which Neither Leaving Atom Is Hydrogen

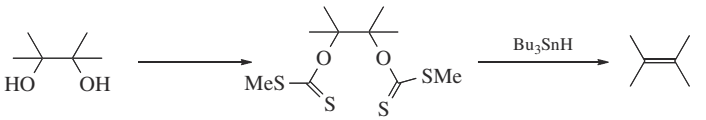
17-18 Deoxygenation of Vicinal Diols

Dihydroxy-elimination

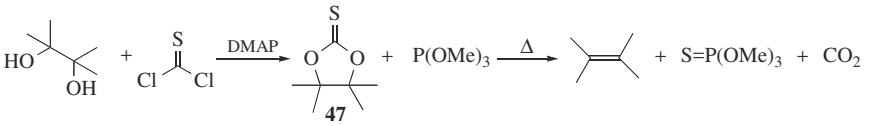


vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide (K_2WCl_6), or with certain other tungsten reagents, in refluxing THF.[331] Tetrasubstituted diols react most rapidly. The elimination is largely, but not entirely, syn. Several other methods have been reported,[332] in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with Ti metal,[333] with TsOH—NaI,[334] and by heating with $CpReO_3$,[335] where Cp is cyclopentadienyl.

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene–sodium[336] and with NaI in DMF.[337] In another procedure, the diols are converted to bis(dithiocarbonates) [bis(xanthates)], which undergo elimination (probably by a free radical mechanism) when treated with tri-*n*-butylstannane in toluene or benzene.[338] *vic*-Diols can also be deoxygenated through cyclic derivatives (Reaction **17-19**).



17-19 Cleavage of Cyclic Thionocarbonates



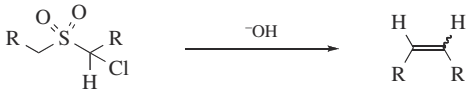
Cyclic thionocarbonates (**47**) can be cleaved to alkenes (the *Corey–Winter reaction*)[339] by heating with trimethyl phosphite[340] or other trivalent phosphorus compounds[341] or by treatment with bis(1,5-cyclooctadiene)nickel.[342] The thionocarbonates (e.g., **47**) can be

[331] Sharpless, K.B.; Umbreit, M.A.; Nieh, T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972****, 94*, 6538.
[332] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 297–299.
[333] McMurry, J.E. *Acc. Chem. Res.* ***1983****, 16*, 405 and references cited therein.
[334] Sarma, J.C.; Sharma, R.P. *Chem. Ind. (London)* ***1987***, 96.
[335] Cook, G.K.; Andrews, M.A. *J. Am. Chem. Soc.* ***1996****, 118*, 9448.
[336] Carnahan, Jr., J.C.; Closson, W.D. *Tetrahedron Lett.* ***1972***, 3447.
[337] Dafaye, J. *Bull. Soc. Chim. Fr.* ***1968***, 2099.
[338] Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2378.
[339] See Block, E. *Org. React.* ***1984****, 30,* 457; Sonnet, P.E. *Tetrahedron* ***1980****, 36*, 557, pp. 593–598; Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 354–359.
[340] Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1963****, 85,* 2677.
[341] Corey, E.J. *Pure Appl. Chem.* ***1967****, 14,* 19, see pp. 32–33.
[342] Semmelhack, M.F.; Stauffer, R.D. *Tetrahedron Lett.* ***1973***, 2667. For another method, see Vedejs, E.; Wu, E.S. C. *J. Org. Chem.* ***1974****, 39*, 3641.

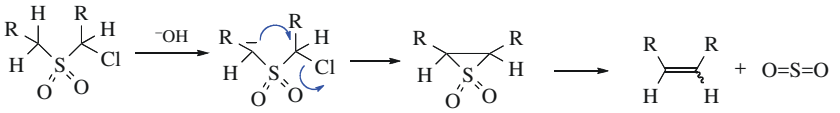
prepared by treatment of 1,2-diols with thiophosgene and DMAP.[343] The elimination is of course syn, so the product is sterically controlled. Alkenes that are not sterically favored can be made this way in high yield (e.g., *cis*-$PhCH_2CH{=}CHCH_2Ph$).[344] Certain other five-membered cyclic derivatives of 1,2-diols can also be converted to alkenes.[345]

17-20 The Ramberg–Bäcklund Reaction

Ramberg–Bäcklund halosulfone transformation



The reaction of an α-halo sulfone with a base to give an alkene is called the *Ramberg–Bäcklund reaction*.[346] The reaction is quite general for α-halo sulfones with an α′ hydrogen, despite the unreactive nature of α-halo sulfones in normal S_N2 reactions (Sec. 10.G.i, category 6). Halogen reactivity is in the order $I > Br \gg Cl$. Phase-transfer catalysis has been used.[347] In general, mixtures of cis and trans isomers are obtained, but usually the less stable cis isomer predominates. The mechanism involves formation of an episulfone, and then elimination of SO_2. There is much evidence for this mechanism,[348]

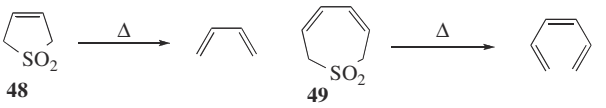


including the isolation of the episulfone intermediate,[349] and also the preparation of episulfones in other ways and the demonstration that they give alkenes under the reaction conditions faster than the corresponding α-halo sulfones.[350] Episulfones synthesized in other ways (e.g., Reaction **16-48**) are reasonably stable compounds, but eliminate SO_2 to give alkenes when heated or treated with base.

If the reaction is run on the unsaturated bromosulfones ($RCH_2CH{=}CHSO_2CH_2Br$, prepared by reaction of $BrCH_2SO_2Br$ with $RCH_2CH{=}CH_2$ followed by treatment with Et_3N), $RCH{=}CHCH{=}CH_2$ is produced in moderate-to-good yields.[351] The compound mesyltriflone ($CF_3SO_2CH_2SO_2CH_3$) can be used as a synthon for the tetraion $^{2-}C{=}C^{2-}$. Successive alkylation (Reaction **10-67**) converts it to $CF_3SO_2CR^1R^2SO_2CHR^3R^4$

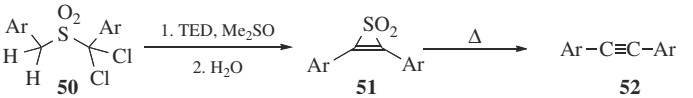
[343] Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett.* ***1982****, 23*, 1979.
[344] Corey, E.J.; Carey, F.A.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1965****, 87*, 934.
[345] See Beels, C.M.D.; Coleman, M.J.; Taylor, R.J.K. *Synlett* ***1990***, 479.
[346] Paquette, L.A. *Org. React.* ***1977****, 25*, 1; *Mech. Mol. Migr.* ***1968****, 1,* 121; *Acc. Chem. Res.* ***1968****, 1*, 209; Meyers, C.Y.; Matthews, W.S.; Ho, L.L.; Kolb, V.M.; Parady, T.E. in Smith, G.V. *Catalysis in Organic Synthesis*, Academic Press, NY, ***1977***, pp. 197–278; Rappe, C. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1105–1110; Bordwell, F.G. *Acc. Chem. Res.* ***1970****, 3*, 281.
[347] Hartman, G.D.; Hartman, R.D. *Synthesis* ***1982***, 504.
[348] See Bordwell, F.G.; Wolfinger, M.D. *J. Org. Chem.* ***1974****, 39,* 2521; Bordwell, F.G.; Doomes, E. *J. Org. Chem.* ***1974****, 39*, 2526, 2531.
[349] Sutherland, A.G.; Taylor, R.J.K. *Tetrahedron Lett.* ***1989****, 30,* 3267.
[350] Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968****, 90,* 429; Bordwell, F. G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968****, 90*, 435.
[351] Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.; Wall, A. *J. Am. Chem. Soc.* ***1986****, 108*, 4568.

(anywhere from one to four alkyl groups can be put in), which, when treated with base, gives $R^1R^2C{=}CR^3R^4$.[352] The nucleofuge here is the $CF_3SO_2^-$ ion. There is an example of a *Ramberg–Bäcklund reaction* that is induced by a *Michael addition*.[353]



48 **49**

2,5-Dihydrothiophene-1,1-dioxides (**48**) and 2,17-dihydrothiepin-1,1-dioxides (**49**) undergo analogous 1,4- and 1,6-eliminations, respectively (see also, Reaction **17-36**). These are concerted reactions and, as predicted by the orbital-symmetry rules (Reaction **15-50**. A, and immediately preceding pages), the former[354] is a suprafacial process and the latter[355] an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and evidence shows that this reaction occurs by a nonconcerted pathway.[356] The eliminations of SO_2 from **48** and **49** are examples of *cheletropic reactions*,[357] which are defined as reactions in which two σ bonds that terminate at a single atom (in this case the sulfur atom) are made or broken in concert.[358]



50 **51** **52**

α,α-Dichlorobenzyl sulfones (**50**) react with an excess of the base triethylenediamine (TED) in DMSO at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**51**), which can be isolated.[359] Thermal decomposition of **51** gives the alkynes **52**.[360]

A *Ramberg–Bäcklund-type reaction* has been carried out on the α-halo *sulfides* ($ArCHClSCH_2Ar$), which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes ($ArCH{=}CHAr$).[361] Cyclic sulfides lead to ring-contracted cyclic alkenes upon treatment with NCS in CCl_4 followed by oxidation with *m*-chloroperoxybenzoic acid.[362]

[352] Hendrickson, J.B.; Boudreaux, G.J.; Palumbo, P.S. *J. Am. Chem. Soc.* ***1986****, 108*, 2358.
[353] Vasin, V.A.; Bolusheva, I.Yu.; Razin, V.V. *Russ. J. Org. Chem.* ***2010****, 46,* 758.
[354] Mock, W.L. *J. Am. Chem. Soc.* ***1966****, 88*, 2857; McGregor, S.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1966****, 88,* 2858.
[355] Mock, W.L. *J. Am. Chem. Soc.* ***1969****, 91,* 5682.
[356] Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968****, 90,* 429; Bordwell, F.G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968****, 90*, 435. See also, Vilsmaier, E.; Tropitzsch, R.; Vostrowsky, O. *Tetrahedron Lett.* ***1974***, 3987.
[357] See Mock, W.L. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 141–179.
[358] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 152–163.
[359] Philips, J.C.; Swisher, J.V.; Haidukewych, D.; Morales, O. *Chem. Commun.* ***1971***, 22.
[360] Philips, J.C.; Morales, O. *J. Chem. Soc., Chem. Commun.* ***1977***, 713.
[361] Mitchell, R.H. *Tetrahedron Lett.* ***1973***, 4395. For a similar reaction without base treatment, see Pommelet, J.; Nyns, C.; Lahousse, F.; Merényi, R.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1981****, 20,* 585.
[362] MacGee, D.I.; Beck, E.J. *J. Org. Chem.* ***2000****, 65*, 8367.

The *Ramberg–Bäcklund reaction* can be regarded as a type of extrusion reaction (see Sec. 17.F.vi).

OS **V**, 877; **VI**, 454, 555; **VIII**, 212.

17-21 The Conversion of Aziridines to Alkenes

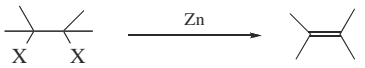
epi-Imino-elimination



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce alkenes.[363] An *N*-nitroso compound is an intermediate (Reaction **12-50**); other reagents that produce such intermediates also give alkenes. The reaction is stereospecific: *cis*-aziridines give *cis*-alkenes and *trans*-aziridines give *trans*-alkenes.[364] Aziridines carrying *N*-alkyl substituents can be converted to alkenes by treatment with ferrous iodide[365] or with *m*-chloroperoxybenzoic acid.[366] An *N*-oxide intermediate (Reaction **19-29**) is presumably involved in the latter case. *N*-Tosylaziridnes give allylic sulfonamides when treated with butyllithium.[367] *N*-Tosyl aziridines are converted to *N*-tosyl imines when treated with boron trifluoride.[368] 2-Tosylmethyl *N*-tosylaziridines react with Te^{2-} in the presence of Adogen 464 to give allylic *N*-tosyl amines.[369] 2-Halomethyl *N*-tosyl aziridines also react with In metal in methanol to give *N*-tosyl allylic amines.[370]

17-22 Elimination of Vicinal Dihalides

Dihalo-elimination



Dehalogenation has been accomplished with many reagents, the most common being Zn, Mg, and iodide ion.[371] Heating in HMPA is often enough to convert a *vic*-dibromide to an alkene.[372] Among reagents used less frequently have been phenyllithium, phenylhydrazine, $CrCl_2$, Na_2S in DMF,[373] and $LiAlH_4$.[374] Electrochemical reduction has also

[363] See Sonnet, P.E. *Tetrahedron* ***1980****, 36*, 557, see p. 591; Dermer, O.C.; Ham, G.E. *Ethylenimine and other Aziridines*, Academic Press, NY, ***1969***, pp. 293–295.
[364] See Carlson, R.M.; Lee, S.Y. *Tetrahedron Lett.* ***1969***, 4001.
[365] Imamoto, T.; Yukawa, Y. *Chem. Lett.* ***1974***, 165.
[366] Heine, H.W.; Myers, J.D.; Peltzer, III, E.T. *Angew. Chem. Int. Ed.* ***1970****, 9,* 374.
[367] Hodgson, D.M.; Ştefane, B.; Miles, T.J.; Witherington, J. *J. Org. Chem.* ***2006****, 71,* 8510.
[368] Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun.* ***2002***, 134.
[369] Chao, B.; Dittmer, D.C. *Tetrahedron Lett.* ***2001****, 42*, 5789.
[370] Yadav, J.S.; Bandyapadhyay, A.; Reddy, B.V.S. *Synlett* ***2001***, 1608.
[371] Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D,* pt. 1, Wiley, NY, ***1983***, pp. 161–201. Also see, Bosser, G.; Paris, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 2057.
[372] Khurana, J.M.; Bansal, G.; Chauhan, S. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1089.
[373] Fukunaga, K.; Yamaguchi, H. *Synthesis* ***1981***, 879. See also, Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* ***1983****, 24* 3001; Landini, D.; Milesi, L.; Quadri, M.L.; Rolla, F. *J. Org. Chem.* ***1984****, 49,* 152.
[374] For a lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 259–263.

been used.[375] Treatment with In[376] or Sm[377] metal in methanol, $InCl_3/NaBH_4$,[378] heating with Zn in acetic acid,[379] or reaction of a *Grignard reagent* and $Ni(dppe)Cl_2$ (dppe = 1,2-diphenylphosphinoethane).[380] When the reagent is Zn, antistereospecificity has been observed in some cases,[381] but not in others.[382] Microwave irradiation of a *vic*-dibromide in an ionic liquid leads to the alkene.[383] The reaction of a vicinal dibromide with triethylamine and DMF with microwave irradiation leads to vinyl bromide.[384] α,β-Dibromo amides are converted to conjugated amides upon photolysis in methanol.[385]

One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from X—C—CX_2—C—X or X—C—CX=C— systems.[386] Cumulenes have been obtained from 1,4-elimination:

$$BrCH_2—C{\equiv}C—CH_2Br + Zn \longrightarrow CH_2{=}C{=}C{=}CH_2$$

Cumulenes have also been prepared by treating alkynyl epoxides with boron trifluoride.[387] 1,4-Elimination of BrC—C=C—CBr has been used to prepare conjugated dienes C=C—C=C.[388] Allenes are formed by heating propargylic alcohols with arylboronic acids (Reaction **12-28**) and a Pd catalyst.[389] Allenes are also formed from propargylic amines using a CuI and a Pd catalyst.[390] In addition, allenes are formed from lithium bromocyclopropylidenoids.[391]

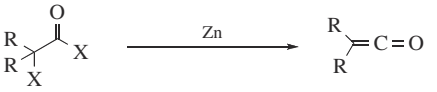
The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.[392] For different reagents, mechanisms involving carbocations, carbanions, and free radical intermediates, as well as concerted mechanisms, have been proposed.

OS **III**, 526, 531; **IV**, 195, 268; **V**, 22, 255, 393, 901; **VI**, 310, **VII**, 241. Also see, OS **IV**, 877, 914, 964.

[375] See Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 145–147; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 151–154.
[376] Ranu, B.C.; Guchhait, S.K.; Sarkar, A. *Chem. Commun.* ***1998***, 2113.
[377] Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* ***1996****, 37*, 9313.
[378] Ranu, B.C.; Das, A.; Hajra, A. *Synthesis* ***2003***, 1012.
[379] Gaenzler, F.C.; Smith, M.B. *Synlett* ***2007***, 1299.
[380] Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995****, 36*, 9189.
[381] See Gordon, M.; Hay, J.V. *J. Org. Chem.* ***1968****, 33,* 427.
[382] See Sicher, J.; Havel, M.; Svoboda, M. *Tetrahedron Lett.* ***1968***, 4269.
[383] Ranu, B.C.; Jana, R. *J. Org. Chem.* ***2005****, 70*, 8621.
[384] Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* ***2001****, 42*, 3893.
[385] Aruna, S.; Kalyanakumar, R.; Ramakrishnan, V.T. *Synth. Commun.* ***2001****, 31*, 3125.
[386] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 9–56; Landor, P.D. in Landor, S.R. *The Chemistry of the Allenes*, Vol. 1, Academic Press, NY, ***1982***; pp. 19–233; Taylor, D.R. *Chem. Rev.* ***1967****, 67*, 317.
[387] Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* ***1994****, 35*, 6977.
[388] Engman, L.; Byström, S.E. *J. Org. Chem.* ***1985****, 50,* 3170.
[389] Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* ***2004****, 45,* 5573.
[390] Nakmura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* ***2004****, 126,* 5958.
[391] Azizoglu, A.; Balci, M.; Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* ***2008****, 73*, 8182.
[392] See Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 332–368; Baciocchi, W. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D,* pt. 2, Wiley, NY, ***1983***, p. 161.

17-23 Dehalogenation of α-Halo Acyl Halides

Dihalo-elimination

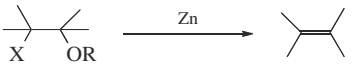


Ketenes can be prepared by dehalogenation of α-halo acyl halides with zinc or with triphenylphosphine.[393] The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.[394]

OS **IV**, 348; **VIII**, 377.

17-24 Elimination of a Halogen and a Hetero Group

Alkoxy-halo-elimination



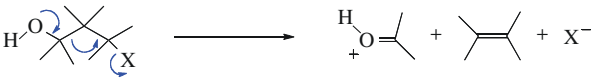
The elimination of OR and halogen from β-halo ethers is called the *Boord reaction*. It can be carried out with Zn, Mg, Na, or certain other reagents.[395] The yields are high and the reaction is of broad scope. β-Halo acetals readily yield vinylic ethers, X—C—C(OR)$_2$ → C=C—OR and 2 molar equivalents of SmI_2 in HMPA is effective.[396] Besides β-halo ethers, the reaction can also be carried out on compounds of the formula Z—C—C—Z where X is halogen and Z is OCOR, OTs,[397] NR_2,[398] or SR.[399] When X = Cl and Z = OAc, heating in THF with an excess of SmI_2 followed by treatment with dilute aq HCl gives an alkene.[400] When Z = I and the other Z is an oxygen of an oxazolone (a carbamate unit), heating with In metal in methanol leads to an allylic amine.[401] The Z group may also be OH, but then X is limited to Br and I.[402] Like Reaction **17-22**, this method ensures that the new double bond will be in a specific position. The fact that Mg causes elimination in these cases limits the preparation of *Grignard reagents* from these compounds. It has been shown that treatment of β-halo ethers and esters with Zn gives nonstereospecific elimination,[403] so the mechanism was not E2. An E1cB mechanism was postulated because of the poor leaving-group ability of OR and OCOR. Bromohydrins can be converted to alkenes (elimination of Br, OH) in high yields by treatment with $LiAlH_4$-$TiCl_3$.[404]

OS **III**, 698, **IV**, 748; **VI**, 675.

[393] Darling, S.D.; Kidwell, R.L. *J. Org. Chem.* ***1968****, 33*, 3974.
[394] See McCarney, C.C.; Ward, R.S. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 1600. See also, Masters, A.P.; Sorensen, T.S.; Ziegler, T. *J. Org. Chem.* ***1986****, 51*, 3558.
[395] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 263–267, for reagents that produce olefins from β-halo ethers and esters, and from halohydrins.
[396] Park, H.S.; Kim, S.H.; Park, M.Y.; Kim, Y.H. *Tetrahedron Lett.* ***2001****, 42*, 3729.
[397] Reeve, W.; Brown, R.; Steckel, T.F. *J. Am. Chem. Soc.* ***1971****, 93*, 4607.
[398] Gurien, H. *J. Org. Chem.* ***1963****, 28*, 878.
[399] Amstutz, E.D. *J. Org. Chem.* ***1944****, 9,* 310.
[400] Concellón, J.M.; Bernad, P.L.; Bardales, E. *Org. Lett.* ***2001****, 3*, 937.
[401] Yadav, J.S.; Bandyopadhyay, A.; Reddy, B.V.S. *Tetrahedron Lett.* ***2001****, 42*, 6385.
[402] Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Chem. Eur. J.* ***2001****, 7*, 3062.
[403] House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* ***1965****, 87*, 838.
[404] McMurry, J.E.; Hoz, T. *J. Org. Chem.* ***1975****, 40,* 3797.

17.F.ii. Fragmentations

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.[405] These processes occur on substrates of the form W—C—C—X, where X is a normal nucleofuge (e.g., halogen, OH_2^+, OTs, NR_3^+) and W is a positive-carbon electrofuge. In most of the cases, W is HO—C— or R_2N—C—, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, for example,

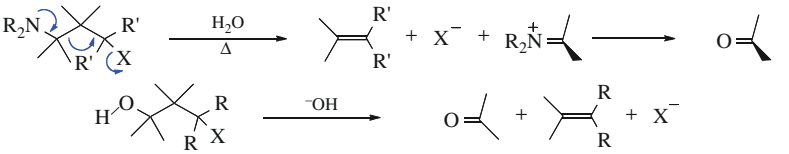


The mechanisms are mostly E1 or E2. We will discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **17-25**–**17-28** and **17-30** may be considered fragmentations (see also, Reactions **19-12** and **19-13**).

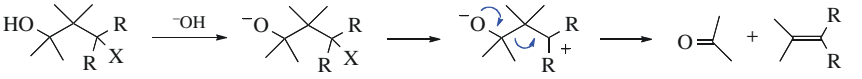
17-25 1,3-Fragmentation of γ-Amino, γ-Hydroxy Halides and 1,3-Diols

Dialkylaminoalkyl-halo-elimination, and so on

Hydroxyalkyl-hydroxy-elimination



γ-Dialkylamino halides undergo fragmentation when heated with water to give an alkene and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (**16-2**).[406] γ-Hydroxy halides and tosylates are fragmented with base. In this instance, the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, which enables the carbon leaving group to come off more easily:



Prelog and Zalán[407] first observed this type of fragmentation in work that solved the structure of quinine and other Cinchona alkaloids in a 1,3-elimination ring-opening reaction. Subsequent work by Grob[408] elucidated the mechanism of the reaction, and this 1,3-elimination is often referred to as *Grob fragmentation*.[409] The mechanism of these

[405] Becker, K.B.; Grob, C.A. in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 2, Wiley, NY, ***1977***, pp. 653–723; Grob, C.A. *Angew. Chem. Int. Ed.* ***1969****, 8,* 535; Grob, C.A.; Schiess, P.W. *Angew. Chem. Int. Ed.* ***1967****, 6,* 1.

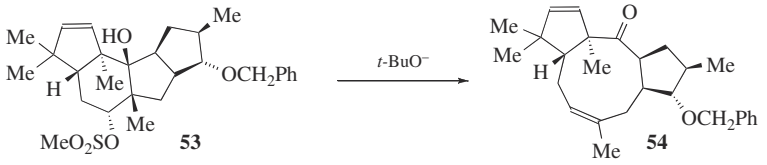
[406] Grob, C.A.; Ostermayer, F.; Raudenbusch, W. *Helv. Chim. Acta* ***1962****, 45*, 1672.

[407] Prelog, V.; Zalán, E. *Helv. Chim. Acta* ***1944****, 27*, 535; Prelog, V.; Häfliger, O. *Helv. Chim. Acta* ***1950****, 33,* 2021.

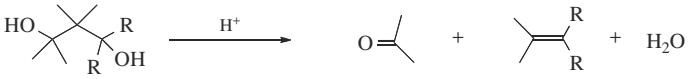
[408] Grob, C.A. *Angew. Chem. Int. Ed.* ***1969****, 8,* 535 and references cited therein; Grob, C.A.; Kiefer, H.R.; Lutz, H. J.; Wilkens, H.J. *Helv. Chim. Acta* ***1967****, 50*, 416.

[409] See Prantz, K.; Mulzer, J. *Chem. Rev.* ***2010****, 110*, 3741.

reactions is often E1, but an E2 mechanism also operates.[410] It has been shown that stereoisomers of cyclic γ-amino halides and tosylates in which the two leaving groups can assume an antiperiplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.[411] An example of a *Grob fragmentation* is the conversion of **53** to **54**.[412]



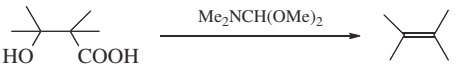
γ-Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to $^{+}OH_2$ and this would convert NR_2 to $^{+}NR_2H$, which does not have the unshared pair necessary to form the double bond with the carbon.[413]



1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved by acid treatment.[414] The reaction is most useful synthetically when at least one of the OH groups is on a ring.[415]

17-26 Decarboxylation of β-Hydroxy Carboxylic Acids and of β-Lactones

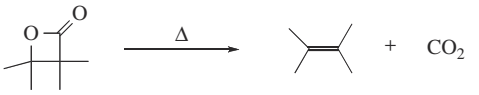
Carboxy-hydroxy-elimination



An OH and a CO_2H group can be eliminated from β-hydroxy carboxylic acids by refluxing with excess DMF dimethyl acetal.[416] Mono-, di-, tri-, and tetrasubstituted alkenes have been prepared by this method in good yields.[417] There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate $^{-}O_2C—C—C—O—C=N^{+}Me_2$.[418] The reaction has also been accomplished[419] under extremely mild conditions (a few seconds at 0 °C) with PPh_3 and $EtO_2C—N=N—CO_2Et$,

[410] Fischer, W.; Grob, C.A. *Helv. Chim. Acta* ***1978****, 61,* 2336 and references cited therein.
[411] Geisel, M.; Grob, C.A.; Wohl, R.A. *Helv. Chim. Acta* ***1969****, 52,* 2206 and references cited therein.
[412] Chass, D.A.; Buddhsukh, D.; Magnus, P.D. *J. Org. Chem.* ***1978****, 43*, 1750.
[413] Grob, C.A.; Hoegerle, R.M.; Ohta, M. *Helv. Chim. Acta* ***1962****, 45*, 1823.
[414] Zimmerman, H.E.; English Jr., J. *J. Am. Chem. Soc.* ***1954****, 76,* 2285, 2291, 2294.
[415] For a review, see Caine, D. *Org. Prep. Proced. Int.* ***1988****, 20*, 1.
[416] Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* ***1975***, 1545.
[417] See Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* ***1975****, 58,* 1450.
[418] Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* ***1979***, 1909.
[419] For another method, see Tanzawa, T.; Schwartz, J. *Organometallics* ***1990****, 9*, 3026.

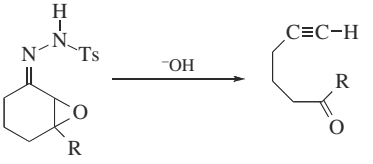
diethyl azodicarboxylate.[420] In a related procedure, β-lactones undergo thermal decarboxylation to give alkenes in high yields. The reaction has been shown to be stereospecific syn elimination.[421] There is evidence that this reaction also involves a zwitterionic intermediate.[422]



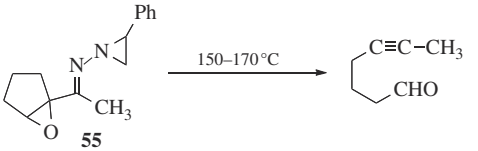
There are no OS references, but see OS **VII**, 172, for a related reaction.

17-27 Fragmentation of α,β-Epoxy Hydrazones

Eschenmoser–Tanabe ring cleavage



Cyclic α,β-unsaturated ketones[423] can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones,[424] in what is known as the *Eschenmoser–Tanabe ring cleavage*. The reaction can be applied to the formation of acetylenic aldehydes (R = H) by using the corresponding, 2,4-dinitro-tosylhydrazone derivatives.[425] Hydrazones (e.g., **55**) prepared from epoxy ketones and ring-substituted *N*-aminoaziridines undergo similar fragmentation when heated.[426]

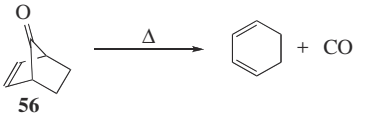


55

OS **VI**, 679.

17-28 Elimination of CO and CO_2 from Bridged Bicyclic Compounds

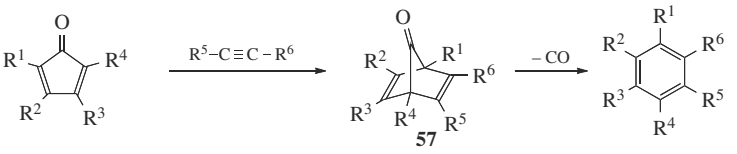
seco-Carbonyl-1, 4-elimination



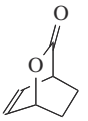
56

[420] Mulzer, J.; Lammer, O. *Angew. Chem. Int. Ed.* ***1983****, 22,* 628.
[421] See Adam, W.; Martinez, G.; Thompson, J.; Yany, F. *J. Org. Chem.* ***1981****, 46,* 3359.
[422] Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem. Int. Ed.* ***1980****, 19,* 465; Mulzer, J.; Zippel, M. *Tetrahedron Lett.* ***1980****, 21*, 751. See also, Moyano, A.; Pericàs, M.A.; Valentí, E. *J. Org. Chem.* ***1989***, 573.
[423] See MacAlpine, G.A.; Warkentin, J. *Can. J. Chem.* ***1978****, 56,* 308, and references cited therein.
[424] Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* ***1967****, 50*, 708; Tanabe, M.; Crowe, D.F.; Dehn, R.L.; Detre, G. *Tetrahedron Lett.* ***1967***, 3739; Tanabe, M.; Crowe, D.F.; Dehn, R.L. *Tetrahedron Lett.* ***1967***, 3943.
[425] Corey, E.J.; Sachdev, H.S. *J. Org. Chem.* ***1975****, 40*, 579.
[426] Felix, D.; Müller, R.K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1972****, 55,* 1276.

On heating, bicyclo[2.2.1]hept-2,3-en-17-ones (**56**) usually lose CO to give cyclohexadienes,[427] in a type of *reverse Diels–Alder reaction*. Bicyclo[2.2.1]heptadienones (**57**) undergo the reaction so readily (because of the stability of the benzene ring produced) that



57



58

they cannot generally be isolated. The parent (**57**) has been obtained at 10–15 K in an Ar matrix, where its spectrum could be studied.[428] Both **56** and **57** can be prepared by a *Diels-Alder reactions* between a cyclopentadienone and an alkyne or alkene, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.[429] Unsaturated bicyclic lactones of the type **58** can also undergo the reaction, losing CO_2 (see also, **17-35**).

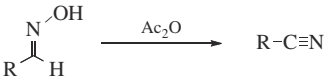
OS **III**, 807; **V**, 604, 1037.

Reversal of the *Diels–Alder reaction* may be considered a fragmentation (see **15-50**).

17.F.iii. Reactions in which C≡N or C=N Bonds Are Formed

17-29 Dehydration of Oximes and Similar Compounds

***C*- Hydro-** *N*- **hydroxy-elimination; *C*- Acyl-** *N*- **hydroxy-elimination**



Aldoximes can be dehydrated to nitriles[430] by many dehydrating agents, of which acetic anhydride is the most common. Among reagents that are effective under mild conditions[431]

[427] See Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 16–46.

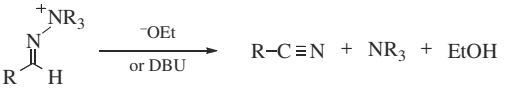
[428] Birney, D.M.; Wiberg, K.B.; Berson, J.A. *J. Am. Chem. Soc.* ***1988****, 110*, 6631.

[429] See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965****, 65*, 261, pp. 300–348. For references to this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 207–213.

[430] Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 92–96; Fatiadi, K. in Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1057–1303.

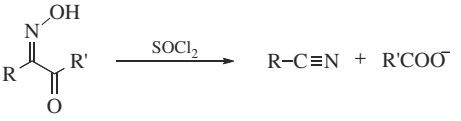
[431] Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* ***1983***, 741; Jursic, B. *Synth. Commun.* ***1989****, 19,* 689.

(room temperature) are $Ph_3P—CCl_4$,[432] $PPh_3—I_2$,[433] $Pd(OAc)_2/PPh_3$ in refluxing CH_3CN,[434] ferric sulfate,[435] Cu(II) with ultrasound,[436] and ZnO/CH_3COCl under solvent-free conditions.[437] *N,N*-Dimethylformamide catalyzes the thermal dehydration of aldoximes.[438] Heating an oxime with a Ru catalyst gives the nitrile.[439] Heating with the *Burgess reagent* [$Et_3N^{+-}SO_2N$-CO_2Me] in PEG is effective for this transformation.[440] Sulfuric acid impregnated silica gel[441] gives the nitrile, as does microwave irradiation of an oxime with tetrachloropyridine on alumina.[442] Aldehydes can be converted to oximes *in situ* and microwave irradiation on alumina[443] or with ammonium acetate[444] gives the nitrile. Solvent-free reactions are known.[445] The reaction is most successful when the H and OH are anti. Various alkyl and acyl derivatives of aldoximes (RCH=NOR,[446] RCH=NOCOR, $RCH=NOSO_2Ar$, etc.), also give nitriles, as do chlorimines (RCH=NCl; the latter with base treatment).[447] *N,N*-Dichloro derivatives of primary amines give nitriles upon pyrolysis: $RCH_2NCl_2 \rightarrow RCN$.[448]



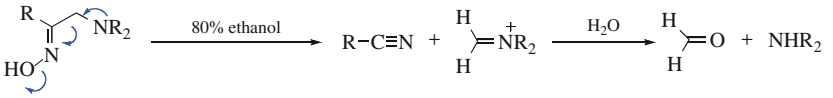
Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with ^-OEt[449] or DBU (see Reaction **17-13**):[450] as do dimethylhydrazones ($RCH=NNMe_2$), when treated with Et_2NLi and HMPA.[451] All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates (see Reaction **16-16**).

Hydroxylamines that have an α-proton are converted to nitrones when treated with a Mn–salen complex.[452]

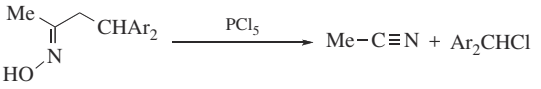


[432] Kim, J.N.; Chung, K.H.; Ryu, E.K. *Synth. Commun.* ***1990****, 20,* 2785.
[433] Narsaiah, A.V.; Sreenu, D.; Nagaiah, K. *Synth. Commun.* ***2006****, 36,* 137.
[434] Kim, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* ***2009****, 50*, 1717.
[435] Desai, D.G.; Swami, S.S.; Mahale, G.D. *Synth. Commun.* ***2000****, 30*, 1623.
[436] Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* ***2010****, 51*, 4479.
[437] Hosseini Sarvari, M. *Synthesis* ***2005***, 787.
[438] Supsana, P.; Liaskopoulos, T.; Tsoungas, P.G.; Varvounis, G. *Synlett* ***2007***, 267.
[439] Yang, S.H.; Chang, S. *Org. Lett.* ***2001****, 3*, 4209.
[440] Miller, C.P.; Kaufman, D.H. *Synlett* ***2000***, 1169.
[441] Sarvari, M.H. *Synthesis* ***2005***, 787.
[442] Lingaiah, N.; Narender, R. *Synth. Commun.* ***2002****, 32,* 2391.
[443] Bose, D.S.; Narsaiah, A.V. *Tetrahedron Lett.* ***1998****, 39*, 6533.
[444] Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.
[445] See Sharghi, H.; Sarvari, M.H. *Synthesis* ***2003***, 243.
[446] Anand, N.; Owston, N.A.; Parker, A.J.; Slatford, P.A.; Willia, J.M.J. *Tetrahedron Lett.* ***2007****, 48*, 7761.
[447] Hauser, C.R.; Le Maistre, J.W.; Rainsford, A.E. *J. Am. Chem. Soc.* ***1935****, 57,* 1056; Pyun, S.Y.; Lee, D.C.; Seung, Y.J.; Cho, B.R. *J. Org. Chem.* ***2005****, 70,* 5327.
[448] Roberts, J.T.; Rittberg, B.R.; Kovacic, P. *J. Org. Chem.* ***1981****, 46*, 4111.
[449] See Ioffe, B.V.; Zelenina, N.L. *J. Org. Chem. USSR,* ***1968****, 4,* 1496.
[450] Moore, J.S.; Stupp, S.I. *J. Org. Chem.* ***1990****, 55,* 3374.
[451] Cuvigny, T.; Le Borgne, J.F.; Larchevêque, M.; Normant, H. *Synthesis* ***1976***, 237.
[452] Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* ***1999****, 40*, 1989.

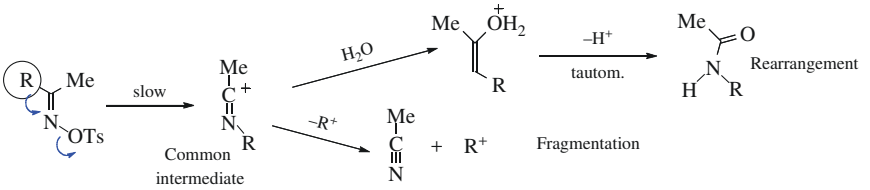
Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.[453] Among these are oximes of α-diketones (illustrated above), α-keto acids, α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[454] These are fragmentation reactions, analogous to **17-25**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles:[455]



The reaction that normally occurs on treatment of a ketoxime with a Lewis or proton acid is the *Beckmann rearrangement* (**18-17**); fragmentations are considered side reactions, often called "abnormal" or "second-order" *Beckmann rearrangements*.[456] Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[457] and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction:[458]



There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to *Beckmann rearrangement* of a series of oxime tosylates [RC(=NOTs)Me] was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[459] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



[453] Gawley, R.E. *Org. React.* ***1988****, 35,* 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 416–439; Casanova, J. in Rappoport, Z. *The Chemistry of the Cyano Group,* Wiley, NY, ***1970***, pp. 915–932.

[454] See Olah, G.A.; Vankar, Y.D.; Berrier, A.L. *Synthesis* ***1980***, 45; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971****, 4*, 197.

[455] Fischer, H.P.; Grob, C.A. *Helv. Chim. Acta* ***1963****, 46,* 936.

[456] See Ferris, A.F. *J. Org. Chem.* ***1960****, 25,* 12.

[457] See Hill, R.K.; Conley, R.T. *J. Am. Chem. Soc.* ***1960****, 82,* 645.

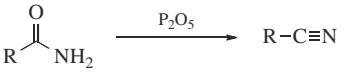
[458] Hassner, A.; Nash, E.G. *Tetrahedron Lett.* ***1965***, 525.

[459] Grob, C.A.; Fischer, H.P.; Raudenbusch, W.; Zergenyi, J. *Helv. Chim. Acta* ***1964****, 47,* 1003.

However, in other cases the simple E1 or E2 mechanisms operate.[460]
OS **V**, 266; **IX**, 281; OS **II**, 622; **III**, 690.

17-30 Dehydration of Unsubstituted Amides

N,N- Dihydro- *C-* oxo-bielimination



Unsubstituted amides can be dehydrated to nitriles.[461] Phosphorous pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, CCl_4—Ph_3P,[462] HMPA,[463] LiCl with a Zr catalyst,[464] $MeOOCNSO_2NEt_3$ (the *Burgess reagent*),[465] $Me_2N{=}CHCl^+\ Cl^-$,[466] $AlCl_3/KI/H_2O$,[467] PPh_3/NCS,[468] oxalyl chloride/DMSO/ −78 °C[469] (*Swern* conditions, see Reaction **19-3**), *o*-iodoxybenzoic acid/Et_4NBr,[470] $PdCl_2$ in aq media,[471] TBAF and hydrosilanes,[472] Fe complexes,[473] and $SOCl_2$ have also been used.[474] Heating an amide with paraformaldehyde and formic acid gives the nitrile.[475] It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,[476] or by other methods.[477] *N,N*-Disubstituted ureas give cyanamides (R_2N–CO–$NH_2 \rightarrow R_2N$–CN) when dehydrated with $CHCl_3$—NaOH under phase-transfer conditions.[478] Treatment of an amide with aq NaOH and ultrasound leads to the nitrile.[479]

N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5. This is called the *von Braun reaction* (not to be confused with the other von Braun reaction, **10-54**).

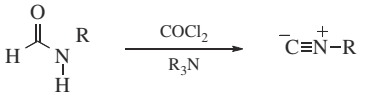


OS **I**, 428; **II**, 379; **III**, 493, 535, 584, 646, 768; **IV**, 62, 144, 166, 172, 436, 486, 706; **VI**, 304, 465.

[460] Grob, C.A.; Sieber, A. *Helv. Chim. Acta* ***1967****, 50,* 2520; Green, M.; Pearson, S.C. *J. Chem. Soc. B* ***1969***, 593.
[461] Bieron J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 274–283; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group,* Wiley, NY, ***1970***, pp. 96–103; Friedrich, K. in Patai, S.; Rapoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1978***, p. 1345.
[462] Harrison, C.R.; Hodge, P.; Rogers, W.J. *Synthesis* ***1977***, 41.
[463] Monson, R.S.; Priest, D.N. *Can. J. Chem.* ***1971****, 49*, 2897.
[464] Ruck, R.T.; Bergman, R.G. *Angew. Chem. Int. Ed.* ***2004****, 43,* 5375.
[465] Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* ***1988****, 29,* 2155.
[466] Barger, T.M.; Riley, C.M. *Synth. Commun.* ***1980****, 10*, 479.
[467] Boruah, M.; Konwar, D. *J. Org. Chem.* ***2002****, 67*, 7138.
[468] Iranpoor, N.; Firouzabadi, H.; Aghapoor, G. *Synth. Commun.* ***2002****, 32*, 2535.
[469] Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* ***1997****, 38*, 2099.
[470] Bhalerao, D.S.; Mahajan, U.S.; Chaudhari, K.H.; Akamanchi, K.G. *J. Org. Chem.* ***2007****, 72*, 662.
[471] Maffioli, S.I.; Marzorati, E.; Marazzi, A. *Org. Lett.* ***2005****, 7,* 5237.
[472] Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett.* ***2009****, 11*, 2461.
[473] Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. *Chem. Commun.* ***2009***, 4883.
[474] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1983–1985.
[475] Heck, M.-P.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1996****, 61*, 6486.
[476] See Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* ***1983***, 142.
[477] For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1949–1950.
[478] Schroth, W.; Kluge, H.; Frach, R.; Hodek, W.; Schädler, H.D. *J. Prakt. Chem.* ***1983****, 325,* 787.
[479] Sivakumar, M.; Senthilkumar, P.; Pandit, A.B. *Synth. Commun.* ***2001****, 31*, 2583.

17-31 Conversion of N-Alkylformamides to Isonitriles (Isocyanides)

***CN*-Dihydro-*C*-oxo-bielimination**



Isocyanides (isonitriles) can be prepared by elimination of water from *N*-alkylformamides[480] with phosgene and a tertiary amine.[481] Other reagents, among them TsCl in quinoline, $POCl_3$ and a tertiary amine,[482] triflic anhydride/$(i\text{Pr})_2\text{NEt}$,[483] 2,4,6-Trichloro [1,3,5]triazine (cyanuric chloride, TCT), with microwave irradiation),[484] and $Ph_3P—CCl_4—Et_3N$[485] have also been employed. Formamides react with thionyl chloride (two sequential treatments) to give an intermediate that gives an isonitrile upon electrolysis in DMF with $LiClO_4$.[486]

A variation of this process uses carbodiimides,[487] which can be prepared by the dehydration of *N,N′*-disubstituted ureas with various dehydrating agents,[488] among which are TsCl in pyridine, $POCl_3$, PCl_5, P_2O_5–pyridine, and TsCl (with phase-transfer catalysis).[489] Hydrogen sulfide can be removed from the corresponding thioureas by treatment with HgO, NaOCl, or diethyl azodicarboxylate–triphenylphosphine.[490]

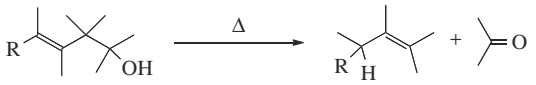
OS **V**, 300, 772; **VI**, 620, 751, 987. See also, OS **VII**, 27. For the carbodiimide/thiourea dehydration, see OS **V**, 555; **VI**, 951.

17.F.iv. Reactions in which C=O Bonds Are Formed

Many elimination-type reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions (also see, Reactions **12-40** and **12-41**).

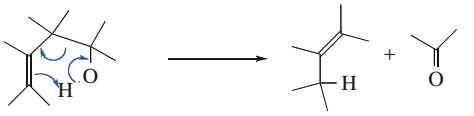
17-32 Pyrolysis of β-Hydroxy Alkenes

***O*- Hydro-*C*-allyl-elimination**

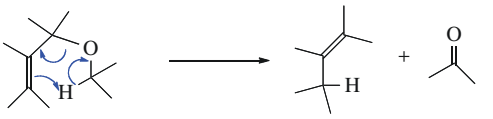


[480] See Creedon, S.M.; Crowley, H.K.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1015.
[481] Hoffmann, P.; Gokel, G.W.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 10–17; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed.* ***1965****, 4,* 472; *Newer Methods Prep. Org. Chem.* ***1968****, 4,* 37.
[482] See Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* ***1985***, 400.
[483] Baldwin, J.E.; O'Neil, I.A. *Synlett* ***1991***, 603.
[484] Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* ***2005****, 70,* 2361.
[485] Appel, R.; Kleinstück, R.; Ziehn, K. *Angew. Chem. Int. Ed.* ***1971****, 10,* 132.
[486] Guirado, A.; Zapata, A.; Gómez, J.L.; Trebalón, L.; Gálvez, J. *Tetrahedron* ***1999****, 55,* 9631.
[487] Bocharov, B.V. *Russ. Chem. Rev.* ***1965****, 34*, 212;Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981****, 81*, 589.
[488] Also see Kim, S.; Yi, K.Y. *J. Org. Chem.* ***1986****, 51,* 2613, *Tetrahedron Lett.* ***1986****, 27*, 1925.
[489] Jászay, Z.M.; Petneházy, I.; Töke, L.; Szajáni, B. *Synthesis* ***1987***, 520.
[490] Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* ***1970****, 26,* 5731.

When pyrolyzed, β-hydroxy alkenes cleave to give alkenes and aldehydes or ketones.[491] Alkenes produced this way are quite pure, since there are no side reactions. The mechanism has been shown to be pericyclic, primarily by observations that the kinetics are first order[492] and that, for ROD, the deuterium appeared in the allylic position of the new alkene.[493] This mechanism is the reverse of that for the oxygen analogue of the ene synthesis (Reaction **16-54**). β-Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.[494] The mechanism is the same despite the linear geometry of the triple bonds.



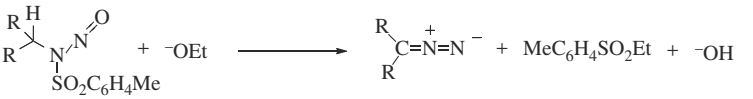
In a related reaction, pyrolysis of allylic ethers that contain at least one α hydrogen gives alkenes and aldehydes or ketones. The mechanism is also pericyclic[495]



17.F.v. Reactions in which N=N Bonds Are Formed

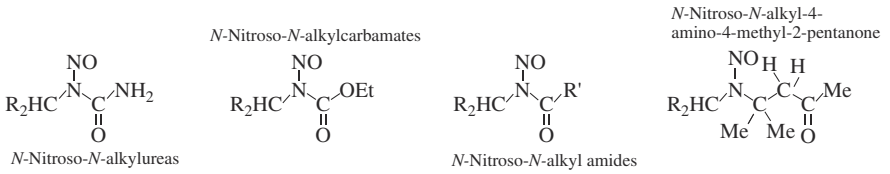
17-33 Eliminations to Give Diazoalkanes

_N_-Nitrosoamine-diazoalkane transformation



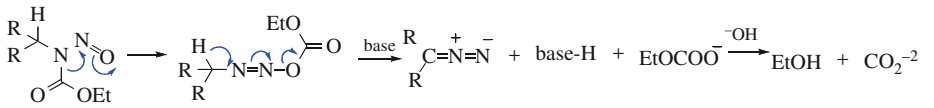
Various *N*-nitroso-*N*-alkyl compounds undergo elimination to give diazoalkanes.[496] One of the most convenient methods for the preparation of diazomethane involves base treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[497] However, other compounds commonly used are (base treatment is required in all cases):

[491] Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1959****, 81,* 6643. For a review, see Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group,* pt. 2, Wiley, NY, ***1971***, pp. 729–734.
[492] Voorhees, K.J.; Smith, G.G. *J. Org. Chem.* ***1971****, 36,* 1755.
[493] Arnold, R.T.; Smolinsky, G. *J. Org. Chem.* ***1960****, 25,* 128; Smith, G.G.; Taylor, R. *Chem. Ind. (London)* ***1961***, 949.
[494] Viola, A.; Proverb, R.J.; Yates, B.L.; Larrahondo, J. *J. Am. Chem. Soc.* ***1973****, 95*, 3609.
[495] Kwart, H.; Slutsky, J.; Sarner, S.F. *J. Am. Chem. Soc.* ***1973****, 95,* 5242; Egger, K.W.; Vitins, P. *Int. J. Chem. Kinet.* ***1974****, 6*, 429.
[496] Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, ***1986***, pp. 296–325; Black, T.H. *Aldrichimica Acta* ***1983****, 16,* 3. See Cowell, G.W.; Ledwith, A. *Q. Rev. Chem. Soc.* ***1970****, 24*, 119, pp. 126–131; Smith, P.A.S. *Open-chain Nitrogen Compounds*, W. A. Benjamin, NY, ***1966***, pp. 257–258, 474–475, in Vol. 2.
[497] de Boer, T.J.; Backer, H.J. *Org. Synth.* ***IV***, 225, 250; Hudlicky, M. *J. Org. Chem.* ***1980****, 45*, 5377.



All of these compounds can be used to prepare diazomethane, although the sulfonamide, which is commercially available, is most satisfactory. *N*-Nitroso-*N*-methylcarbamate and *N*-nitroso-*N*-methylurea give good yields, but are highly irritating and carcinogenic.[498] For higher diazoalkanes, the preferred substrates are nitrosoalkylcarbamates.

Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS **II**, 165; **III**, 119, 244; **IV**, 225, 250; **V**, 351; **VI**, 981.

17.F.vi. Extrusion Reactions

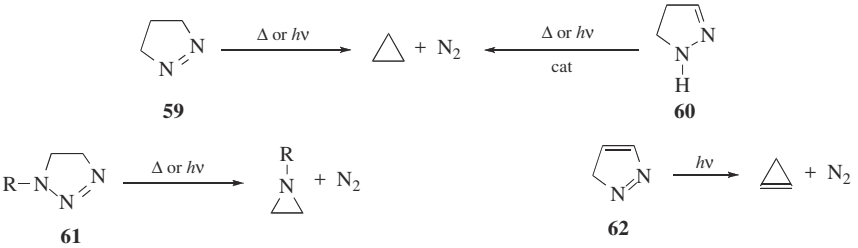
We consider an *extrusion reaction*[499] to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z.

$$X{-}Y{-}Z \longrightarrow X{-}Z + Y$$

Reactions **14-32** and **17-20** also fit this definition. Reaction **17-28** does not fit the definition, but is often also classified as an extrusion reaction. A scale of extrusion facility has been developed, showing that the ease of extrusion of the common Y groups is in the order: $-N{=}N- > -COO- > -SO_2- > -CO-$.[500]

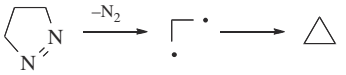
17-34 Extrusion of N_2 from Pyrazolines, Pyrazoles, and Triazolines

Azo-extrusion

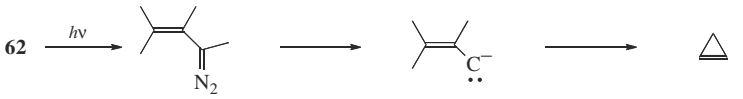


[498] Searle, C.E. *Chem. Br.* ***1970****, 6*, 5.
[499] Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***. For a review of extrusions that are photochemically induced, see Givens, R.S. *Org. Photochem.* ***1981****, 5,* 227.
[500] Paine, A.J.; Warkentin, J. *Can. J. Chem.* ***1981****, 59*, 491.

1-Pyrazolines (**59**) can be converted to cyclopropane and N_2 on photolysis[501] or pyrolysis.[502] The tautomeric 2-pyrazolines (**60**), which are more stable than **59**, also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **60** to **59**.[503] In the absence of such catalysts, **60** does not react.[504] In a similar manner, triazolines (**61**) are converted to aziridines.[505] Side reactions are frequent with both **59** and **61**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **59** and **61**. 3*H*-Pyrazoles[506] (**62**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,[507] although in other cases other types of products are obtained.



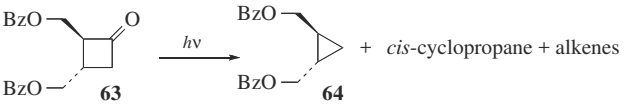
There is much evidence that the mechanism[508] of the 1-pyrazoline reactions generally involves diradicals, although the mode of formation and detailed structure (e.g., singlet vs triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles (**62**) have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.[509]



OS **V**, 96, 929. See also, OS **VIII**, 597.

17-35 Extrusion of CO or CO_2

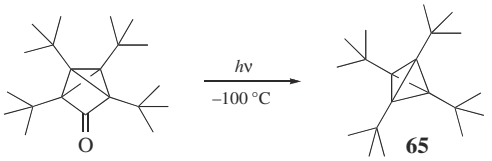
Carbonyl-extrusion



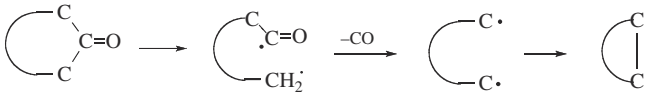
Although the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.[510] In the example above, the cyclobutanone (**63**) was

[501] Van Auken, T.V.; Rinehart, Jr., K.L. *J. Am. Chem. Soc.* ***1962****, 84,* 3736.
[502] Adam, W.; De Lucchi, O. *Angew. Chem. Int. Ed.* ***1980****, 19*, 762; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 116–151. See Mackenzie, K. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 329–442.
[503] See Jones, W.M.; Sanderfer, P.O.; Baarda, D.G. *J. Org. Chem.* ***1967****, 32,* 1367.
[504] McGreer, D.E.; Wai, W.; Carmichael, G. *Can. J. Chem.* ***1960****, 38,* 2410; Kocsis K.; Ferrini, P.G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* ***1960****, 43*, 2178.
[505] For a review, see Scheiner, P. *Sel. Org. Transform.* ***1970****, 1,* 327.
[506] See Sammes, M.P.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1983****, 34,* 2.
[507] See Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973****, 95*, 7536.
[508] Engel, P.S. *Chem. Rev.* ***1980****, 80,* 99; Engel, P.S.; Nalepa, C.J. *Pure Appl. Chem.* ***1980****, 52*, 2621; Reedich, D.E.; Sheridan, R.S. *J. Am. Chem. Soc.* ***1988****, 110*, 3697.
[509] Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973****, 95*, 7536.
[510] See Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971****, 3*, 1, see pp. 91–107; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 47–71.

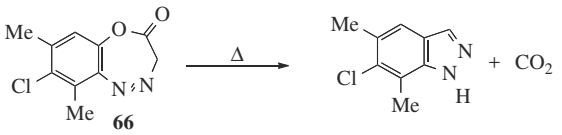
photolyzed to give **64**.[511] This reaction was used to synthesize tetra-*tert*-butyltetrahedrane, (**65**).[512]



The mechanism probably involves a *Norrish-type I cleavage* (Sec. 7.A.vii), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO_2 on heating or on irradiation (e.g., the pyrolysis of **66**).[513]

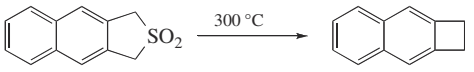


Decarboxylation of β-lactones (see **17-26**) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides (RCO—OO—COR′) lose two molecules of CO_2 when photolyzed in the solid state to give the product RR′.[514] Electrolysis was also used, but yields were lower. This is an alternative to the *Kolbe reaction* (**11-34**) (see also, **17-28** and **17-38**).

There are no OS references, but see OS **VI**, 418, for a related reaction.

17-36 Extrusion of SO_2

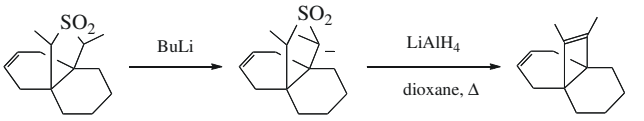
Sulfonyl-extrusion



In a reaction similar to **17-35**, certain sulfones, both cyclic and acyclic,[515] extrude SO_2 on heating or photolysis to give ring-contracted products.[516] An example is the preparation of naphtho(*b*)cyclobutene shown above.[517] In a different kind of reaction, five-membered

[511] Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***1997****, 75*, 518. See also, Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***2001****, 79*, 114.
[512] Maier, G.; Pfriem, S.; Schäfer, U.; Matusch, R. *Angew. Chem. Int. Ed.* ***1978****, 17,* 520.
[513] Ried, W.; Wagner, K. *Liebigs Ann. Chem.* ***1965****, 681,* 45.
[514] Lomölder, R.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1987****, 26*, 1253.
[515] Gould, I.R.; Tung, C.; Turro, N.J.; Givens, R.S.; Matuszewski, B. *J. Am. Chem. Soc.* ***1984****, 106*, 1789.
[516] Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed.* ***1979****, 18,* 515; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 72–90; Kice, J.L. in Kharasch, N.; Meyers, C.Y. *The Chemisry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 115–136. For a review of extrusion reactions of S, Se, and Te compounds, see Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988****, 44,* 6241.
[517] Cava, M.P.; Shirley, R.L. *J. Am. Chem. Soc.* ***1960****, 82*, 654.

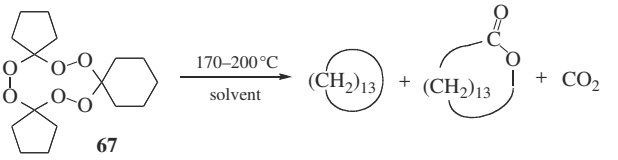
cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by $LiAlH_4$,[518] for example,



This method is most successful when both the α and α′ position of the sulfone bear alkyl substituents (see also, Reaction **17-20**). Treating four-membered ring sultams with $SnCl_2$ led to aziridine products via loss of SO_2.[519]

OS **VI**, 482.

17-37 The Story Synthesis



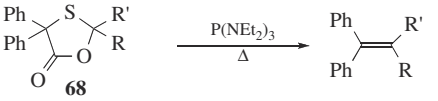
67

When cycloalkylidine peroxides (e.g., **60**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place; the products are the cycloalkane containing three carbon atoms less than the starting peroxide and the lactone containing two carbon atoms less[520] (the *Story synthesis*).[521] The two products are formed in comparable yields, usually ∼ 15–25% each. Although the yields are low, the reaction is useful because there are not many other ways to prepare large rings. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members.

Both dimeric and trimeric cycloalkylidine peroxides can be synthesized[522] by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.[523] The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.[524]

17-38 Alkene synthesis by Twofold Extrusion

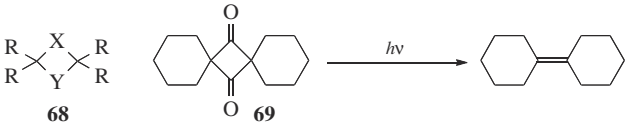
Carbon dioxide,thio-extrusion



68

[518] Photis, J.M.; Paquette, L.A. *J. Am. Chem. Soc.* ***1974****, 96,* 4715.
[519] Kataoka, T.; Iwama, T. *Tetrahedron Lett.* ***1995****, 36*, 5559.
[520] Sanderson, J.R.; Story, P.R.; Paul, K. *J. Org. Chem.* ***1975****, 40,* 691; Sanderson, J.R.; Paul, K.; Story, P.R. *Synthesis* ***1975***, 275.
[521] See Story, P.R.; Busch, P. *Adv. Org. Chem.* ***1972****, 8*, 67, see pp. 79–94.
[522] See Paul, K.; Story, P.R.; Busch, P.; Sanderson, J.R. *J. Org. Chem.* ***1976****, 41,* 1283.
[523] Kharasch, M.S.; Sosnovsky, G. *J. Org. Chem.* ***1958****, 23,* 1322; Ledaal, T. *Acta Chem. Scand.,* ***1967****, 21,* 1656. For another method, see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 125.
[524] Story, P.R.; Lee, B.; Bishop, C.E.; Denson, D.D.; Busch, P. *J. Org. Chem.* ***1970****, 35,* 3059. See also, Sanderson, J.R.; Wilterdink, R.J.; Zeiler, A.G. *Synthesis* ***1976***, 479.

4,4-Diphenyloxathiolan-5-ones (**68**) give good yields of the corresponding alkenes when heated with tris(diethylamino)phosphine.[525] This reaction is an example of a general type: alkene synthesis by twofold extrusion of X and Y from a molecule of the type **69**.[526] Other examples are photolysis of 1,4-diones[527] (e.g., **70**) and treatment of acetoxy sulfones [$RCH(OAc)CH_2SO_2Ph$] with Mg/EtOH and a catalytic amount of $HgCl_2$.[528] **68** can be prepared by the condensation of thiobenzilic acid [$Ph_2C(SH)COOH$] with aldehydes or ketones.



68 **69**

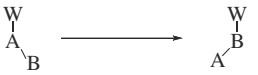
OS **V**, 297.

[525] Barton, D.H.R.; Willis, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 305.
[526] See Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988****, 44*, 6241.
[527] Turro, N.J.; Leermakers, P.A.; Wilson, H.R.; Neckers, D.C.; Byers, G.W.; Vesley, G.F. *J. Am. Chem. Soc.* ***1965****, 87,* 2613.
[528] Lee, G.H.; Lee, H.K.; Choi, E.B.; Kim, B.T.; Pak, C.S. *Tetrahedron Lett.* ***1995****, 36*, 5607.

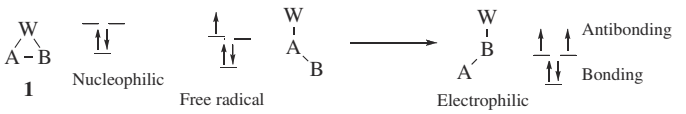
CHAPTER 18

Rearrangements

In a rearrangement reaction, a group moves from one atom to another in the same molecule.[1] Most are migrations from an atom to an adjacent one (called 1,2-shifts), but some are over longer distances. The group



that migrates (W) may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (radical rearrangements). The atom A is called the *migration origin* and B is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (Reactions **18-27**–**18-36**).



1

As will be seen, nucleophilic 1,2-shifts are much more common than electrophilic or free radical 1,2-shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. The transition state or intermediate for all three cases can be represented by **1**, in which the two-electron A—W bond overlaps with the orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those in Section 2.K.i (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and **1** is a low-energy transition state, In a free radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated, and antibonding orbitals

[1] de Mayo, P. *Rearrangements in Ground and Excited States*, 3 Vols., Academic Press, NY, ***1980***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 761–821. See also, the series *Mechanisms of Molecular Migrations.*

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

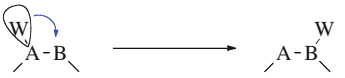
must be occupied. It is not surprising therefore that, when 1,2-electrophilic or free radical shifts are found, the migrating group W is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see **41**).

In any rearrangement two possible modes of reaction can, in principle, be distinguished. In one of these, the group W becomes completely detached from A and may end up on the B atom of a different molecule (*intermolecular* rearrangement). In the other, W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A—B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice, which is followed here, is to include under the title "rearrangement" all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is inter- or intramolecular. The most common method involves the use of *cross over* experiments. In this type of experiment, rearrangement is carried out on a mixture of W—A—B and V—A—C, where V is closely related to W (say, methyl vs ethyl) and B to C. In an intramolecular process, only A—B—W and A—C—V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A—B—V and A—C—W.

18.A. MECHANISMS

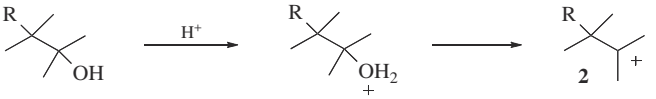
18.A.i. Nucleophilic Rearrangements[2]

Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:



This process has been called the *Whitmore 1,2-shift*.[3] Since the migrating group carries the electron pair with it, the migration terminus B must be an atom with only six electrons in its outer shell (an open sextet). The first step therefore is creation of a system with an open sextet. Such a system can arise in various ways, but two of these are the most important:

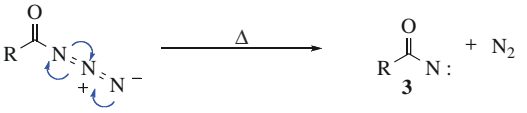
1. *Formation of a Carbocation*: These can be formed in a number of ways (see Sec. 5. A.iii), but one of the most common methods is the acid treatment of an alcohol to give **2** from an intermediate oxonium ion. Such carbocations are subject to rearrangement to a more stable carbocation. These two steps are of course the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.



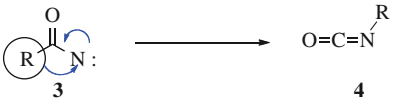
[2] Vogel, P. *Carbocation Chemistry*; Elsevier, NY, ***1985***, pp. 323–372; Shubin, V.G. *Top. Curr. Chem.* ***1984****, 116/117*, 267; Saunders, M.; Chandrasekhar, J.; Schleyer, P.v.R. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 1–53; Kirmse, W. *Top. Curr. Chem.* ***1979****, 80,* 89. For reviews of rearrangements in vinylic cations, see Shchegolev, A.A.; Kanishchev, M.I. *Russ. Chem. Rev.* ***1981****, 50,* 553; Lee, C.C. *Isot. Org. Chem.* ***1980****, 5,* 1.

[3] It was first postulated by Whitmore, F.C. *J. Am. Chem. Soc.* ***1932****, 54,* 3274.

2. *Formation of a Nitrene*: The decomposition of acyl azides is one of several ways in which acyl nitrenes (**3**) are formed (see Sec. 5.E). After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step, this atom acquires an octet. In the case of carbocations, combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination). Constitute the most common third stop.



Although this mechanism is presented as taking place in three steps, and some reactions do take place in this way, in others the transformation is simultaneous. For example, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C—N bond to give a stable isocyanate, (**4**). In this example, what are shown as the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the "third" step involves more than just a simple motion of a pair of electrons. Similarly, there are many reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species (e.g., **2** or **3**). In these instances, it may be said that R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as (**2**) or (**3**) actually form, or whether the steps are simultaneous (see, e.g., the discussions in Reaction **16-45** and Sec. 18.A.ii), but the difference between the two possibilities is often subtle, and the question is not always easily answered.[4]

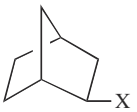


Evidence for this mechanism is that rearrangements of this sort occur under conditions where previously carbocations have been encountered: S_N1 conditions, *Friedel–Crafts alkylation*, and so on. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent, but is unaffected by concentration of base,[5] so that the first step is carbocation formation. The same compound under S_N2 conditions gave no rearrangement, but slowly gave only ordinary substitution. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary → secondary → tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **5**) type systems are especially prone to carbocation rearrangement

[4] The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie, R.D. *Pure Appl. Chem.* ***1989****, 61,* 23, pp. 44–45.

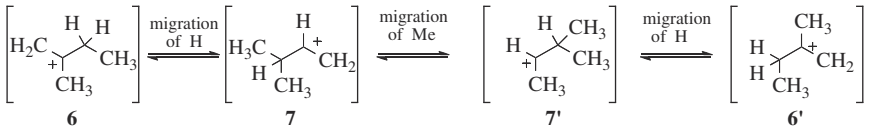
[5] Dostrovsky, I.; Hughes, E.D. *J. Chem. Soc.* ***1946***, 166.

reactions. It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.[6]



5

It was previously mentioned (Sec. 5.A.ii) that stable tertiary carbocations could be obtained, in solution, at very low temperatures. The NMR studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.[7] For example, the *tert*-pentyl cation (**5**)[8] equilibrates as follows:

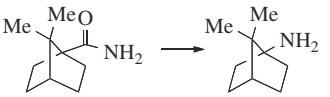


6 **7** **7'** **6'**

Carbocations that rearrange to give products of identical structure (**6**⇄**6′**, **7**⇄**7′**) are called *degenerate carbocations*. Such rearrangements are *degenerate rearrangements* and many examples are known.[9]

18.A.ii. The Actual Nature of the Migration

Most nucleophilic 1,2-shifts are intramolecular. The W group does not become free, but always remains connected in some way to the substrate. Apart from the evidence from cross-over experiments, the strongest evidence is that when the W group is chiral, the configuration is *retained* in the product. For example, (+)-PhCHMeCO$_2$H was converted to (−)-PhCHMeNH$_2$ by the *Curtius* (**18-14**), *Hofmann* (**18-13**), *Lossen* (**18-15**), and *Schmidt* (**18-16**) reactions.[10] In these reactions, the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.[11] Another experiment demonstrating retention was the easy conversion of **8** to **9**.[11] Neither inversion nor racemization could take place at a bridgehead.



8 **9**

[6] Borodkin, G.I.; Shakirov, M.M.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1978****, 14*, 290, 924.

[7] Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972****, 9,* 179, see pp. 203–237; Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 751–760, 766–778. For a discussion of the rates of these reactions, see Sorensen, T.S. *Acc. Chem. Res.* ***1976****, 9,* 257.

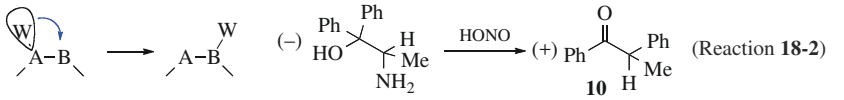
[8] Brouwer, D.M. *Recl. Trav. Chim. Pays-Bas* ***1968****, 87,* 210; Saunders, M.; Hagen, E.L. *J. Am. Chem. Soc.* ***1968****, 90,* 2436.

[9] Ahlberg, P.; Jonsäll, G.; Engdahl, C. *Adv. Phys. Org. Chem.* ***1983****, 19,* 223; Leone, R.E.; Barborak, J.C.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1970***, pp. 1837–1939; Leone, R.E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1970****, 9*, 860.

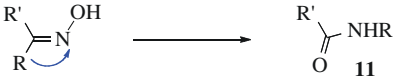
[10] Campbell, A.; Kenyon, J. *J. Chem. Soc.* ***1946***, 25, and references cited therein.

[11] See Kirmse, W.; Gruber, W.; Knist, J. *Chem. Ber.* ***1973****, 106,* 1376; Borodkin, G.I.; Panova, Y.B.; Shakirov, M.M.; Shubin, V.G. *J. Org. Chem. USSR* ***1983****, 19,* 103.

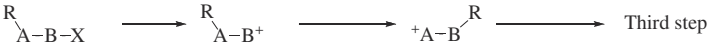
Using the simple example W-A-B, there is much evidence that retention of configuration usually occurs in W, and inversion never occurs.[12] However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W—A—B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. One example is **10**, where the conversion proceeded with inversion (equivalent to inversion at B.[13] Inversion at A has been



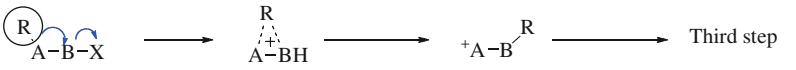
shown in other cases.[14] However, in many other cases, racemization occurs at A or B or both.[15] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most *Beckmann rearrangements* (**18-17**), only the group trans (usually called *anti*) to the hydroxyl group migrates, as illustrated by formation of **11**, which shows inversion at B.



This information tells us about the degree of concertedness of the three steps of the rearrangement. First, consider the migration terminus B in R—A—B—X. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:



With respect to B this is an S_N1 type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation is *not* an intermediate, and that the process is S_N2 like:



In this case, participation by R assists in removal of X in the same way that neighboring groups do (Sec. 10.C). Indeed, R *is* a neighboring group here. The only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken.

[12] See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***; pp. 251–254; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 597–604.

[13] Bernstein, H.I.; Whitmore, F.C. *J. Am. Chem. Soc.* ***1939***, *61,* 1324. For other examples, see Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* ***1984***, *25,* 4253.

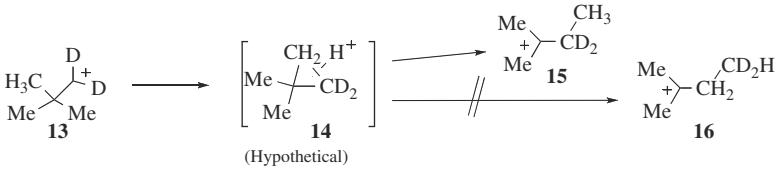
[14] See Meerwein, H.; van Emster, K. *Ber.* ***1920***, *53,* 1815; ***1922***, *55,* 2500; Meerwein, H.; Gérard, L. *Liebigs Ann. Chem.* ***1923***, *435,* 174.

[15] See Winstein, S.; Morse, B.K. *J. Am. Chem. Soc.* ***1952***, *74,* 1133.

In either case, the anchimeric assistance results in an increased rate of reaction. Of course, for such a process to take place, R must be in a favorable geometrical position (R and X antiperiplanar). Intermediate **12** may be a true intermediate, or there may only be a transition state, depending on what migrates. In certain cases of the S_N1 type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbocation.[16]

A few conclusions may be summarized:

1. The S_N1 type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2 type process is more likely. Inversion of configuration (indicating an S_N2 type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[17] There is other evidence that neopentyl systems undergo rearrangement by a carbocation (S_N1 type) mechanism.[18]
2. The question as to whether **12** is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then **12** is probably an intermediate and the migrating group lends anchimeric assistance[19] (see Sec. 10.C.i, category 3-preceding category 4 for resonance stabilization of this intermediate, when R is aryl). When R is alkyl, **12** is a protonated cyclopropane (edge- or corner protonated; see Sec. 15.B.iv). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (Sec. 10.C.i, category 4c). Further evidence was obtained from experiments involving labeling.



Rearrangement of the neopentyl cation labeled with deuterium in the 1 position (**13**) gave only *tert*-pentyl products with the label in the 3 position (derived from **15**), though if **14** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-pentyl derivatives labeled in the 4 position (derived from **16**).[20] Another experiment that led to the same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. The only *tert*-pentyl products isolated were labeled in C-3, that is, $Me_2C^+—^{13}CH_2CH_3$ derivatives; no derivatives of $Me_2C^+—CH_2{}^{13}CH_3$ were found.[21]

[16] Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972****, 37,* 4358, and references cited therein.
[17] Mosher, H.S. *Tetrahedron* ***1974****, 30*, 1733. See also, Guthrie, R.D. *J. Am. Chem. Soc.* ***1967****, 89*, 6718.
[18] Shiner, Jr., V.J.; Imhoff, M.A. *J. Am. Chem. Soc.* ***1985****, 107,* 2121.
[19] Rachoń, J.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1989****, 54,* 1006. An opposing view: Kirmse, W.; Feyen, P. *Chem. Ber.* ***1975****, 108,* 71; Kirmse, W.; Plath, P.; Schaffrodt, H. *Chem. Ber.* ***1975****, 108*, 79.
[20] Skell, P.S.; Starer, I.; Krapcho, A.P. *J. Am. Chem. Soc.* ***1960****, 82,* 5257.
[21] Karabatsos, G.J.; Orzech, Jr., C.E.; Meyerson, S. *J. Am. Chem. Soc.* ***1964****, 86,* 1994.

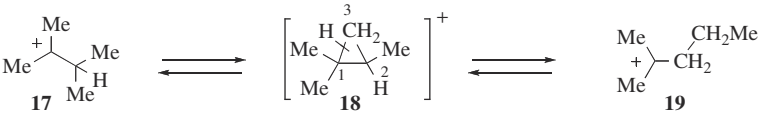
Although the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl systems, a small part of the product can in fact arise from such intermediates.[22] Among this evidence is the isolation of 10–15% cyclopropanes (mentioned in Sec. 10.C.i, category 4c). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CH_2CD_2^+$, $CH_3CD_2CH_2^+$, $CH_3CH_2{}^{14}CH_2^+$), where isotopic distribution in the products indicated that a small amount (∼5%) of the product had to be formed from protonated cyclopropane intermediates, for example,[23]

$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} -1\%\, C_2H_4D{-}CHD{-}OH$$

$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} -1\%\, C_2H_4D{-}CHD{-}OH$$

$$CH_3CH_2{}^{14}CH_2NH_2 \xrightarrow{HONO} -2\%\, {}^{14}CH_3CH_2CH_2OH + -2\%\, CH_3{}^{14}CH_2OH$$

Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[24] However, protonated cyclopropane intermediates accounted for <1% of the products from diazotization of labeled isobutylamine[25] and from formolysis of labeled 1-propyl tosylate.[26]



17 **18** **19**

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in superacid solution, the ions **17** and **19** are in equilibrium. It is not possible for these to interconvert solely by 1,2-alkyl or hydride shifts unless primary carbocations, which are highly unlikely, are intermediates. However, the reaction can be explained[27] by postulating that (in the forward reaction) it is the 1,2-bond of the intermediate or transition state **18** that opens up rather than the 2,3-bond, which is the one that would open if the reaction were a normal 1,2-shift of a methyl group. In this case, opening of the 1,2-bond produces a tertiary cation, while opening of the 2,3-bond would give a secondary cation. (In the reaction **19** → **17**, it is of course the 1,3-bond that opens).

3. There has been much discussion of H as the migrating group. There is no conclusive evidence that **10** in this case is or is not a true intermediate, although both positions have been argued (see Sec. 10.C.i, category 4c).

[22] Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* ***1973****, 6,* 53; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970****, 7,* 129; Collins, C.J. *Chem. Rev.* ***1969****, 69,* 543. See also, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

[23] Karabatsos, G.J.; Orzech, Jr., C.E.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970****, 92*, 606.

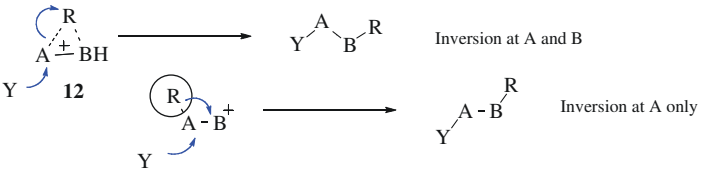
[24] Lee, C.C.; Cessna, A.J.; Ko, E.C.F.; Vassie, S. *J. Am. Chem. Soc.* ***1973****, 95*, 5688. See also, Lee, C.C.; Reichle, R. *J. Org. Chem.* ***1977****, 42*, 2058 and references cited therein.

[25] Karabatsos, G.J.; Hsi, N.; Meyerson, S. *J. Am. Chem. Soc.* ***1970****, 92*, 621. See also, Karabatsos, G.J.; Anand, M.; Rickter, D.O.; Meyerson, S. *J. Am. Chem. Soc.* ***1970****, 92,* 1254.

[26] Karabatsos, G.J.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970****, 92*, 614. See also, Lee, C.C.; Zohdi, H.F. *Can. J. Chem.* ***1983****, 61,* 2092.

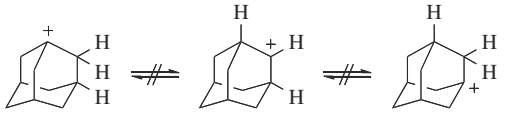
[27] Saunders, M.; Jaffe, M.H.; Vogel, P. *J. Am. Chem. Soc.* ***1971****, 93*, 2558; Saunders, M.; Vogel, P. *J. Am. Chem. Soc.* ***1971****, 93,* 2559, 2561; Kirmse, W.; Loosen, K.; Prolingheuer, E. *Chem. Ber.* ***1980****, 113,* 129.

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2 type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



In some cases, it has been found that, when H is the migrating species, the configuration at A may be *retained*.[28]

There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**20**) does not equilibrate intramolecularly, even at temperatures up to 130 °C,[29] though open-chain (e.g., **6**-**6′**) and cyclic tertiary carbocations undergo such equilibration at 0 °C or below. On the basis of this and other evidence, it has been concluded that for a 1,2-shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,[29] which is not possible for **20**.



18.A.iii. Migratory Aptitudes[30]

In many reactions, there is no question about which group migrates. For example, in the *Hofmann*, *Curtius*, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances, there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The *Beckmann rearrangement* (Reaction **18-17**) provides an example. As seen in the formation of **11**, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see Sec. 17.C), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[31] However, in some reactions, especially the W*agner–Meerwein* (**18-1**) and the *pinacol* (**18-2**) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances

[28] Kirmse, W.; Ratajczak, H.; Rauleder, G. *Chem. Ber.* ***1977****, 110,* 2290.

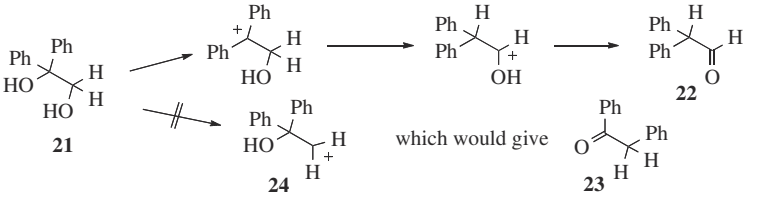
[29] Brouwer, D.M.; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* ***1970****, 89,* 211; Majerski, Z.; Schleyer, P.v.R.; Wolf, A.P. *J. Am. Chem. Soc.* ***1970****, 92,* 5731.

[30] See Koptyug, V.A.; Shubin, V.G. *J. Org. Chem. USSR* ***1980****, 16,* 1685; Wheland, G.W. *Advanced Organic Chemistry,* 3rd ed., Wiley, NY, ***1960***, pp. 573–597.

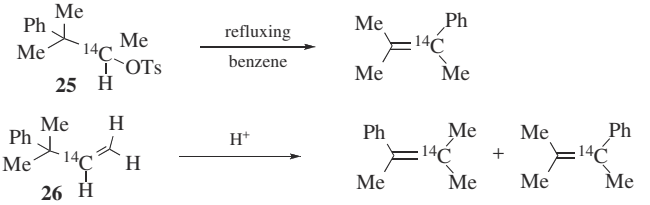
[31] See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry, Wiley, NY,* ***1956***, pp. 270–276. For an interesting example, see Nickon, A.; Weglein, R.C. *J. Am. Chem. Soc.* ***1975****, 97,* 1271.

of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the *pinacol rearrangement*, there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form $R_2C(OH)—C(OH)R'_2$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**21**) gives diphenylacetaldehyde (**22**), not phenylacetophenone (**23**). Obviously, it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **24** is not formed. Remember that carbocation stability is enhanced by groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (e.g., see the reaction of **59**).



In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is R′RC(OH)—COH)RR′, since the same carbocation is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R′ is possible. On closer inspection, however, it is clear that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R′ migrates is determined not only by the relative inherent migrating abilities of R and R′, but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.[32] Thus, migration of R gives rise to the cation $R'C^+(OH)CR_2R_2'$, while migration of R′ gives the cation $R^+C(OH)CRR_2'$ and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R′, not because it actually has a lower inherent migrating tendency, but because it is much



better at stabilizing the positive charge. In addition to this factor, the migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the

[32] See McCall, M.J.; Townsend, J.M.; Bonner, W.A. *J. Am. Chem. Soc.* ***1975****, 97,* 2743; Brownbridge, P.; Hodgson, P.K.G.; Shepherd, R.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 2024.

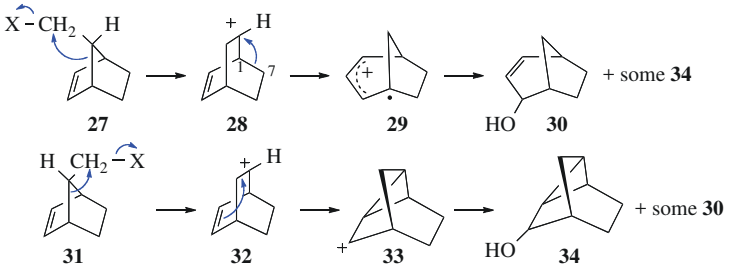
nucleofuge. An example of this effect is the decomposition of tosylate (**25**) where only the phenyl group migrates, while in acid treatment of the corresponding alkene (**26**), there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).[33] Both **25** and **26** give the same carbocation; the differing results must be caused by the fact that in **25** the phenyl group can assist the leaving group, while no such process is possible for **26**. This example clearly illustrates the difference between migration to a relatively free terminus and one that proceeds with the migrating group lending anchimeric assistance.[34]

Therefore, it is not surprising that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases, migration of hydrogen is preferred to aryl migration; in other cases, migration of alkyl is preferred to that of hydrogen. Mixtures are often found, and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.[35] However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups:[36] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.[37]

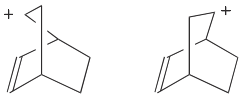
18.A.iv. Memory Effects[38]

Solvolysis of the endo bicyclic compound (**27**, X = ONs, see Sec. 10.G.iii, or Br) gave mostly the bicyclic allylic alcohol (**30**), along with a smaller amount of the tricyclic alcohol (**34**), while solvolysis of the exo isomers, (**31**), gave mostly **34**, with smaller amounts of **30**.[39] Note that endo and exo here refers to the position of the XCH_2 group over the C=C unit or opposite the C=C unit, respectively. The two isomers gave entirely different ratios of products, although the carbocation initially formed seems to be the same for each (marked **28** and **32** for convenience). With **28**, a second rearrangement (a shift of the 1,7 bond) follows to give **29**, while with **32**

[33] Grimaud, J.; Laurent, A. *Bull. Soc. Chim. Fr.* ***1967***, 3599.
[34] See Fischer, A.; Henderson, G.N. *J. Chem. Soc., Chem. Commun.* ***1979***, 279, and references cited therein. See also, Marx, J.N.; Hahn, Y.P. *J. Org. Chem.* ***1988****, 53*, 2866.
[35] See Pilkington, J.W.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1349; Korchagina, D.V.; Derendyaev, B.G.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1976****, 12,* 378; Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981****, 22,* 4069; Jost, R.; Laali, K.; Sommer, J. *Nouv. J. Chim.* ***1983****, 7*, 79.
[36] Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* ***1934****, 56,* 2081.
[37] Le Drian, C.; Vogel, P. *Helv. Chim. Acta* ***1987****, 70,* 1703; *Tetrahedron Lett.* ***1987****, 28,* 1523.
[38] For a review, see Berson, J.A. *Angew. Chem. Int. Ed.* ***1968****, 7,* 779.
[39] Berson, J.A.; Poonian, M.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969****, 91*, 5567; Berson, J.A.; Donald, D.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969****, 91,* 5580; Berson, J.A.; Wege, D.; Clarke, G.M.; Bergman, R.G. *J. Am. Chem. Soc.* ***1969****, 91*, 5594, 5601.



an intramolecular addition of the positive carbon to the double bond gives **33**. It seems as if **28** and **32** "remember" how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.[40] The causes of these effects are not well understood, although there has been much discussion. One possible cause is differential solvation of the apparently identical ions **28** and **32**. Other possibilities are (1) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **32** might have its positive



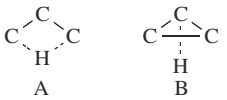
carbon closer to the double bond than a twisted **28**); (*2*) that ion pairing is responsible[41]; and (3) that nonclassical carbocations are involved.[42] One possibility that has been ruled out is that steps **27** → **28** → **29** and **31** → **32** → **33** are concerted, so that **28/32** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **27** gives not only **30**, but also some **34**; and **31** gives some **30** along with **34**. This means that some of the **28** and **32** ions interconvert, a phenomenon known as *leakage*.

18.B. LONGER NUCLEOPHILIC REARRANGEMENTS

The question as to whether a group can migrate with its electron pair from A to C in W—A—B—C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation ($Me_3CCH_2CH_2^+$). If 1,3-methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation ($Me_2C^+CH_2CH_2CH_3$), while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2-hydride migration.[43] 1,3-Migration of bromine has been reported.[44]

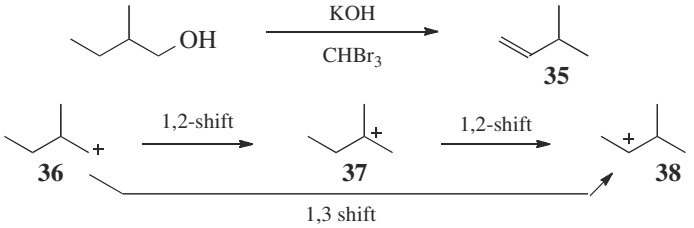
[40] See Collins, C.J. *Acc. Chem. Res.* ***1971****, 4,* 315; Collins, J.A.; Glover, I.T.; Eckart, M.D.; Raaen, V.F.; Benjamin, B.M.; Benjaminov, B.S. *J. Am. Chem. Soc.* ***1972****, 94*, 899; Svensson, T. *Chem. Scr.* ***1974****, 6,* 22.
[41] See Collins, C.J. *Chem. Soc. Rev.* ***1975****, 4,* 251.
[42] See Kirmse, W.; Günther, B. *J. Am. Chem. Soc.* ***1978****, 100,* 3619.
[43] Skell, P.S.; Reichenbacher, P.H. *J. Am. Chem. Soc.* ***1968****, 90,* 2309.
[44] Reineke, C.E.; McCarthy, Jr., J.R. *J. Am. Chem. Soc.* ***1970****, 92,* 6376; Smolina, T.A.; Gopius, E.D.; Gruzdneva, V.N.; Reutov, O.A. *Doklad. Chem.* ***1973****, 209,* 280.

Most of the debate over the possibility of 1,3-migrations has concerned not methyl or bromine but 1,3-hydride shifts.[45] Many instances have been found of *apparent* 1,3-hydride shifts, but the question is whether they are truly direct hydride shifts or whether they occur by another mechanism. There are at least two ways in



A B

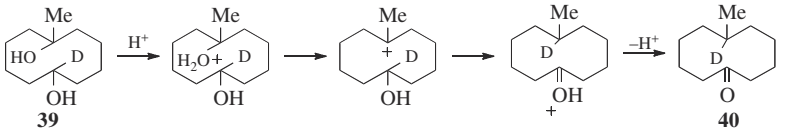
which indirect 1,3-hydride shifts can take place: (1) by successive 1,2-shifts or (2) through the intervention of protonated cyclopropanes (see Sec. 18.A.ii, category 2). A direct 1,3-shift would have transition state **A**, while the transition state for a 1,3-shift involving a protonated cyclopropane intermediate would resemble **B**. The evidence is that most reported 1,3-hydride shifts are actually the result of successive 1,2-migrations,[46] but in some cases small amounts of products cannot be accounted for in this way. The reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of alkenes, nearly all of which could have arisen from simple elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was **35**.[47] Hypothetically, **35** could have arisen from a 1,3 shift (direct or through a protonated cyclopropane) or from two successive 1,2-shifts:



However, the same reaction applied to 2-methyl-2-butanol gave no **35**, which demonstrated that **38** was not formed from **37**. The conclusion made was that **38** was formed directly from **36**. This experiment does not answer the question as to whether **38** was formed by a direct shift or through a protonated cyclopropane, but from other evidence[48] it appears that 1,3-hydride shifts that do not result from successive 1,2-migrations usually take place through protonated cyclopropane intermediates, which (as seen in Sec. 18.A.ii, category 2) account for only a small percentage of the product in any case. However, there is evidence that direct 1,3-hydride shifts by way of **A** (see above) may take place in superacid solutions.[49] Although direct nucleophilic rearrangements over distances >1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8–11 members. Many such transannular rearrangements are known[50] (see Sec. 4.Q.ii): the mechanism for the

[45] See Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.
[46] See Kirmse, W.; Knist, J.; Ratajczak, H. *Chem. Ber.* ***1976****, 109*, 2296.
[47] Skell, P.S.; Maxwell, R.J. *J. Am. Chem. Soc.* ***1962****, 84*, 3963. See also, Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1962****, 84*, 3962.
[48] Hudson, H.R.; Koplick, A.J.; Poulton, D.J. *Tetrahedron Lett.* ***1975***, 1449; Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.
[49] Saunders, M.; Stofko, Jr., J.J. *J. Am. Chem. Soc.* ***1973****, 95,* 252.
[50] See Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966****, 20*, 119.

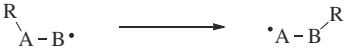
conversion of **39** to **40** is shown.[51]



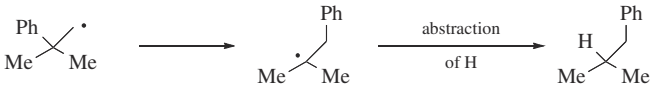
Note that the *methyl* group does not migrate in this system. *It is generally true that alkyl groups do not undergo transannular migration*.[52] In most cases, it is the hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.[53]

18.C. FREE RADICAL REARRANGEMENTS[54]

1,2-Free radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned in the introductory Section 18.A. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



Finally, the new free radical will undergo a further reaction to generate a neutral molecule. The order of radical stability leads to a prediction that here too, as with carbocation rearrangements, migrations should be in the order primary → secondary → tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (Reaction **14-32**). In this manner, it was found that neophyl radicals *do* undergo rearrangement.[55] Thus, $PhCMe_2CH_2CHO$ treated with di-*tert*-butyl peroxide gave about equal amounts of the normal product $PhCMe_2CH_3$ and the product arising from migration of phenyl[56]:



[51] Prelog, V.; Küng, W. *Helv. Chim. Acta* ***1956****, 39*, 1394.

[52] For an apparent exception, see Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D.B.; Sevin, A. *J. Am. Chem. Soc.* ***1989****, 111,* 8466.

[53] Cope, A.C.; Burton, P.E.; Caspar, M.L. *J. Am. Chem. Soc.* ***1962****, 84,* 4855.

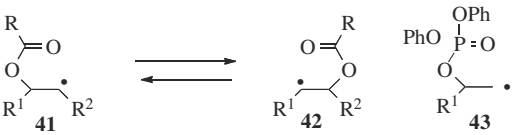
[54] Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 161–310; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 333–501; Stepukhovich, A.D.; Babayan, V.I. *Russ. Chem. Rev.* ***1972****, 41,* 750; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 498–552; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 235–255; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965****, 1,* 211-278; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***, pp. 266–284.

[55] Antunes, C.S.A.; Bietti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* ***2005****, 70,* 3884.

[56] Seubold Jr., F.H. *J. Am. Chem. Soc.* ***1953****, 75*, 2532. For the observation of this rearrangement by ESR, see Hamilton, Jr., E.J.; Fischer, H. *Helv. Chim. Acta* ***1973****, 56*, 795.

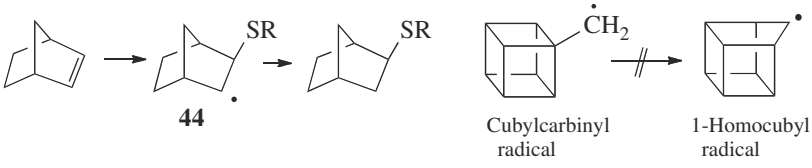
Many other cases of free radical migration of aryl groups have been found.[57] Intramolecular radical rearrangements are known.[58] The C-4 radicals of α-and β-thujone undergo two distinct rearrangement reactions, and it has been proposed that these could serve as simultaneous but independent radical clocks.[59]

A 1,2-shift has been observed in radicals bearing an OCOR group at the β-carbon where the oxygen group migrates as shown in the interconversion of **41** and **42**. This has been proven by ^{18}O isotopic labeling experiments[60] and other mechanistic explorations.[61] A similar rearrangement was observed with phosphatoxy alkyl radicals (e.g., as **43**.[62] A 1,2-shift of hydrogen atoms has been observed in aryl radicals.[63]



Note that the extent of migration is much less than with corresponding carbocations: Thus in the example given, there was only ∼50% migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general, it may be said that free radical migration of alkyl groups does not occur at ordinary temperatures. *Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo facile rearrangement*.[64] Another type of migration that is very common for carbocations, but not observed for free radicals, is 1,2-migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

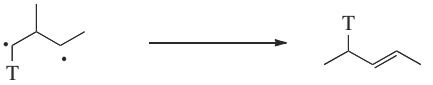
1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products on decarbonylation.[65]
2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **44** is an intermediate, and the corresponding carbocation cannot be formed without rearrangement.[66]



[57] See Walter, D.W.; McBride, J.M. *J. Am. Chem. Soc.* ***1981****, 103,* 7069, 7074. For a review, see Studer, A.; Bossart, M. *Tetrahedron* ***2001****, 57*, 9649.
[58] Prévost, N.; Shipman, M. *Org. Lett.* ***2001****, 3*, 2383.
[59] He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* ***2004****, 69,* 5684.
[60] Crich, D.; Filzen, G.F. *J. Org. Chem.* ***1995****, 60*, 4834.
[61] Beckwith, A.L.J.; Duggan, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1777; ***1993***, 1673.
[62] Crich, D.; Yao, Q. *Tetrahedron Lett.* ***1993****, 34,* 5677. See Ganapathy, S.; Cambron R.T.; Dockery, K.P.; Wu, Y.-W.; Harris, J.M.; Bentrude, W.G. *Tetrahedron Lett.* ***1993****, 34*, 5987.
[63] Brooks, M.A.; Scott, L.T. *J. Am. Chem. Soc.* ***1999****, 121*,5444.
[64] Several unsuccessful attempts: Slaugh, L.H.; Magoon, E.F.; Guinn, V.P. *J. Org. Chem.* ***1963****, 28*, 2643.
[65] Seubold Jr., F.H. *J. Am. Chem. Soc.* ***1954****, 76*, 3732.
[66] Cristol, S.J.; Brindell, G.D. *J. Am. Chem. Soc.* ***1954****, 76,* 5699.

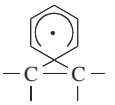
3. The cubylcarbinyl radical did not rearrange to the 1-homocubyl radical, though doing so would result in a considerable decrease in strain.[67]
4. It was shown[68] that no rearrangement of isobutyl radical to *tert*-butyl radical, which would involve the formation of a more stable radical by a hydrogen shift, took place during the chlorination of isobutane.

However, 1,2-migration of alkyl groups has been shown to occur in certain *diradicals*.[69] For example, the following rearrangement has been established by tritium labeling.[70]



In this case, the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **45**, in which the odd electron is not found in the three-membered ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **45** is a transition state, not an intermediate.[71] Among the evidence is the failure to observe **45** either by ESR[72] or CIDNP.[73] Both of these techniques can detect free radicals with extremely short lifetimes (Sec. 5.C.i).[74]

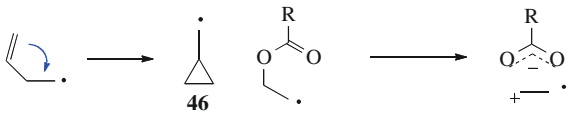


45

In addition, aryl, vinylic[75] and acetoxy groups[76] also migrate. Vinylic groups migrate via a cyclopropylcarbinyl radical intermediate (**46**),[77] while the migration of acetoxy groups may involve the charge-separated structure shown.[78] Thermal isomerization of 1-(3-butenyl)cyclopropane at 415 °C leads to bicyclo[2.2.1]heptane.[79] Migration has been

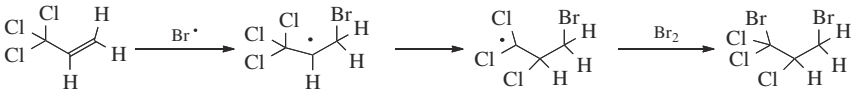
[67] Eaton, P.E.; Yip, Y. *J. Am. Chem. Soc.* ***1991****, 113*, 7692.
[68] Brown, H.C.; Russel, G.A. *J. Am. Chem. Soc.* ***1952****, 74,* 3995. See also, Desai, V.R.; Nechvatal, A.; Tedder, J.M. *J. Chem. Soc. B* ***1970***, 386.
[69] See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1974****, 43,* 129.
[70] McKnight, C.; Rowland, F.S. *J. Am. Chem. Soc.* ***1966****, 88,* 3179. See Gajewski, J.J.; Burka, L.T. *J. Am. Chem. Soc.* ***1972****, 94*, 8857, 8860, 8865; Adam, W.; Aponte, G.S. *J. Am. Chem. Soc.* ***1971****, 93,* 4300.
[71] For MO calcualtions indicating that **45** is an intermediate, see Yamabe, S. *Chem. Lett.* ***1989***, 1523.
[72] Edge, D.J.; Kochi, J.K. *J. Am. Chem. Soc.* ***1972****, 94*, 7695.
[73] Olah, G.A.; Krishnamurthy, V.V.; Singh, B.P.; Iyer, P.S. *J. Org. Chem.* ***1983****, 48,* 955. **45** has been detected as an intemediate in a different reaction: Effio, A.; Griller, D.; Ingold, K.U.; Scaiano, J.C.; Sheng, S.J. *J. Am. Chem. Soc.* ***1980****, 102*, 6063; Leardini, R.; Nanni, D.; Pedulli, G.F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* ***1989****, 111*, 7723.
[74] See Martin, M.M. *J. Am. Chem. Soc.* ***1962****, 84,* 1986; Rüchardt, C.; Hecht, R. *Chem. Ber.* ***1965****, 98,* 2460, 2471; Rüchardt, C.; Trautwein, H. *Chem. Ber.* ***1965****, 98,* 2478.
[75] See Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* ***1989****, 54*, 2675.
[76] See Lewis, S.N.; Miller, J.J.; Winstein, S. *J. Org. Chem.* ***1972****, 37*, 1478.
[77] See Montgomery, L.K.; Matt, J.W. *J. Am. Chem. Soc.* ***1967****, 89,* 934, 6556; Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* ***1986****, 119,* 3528.
[78] Barclay, L.R.C.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984****, 106*, 1793.
[79] Baldwin, J.E.; Burrell, R.C.; Shukla, R. *Org. Lett.* ***2002****, 4*, 3305.

observed for chloro (and to a much lesser extent bromo) groups.



46

For example, in the reaction of $Cl_3CCH{=}CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$ (the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which arose by rearrangement:

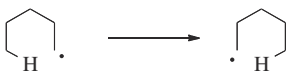


In this particular case, the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals.[80] It has been shown that the 1,2-migration of Cl readily occurs if the migration origin is tertiary and the migration terminus is primary.[81] Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $RCMe_2CH_2^{\bullet} \rightarrow Me_2OC^{\bullet}CH_2R$. These were found to be in the order $R = H_2C{=}CH_2 > Me_3CC{=}O > Ph > Me_3CC{\equiv}C > CN$.[82]

In summary, 1,2 free radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[83]

Despite the fact that hydrogen atoms do not migrate 1,2, longer free radical migrations of hydrogen are known.[84] The most common are 1,5-shifts, but 1,6 and longer shifts have also been found (see Reaction **18-29**). The possibility of 1,3-hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for $C\cdots H\cdots C$ in the transition state is linear and this geometry cannot be achieved in a 1,3-shift. 1,4-Shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for Reactions, see **14-6** and **18-40**):

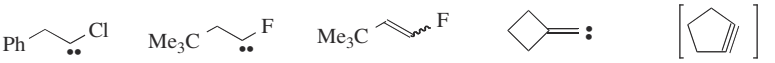


Transannular shifts of hydrogen atoms have also been observed.[85]

[80] See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1979****, 48*, 828; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965****, 1*, 211, pp. 231–249.
[81] See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974****, 96*, 2201.
[82] Lindsay, D.A.; Lusztyk, J.L.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984****, 106,* 7087.
[83] See Dannenberg, J.J.; Dill, K. *Tetrahedron Lett.* ***1972***, 1571.
[84] See Freidlina, R.Kh.; Terent'ev, A.B. *Acc. Chem. Res.* ***1977****, 10,* 9.
[85] Traynham, J.G.; Couvillon, T.M. *J. Am. Chem. Soc.* ***1967****, 89*, 3205.

18.D. CARBENE REARRANGEMENTS[86]

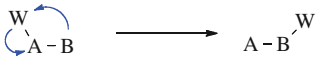
Carbenes can rearrange to alkenes in many cases.[87] A 1,2-hydrogen shift leads to an alkene, and this is often competitive with insertion reactions.[88] Benzylchlorocarbene (**47**) rearranges via a 1,2-hydrogen shift to give the alkene.[89] Similarly, carbene **48** rearranges to alkene **49**, and replacement of H on the α-carbon with D showed a deuterium isotope effect of ∼5.[90] Vinylidene carbene ($H_2C{=}C{:}$) rearranges to acetylene.[91] Rearrangement of alkylidene carbene (**50**) has been calculated to give the highly unstable cyclopentyne (**51**), which cannot be isolated, but can give a [2 + 2] cycloaddition product (Reaction **15-63**) when generated in the presence of a simple alkene.[92] The spiro carbenes undergo rearrangement reactions.[93]



47 **48** **49** **50** **51**

18.E. ELECTROPHILIC REARRANGEMENTS[94]

Rearrangements in which a group migrates without its electrons are rarer than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also, Reaction **18-2**). An *ab initio* study predicts that a [1,2]-alkyl shift in alkyne anions should be facile.[95]

18.F. REACTIONS

The reactions in this chapter are classified into three main groups and 1,2-shifts are considered first. Within this group, reactions are classified according to (1) the identity of the substrate atoms A and B and (2) the nature of the migrating group W. The cyclic

[86] See Baird, M.S. *Chem. Rev.* ***2003****, 103*, 1271.
[87] de Meijere, A.; Kozhushkov, S.I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3607.
[88] Nickon, A.; Stern, A.G.; Ilao, M.C. *Tetrahedron Lett.* ***1993****, 34*, 1391.
[89] Merrer, D.C.; Moss, R.A.; Liu, M.T.H.; Banks, J.-T.; Ingold, K.U. *J. Org. Chem.* ***1998****, 63*, 3010.
[90] Moss, R.A.; Ho, C.-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* ***1992****, 33*, 4287.
[91] Hayes, R.L.; Fattal, E.; Govind, N.; Carter, E.A. *J. Am. Chem. Soc.* ***2001****, 123*, 641.
[92] Gilbert, J.C.; Kirschner, S. *Tetrahedron Lett.* ***1993****, 34*, 599, 603.
[93] Moss, R.A.; Zheng, F.; Krough-Jespersen, K. *Org. Lett.* ***2001****, 3*, 1439.
[94] See Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangments in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 391–470; Grovenstein Jr., E. *Angew. Chem. Int. Ed.* ***1978****, 17*, 313; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 21–30; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 223–243.
[95] Borosky, G.L. *J. Org. Chem.* ***1998****, 63*, 3337.

rearrangements are in the second group. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

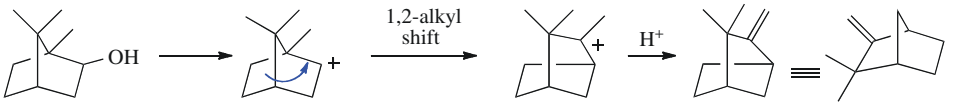
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are Reactions **11-27**–**11-32**, **11-36**, **13-30**-**13-32**, and, partially, **11-33**, **11-38**, and **11-39**. Double-bond shifts have also been treated in other chapters, although they may be considered rearrangements (Sec. 8.A and Reactions **12-**4, and **12-2**). Other reactions that may be regarded as rearrangements are the *Pummerer* (**19-83**) and *Willgerodt* (**19-84**) reactions.

18.F.i. 1,2-Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

18-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/→1/alkyl)- *migro-* elimination, and so on



Isoborneol **52** **53** Camphene

Wagner-Meerwein rearrangements were first discovered in reactions of bicyclic terpenes, and most of the early development of this reaction was with these compounds.[96] An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2-alkyl shift of an intermediate carbocation, (e.g., **52** → **53**). When alcohols are treated with acids, simple substitution (e.g., Reaction **10-48**) or elimination (Reaction **17-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements have been called *Wagner–Meerwein rearrangements*, although this term is nowadays reserved for relatively specific transformations (e.g., isoborneol to camphene and related reactions). As pointed out previously, the carbocation that is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss of a hydrogen β to it, so the rearrangement product is usually an alkene.[97] If there is a choice of protons, *Zaitsev's rule* (Sec. 17.A.i, category 3) governs the direction, as expected. Sometimes a different positive group is lost instead of a proton. Less often, the new carbocation reacts with a nucleophile instead of losing a proton. The nucleophile may be the water that is the original leaving group, in which case the product is a rearranged alcohol; or it may be some other species present (solvent, added nucleophile, etc.).

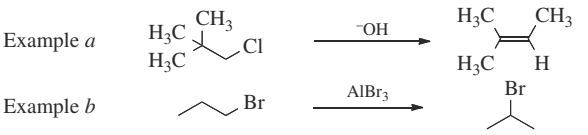
Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under S_N2 conditions, substitution is extremely slow[98]; and under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free radical

[96] See Hogeveen, H.; van Kruchten, E.M.G.A. *Top. Curr. Chem.* ***1979****, 80*, 89; Arbuzov, B.A.; Isaeva, Z.G. *Russ. Chem. Rev.* ***1976****, 45,* 673; Banthorpe, D.V.; Whittaker, D. *Q. Rev. Chem. Soc.* ***1966****, 20*, 373.

[97] See Kaupp, G. *Top. Curr. Chem.* ***1988****, 146,* 57.

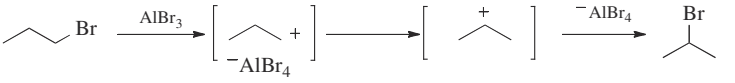
[98] See, however, Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, although, as seen previously (Sec. 18.C), neophyl systems undergo rearrangement as well as substitution.



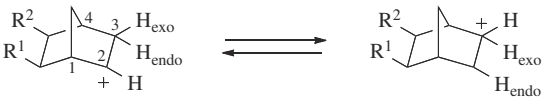
Examples of carbocation rearrangements are found in simpler systems (e.g., neopentyl chloride, example *a*) and even 1-bromopropane (example *b*). These examples illustrate the following points:

1. Hydride ion can migrate. In example *b*, it was hydride that shifted, not bromine:



2. The leaving group does not have to be H_2O, but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions[99] (see the section on leaving groups in nucleophilic substitution in Sec. 10.A.ii, category 1). Rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond.
3. Example *b* illustrates that the last step can be substitution instead of elimination.
4. Example *a* illustrates that the new double bond is formed in accord with *Zaitsev's rule*.

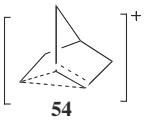
2-Norbornyl cations (see **52**), besides displaying the 1,2-shifts of a CH_2 group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2-shifts). These 3,2-shifts usually take place from the exo side[100]; that is, the 3-exo hydrogen migrates to the 2-exo position.[101] This stereoselectivity is analogous to the behavior previously seen for norbornyl systems, namely, that nucleophiles attack norbornyl cations from the exo side (Sec. 10.C.i, category 4) and that addition to norbornenes is also usually from the exo direction (Sec. 15.B.iii).



For rearrangements of alkyl carbocations, the direction of rearrangement is usually toward the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,[102] and the product is

[99] See, in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, the articles by White, E.H.; Woodcock, D.J. pp. 407–497 (473–483) and by Banthorpe, D.V. pp. 585–667 (pp. 586–612).
[100] See Berson, J.A.; Hammons, J.H.; McRowe, A.W.; Bergman, R.G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* ***1967****, 89,* 2590.
[101] For an example of a 3,2-endo shift, see Wilder, Jr., P.; Hsieh, W. *J. Org. Chem.* ***1971****, 36*, 2552.
[102] See Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

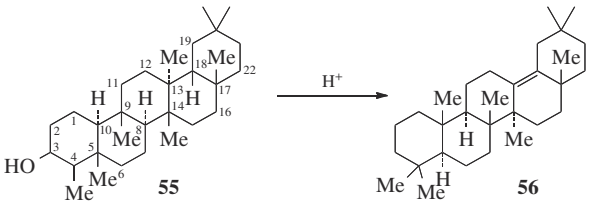
sometimes a mixture corresponding to an equilibrium mixture of the possible carbocations. The *Wagner–Meerwein rearrangement* has been observed for a secondary to a secondary carbocation rearrangement, leading to some controversy. Winstein[103] described norbornyl cations in terms of the resonance structures represented by the nonclassical ion **54**.[104] This view was questioned, primarily by Brown,[105] who suggested that the facile rearrangements could be explained by a series of fast *1,3-Wagner–Meerwein shifts*.[106] There is considerable evidence, however, that *the norbornyl cation rearranges with σ participation*,[107] and there is strong NMr evidence for the nonclassical ion in superacids at low temperatures.[108]



54

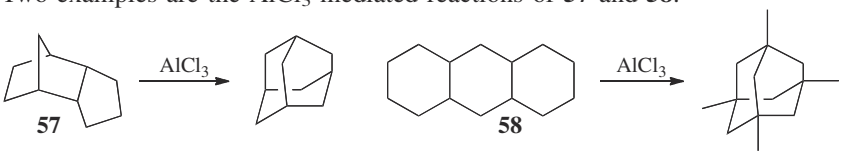
As alluded to above, the term "*Wagner–Meerwein rearrangement*" is not precise. Some use it to refer to all the rearrangements in this section and in Reaction **18-2**. Others use it only when an alcohol is converted to a rearranged alkene. Many use the term only for rearrangements that involve a nonclassical carbocation intermediate. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion. Catalytic asymmetric *Wagner–Meerwein shifts* have been observed.[109] An asymmetric, Pd catalyzed *Wagner–Meerwein shift* has been reported with allenic alcohols.[110]

Several of these rearrangements sometimes occur in one molecule, either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3β-friedelanol (**55**). When this compound is treated with acid, 13(18)-oleanene (**56**) is formed.[111] In this case, *seven* 1,2-shifts take place. Loss of H_2O from position 3 leaves a positive charge, and


H+
HO
Me
H
Me
Me
Me

the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **56**. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **55**) moves above the plane, and a group below the plane (dashed line) moves below it. It is probable that the seven shifts are not all concerted, although some of them may be, for intermediate products can be isolated.[112] As an illustration of point 2 (see above), it may be mentioned that friedelene, derived from dehydration of **55**, also gives **56** on treatment with acid.[113]

Some alkanes undergo *Wagner–Meerwein rearrangements* if treated with Lewis acids and a small amount of initiator. An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.[114] It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, (e.g., $AlCl_3$). If the substrate contains $>$ 10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is *Schleyer adamantization*. Two examples are the $AlCl_3$-mediated reactions of **57** and **58**.



57 **58**

If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[115] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equilibrium.[116] Best yields are obtained by the use of "sludge" catalysts[117] (i.e., a mixture of AlX_3 and *tert*-butyl bromide or *sec*-butyl bromide).[118] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2 shifts, the exact pathways are not easy to unravel because of their complexity.[119] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[120]

As already indicated, the mechanism of the *Wagner–Meerwein rearrangement* is usually nucleophilic. Free radical rearrangements are also known (see Section 18.A), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic)

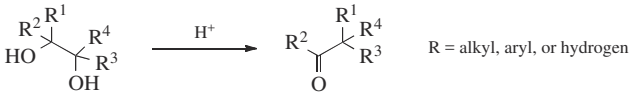
[112] See Whitlock Jr., H.W.; Olson, A.H. *J. Am. Chem. Soc.* ***1970****, 92*, 5383.
[113] Dutler, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* ***1955****, 38,* 1268; Brownlie, G.; Spring, F.S.; Stevenson, R.; Strachan, W.S. *J. Chem. Soc.* ***1956***, 2419; Coates, R.M. *Tetrahedron Lett.* ***1967***, 4143.
[114] See McKervey, M.A.; Rooney, J.J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 39–64; McKervey, M.A. *Tetrahedron* ***1980****, 36*, 971; *Chem. Soc. Rev.* ***1974****, 3,* 479; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 178–202; Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971****, 18,* 1, pp. 3–23.
[115] See Gund, T.M.; Osawa, E.; Williams, Jr., V.Z.; Schleyer, P.v.R. *J. Org. Chem.* ***1974****, 39,* 2979.
[116] See Godleski, S.A.; Schleyer, P.v.R.; Osawa, E.; Wipke, W.T. *Prog. Phys. Org. Chem.* ***1981****, 13,* 63.
[117] Schneider, A.; Warren, R.W.; Janoski, E.J. *J. Org. Chem.* ***1966****, 31,* 1617; Williams, Jr., V.Z.; Schleyer, P.v.R.; Gleicher, G.J.; Rodewald, L.B. *J. Am. Chem. Soc.* ***1966****, 88,* 3862; Robinson, M.J.T.; Tarratt, H.J.F. *Tetrahedron Lett.* ***1968***, 5.
[118] See Olah, G.A.; Wu, A.; Farooq, O.; Prakash, G.K.S. *J. Org. Chem.* ***1989****, 54,* 1450.
[119] See Klester, A.M.; Ganter, C. *Helv. Chim. Acta* ***1985****, 68*, 734.
[120] Majerski, Z.; Liggero, S.H.; Schleyer, P.v.R.; Wolf, A.P. *Chem. Commun.* ***1970***, 1596.

have also been found.[94] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[121] This is called the *Grovenstein-Zimmerman rearrangement*. The intermediate is $Ph_3CCH_2^-$, and the phenyl moves without its electron pair. Only aryl and vinylic,[122] and not alkyl, groups migrate by the electrophilic mechanism (see the introductory section preceding Sec. 18.A) and transition states or intermediates analogous to **41** and **42** are likely.[123]

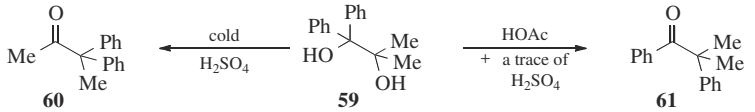
OS **V**, 16, 194; **VI**, 378, 845.

18-2 The Pinacol Rearrangement

1/*O*-Hydro,3/hydroxy-(2/→3/alkyl)-*migro*-elimination



When 1.2-diols (*vic*-diols; glycols) are treated with acids,[124] they rearrange to give aldehydes or ketones, although elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from a prototype compound pinacol ($Me_2COHCOHMe_2$), which is rearranged to pinacolone (Me_3C-$COCH_3$).[125] In this type of reaction, reduction can compete with rearrangement.[126] The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (CO_2Et)[127] as migrating groups. In most cases, each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see Sec. 18.A.iii for a discussion of migratory aptitudes). A noncatalytic reaction is possible in supercritical water.[128]



Stereodifferentiation is possible in this reaction.[129] When TMSOTf was used to initiate the reaction, it was shown to be highly regioselective.[130] Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions as well as on the nature

[121] Grovenstein, Jr., E.; Williams Jr., L.P. *J. Am. Chem. Soc.* ***1961****, 83,* 412; Zimmerman, H.E.; Zweig, A. *J. Am. Chem. Soc.* ***1961****, 83,* 1196. See also, Grovenstein, Jr., E.; Cheng, Y. *J. Am. Chem. Soc.* ***1972****, 94*, 4971.

[122] See Grovenstein, Jr., E.; Black, K.W.; Goel, S.C.; Hughes, R.L.; Northrop, J.H.; Streeter, D.L.; VanDerveer, D. *J. Org. Chem.* ***1989****, 54,* 1671, and references cited therein.

[123] Bertrand, J.A.; Grovenstein, Jr., E.; Lu, P.; VanDerveer, D. *J. Am. Chem. Soc.* ***1976****, 98*, 7835.

[124] See Lopez, L.; Mele, G.; Mazzeo, C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 779; de Sanabia, J.A.; Carrión, A.E. *Tetrahedron Lett.* ***1993****, 34*, 7837; Harada, T.; Mukaiyama, T. *Chem. Lett.* ***1992***, 81.

[125] Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 722–732; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group,* Vol. 1, Wiley, NY, ***1966***, pp. 762–771.

[126] Grant, A.A.; Allukian, M.; Fry, A.J. *Tetrahedron Lett.* ***2002****, 43*, 4391.

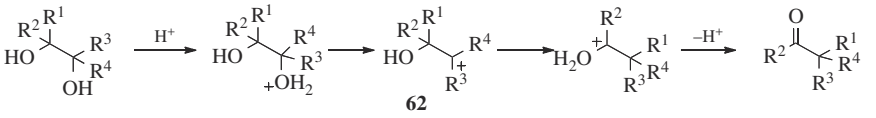
[127] Kagan, J.; Agdeppa Jr., D.A.; Mayers, D.A.; Singh, S.P.; Walters, M.J.; Wintermute, R.D. *J. Org. Chem.* ***1976****, 41,* 2355. Also see Berner, D.; Cox, D.P.; Dahn, H. *J. Am. Chem. Soc.* ***1982****, 104*, 2631.

[128] Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000****, 122*, 1908.

[129] Paquette, L.A.; Lanter, J.C.; Johnston, J.N. *J. Org. Chem.* ***1997****, 62*, 1702.

[130] Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* ***1992***, 1449.

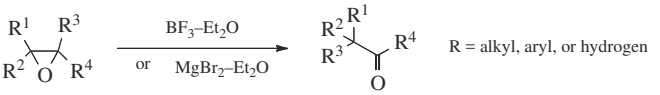
of the substrate. Thus the action of cold, concentrated sulfuric acid on **59** produces mainly the ketone **60** (methyl migration), while treatment of **59** with acetic acid containing a trace of sulfuric acid gives mostly **61** (phenyl migration).[131] If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (Reaction **18-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with a solid organic acid.[132]



62

The mechanism involves a simple 1,2-shift. The ion **62** (where all four R groups are Me) has been trapped by the addition of tetrahydrothiophene.[133] A migration takes place from the tertiary position because carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (Sec. 5.A.ii). In addition, the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β-amino alcohols, which rearrange on treatment with nitrous acid (this is called the *semipinacol rearrangement*), for iodohydrins, for which the reagent is mercuric oxide or silver nitrate, for β-hydroxyalkyl selenides [$R^1R^2C(OH)C(SeR^5)R^3R^4$],[134] and for allylic alcohols,[135] which can rearrange on treatment with a strong acid that protonates the double bond. A related rearrangement is the Et_2Zn mediated rearrangement of bromohydrins to give ketones.[136]



A similar rearrangement is given by epoxides, when treated with acidic reagents (e.g., BF_3–etherate or $MgBr_2$–etherate), 5M $LiClO_4$ in ether,[137] $InCl_3$,[138] $Bi(OTf)_3$,[139] or sometimes by heat alone.[140] Epoxides are converted to aldehydes or ketones on treatment with certain metallic catalysts[141] including treatment with iron complexes,[142] $IrCl_3$,[143] or

[131] Ramart-Lucas, P.; Salmon-Legagneur, F. *C. R. Acad. Sci.* ***1928****, 188,* 1301.
[132] Toda, F.; Shigemasa, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 209.
[133] Bosshard, H.; Baumann, M.E.; Schetty, G. *Helv. Chim. Acta* ***1970****, 53*, 1271.
[134] For a review, see Krief, A.; Laboureur, J.L.; Dumont, W.; Labar, D. *Bull. Soc. Chim. Fr.* ***1990***, 681.
[135] See Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Chen, W.M. *Synlett* ***2003***, 1497; Hurley, P.B.; Dake, G.R. *Synlett* ***2003***, 2131.
[136] Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* ***2008****, 73,* 3516.
[137] Sankararaman, S.; Nesakumar, J.E. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3173.
[138] Ranu, B.C.; Jana, U. *J. Org. Chem.* ***1998****, 63*, 8212.
[139] Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001****, 42*, 8129.
[140] For a list of reagents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1277–1280.
[141] See Prandi, J.; Namy, J.L.; Menoret, G.; Kagan, H.B. *J. Organomet. Chem.* ***1985****, 285*, 449; Miyashita, A.; Shimada, T.; Sugawara, A.; Nohira, H. *Chem. Lett.* ***1986***, 1323; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* ***1989****, 30*, 5607.
[142] Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* ***1999****, 40*, 7243.
[143] Karamé, I.; Tommasino, M.L.; LeMaire, M. *Tetrahedron Lett.* ***2003****, 44*, 7687.

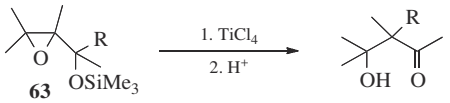
with $BiOClO_4$.[144] Base-induced rearrangement is also known, but the products are usually different.[145]

The *Meinwald rearrangement* converts epoxides to carbonyl compounds.[146] Several reagents mediate this transformation, including Cu compounds.[147] A closely related reaction of vinyl epoxides gives alkenyl ketones upon treatment with Ga compounds.[148] It has been shown that epoxides are intermediates in the pinacol rearrangements of certain glycols.[149] Among the evidence for the mechanism given is that $Me_2COHCOHMe_2$, $Me_2COHC(NH_2)Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as expected), but yielded the *same mixture* of two products, pinacol and pinacolone, indicating a common intermediate.[150]

A good way to prepare β-diketones consists of heating α,β-epoxy ketones at 80–140 °C in toluene with small amounts of $(Ph_3P)_4Pd$ and dppe.[151] Epoxides are converted to 1,2-diketones with Bi, DMSO, O_2 and a catalytic amounts of $Cu(OTf)_2$ at 100 °C.[152] α,β-Epoxy ketones are also converted to 1,2-diketones with a Ru catalyst[153] or an Fe catalyst.[154] Epoxides with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of a $ZnBr_2$[155] or $Tb(OTf)_3$[156] catalyst to give a γ-hydroxy ketone.

Oxaziridines are converted to ring-expanded lactams under photochemical conditions.[157] *N*-Tosyl aziridines with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of Lewis acids (e.g., SmI_2), in this case a keto-*N*-tosyl amide.[158]

β-Hydroxy ketones can be prepared by treating the silyl ethers (**63**) of α,β-epoxy alcohols with $TiCl_4$.[159]



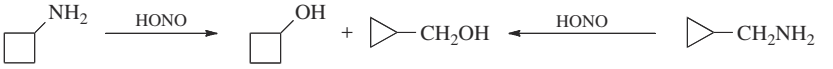
63

OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **V**, 326, 647; **VI**, 39, 320; **VII**, 129. See also, OS **VII**, 456.

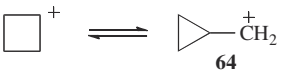
[144] Anderson, A.M.; Blazek, J.M.; Garg, P.; Payne, B.J.; Mohan, R.S. *Tetrahedron Lett.* ***2000****, 41*, 1527.
[145] See Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* ***1972****, 41*, 403, 410. Also see Hodgson, D.M.; Robinson, L.A.; Jones, M.L. *Tetrahedron Lett.* ***1999****, 40*, 8637.
[146] See Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* ***1963****, 85*, 582.
[147] Robinson, M.W.C.; Pillinger, K.S.; Graham, A.E. *Tetrahedron Lett.* ***2006****, 47,* 5919; Robinson, M.W.C.; Pillinger, K.S.; Mabbett, I.; Timms, D.A.; Graham, A.E. *Tetrahedron* ***2010****, 66,* 8377.
[148] Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* ***2005****, 70,* 6537.
[149] See Pocker, Y.; Ronald, B.P. *J. Am. Chem. Soc.* ***1970****, 92,* 3385; *J. Org. Chem.* ***1970****, 35,* 3362; Tamura, K.; Moriyoshi, T. *Bull. Chem. Soc. Jpn.* ***1974****, 47*, 2942.
[150] Pocker, Y. *Chem. Ind. (London),* ***1959***, 332. See also, Herlihy, K.P. *Aust. J. Chem.* ***1981****, 34,* 107.
[151] Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* ***1980****, 102,* 2095.
[152] Antoniotti, S.; Duñach, E. *Chem. Commun.* ***2001***, 2566.
[153] Chang, C.-L.; Kumar, M.P.; Liu, R.-S. *J. Org. Chem.* ***2004****, 69*, 2793.
[154] Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* ***2002***, 2570.
[155] Tu, Y.Q.; Fan, C.A.; Ren, S.K.; Chan, A.S.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3791.
[156] Bickley, J.F.; Hauer, B.; Pena, P.C.A.; Roberts, S.M.; Skidmore, J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1253.
[157] Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declerzq, J.-P. *Org. Lett.* ***2001****, 3*, 3067.
[158] Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Shi, Y. *Org. Lett.* ***2002****, 4*, 363.
[159] Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* ***1986****, 108*, 3827.

18-3 Expansion and Contraction of Rings

Demyanov ring contraction; Demyanov ring expansion



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller than the original, as in the interconversion of the cyclobutyl cation and the cyclopropylcarbinyl cation (**64**). Note that this change involves conversion of a



64

secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring expansion can take place.[160] The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **18-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,[161] but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C_3–C_8,[162] but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion (for a discussion of this interconversion, see Sec. 10.C.i). The influence of substituents on this rearrangement has been examined.[163] Note that a hybrid of a [1,2]-sigmatropic hydrogen shift (also See **18-29**) and a two-electron-electrocyclic ring opening has been discovered for cyclopropylcarbinyl cations that was labeled as a "hiscotropic" rearrangement."[164] The contraction reaction has been applied to four-membered rings and to rings of C_6–C_8, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved.

A related rearrangement involves cyclopropyl propargylic alcohols, which gives an alkylidene cyclobutanone in the presence of Ag and Au catalysts,[165] or Ru and In catalysts.[166] Cyclopropylcarbinyl rearrangements are catalyzed by ionic liquids under

[160] See Hesse, M. *Ring Enlargement in Organic Chemistry*, VCH, NY, ***1991***; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***; Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron* ***1989****, 45,* 909; Salaün, J. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 809–878; Conia, J.M.; Robson, M.J. *Angew. Chem. Int. Ed.* ***1975****, 14,* 473. For a list of ring expansions and contractions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1283–1302.

[161] See Smith, P.A.S.; Baer, D.R. *Org. React.* ***1960****, 11*, 157. See also, Chow, L.; McClure, M.; White, J. *Org. Biomol. Chem.* ***2004****, 2*, 648.

[162] See Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989****, 89,* 165, see pp. 182–186; Breslow, R. in Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 233–294.

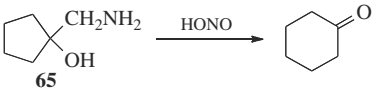
[163] Wiberg, K.B.; Shobe, D.; Nelson, G.C. *J. Am. Chem. Soc.* ***1993****, 115*, 10645.

[164] Nouri, D.H.; Tantillo, D.J. *J. Org. Chem.* ***2006****, 71,* 3686.

[165] Markham, J.P.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2005****, 127,* 9708.

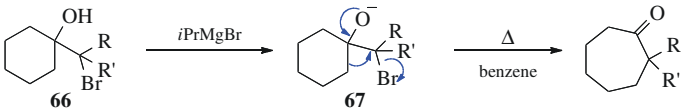
[166] Trost, B.M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* ***2008****, 130,* 17258.

solvent-free conditions.[167] Methylenecyclopropanes rearrange to cyclobutenes in the presence of 1 atm of CO and Pt catalyst[168] or a Pd catalyst, mediated by a Cu catalyst.[169] Arylvinylidenecyclopropanes rearrange to bicyclic systems in the presence of a Lewis acid.[170]



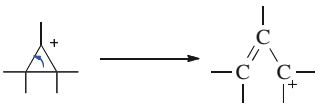
65

Ring expansions of certain hydroxyamines (e.g., **65**) are analogous to the semipinacol rearrangement (Reaction **18-2**). This reaction is called the *Tiffeneau–Demyanov ring expansion*. These have been performed on rings of C_4–C_8 and the yields are better than for the simple *Demyanov ring expansion*. A similar reaction has been used to expand rings of from five to eight members.[171] In this case, a cyclic bromohydrin of the form **66** is treated with a *Grignard reagent*, which, acting as a base, removes the OH proton to give the alkoxide **67**. When **67** is heated to reflux, ring enlargement occurs. The reaction has been done with **66** in which at least one R group is phenyl or methyl,[172] but fails when both R groups are hydrogen.[173]

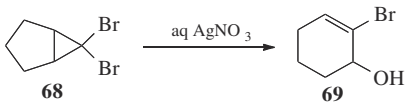


66 **67**

A positive charge generated on a three-membered ring gives "contraction" to an allylic cation, as shown.[174]



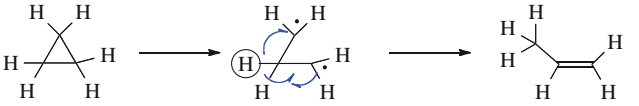
As seen in Section 10.G.i, category 7, this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being the conversion of **68** to **69**.[175] The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see Reaction **18-27**, the *Möbius–Hückel method*).



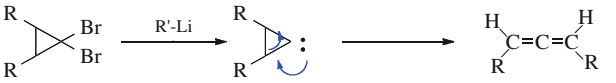
68 **69**

[167] Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* ***2006****, 47*, 881.
[168] Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* ***2006****, 128,* 6306.
[169] Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* ***2006****, 128,* 7430.
[170] Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* ***2005****, 127,* 14552.
[171] Sisti, A.J. *J. Org. Chem.* ***1968****, 33,* 453. See also, Sisti, A.J.; Vitale, A.C. *J. Org. Chem.* ***1972****, 37,* 4090.
[172] Sisti, A.J.; Rusch, G.M. *J. Org. Chem.* ***1974****, 39*, 1182.
[173] Sisti, A.J. *J. Org. Chem.* ***1968****, 33*, 3953.
[174] Marvell, E.N. *Thermal Electrocylic Reactions*, Academic Press, NY, ***1980***, pp. 23–53; Sorensen, T.S.; Rauk, A. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 1–78.
[175] Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc.* ***1958****, 80,* 2024.

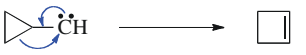
Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (1) Upon pyrolysis, cyclopropanes can undergo "contraction" to propenes.[176] In the simplest case, cyclopropane gives propene when heated to 400–500 °C. The mechanism is generally regarded[177] as involving a diradical



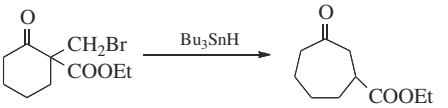
intermediate[178] (recall that free radical 1,2-migration is possible for diradicals, Sec. 18.C). (2) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in



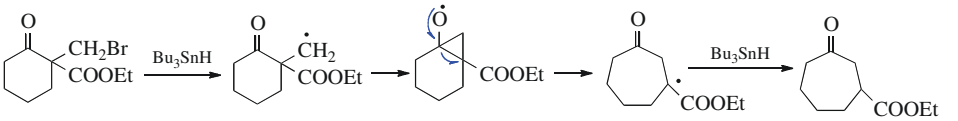
this way.[179] Flash vacuum pyrolysis of 1-chlorocyclopropene thermally rearranges to chloroallene.[180] One way to generate such a species is treatment of a 1,1-dihalocyclopropane with an alkyllithium compound (Reaction **12-39**).[181] In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion.[182]



Some free radical ring enlargements are also known, an example being[183]:



This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is



[176] See Berson, J.A. in de Mayo, P. *Rearrangaements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 324–352; *Ann. Rev. Phys. Chem.* ***1977****, 28*, 111; Bergman, R.G. in Kochi, J.K. *Free Radicals,* Vol. 1, Wiley, NY, ***1973***, pp. 191–237; Frey, H.M. *Adv. Phys. Org. Chem.* ***1966****, 4,* 147, see pp. 148–170. Also see Baldwin, J.E.; Day, L.S.; Singer, S.R. *J. Am. Chem. Soc.* ***2005****, 127*, 9370.

[177] See Baldwin, J.E.; Grayston, M.W. *J. Am. Chem. Soc.* ***1974****, 96,* 1629, 1630.

[178] See Bergman, R.G.; Carter, W.L. *J. Am. Chem. Soc.* ***1969****, 91,* 7411.

[179] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 20–23; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 462–467.

[180] Billups, W.E.; Bachman, R.E. *Tetrahedron Lett.* ***1992****, 33*, 1825.

[181] See Baird, M.S.; Baxter, A.G.W. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2317, and references cited therein.

[182] See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 111–117.

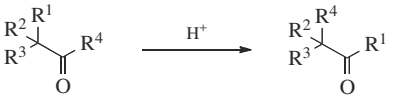
[183] Dowd, P.; Choi, S. *Tetrahedron* ***1991****, 47*, 4847. For a related ring expansion, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* ***1988***, 1404.

This reaction has been extended to the expansion of rings by three or four carbons, by the use of a substrate containing $(CH_2)_nX$ ($n = 3$ or 4) instead of CH_2Br.[184] By this means, 5-, 6-, and 7-membered rings were enlarged to 18–11-membered rings. A β-keto ester (e.g., 2-carboxyethyl cyclohexanone) is converted to 3-carboxyethyl cylcoheptanone when treated with $CF_3CO_2ZnCH_2I$.[185]

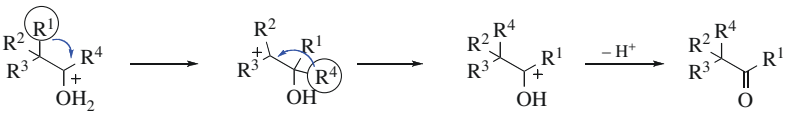
OS **III**, 276; **IV**, 221, 957; **V**, 306, 320; **VI**, 142, 187; **VII**, 12, 114, 117, 129, 135; **VIII**, 179, 467, 556, 578.

18-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones

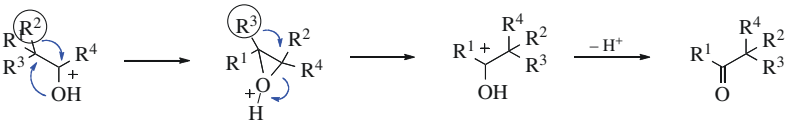
1/Alkyl,2/alkyl-interchange, and so on



Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[186] The R^2, R^3, and R^4 groups may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($R^1 = H$) has so far been reported. There are two mechanisms,[187] each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions[188]:



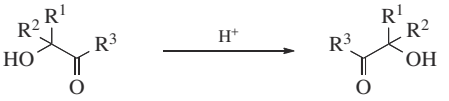
In the other pathway, the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate[189] is one possibility[190]:



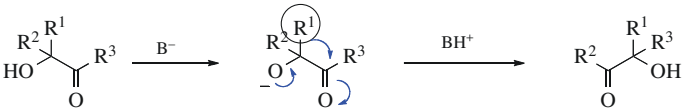
If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, the first pathway predicts that the product will contain all the ^{14}C in the C=O carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments[191] have shown that in some cases only the C=O carbon was

[184] Dowd, P.; Choi, S. *J. Am. Chem. Soc.* ***1987****, 109,* 6548; *Tetrahedron Lett.* ***1991****, 32,* 565.
[185] Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* ***2005****, 70,* 8245.
[186] See Fry, A. *Mech. Mol. Migr.* ***1971****, 4,* 113; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 771–790.
[187] Favorskii, A.; Chilingaren, A. *C. R. Acad. Sci.* ***1926****, 182,* 221.
[188] Collins, C.J.; Bowman, N.S. *J. Am. Chem. Soc.* ***1959****, 81,* 3614.
[189] Zook, H.D.; Smith, W.E.; Greene, J.L. *J. Am. Chem. Soc.* ***1957****, 79,* 4436.
[190] Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2-shift of an OH group.
[191] See Fry, A.; Oka, M. *J. Am. Chem. Soc.* ***1979****, 101,* 6353.

labeled, in other cases only the α carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α-hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the α-*ketol rearrangement*).

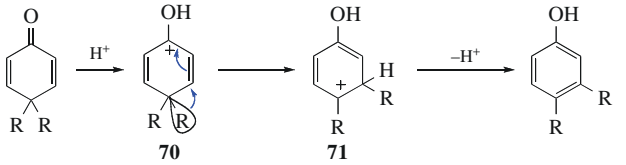


The α-ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.



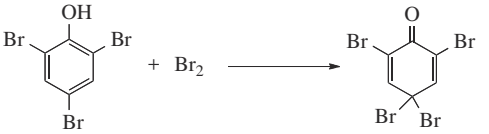
18-5 The Dienone–Phenol Rearrangement

2/*C*→5/*O*-Hydro,1/*C*→2/*C*-alkyl-bis-migration



70 **71**

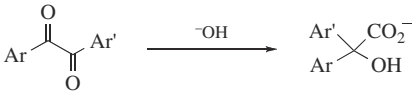
Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,[192] 1,2-migration of one of these groups from **70** to give the phenol. Note that a photochemical version of this reaction has been observed.[193] The driving force in the overall reaction (the *dienone–phenol rearrangement*) is of course creation of an aromatic system.[194] Note that **70** and **71** are arenium ions (Sec. 5.A.ii), the same as those generated by attack of a phenol on an electrophile.[195] Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol–dienone rearrangement)* takes place, though without an actual migration.[196] An example is



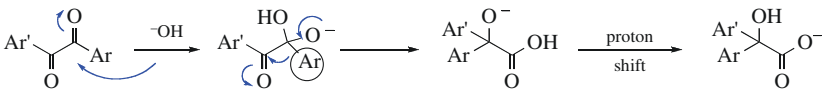
[192] See Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* ***1986****, 27,* 2627.
[193] Guo, Z.; Schultz, A.G. *Org. Lett.* ***2001****, 3,* 1177.
[194] Perkins, M.J.; Ward, P. *Mech. Mol. Migr.* ***1971****, 4,* 55, pp. 90–103; Miller, B. *Mech. Mol. Migr.* ***1968****, 1,* 247; Shine, H.J. *Aromatic Rearrangements*; Elsevier, NY, ***1967***, pp. 55–68; Waring, A.J. *Adv. Alicyclic Chem.* ***1966****, 1,* 129, pp. 207–223. See Miller, B. *Acc. Chem. Res.* ***1975****, 8,* 245.
[195] See Vitullo, V.P.; Grossman, N. *J. Am. Chem. Soc.* ***1972****, 94*, 3844; Planas, A.; Tomás, J.; Bonet, J. *Tetrahedron Lett.* ***1987****, 28,* 471.
[196] See Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. *Russ. Chem. Rev.* ***1963****, 32,* 75.

18-6 The Benzil–Benzilic Acid Rearrangement

1/*O*-Hydro,3/oxido-(1/→2/aryl)-*migro*-addition



When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil–benzilic acid rearrangement* (benzil is PhCOCOPh; benzilic acid is Ph_2COHCO_2H).[197] A Rh catalyzed version of this reaction has also been reported.[198] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones[199] and to α-keto aldehydes. The use of an alkoxide instead of hydroxide gives the corresponding ester directly,[200] although alkoxide ions that are readily oxidized (e.g., OEt^- or $OCHMe_2^-$) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in Reaction **18-1**–**18-4**, but there is a difference: The migrating group does not move to a carbocation. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (Sec. 16.A.i) and of many additions to the C=O bond (Chapter 16):

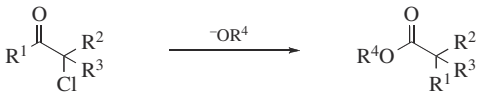


The mechanism has been intensely studied,[188] and there is much evidence for it.[201] The reaction is irreversible.

OS **I**, 89.

18-7 The Favorskii Rearrangement

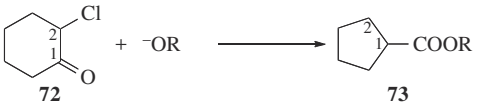
2/Alkoxy-de-chloro(2/→1/alkyl)-*migro*-substitution



The reaction of α-halo ketones (chloro, bromo, or iodo) with alkoxide ions[202] to give rearranged esters is called the *Favorskii rearrangement*.[203] The use of hydroxide ions or amines as bases leads to the free carboxylic acid (salt) or amide, respectively,

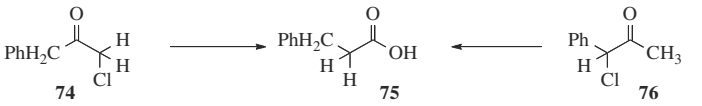
[197] See Selman, S.; Eastham, J.F. *Q. Rev. Chem. Soc.* ***1960****, 14,* 221.
[198] Shimizu, I.; Tekawa, M.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1992***, 1365.
[199] For an example, see Schaltegger, A.; Bigler, P. *Helv. Chim. Acta* ***1986****, 69,* 1666.
[200] Doering, W. von E.; Urban, R.S. *J. Am. Chem. Soc.* ***1956****, 78,* 5938.
[201] However, see Screttas, C.G.; Micha-Screttas, M.; Cazianis, C.T. *Tetrahedron Lett.* ***1983****, 24,* 3287.
[202] See Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* ***1982****, 23*, 1385.
[203] Boyer, L.E.; Brazzillo, J.; Forman, M.A.; Zanoni, B. *J. Org. Chem.* ***1996****, 61*, 7611; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 437–461; Rappe, C. in Patai, S. *The Chemistry of the Carbon–Halogen Bond,* pt. 2, Wiley, NY, ***1973***, pp. 1084–1101; Redmore, D.; Gutsche, C.D. *Carbocylcic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 46–69; Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* ***1993****, 34*, 4823.

instead of the ester. Cyclic α-halo ketones give ring contraction, as in the conversion of **72** to **73**.



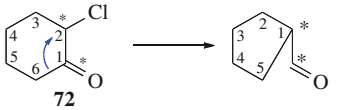
72 **73**

The reaction has also been carried out on α-hydroxy ketones[204] and on α,β-epoxy ketones, which give β-hydroxy acids.[205] The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.



74 **75** **76**

Investigation of the mechanism[206] of the *Favorskii rearrangement* has led to proposals for at least five different mechanisms. However, the finding[207] that **74** and **75** *both* give **76** (this behavior is typical) shows that any mechanism where the halogen leaves and R^1 takes its place is invalid, since in such a case **74** would be expected to give **76** (with $PhCH_2$ migrating), but **75** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **75**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. Chloroketone (**72**), in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **73**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[208] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:

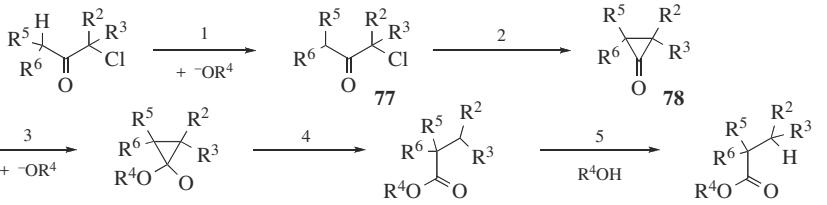


72

On the other hand, if the migration had gone the other way (if the C-2 carbon had migrated to C-6), then this half of the radioactivity would be found solely on C-2 of the product. The fact that C-1 and C-2 were equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **72** are not equivalent, this means that there must be a symmetrical intermediate.[209] The type of intermediate that best fits the circumstances is a cyclopropanone,[210] and the mechanism (for the general case) is formulated (replacing R^1

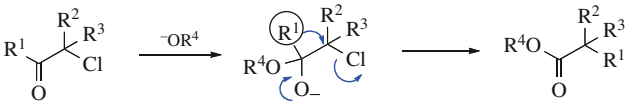
[204] Craig, J.C.; Dinner, A.; Mulligan, P.J. *J. Org. Chem.* ***1972****, 37,* 3539.
[205] See Mouk, R.W.; Patel, K.M.; Reusch, W. *Tetrahedron* ***1975****, 31*, 13.
[206] See Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* ***1982****, 2,* 527. For a theoretical study, see Hamblin, G. D.; Jimenez, R.P.; Sorensen, T.S. *J. Org. Chem.* ***2007****, 72,* 8033.
[207] Bordwell, F.G.; Scamehorn, R.G.; Springer, W.R. *J. Am. Chem. Soc.* ***1969****, 91*, 2087.
[208] Loftfield, R.B. *J. Am. Chem. Soc.* ***1951****, 73*, 4707.
[209] A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **72** had the same isotopic distribution as the starting **72**.
[210] See Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974****, 47,* 73; Turro, N.J. *Acc. Chem. Res.* ***1969****, 2*, 25.

of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α hydrogen is required on the non-halogenated side of the carbonyl):



The intermediate corresponding to **78**, in the case of **72**, is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, **78** is not symmetrical and should open on the side that gives the more stable carbanion.[211] This accounts for the fact that **74** and **75** give the same product. The intermediate in both cases is **77**, which always opens to give the carbanion stabilized by resonance. The cyclopropanone intermediate (**78**) has been isolated in the case where $R^2 = R^5 =$ *t*-Bu and $R^3 = R^6 = H$,[212] and it has also been trapped.[213] Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[214]

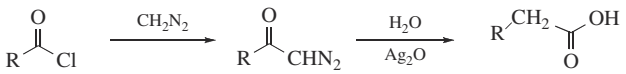
The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have an α hydrogen also rearrange to give the same type of product in what is usually called the *quasi-Favorskii rearrangement*. The *quasi-Favorskii rearrangement* cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*[215]) is a base-catalyzed pinacol rearrangement-type mechanism similar to that of **18-6**. This mechanism requires inversion at the migration terminus and this has been found.[216] It has been shown that even where there *is* an appropriately situated α hydrogen, the semibenzilic mechanism may still operate.[217]



An interesting analogue of the *Favorskii rearrangement* treats a ketone, (e.g., 4-*tert*-butylcyclohexanone), without an α-halogen with $Tl(NO_3)_3$ to give 3-*tert*-butylcyclopentane-1-carboxylic acid.[218]

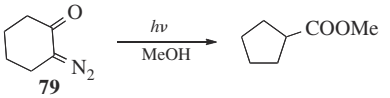
OS **IV**, 594; **VI**, 368, 711.

18-8 The Arndt–Eistert Synthesis



[211] See Rappe, C.; Knutsson, L.; Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970****, 92,* 2032.
[212] Pazos, J.F.; Pacifici, J.G.; Pierson, G.O.; Sclove, D.B.; Greene, F.D. *J. Org. Chem.* ***1974****, 39,* 1990.
[213] See Baldwin, J.E.; Cardellina, J.H.I. *Chem. Commun.* ***1968***, 558.
[214] Wharton, P.S.; Fritzberg, A.R. *J. Org. Chem.* ***1972****, 37,* 1899.
[215] Tchoubar, B.; Sackur, O. *C. R. Acad. Sci.* ***1939****, 208*, 1020.
[216] Baudry, D.; Bégué, J.; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1971***, 1416.
[217] See Salaun, J.R.; Garnier, B.; Conia, J.M. *Tetrahedron* ***1973****, 29,* 2895.
[218] Ferraz, H.M.; Silva, Jr., J.F. *Tetrahedron Lett.* ***1997****, 38*, 1899.

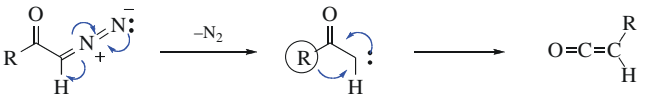
In the *Arndt–Eistert synthesis*, an acyl halide is converted to a carboxylic acid with one additional carbon.[219] The first step of this process is Reaction **16-89**. The actual rearrangement occurs in the second step after treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*.[220] It is the best method of increasing a carbon chain by one from a *carboxylic acid* (see Reaction **10-75** and **16-30**). If an alcohol (R′OH) is used instead of water, the ester (RCH_2CO_2R') is isolated.[221] Similarly, treatment with ammonia gives the amide. Other catalysts are sometimes used (colloidal Pt, Cu, etc.), but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all using ultrasound.[222] The photolysis method[223] often gives better results than the Ag catalysis method. Of course, diazo ketones prepared in any other way also give the rearrangement.[224] The reaction is of wide scope. The R group may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., Reaction **10-5** and **10-19**). Sometimes the reaction is performed with other diazoalkanes (i.e., $R'CHN_2$) to give RCHR′COOH. The reaction has been used for ring contraction of cyclic diazo ketones[225] (e.g., **79**).[226]



79

An asymmetric variation converted ketones to esters using an azaferrocene catalyst.[227]

The mechanism is generally regarded as involving formation of a carbene.[228] It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**15-3**), an alcohol (**15-5**), or ammonia or an amine (**15-8**). Particularly stable ketenes[229]

[219] Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* ***1975****, 14,* 32; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 475–493; Whittaker, D. in Patai, S. *The Chemistry of Diazonium and Diazo Compounds*, pt. 2, Wiley, NY, ***1978***, pp. 593–644.

[220] Kirmse, W. *Eur. J. Org. Chem.* ***2002***, 2193. See Sudrik, S.G.; Sharma, J.; Chavan, V.B.; Chaki, N.K.; Sonawane, H.R.; Vijayamohanan, K.P. *Org. Lett.* ***2006****, 8,* 1089.

[221] Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* ***1996****, 37*, 1781.

[222] For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1850–1851.

[223] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 185–195; Ando, W. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***,78, pp. 458–475.

[224] See Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1980****, 21*, 4461.

[225] Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 125–136.

[226] Korobitsyna, I.K.; Rodina, L.L.; Sushko, T.P. *J. Org. Chem. USSR* ***1968****, 4,* 165; Jones, Jr., M.; Ando, W. *J. Am. Chem. Soc.* ***1968****, 90,* 2200. See Lee, Y.R.; Suk, J.Y.; Kim, B.S. *Tetrahedron Lett.* ***1999****, 40*, 8219.

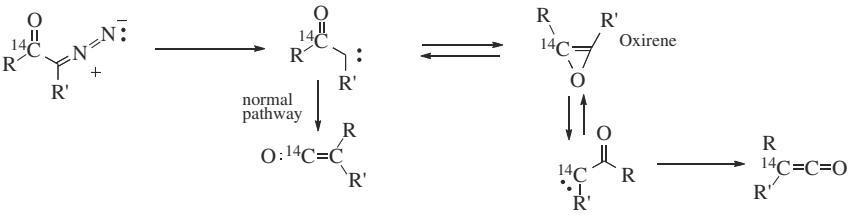
[227] Wiskur, S.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2005****, 127*, 6176.

[228] See Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* ***2001****, 123*, 6069.

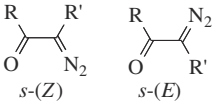
[229] See Farlow, R.A.; Thamatloor, D.A.; Sunoj, R.B.; Hadad, C.M. *J. Org. Chem.* ***2002****, 67*, 3257.

(e.g., $Ph_2C{=}C{=}O$) have been isolated and others have been trapped in other ways (e.g., as β-lactams,[230] reaction **16-96**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the *Curtius rearrangement* (Reaction **18-14**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,[231] it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the *Wolff rearrangement* is carried out photochemically, the mechanism is basically the same,[223] but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene–carbene rearrangement, through an oxirene intermediate.[232] This was shown by ^{14}C labeling experiments, where



diazoketones labeled in the carbonyl group gave rise to ketenes that bore the label at both C=C carbons.[233] In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when R′ = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.[234] The oxirene pathway is not found in the thermal *Wolff rearrangement*. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.[235] In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by UV–visible, IR, and ESR spectra.[236] These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.



The diazo ketone can exist in two conformations, called *s*-(*E*) and *s*-(*Z*). Studies have shown that *Wolff rearrangement* takes place preferentially from the *s*-(*Z*) conformation.[237]

OS **III**, 356; **VI**, 613, 840.

[230] Kirmse, W.; Horner, L. *Chem. Ber.* ***1956****, 89,* 2759. Also see, Horner, L.; Spietschka, E. *Chem. Ber.* ***1956****, 89,* 2765.

[231] See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 476–480. See also, Torres, M.; Ribo, J.; Clement, A.; Strausz, O.P. *Can. J. Chem.* ***1983****, 61*, 996; Tomoika, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull. Chem. Soc. Jpn.* ***1983****, 56,* 758.

[232] See Lewars, Y. *Chem. Rev.* ***1983****, 83,* 519.

[233] Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973****, 95,* 124; Zeller, K. *Chem. Ber.* ***1978****, 112,* 678. See also, Majerski, Z.; Redvanly, C.S. *J. Chem. Soc., Chem. Commun.* ***1972***, 694.

[234] Tanigaki, K.; Ebbesen, T.W. *J. Am. Chem. Soc.* ***1987****, 109,* 5883. See also, Bachmann, C.; N'Guessan, T.Y.; Debû, F.; Monnier, M.; Pourcin, J.; Aycard, J.; Bodot, H. *J. Am. Chem. Soc.* ***1990****, 112*, 7488.

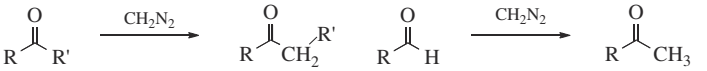
[235] Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973****, 95*, 133.

[236] McMahon, R.J.; Chapman, O.L.; Hayes, R.A.; Hess, T.C.; Krimmer, H. *J. Am. Chem. Soc.* ***1985****, 107*, 7597.

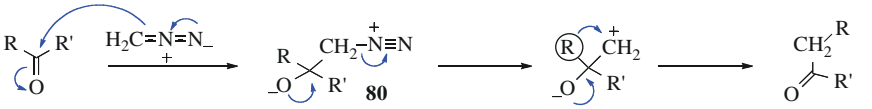
[237] Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* ***1980****, 45,* 5278.

18-9 Homologation of Aldehydes and Ketones

Methylene-insertion



Aldehydes and ketones[238] can be converted to their homologues with diazomethane.[239] Several other reagents[240] are also effective, including Me_3SiI, and then silica gel.[241] With the diazomethane reaction, formation of an epoxide (**16-46**) is a side reaction. Superficially, this reaction appears to be similar to the insertion of carbenes into C—H bonds, (Reaction **12-21**, and IUPAC names it as an insertion), but the mechanism is quite different. However, it is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:



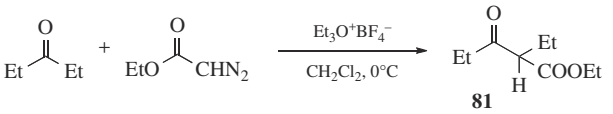
The betaine (**80**) can sometimes be isolated. As shown in Reaction **16-46**, intermediate **80** can also go to the epoxide. The evidence for this mechanism has been summarized in the review by Gutsche.[239] Note that this mechanism is essentially the same as in the apparent "insertions" of oxygen (Reaction **18-19**) and nitrogen (Reaction **18-16**) into ketones.

1,3-Diketones are converted to 1,4-diketones upon treatment with $CF_3CO_2ZnCH_2I$.[242] In a related reaction, alkenes insert into aldehydes in the presence of a Rh catalyst to give the corresponding ketone.[243]

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of a Lewis acid increases the yield of ketone.[244] Cyclic ketones,[245] three membered[246] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[247] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of

[238] See Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* ***1996***, 2353.
[239] See Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.
[240] See Aoyama, T.; Shioiri, T. *Synthesis* ***1988***, 228.
[241] Lemini, C.; Ordoñez, M.; Pérez–Flores, J.; Cruz-Almanza, R. *Synth. Commun.* ***1995***, *25*, 2695.
[242] Xue, S.; Li, L.-Z.; Liu, Y.-K.; Guo, Q.-X. *J. Org. Chem.* ***2006***, *71*, 215.
[243] Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* ***2007***, *129*, 14836.
[244] See Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128, see pp. 137–150.
[245] See Krief, A.; Laboureur, J.L. *Tetrahedron Lett.* ***1987***, *28*, 1545; Krief, A.; Laboureur, J.L.; Dumont, W. *Tetrahedron Lett.* ***1987***, *28*, 1549; Abraham, W.D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* ***1987***, *28*, 2203; Trost, B.M.; Mikhail, G.K. *J. Am. Chem. Soc.* ***1987***, *109*, 4124.
[246] See Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2036.
[247] See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 81–98. For a review pertaining to bridged bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1987***, *43*, 3.

diazomethane, with the expected results.[248] Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[249] to give a β-keto ester, (e.g., **81**).



81

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[250] The reaction can be made regioselective by applying this method to the α-halo ketone, in which case only the other carbon migrates.[251] The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β-unsaturated aldehydes and ketones.[252]

Bicyclic ketones can be expanded to form monocyclic ketones in the presence of certain reagents. Treatment of a bicyclo[4.1.0]hexan-4-one derivative with SmI_2 led to a cyclohexanone.[253] The SmI_2 also converts α-halomethyl cyclic ketones to the next larger ring ketone[254] and cyclic ketones to the next larger ring ketone in the presence of CH_2I_2.[255]

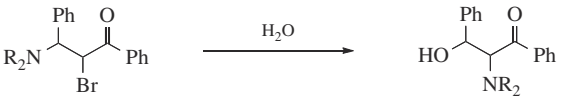
Another homologation reaction converts an aldehyde to its tosyl hydrazone, and subsequent reaction with an aldehyde and NaOEt/EtOH give a ketone.[256] The reaction of an aldehyde with vinyl acetate and $Ba(OH)_2$ gives the homologated conjugated aldehyde.[257]

OS **IV**, 225, 780. For homologation of carboxyl acid derivatives, see OS **IX**, 426

B. Carbon-to-Carbon Migrations of Other Groups

18-10 Migrations of Halogen, Hydroxyl, Amino, and so on

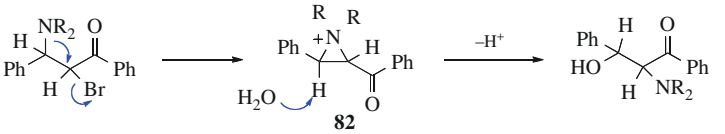
Hydroxy-de-bromo-*cine*-substitution, and so on



When a nucleophilic substitution is carried out on a substrate that has a neighboring group (Sec. 10.C) on the adjacent carbon, a cyclic intermediate can be generated that is opened on the opposite side, resulting in migration of the neighboring group. In the example shown above (NR_2 = morpholino),[258] the reaction took place via an aziridinium salt (**82**) to give an α-amino-β-hydroxy ketone. Sulfonate esters and halides can also

[248] See Loeschorn, C.A.; Nakajima, M.; Anselme, J. *Bull. Soc. Chim. Belg.* ***1981****, 90,* 985.
[249] Mock, W.L.; Hartman, M.E. *J. Org. Chem.* ***1977****, 42,* 459, 466; Baldwin, S.W.; Landmesser, N.G. *Synth. Commun.* ***1978****, 8*, 413.
[250] Liu, H.J.; Majumdar, S.P. *Synth. Commun.* ***1975****, 5,* 125.
[251] Dave, V.; Warnhoff, E.W. *J. Org. Chem.* ***1983****, 48,* 2590.
[252] Doyle, M.P.; Trudell, M.L.; Terpstra, J.W. *J. Org. Chem.* ***1983****, 48,* 5146.
[253] Lee, P.H.; Lee, J. *Tetrahedron Lett.* ***1998****, 39*, 7889.
[254] Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* ***1998****, 39*, 4059.
[255] Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* ***1995****, 36*, 5937.
[256] Angle, S.R.; Neitzel, M.L. *J. Org. Chem.* ***2000****, 65*, 6458.
[257] Mahata, P.K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* ***2000***, 1345.
[258] Southwick, P.L.; Walsh, W.L. *J. Am. Chem. Soc.* ***1955****, 77,* 405. See also, Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* ***2007****, 9,* 4399.

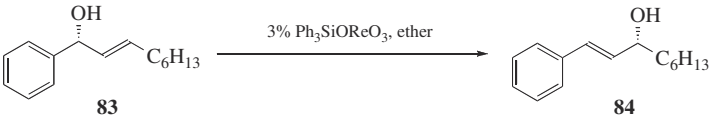
migrate in this reaction.[259]



α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[260] These substrates are prone to rearrange, and often do so upon standing without a catalyst, although an acid catalyst is necessary in some cases. The reaction is essentially the same as the rearrangement of epoxides shown in **18-2**, except that halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups (alkyl, aryl, or hydrogen) to migrate instead, and mixtures are sometimes obtained). In a related reaction, α-bromoaziridines undergo rearrangement to the isomerized α-bromoaziridine in the presence of $MgBr_2$.[261]

In the presence of a Cu catalyst, alkenyl epoxides (vinyl oxiranes) rearrange to a 2,5-dihydrofuran.[262] Alkenyl thiiranes are similarly converted to 2,5-dihydrothiophenes with a Cu catalyst.[263]

Allylic alcohols migrate to give a new allylic alcohol in the presence of a Re catalyst. An example is the conversion of **83** to **84**.[264] Variations using Rh[265] or Ir[266] catalysts are known, and methanesulfonic acid catalyzes the isomerization.[267] In the presence of a Ru catalyst, an allylic alcohol was isomerized to an aliphatic ketone.[268] There is a similar Au catalyzed isomerization of allylic acetates.[269]



83 **84**

The *Meyer–Schuster Rearrangement* is an acid-catalyzed rearrangement of a propargyl alcohol to a conjugated carbonyl compound.[270] Rearrangement was also catalyzed by a cationic Rh–bisphosphane complex.[271] An Au catalyzed rearrangement of ethoxyalkynyl carbinols gave α,β-unsaturated esters.[272] The base-induced isomerization of a propargylic

[259] See Peterson, P.E. *Acc. Chem. Res.* ***1971****, 4,* 407. See also, Brusova, G.P.; Gopius, E.D.; Smolina, T.A.; Reutov, O.A. *Doklad. Chem.* ***1980****, 253,* 334; Kobrina, L.S.; Kovtonyuk, V.N. *Russ. Chem. Rev.* ***1988****, 57*, 62; Warren, S. *Acc. Chem. Res.* ***1978****, 11*, 403. See also, Aggarwal, V.K.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2579.

[260] For a review, see McDonald, R.N. *Mech. Mol. Migr.* ***1971****, 3,* 67.

[261] Karikomi, M.; Takayama, T.; Haga, K.; Hiratani, K. *Tetrahedron Lett.* ***2005****, 46,* 6541.

[262] Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* ***2006****, 128*, 16054.

[263] Rogers, E.; Araki, H.; Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* ***2007****, 129*, 2768.

[264] Morrill, C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2005****, 127,* 2842; Morrill, C.; Beutner, G.L.; Grubbs, R.H. *J. Org. Chem.* ***2006****, 71,* 7813.

[265] Boeda, F.; Mosset, P.; Crévisy, C. *Tetrahedron Lett.* ***2006****, 47*, 5021.

[266] Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. *Pure Appl. Chem.* ***2010****, 82*, 1461.

[267] Leleti, R.R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* ***2007****, 48*, 8505.

[268] Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* ***2005****, 127*, 6172.

[269] Marion, N.; Gealageas, R.; Nolan, S.P. *Org. Lett.* ***2007****, 9*, 2653.

[270] Meyer, K.H.; Schuster, K. Ber. **1922**, 55, 819; Swaminathan, S.; Narayan, K.V. Chem. Rev. **1971**, 71, 429.

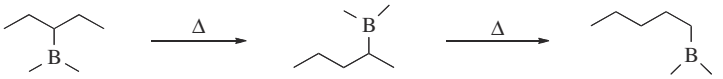
[271] Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* ***2007***, 2687.

[272] Lopez, S.S.; Engel, D.A.; Dudley, G.B. *Synlett* ***2007***, 949.

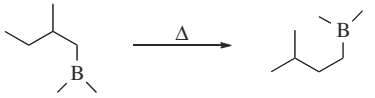
alcohol gave a conjugated ketone,[273] and a combination of Mo—Au led to rapid 1,3-rearrangement of propargyl alcohols.[274] An Au—Ag catalyzed reaction with propargyl esters gave a 2-O-pivaloyl conjugated aldehyde.[275] A similar reaction with a Pt catalyst converted a 1-ethoxy propargylic ester to a 2-carboethoxy conjugated ketone.[276] An Au catalyzed isomerization of allenyl carbinol esters is also known.[277]

18-11 Migration of Boron

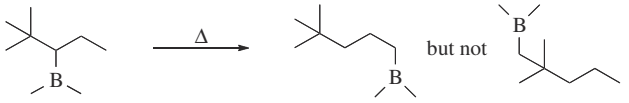
Hydro,dialkylboro-interchange, and so on



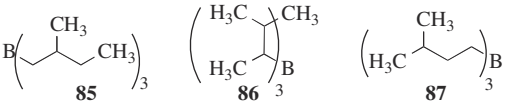
Boranes are prepared by the reaction of BH_3 (B_2H_6) or an alkylborane with an alkene (**15-16**). When a nonterminal borane is heated at temperatures ranging from 100 to 200 °C, the boron moves toward the end of the chain.[278] The reaction is catalyzed by small amounts of borane or other species containing B—H bonds. The boron can move past a branch, for example,



but not past a double branch, for example,



The reaction is an equilibrium: **85**, **86**, and **87** each gave a mixture containing ~40% **85**, 1% **86**, and 59% **87**. The migration can go quite a long distance, including a migration of 11 positions.[279] If the boron is on a cycloalkyl ring, it can move around the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.[280] The reaction is useful for the migration of double bonds in a controlled way (see **12-2**). The mechanism may involve a π complex, at least partially.[281]

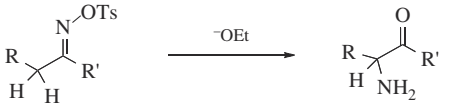


85 **86** **87**

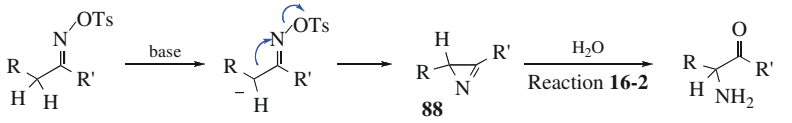
[273] Sonye, J.P.; Koide, K. *J. Org. Chem.* ***2007****, 72,* 1846.
[274] Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* ***2008****, 10*, 1867.
[275] Witham, C.A.; Mauleón, P.; Shapiro, N.D.; Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc.* ***2007****, 129*, 5838.
[276] Barluenga, J.; Riesgo, L.; Vicente, R.; López, L.A.; Tomás, M. *J. Am. Chem. Soc.* ***2007****, 129*, 7772.
[277] Buzas, A.K.; Istrate, F.M.; Gagosz, F. *Org. Lett.* ***2007****, 9*, 985.
[278] Brown, H.C. *Hydroboration*, W. A. Benjamin, NY, ***1962***, pp. 136–149, Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1966****, 88,* 1433. See also, Brown, H.C.; Racherla, U.S. *J. Organomet. Chem.* ***1982****, 241*, C37.
[279] Logan, T.J. *J. Org. Chem.* ***1961****, 26,* 3657.
[280] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1967****, 89,* 561.
[281] See Wood, S.E.; Rickborn, B. *J. Org. Chem.* ***1983****, 48,* 555; Field, L.D.; Gallagher, S.P. *Tetrahedron Lett.* ***1985****, 26*, 6125.

18-12 The Neber Rearrangement

Neber oxime tosylate-amino ketone rearrangement



α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base (e.g., ethoxide or pyridine).[282] This reaction is called the *Neber rearrangement*. The R group is usually aryl, although the reaction has been carried out with R = alkyl or hydrogen. The R′ group may be alkyl or aryl, but not hydrogen. The *Beckmann rearrangement* (Reaction **18-17**) and the abnormal *Beckmann reaction* (elimination to the nitrile, Reaction **17-30**) may be side reactions, although these generally occur in acid media. A similar rearrangement is given by *N,N*-dichloroamines of the type $RCH_2CH(NCl_2)R'$, where the product is also $RCH(NH_2)COR'$.[283] The mechanism of the Neber rearrangement involves an azirine intermediate (**88**).[284] The best evidence for this mechanism is that the azirine intermediate has been isolated.[285,] In contrast to the *Beckmann rearrangement*, this one is sterically indiscriminate:[286] Both a syn and an anti ketoxime give the same product. The mechanism, as shown above, consists of three steps. However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give $RCH_2C(=NCl)R'$, which then behaves analogously.[287] *N*-Chloroimines prepared in other ways also give the reaction.[288] Indoles have been prepared via a *Neber rearrangement*.[289]



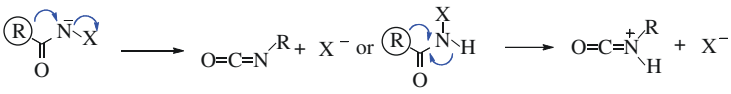
OS **V**, 909; **VII**, 149.

C. Carbon-to-Nitrogen Migrations of R and Ar

The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case, the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (Sec. 18.A.i). Reactions **18-13**–**18-16** are used to prepare amines from acid derivatives. Reactions **18-16** and **18-17** are used to prepare amines from ketones. The mechanisms of Reaction **18-13**–**18-16** (with carboxylic acids) are very similar and follow

[282] For a review, see Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971****, 4,* 197, pp. 289–304.
[283] Baumgarten, H.E.; Petersen, H.E. *J. Am. Chem. Soc.* ***1960****, 82,* 459, and references cited therein.
[284] Cram, D.J.; Hatch, M.J. *J. Am. Chem. Soc.* ***1953****, 75,* 33; Hatch, M.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1953****, 75,* 38.
[285] Neber, P.W.; Burgard, A. *Liebigs Ann. Chem.* ***1932****, 493,* 281; Parcell, R.F. *Chem. Ind. (London)* ***1963***, 1396. Also see Ref. 284.
[286] House, H.O.; Berkowitz, W.F. *J. Org. Chem.* ***1963****, 28,* 2271.
[287] See Nakai, M.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969****, 42,* 2917.
[288] Baumgarten, H.E.; Petersen, J.M.; Wolf, D.C. *J. Org. Chem.* ***1963****, 28,* 2369.
[289] Taber, D.F.; Tian, W. *J. Am. Chem. Soc.* ***2006****, 128*, 1058.

one of two patterns:

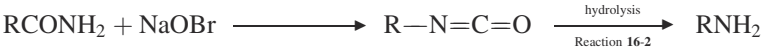


Some of the evidence[290] is (1) configuration is retained in R (Sec. 18.A.ii); (2) the kinetics are first order; (3) intramolecular rearrangement is shown by labeling; and (4) no rearrangement occurs *within* the migrating group, for example, a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases, it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene[291] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.[292] It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

18-13 The Hofmann Rearrangement

Bishydrogen-(2/→1/*N*-alkyl)-*migro*-detachment (formation of isocyanate)



In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give an isocyanate, but this compound is seldom isolated[293] since it is usually hydrolyzed under the reaction conditions. The final isolated product is a primary amine that has one carbon fewer than the starting amide.[294] The R group may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.[295] Another modification uses NBS/NaOMe.[296] Under these conditions, the product of addition to the isocyanate is the carbamate (RNHCOOMe, Reaction **16-8**), which is easily isolated or can be hydrolyzed to the amine.[297] A mixture of NBS and DBU (see Reaction **17-13**) in methanol gives the carbamate,[298] as does electrolysis in methanol.[299]

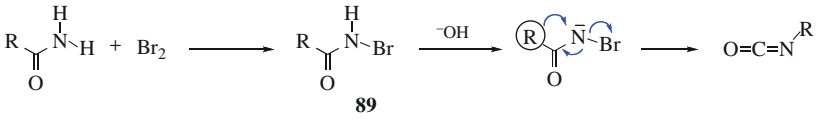
Side reactions when NaOH is the base are formation of ureas (RNHCONHR) and acylureas (RCONHCONHR) by addition, respectively, of RNH_2 and $RCONH_2$ to RNCO (**16-20**). If acylureas are desired, they can be made the main products by using only one-half of the usual quantities of Br_2 and NaOH. Another side product, but only from primary R, is the nitrile derived from oxidation of RNH_2 (Reaction **19-5**).

Imides react to give amino acids, (e.g., phthalimide gives *o*-aminobenzoic acid). α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable

[290] Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, Vol. 1, pp. 258–550.
[291] See Boyer, J.H. *Mech. Mol. Migr.* ***1969****, 2,* 267.
[292] The question is discussed by Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 217–221.
[293] See Sy, A.O.; Raksis, J.W. *Tetrahedron Lett.* ***1980****, 21,* 2223.
[294] See Wallis, E.S.; Lane, J.F. *Org. React.* ***1946****, 3,* 267.
[295] See Radlick, P.; Brown, L.R. *Synthesis* ***1974***, 290.
[296] Huang, X.; Keillor, J.W. *Tetrahedron Lett.* ***1997****, 38*, 313.
[297] See Gogoi, P.; Konwar, D. *Tetrahedron Lett.* ***2007****, 48*, 531.
[298] Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* ***1997****, 62*, 7495.
[299] Matsumura, Y.; Maki, T. ; Satoh, Y. *Tetrahedron Lett.* ***1997****, 38*, 8879.

α-hydroxy- or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

The mechanism follows the pattern outlined in the discussion preceding Reaction **18-13**.



The first step is an example of Reaction **12-52** and intermediate *N*-halo amides (**89**) have been isolated. Compound **89** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen, and in the second step, **89** loses a proton to the base. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.[300] A similar reaction can be effected by the treatment of amides with lead tetraacetate.[301] Among other reagents that convert $RCONH_2$ to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) [$PhI(OCOCF_3)_2$][302] and hydroxy(tosyloxy) iodobenzene [PhI(OH)OTs].[303]

A variation of the *Hofmann rearrangement* treated a β-hydroxy primary amide with $PhI(O_2CCF_3)_3$ in aq acetonitrile, giving an isocyanate via –CON-I, which reacts with the hydroxyl group intramolecularly to give a cyclic carbamate.[304] Note that carbamates are converted to isocyanates by heating with Montmorillonite K-10.[305]

OS **II**, 19, 44, 462; **IV**, 45; **VIII**, 26, 132.

18-14 The Curtius Rearrangement

Dinitrogen-(2/→1/*N*-alkyl)-*migro*-detachment

$$RCON_3 \xrightarrow{\Delta} R{-}N{=}C{=}O$$

The *Curtius rearrangement* involves heating acyl azides to yield isocyanates.[306] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in **18-13**.[307] This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in Reaction **10-43** or by treatment

[300] Imamoto, T.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 1632, 1639, 1644; Imamoto, T.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971****, 44*, 2776.

[301] Baumgarten, H.E.; Smith, H.L.; Staklis, A. *J. Org. Chem.* ***1975****, 40,* 3554.

[302] Loudon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.; Boutin, R.H. *J. Org. Chem.* ***1984****, 49,* 4272; Boutin, R.H.; Loudon, G.M. *J. Org. Chem.* ***1984****, 49*, 4277; Pavlides, V.H.; Chan, E.D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I.G.C. *Synth. Commun.* ***1988****, 18,* 1615.

[303] Vasudevan, A.; Koser, G.F. *J. Org. Chem.* ***1988****, 53,* 5158.

[304] Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* ***2001****, 42*, 1449.

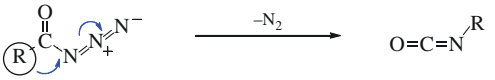
[305] Uriz, P.; Serra, M.; Salagre, P.; Castillon, S.; Claver, C.; Fernandez, E. *Tetrahedron Lett.* ***2002****, 43*, 1673.

[306] See Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 397–405.

[307] See Pfister, J.R.; Wyman, W.E. *Synthesis* ***1983***, 38. See also, Lebel, H.; Leogane, O. *Org. Lett.* ***2005****, 7*, 4107. See also, Ma, B.; Lee, W.-C. *Tetrahedron Lett.* ***2010****, 51*, 385.

of acylhydrazines (hydrazides) with nitrous acid (analogous to Reaction **12-49**). The Curtius rearrangement is catalyzed by Lewis acids or protic acids, but these are usually not necessary for good results.

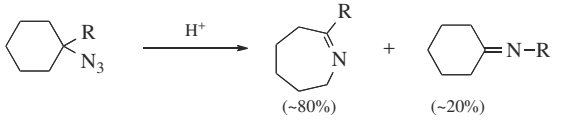
The mechanism is similar to that in Reaction **18-13** to give an isocyanate. Also note the exact analogy between this Reaction and **18-8**. However, in this case, there is no evidence for a free nitrene and it is probable that the conversion is concerted.[308]



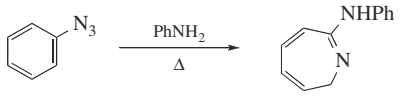
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction[309]:

$$R_3CN_3 \xrightarrow{\Delta} R_2C{=}NR$$

The R groups may be alkyl, aryl, or hydrogen, although if hydrogen migrates, the product is the unstable $R_2C{=}NH$. The mechanism is essentially the same as that of the *Curtius rearrangement*. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.[310] The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, although the acid may hydrolyze the imine (**16-2**). Cycloalkyl azides give ring expansion as shown.[311]



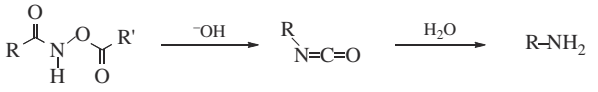
Aryl azides also give ring expansion on heating, for example,[312]



OS **III**, 846; **IV**, 819; **V**, 273; **VI**, 95, 910. Also see, OS **VI**, 210.

18-15 The Lossen Rearrangement

Hydro,acetoxy-(2/→1*N*-alkyl)-*migro*-detachment



[308] See, Smalley, R.K.; Bingham, T.E. *J. Chem. Soc. C* ***1969***, 2481.

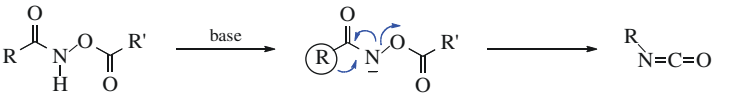
[309] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrnagements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 45–52; in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, the chapters by Lewis, F.D.; Saunders Jr., W.H. pp. 47–97, pp. 47–78 and by Smith, P.A.S. pp. 99–162.

[310] Montgomery, F.C.; Saunders, Jr., W.H. *J. Org. Chem.* ***1976****, 41,* 2368.

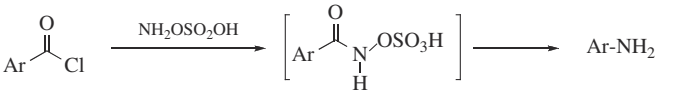
[311] Smith, P.A.S.; Lakritz, J. cited in Smith, P.A.S. in de Mayo, P. *Molecular Rearrangments,* Vol. 1, Wiley, NY, ***1963***, p. 474.

[312] Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* ***1958****, 91,* 1,12.

The *O*-acyl derivatives of hydroxamic acids[313] give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*.[314] The mechanism is similar to that of Reaction **18-13** and **18-14**:

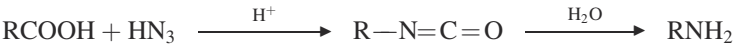


In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-*O*-sulfonic acid.[315]



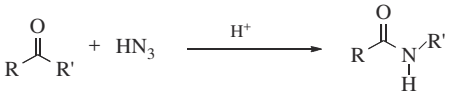
A chiral *Lossen rearrangement* is known.[316]

18-16 The Schmidt Reaction



There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes.[317] The most common is the reaction with carboxylic acids, illustrated above.[318] Sulfuric acid is a common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over Reaction **18-13** and **18-14** in that there is just one laboratory step from the acid to the amine, but conditions are more drastic.[319] Under the acid conditions employed, the isocyanate is virtually never isolated.

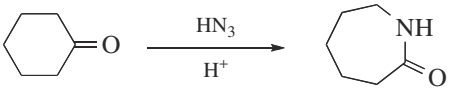
The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, converting a ketone into an amide.[320]



Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for

[313] See Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* ***1974****, 13,* 376.
[314] See Salomon, C.J.; Breuer, E. *J. Org. Chem,* ***1997****, 62*, 3858.
[315] Wallace, R.G.; Barker, J.M.; Wood, M.L. *Synthesis* ***1990***, 1143.
[316] Chandrasekhar, S.; Sridhar, M. *Tetrahedron Asymmetry* ***2000****, 11*, 3467.
[317] See Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 405–434.
[318] See Koldobskii, G.I.; Ostrovskii, V.A.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1978****, 47,* 1084.
[319] See Smith, P.A.S. *Org. React.* ***1946****, 3,* 337, pp. 363–366.
[320] See Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. *Russ. Chem. Rev.* ***1971****, 40*, 835; Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 137–145.

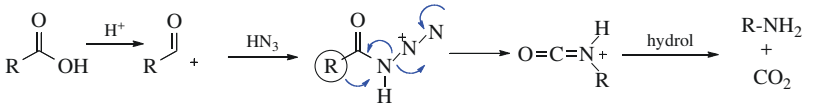
dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols so that these functions may be present in the same molecule without interference. Cyclic ketones give lactams[321]: With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[322]



The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (Reaction **16-16**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **17-30**. A useful variation of the Schmidt reaction treats a cyclic ketone with an alkyl azide (RN_3)[323] in the presence of $TiCl_4$, generating a lactam.[324] An intramolecular *Schmidt reaction* gives bicyclic amines.[325] Another variation treats a silyl enol ether of a cyclic ketone with $TMSN_3$ and photolyzes the product with UV light to give a lactam.[326] An α–azido cyclic ketone rearrangement to lactams under radical conditions (Bu_3SnH/AIBN).[327]

Alcohols and alkenes react with HN_3 to give alkyl azides,[328] which in the course of reaction rearrange in the same way as discussed in Reaction **18-14**.[309] The *Mitsunobu Reaction* (**10-17**) can be used to convert alcohols to alkyl azides, and an alternative reagent for azides [$(PhO)_2PON_3$], for use in the *Mitsunobu* is now available.[329] In the presence of an Au catalyst, an acetylenic azide was converted to a pyrrole derivative.[330] An intramolecular *Schmidt reaction* gives bicyclic lactams in the presence of $MeAlCl_2$.[331]

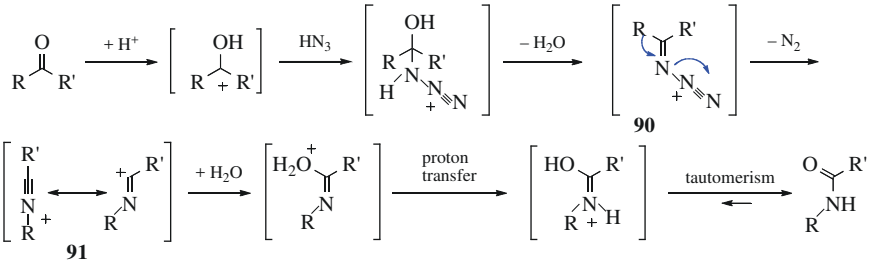
There is evidence that the mechanism with carboxylic acids[320] is similar to that of Reaction **18-14**, except that it is the protonated azide that undergoes the rearrangement[332]:



The first step is the same as that of the $A_{AC}1$ mechanism (Reaction **16-59**, which explains why good results are obtained with hindered substrates. The mechanism with ketones

[321] See Krow, G.R. *Tetrahedron* ***1981***, *37,* 1283.
[322] Exceptions to this statement are found in Bhalerao, U.T.; Thyagarajan, G. *Can. J. Chem.* ***1968***, *46,* 3367; Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* ***1969***, 183.
[323] See Furness, K.; Aubé, J. *Org. Lett.* ***1999***, *1*, 495.
[324] Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B.T.; Katz, C.E.; Reddy, D.S.; Aubé, J. *J. Am. Chem. Soc.* ***2003***, *125*, 7914. See Mossman, C.J.; Aubé, J. *Tetrahedron* , ***1996***, *52*, 3403.
[325] Pearson, W.H.; Hutta, D.A.; Fang, W.-k. *J. Org. Chem.* ***2000***, *65*, 8326. See also, Wrobleski, A.; Aubé, J. *J. Org. Chem.* ***2001***, *66*, 886.
[326] Evans, P.A.; Modi, D.P. *J. Org. Chem.* ***1995***, *60*, 6662.
[327] Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* ***1999***, *64*, 7836.
[328] See Kumar, H.M.S.; Reddy, B.V.S.; Anjaneyulu, S.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 7385. Also see, Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* ***1997***, *38*, 3955.
[329] Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. *J. Org. Chem.* ***1993***, *58*, 5886.
[330] Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* ***2005***, *127*, 11260.
[331] Yao, L.; Aubé, J. *J. Am. Chem. Soc.* ***2007***, *129*, 2766.
[332] This mechanism has been controversial, see Vogler, E.A.; Hayes, J.M. *J. Org. Chem.* ***1979***, *44,* 3682.

involves formation of a nitrilium ion (**82**), which reacts with water.

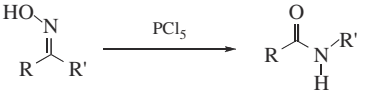


Intermediates (e.g., **90**) have been independently generated in aqueous solution.[333] Note the similarity of this mechanism to those of "insertion" of CH_2 (Reaction **18-9**) and of O (Reaction **18-19**). The three reactions are essentially analogous, both in products and in mechanism.[334,320] Also note the similarity of the latter part of this mechanism to that of the *Beckmann rearrangement* (Reaction **18-17**).

OS **V**, 408; **VI**, 368; **VII**, 254; **X**, 207. See also, OS **V**, 623.

18-17 The Beckmann Rearrangement

Beckmann oxime–amide rearrangement



When oximes are treated with PCl_5 or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.[335] Reagents used include concentrated H_2SO_4 acid, formic acid, liquid SO_2, silica gel,[336] $RuCl_3$,[337] $Y(OTf)_3$,[338] I_2,[339] $HgCl_2$,[340] triphosphazene,[341] bromodimethylsulfonium bromide–$ZnCl_2$,[342] neat with $FeCl_3$,[343] cyanuric acid,[344] and polyphosphoric acid.[345] Simply heating the oxime of benzophenone neat leads to *N*-phenyl benzamide.[346] The reaction has been

[333] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1991****, 113,* 1867.
[334] See Ostrovskii, V.A.; Koshtaleva, T.M.; Shirokova, N.P.; Koldobskii, G.I.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1974****, 10*, 2365 and references cited therein.
[335] Gawley, R.E. *Org. React.* ***1988****, 35*, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 408–439. Also see, Nguyen, M.T.; Raspoet, G.; Vanquickenborne, L.G. *J. Am. Chem. Soc.* ***1997****, 119*, 2552.
[336] Costa, A.; Mestres, R.; Riego, J.M. *Synth. Commun.* ***1982****, 12,* 1003.
[337] De, S.K. *Synth. Commun.* ***2004****, 34*, 3431.
[338] De, S.K. *Org. Prep. Proceed. Int.* ***2004****, 36*, 383.
[339] Ganguly, N.C.; Mondal, P. *Synthesis* ***2010***, 3705.
[340] Ramalingan, C.; Park, Y.-T. *J. Org. Chem.* ***2007****, 72,* 4536.
[341] Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2008****, 73*, 2894.
[342] Yadav, L.D.S.; Patel, R.; Srivastava, V.P. *Synthesis* ***2010***, 1771. See also Yadav, L.D.S.; Garima, Srivastava, V.P. *Tetrahedron Lett.* ***2010****, 51*, 739.
[343] Khodaei, M.M.; Meybodi, F.A.; Rezai, N.; Salehi, P. *Synth. Commun.* ***2001****, 31,* 2047.
[344] Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***2005****, 127*, 11240. In ionic liquids, see Betti, C.; Landini, D.; Maia, A.; Pasi, M. *Synlett* ***2008***, 908.
[345] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 131–137.
[346] Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2001****, 42*, 8123.

done in supercritical water[347] and in ionic liquids.[348] A polymer-bound Beckman rearrangement has been reported.[349] Microwave assisted *Beckmann rearrangements* are known.[350] Note that the reaction of an imine with $BF_3{\cdot}OEt_2$ and *m*-chloroperoxybenzoic acid leads to a formamide.[351]

The oximes of cyclic ketones give ring enlargement and form the lactam,[352] as in the formation of caprolactam (see Reaction **18-16**) from the oxime of cyclohexanone. Solvent-free reactions are known.[353] Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with NH_2OSO_2OH and formic acid (Reaction **16-14** takes place first, then the *Beckmann rearrangement*).[354]

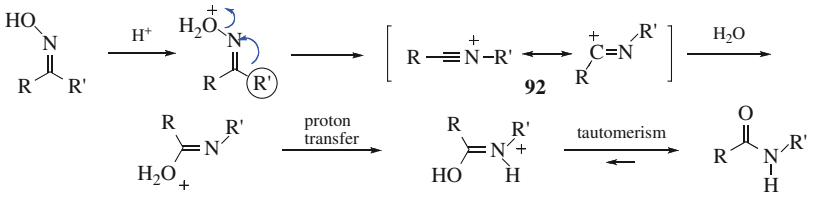
Of the groups attached to the carbon of the C=N unit, the one that migrates in the *Beckman rearrangement* is generally the one anti to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the syn group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the syn group actually undergoes migration. In most cases, the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[355] The scope of the reaction is quite broad and R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom migrates, so the reaction is not generally a means of converting aldoximes to unsubstituted amides ($RCONH_2$). This latter conversion can be accomplished, however, by treatment of the aldoxime with nickel acetate under neutral conditions[356] or by heating the aldoxime for 60 h at 100 °C after it has been adsorbed onto silica gel.[357] As in the case of the *Schmidt rearrangement* (Reaction **18-16**), when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates.[358]

Not only do oximes undergo the *Beckmann rearrangement*, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" *Beckmann rearrangement*, Reaction **17-30**). The *O*-carbonates of imines (e.g., $Ph_2C{=}N{-}OCO_2Et$) react with $BF_3{\cdot}OEt_2$ to give the corresponding amide in this case *N*-phenyl benzamide.[359]

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, for example, proton acids convert it to OH_2^+. After that, the mechanism[360] follows a course analogous to that for the *Schmidt reaction* of ketones (**18-16**) from the

[347] Boero, M.; Ikeshoji, T.; Liew, C.C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* ***2004****, 126*, 6280.
[348] Peng, J.; Deng, Y. *Tetrahedron Lett.* ***2001****, 42,* 403; Ren, R.X.; Zueva, L.D.; Ou, X. *Tetrahedron Lett.* ***2001****, 42*, 8441.
[349] His, S.; Meyer, C.; Cossy, J.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* ***2003****, 44*, 8581.
[350] Thakur, A.J.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2000****, 30*, 2105; On silica with microwave irradiation, see Loupy, A.; Régnier, S. *Tetrahedron Lett.* ***1999****, 40*, 6221.
[351] An, G.-i.; Kim, M.; Kim. J.Y.; Rhee, H. *Tetrahedron Lett.* ***2003****, 44*, 2183.
[352] Vinnik, M.I.; Zarakhani, N.G. *Russ. Chem. Rev.* ***1967****, 36*, 51; Krow, G.R. *Tetrahedron* ***1981****, 37*, 1283.
[353] Sharghi, H.; Hosseini, M. *Synthesis* ***2002***, 1057; Eshghi, H.; Gordi, Z. *Synth. Commun.* ***2003****, 33*, 2971; Moghaddam, F.M.; Rad, A.A.R.; Zali-Boinee, H. *Synth. Commun.* ***2004****, 34*, 2071.
[354] Olah, G.A.; Fung, A.P. *Synthesis* ***1979***, 537. See also, Novoselov, E.F.; Isaev, S.D.; Yurchenko, A.G.; Vodichka, L.; Trshiska, Ya. *J. Org. Chem. USSR* ***1981****, 17*, 2284.
[355] See Lansbury, P.T.; Mancuso, N.R. *Tetrahedron Lett.* ***1965***, 2445.
[356] Field, L.; Hughmark, P.B.; Shumaker, S.H.; Marshall, W.S. *J. Am. Chem. Soc.* ***1961****, 83,* 1983. See also, Leusink, A.J.; Meerbeek, T.G.; Noltes, J.G. *Recl. Trav. Chim. Pays-Bas* ***1976****, 95*, 123; ***1977****, 96,* 142.
[357] Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron* ***1974****, 30,* 2899.
[358] See Arisawa, M.; Yamaguchi, M. *Org. Lett.* ***2001****, 3*, 311.
[359] Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* ***2000****, 41,* 5427.
[360] See Nguyen, M.T.; Vanquickenborne, L.G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1969.

formation of nitrilium ion (**92**) on[361]: Alternative modes of reaction are possible. For example, when PCl_5 is used to induce the reaction, a N-O-PCl_4 species is formed, which generates **92**. Intermediates of the form **92** have been detected by NMR and UV spectroscopy.[362] The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a *Ritter Reaction* (**16-91**).[363] *Beckmann rearrangements* have also been carried out photochemically.[364] A computational study compared converted versus stepwise mechanisms for the *Beckmann rearrangement*, and found that proton relay between the substrate and the solvent molecules controls the reaction, and migration and N—O bond scission occur simultaneously.[365]



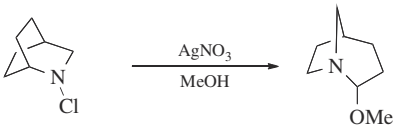
If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,[366] the nitrilium ion intermediate (**92**) is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether (R—N=C—SR), or an imino nitrile (R—N=C—CN).[367] In the last case, the nucleophile comes from added trimethylsilyl cyanide. In the presence of LiI, 2-benzyloxypyridine is converted to *N*-benzyl-2-pyridone.[368]

In a related reaction, treatment of spirocyclic oxaziridines with MnCl(tpp) (tpp = triphenylphosphine, ligand)[369] or photolysis[370] leads to a lactam.

OS **II**, 76, 371; **VIII**, 568.

18-18 Stieglitz and Related Rearrangements

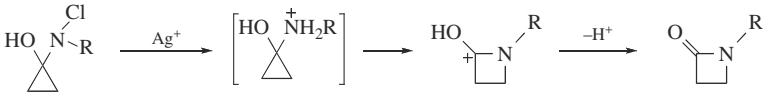
Methoxy-de-*N*-chloro-(2/→1/*N*-alkyl)-*migro*-substitution, and so on



In addition to the reactions discussed at **18-13**–**18-17**, other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic *N*-haloamines (e.g.,

[361] Donaruma, L.G.; Heldt, W.Z. *Org. React.* ***1960****, 11,* 1, pp. 5–14; Smith, P.A.S. in de Mayo, P. *Molecular Rearrangments,* Vol. 1, Wiley, NY, ***1963***, 483–507, pp. 488–493.
[362] Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338.
[363] Palmere, R.M.; Conley, R.T.; Rabinowitz, J.L. *J. Org. Chem.* ***1972****, 37,* 4095.
[364] See, Suginome, H.; Yagihashi, F. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 2488.
[365] Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Org. Chem.* ***2005****, 70,* 10638.
[366] For a review, see Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1985****, 24*, 668.
[367] Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1983****, 105*, 2831; Maruoka, K.; Nakai, S.; Yamamoto, H. *Org. Synth. 66*, 185.
[368] Lanni, E.L.; Bosscher, M.A.; Ooms, B.; Shandro, C.A.; Ellsworth, B.A.; Anderson, C.E. *J. Org. Chem.* ***2008****, 73*, 6425.
[369] Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* ***1994***, 949.
[370] Post, A.J.; Nwaukwa, S.; Morrison, H. *J. Am. Chem. Soc.* ***1994****, 116*, 6439.

N-chloro-2-azabicyclo[2.2.2]octane, above), undergo rearrangement when solvolyzed in the presence of silver nitrate.[371] This reaction is similar to the *Wagner–Meerwein rearrangement* (**18-1**) and is initiated by the silver-catalyzed departure of the chloride ion.[372] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for Reaction **18-3**.[373] An example is the conversion of 1-(*N*-chloroamino)cyclopropanols to β-lactams.[374] Methyl prolinate was converted to the 2-piperidone upon treatment with SmI_2 and pivalic acid–THF.[375]



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl *N*-haloamines and

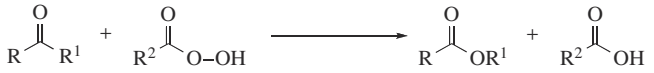


hydroxylamines. These reactions are similar to the rearrangements of alkyl azides (**18-14**), and the name *Stieglitz rearrangement* is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate ($Ar_3CNH_2 \rightarrow Ar_2C{=}NAr$.[376]

D. Carbon-to-Oxygen Migrations of R and Ar

18-19 The Baeyer–Villiger Rearrangement[377]

Oxy-insertion



The treatment of ketones with peroxyacids (e.g., peroxybenzoic or peroxyacetic acid or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by migration of an alkyl group oxygen[378] and the carboxylic acid parent of the peroxyacid as a byproduct. In other words, there is a C → O rearrangement, and the reaction is called the *Baeyer–Villiger rearrangement*.[379] A particularly good reagent is peroxytrifluoroacetic

[371] Gassman, P.G.; Fox, B.L. *J. Am. Chem. Soc.* ***1967****, 89*, 338. See also, Davies, J.W.; Malpass, J.R.; Walker, M.P. *J. Chem. Soc., Chem. Commun.* ***1985***, 686; Hoffman, R.V.; Kumar, A.; Buntain, G.A. *J. Am. Chem. Soc.* ***1985****, 107*, 4731.

[372] See Kovacic, P.; Lowery, M.K.; Roskos, P.D. *Tetrahedron* ***1970****, 26*, 529.

[373] Hoffman, R.V.; Buntain, G.A. *J. Org. Chem.* ***1988****, 53*, 3316.

[374] Wasserman, H.H.; Glazer, E.A.; Hearn, M.J. *Tetrahedron Lett.* ***1973***, 4855.

[375] Honda, T.; Ishikawa, F. *Chem. Commun.* ***1999***, 1065.

[376] Sisti, A.J.; Milstein, S.R. *J. Org. Chem.* ***1974****, 39,* 3932.

[377] For a review, see Renz, M.; Meunier, B. *Eur. J. Org. Chem.* ***1999***, 737. For a review of green procedures, see ten Brink, G.-J.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Rev.* ***2004****, 104*, 4105.

[378] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1665–1667.

[379] Hudlicky, M. *Oxidations in Organic Chemistry,* American Chemical Society, Washington, ***1990***, pp. 186–195; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 254–267; House, H.O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin, NY, ***1972***, pp. 321–329; Lewis, S.N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 237–244. Also see, Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* ***2001****, 66*, 1193.

acid. Reactions with this reagent are rapid and clean, giving high yields of product, although it is often necessary to add a buffer (e.g., Na_2HPO_4), to prevent transesterification of the product with trifluoroacetic acid that is also formed during the reaction. The reaction is often applied to cyclic ketones to give lactones.[380] Hydrogen peroxide has been used to convert cyclic ketones to lactones using a catalytic amount of $MeReO_3$[381] or a diselenide catalyst.[382] Heterogeneous catalysts are used for the *Baeyer–Villiger reaction*.[383] Transition metal catalysts have been used with peroxyacids to facilitate the oxidation.[384] Polymer-supported peroxy acids have been used,[385] and solvent-free *Bayer–Villiger reactions* are known.[386] Potassium peroxomonosulfate supported on acidic silica gel has been used.[387]

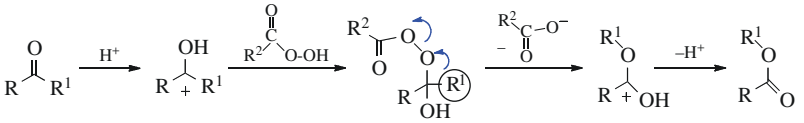
Enantioselective synthesis[388] of chiral lactones from achiral ketones has been achieved by the use of enzymes[389] and other asymmetric reactions are known.[390] Chiral Pd complexes give chiral lactones from cyclic ketones with high enantioselectively.[391] Other chiral catalysts include those based on Al.[392] *Baeyer–Villiger oxidation* of chiral substrates with *m*-chloroperoxybenzoic acid (mcpba) also leads to chiral lactones.[393]

For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[394] with $I_2—H_2O_2$,[395] $BF_3—H_2O_2$,[396] and with $K_2S_2O_8—H_2SO_4$.[397] For unsymmetrical ketones, the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone (R′COMe) to produce an alcohol or phenol (R′OH, by hydrolysis of the ester R′OCOMe). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.[398] There is a preference of *anti*- over *gauche* migration.[399]

[380] See Krow, G.R. *Tetrahedron* ***1981****, 37,* 2697.
[381] Phillips, A.M.F.; Romão, C. *Eur. J. Org. Chem.* ***1999***, 1767. In an ionic liquid, see Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* ***2003****, 44*, 8991.
[382] ten Brink, G.-J.; Vis, J.-M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Org. Chem.* ***2001****, 66,* 2429.
[383] For a review, see Jiménez-Sanchidrián, C.; Ruiz, J.R. *Tetrahedron* ***2008****, 64*, 2011.
[384] Alam, M.M.; Varala, R.; Adapa, S.R. *Synth. Commun.* ***2003****, 33,* 3035.
[385] Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. *Synlett* ***2000***, 1052. See Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2645.
[386] Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* ***2002****, 43*, 6925.
[387] González-Núñez, M.E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* ***2005****, 70*, 10879. In suspercritical CO_2, see González-Núñez, M.E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* ***2006****, 71,* 6432.
[388] See Bolm, C.; Frison, J.-C.; Zhang, Y.; Wulff, W.D. *Synlett* ***2004***, 1619.
[389] See Mihovilovic, M.D.; Müller, B.; Kayser, M.M.; Stewart, J.D.; Stanetty, P. *Synlett* ***2002***, 703. See Clouthier, C.M.; Kayser, M.M.; Reetz, M.T. *J. Org. Chem.* ***2006****, 71,* 8431; Pazmiño, D.E.T.; Snajdrova, R.; Baas, B.-J.; Ghobrial, M.; Mihovilovic, M.D.; Fraaije, M.W. *Angew. Chem. Int. Ed.* ***2008****, 47,* 2275.
[390] See Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***2002****, 43*, 4481; Murhashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* ***2002****, 41*, 2366.
[391] Malkov, A.V.; Friscourt, F.; Bell, M.; Swarbrick, M.E.; Koovský, P. *J. Org. Chem.* ***2008****, 73*, 3996
[392] Frison, J.-C.; Palazzi, C.; Bolm, C. *Tetrahedron* ***2006****, 62,* 6700.
[393] Hunt, KW.; Grieco, P.A. *Org. Lett.* ***2000****, 2*, 1717.
[394] Emmons, W.D.; Lucas, G.B. *J. Am. Chem. Soc.* ***1955****, 77,* 2287.
[395] Gaikwad, D.D.; Dake, S.A.; Kulkarni, R.S.; Jadhav, W.N.; Kakde, S.B.; Pawar, R.P. *Synth. Commun.* ***2007****, 37,* 4093.
[396] McClure, J.D.; Williams, P.H. *J. Org. Chem.* ***1962****, 27*, 24.
[397] Deno, N.C.; Billups, W.E.; Kramer, K.E.; Lastomirsky, R.R. *J. Org. Chem.* ***1970****, 35*, 3080. See Chrobok, A. *Tetrahedron* ***2010****, 66,* 6212.
[398] See Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2661.
[399] Snowden, M.; Bermudez, A.; Kelly, D.R.; Radkiewicz-Poutsma, J.L. *J. Org. Chem.* ***2004****, 69*, 7148.

Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides.[400] With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing Reaction **19-23**. Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H_2O_2 and a selenium compound[401] (see also, the *Dakin Reaction* in **19-11**).

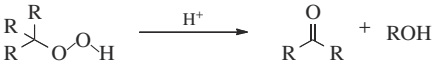
The mechanism[402] is similar to those of the analogous reactions with hydrazoic acid (**18-16** with ketones) and diazomethane (**18-8**):



One important piece of evidence for this mechanism was that benzophenone–^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxyl oxygen.[403] Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,[404] demonstrating that migration of Ar is concerted with departure of $OCOR^2$.[405] It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.

18-20 Rearrangement of Hydroperoxides

C-Alkyl-*O*-hydroxy-elimination



Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[406] The reaction has also been applied to peroxy esters ($R_3COOCOR'$), but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolo ($RCH_2OOH \rightarrow CH_2{=}O + ROH$).

[400] See Cullis, P.M.; Arnold, J.R.P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* ***1987***, 1088.

[401] Syper, L. *Synthesis* ***1989***, 167. See also, Godfrey, I.M.; Sargent, M.V.; Elix, J.A. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1353.

[402] Proposed by Criegee, R. *Liebigs Ann. Chem.* ***1948****, 560,* 127.

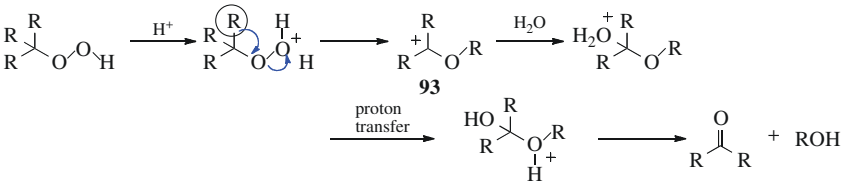
[403] Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* ***1953****, 75,* 5595. Also see Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements* Vol. 1, Wiley, NY, ***1963***, pp. 578–584.

[404] Palmer, B.W.; Fry, A. *J. Am. Chem. Soc.* ***1970****, 92*, 2580. See Mitsuhashi, T.; Miyadera, H.; Simamura, O. *Chem. Commun.* ***1970***, 1301; Winnik, M.A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* ***1974****, 96*, 1977.

[405] Also see Ogata, Y.; Sawaki, Y. *J. Org. Chem.* ***1972****, 37,* 2953.

[406] Yablokov, V.A. *Russ. Chem. Rev.* ***1980****, 49,* 833; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967****, 21*, 429, 445–449.

The mechanism is as follows[407]:



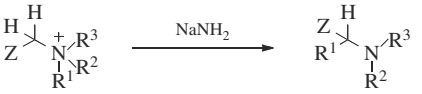
The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbocation intermediates (**93**, R = alkyl) have been isolated in superacid solution[408] at low temperatures, and their structures proved by NMr.[409] The protonated hydroperoxides could not be observed in these solutions, evidently reacting immediately on formation.

OS **V**, 818.

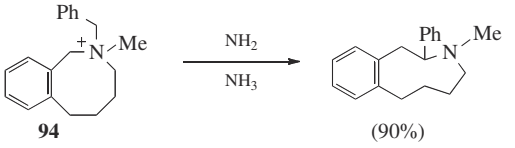
E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

18-21 The Stevens Rearrangement

Hydron-(2/*N*→1/alkyl)-*migro*-detachment

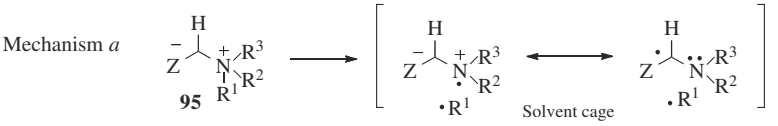


In the *Stevens rearrangement*,[410] a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (e.g., NaOR or $NaNH_2$) to give a rearranged tertiary amine. The Z group may be RCO, ROOC, or phenyl.[411] The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center. Migration of aryl is rare, but has been reported.[412] When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see Reaction **18-35**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,[413] illustrated by the rearrangement of **94**.

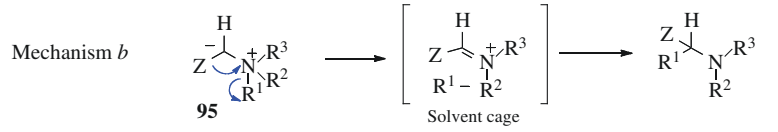


[407] See Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981****, 22,* 3389.
[408] See Olah, G.A.; Parker, D.G.; Yoneda, N. *Angew. Chem. Int. Ed.* ***1978****, 17,* 909.
[409] Sheldon, R.A.; van Doorn, J.A. *Tetrahedron Lett.* ***1973***, 1021.
[410] For syntheses, see Vanecko, J.A.; Wan, H.; West, F.G. *Tetrahedron* ***2006****, 62,* 1043.
[411] Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971****, 3,* 297; Pine, S.H. *Org. React.* ***1970****, 18,* 403; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 81–116; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 448–458; Iwai, I. *Mech. Mol. Migr.* ***1969****, 2,* 73, see pp. 105–113; Stevens, T.S. *Prog. Org. Chem.* ***1968****, 7,* 48.
[412] Heaney, H.; Ward, T.J. *Chem. Commun.* ***1969***, 810; Truce, W.E.; Heuring, D.L. *Chem. Commun.* ***1969***, 1499.
[413] Elmasmodi, A.; Cotelle, P.; Barbry, D.; Hasiak, B.; Couturier, D. *Synthesis* ***1989***, 327.

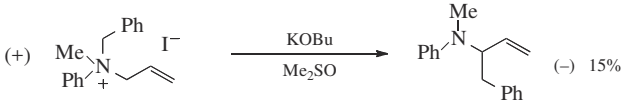
The mechanism has been the subject of much study.[414] The rearrangement is intramolecular, as shown by cross-over experiments, by ^{14}C labeling,[415] and by the fact that retention of configuration is found at R^1.[416] The first step is loss of the acidic proton to give the ylid (**95**), which has been isolated.[417] The finding[418] that CIDNP is observed[419] in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical pair mechanism was proposed[420]:



The radicals do not drift apart because the solvent cage holds them together. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R^1 does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R^1–R^1) have been isolated,[421] which would be expected if some $\bullet R^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.[422] It is possible that another mechanism (*b*), similar to mechanism *a*, but

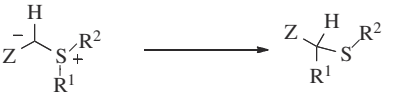


involving ion pairs in a solvent cage instead of radical pairs, operates in some cases. A third possible mechanism would be a concerted 1,2-shift,[423] but the orbital symmetry principle requires that this take place with inversion at R^1.[424] (see Reaction **18-30** and [1,5]-migration). *Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism.* However, in the case where the migrating group is allylic, a concerted mechanism can also operate (Reaction **18-35**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see Sec. 4.C, category 3) gave an optically active product[425]:

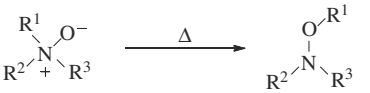


[414] See Heard, G.L.; Yates, B.F. *Aust. J. Chem.* ***1994****, 47*, 1685.
[415] Stevens, T.S. *J. Chem. Soc.* ***1930***, 2107; Johnstone, R.A.W.; Stevens, T.S. *J. Chem. Soc.* ***1955***, 4487.
[416] Brewster, J.H.; Kline, M.W. *J. Am. Chem. Soc.* ***1952****, 74,* 5179; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.
[417] Jemison, R.W.; Mageswaran, S.; Ollis, W.D.; Potter, S.E.; Pretty, A.J.; Sutherland, I.O.; Thebtaranonth, Y. *Chem. Commun.* ***1970***, 1201.
[418] See Lepley, A.R.; Becker, R.H.; Giumanini, A.G. *J. Org. Chem.* ***1971****, 36,* 1222.
[419] For a review of the application of CIDNP to rearrangement reactions, see Lepley, A.R. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 323–384.
[420] Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1009, 1049.
[421] Hennion, G.F.; Shoemaker, M.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1769.
[422] See, for example, Pine, S.H.; Catto, B.A.; Yamagishi, F.G. *J. Org. Chem.* ***1970****, 35,* 3663.
[423] For evidence against this mechanism, see Jenny, E.F.; Druey, J. *Angew. Chem. Int. Ed.* ***1962****, 1,* 155.
[424] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 131.
[425] Hill, R.K.; Chan, T. *J. Am. Chem. Soc.* ***1966****, 88*, 866.

The *Sommelet–Hauser rearrangement* competes when Z is an aryl group (see Reaction **13-31**). *Hofmann elimination* competes when one of the R groups contains a β hydrogen atom (Reaction **17-7** and **17-8**).



Sulfur ylids containing a Z group give an analogous rearrangement (see the reaction), sometimes referred to as a *Stevens rearrangement*.[426] In this case too, there is much evidence (including CIDNP) that a radical-pair cage mechanism is operating,[427] except that when the migrating group is allylic, the mechanism may be different (see Reaction **18-35**).



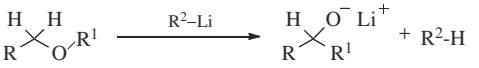
Another reaction with a similar mechanism[428] is the *Meisenheimer rearrangement*,[429] in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines (see reaction).[430] The migrating group R^1 is almost always allylic or benzilic.[431] Both R^2 and R^3 may be alkyl or aryl, but if one of the R groups contains a β hydrogen, *Cope elimination* (Reaction **17-9**) often competes. In a related reaction, when 2-methylpyridine *N*-oxides are treated with trifluoroacetic anhydride, the *Boekelheide reaction* occurs to give 2-hydroxymethylpyridines.[432]

Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the *Wittig rearrangement* (Reaction **18-22**, e.g., $PhCH_2NPh_2 \rightarrow Ph_2CHNHPh$).[433] Only aryl groups migrate in this reaction.

Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles (RNC → RCN).[434] In polar solvents, the mechanism is different.[435]

18-22 The Wittig Rearrangement[436]

Hydron-(2/*O*→1/alkyl)-*migro*-detachment



[426] Olsen, R.K.; Currie, Jr., J.O. in Patai, S. *The Chemistry of The Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 561–566. See Okazaki, Y.; Asai, T.; Ando, F.; Koketsu, J. *Chem. Lett.* ***2006****, 35,* 98.

[427] See Iwamura, H.I.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, T. *Tetrahedron Lett.* ***1971***, 63.

[428] See Ostermann, G.; Schöllkopf, U. *Liebigs Ann. Chem.* ***1970****, 737,* 170; Lorand, J.P.; Grant, R.W.; Samuel, P.A.; O'Connell, E.; Zaro, J. *Tetrahedron Lett.* ***1969***, 4087.

[429] Johnstone, R.A.W. *Mech. Mol. Migr.* ***1969****, 2,* 249. See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2327.

[430] See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *Tetrahedron Asymmetry,* ***1998****, 9*, 1995.

[431] See Khuthier, A.; Al-Mallah, K.Y.; Hanna, S.Y.; Abdulla, N.I. *J. Org. Chem.* ***1987****, 52,* 1710, and references cited therein.

[432] Fontenas, C.; Bejan, E.; Haddon, H.A.; Balavoine, G.G.A. *Synth. Commun.* ***1995****, 25*, 629.

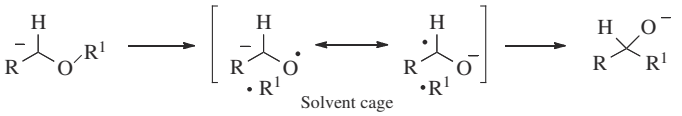
[433] Eisch, J.J.; Kovacs, C.A.; Chobe, P. *J. Org. Chem.* ***1989****, 54,* 1275.

[434] See Pakusch, J.; Rüchardt, C. *Chem. Ber.* ***1991****, 124*, 971 and references cited therein.

[435] Meier, M.; Rüchardt, C. *Chimia* ***1986****, 40,* 238.

[436] See Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* ***2003***, 1088.

The rearrangement of ethers upon treatment with alkyllithium reagents is called the *Wittig rearrangement* (not to be confused with the *Wittig Reaction*, **16-44**) and is similar to **18-21**.[411] However, a stronger base is required (e.g., phenyllithium or sodium amide). The R and R′ groups may be alkyl,[437] aryl, or vinylic.[438] Also, one of the hydrogen atoms may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allylic, benzylic > ethyl > methyl > phenyl.[439] The stereospecificity of the *1,2-Wittig rearrangement* has been discussed.[440] The following radical-pair mechanism[441] (similar to mechanism *a* of Reaction **18-21**) is likely, after removal of the proton by the base. One of the



the radical pair is a ketyl. Evidence for this mechanism includes (1) the rearrangement is largely intramolecular; (2) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities[442] (which rules out an ion-pair mechanism similar to mechanism *b* of Reaction **18-21**); (3) aldehydes are obtained as side products[443]; (4) partial racemization of R′ has been observed[444] (the remainder of the product retained its configuration); (5) cross-over products have been detected[445]; and (6) when ketyl radicals and R• radicals from different precursors were brought together, similar products resulted.[446] However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.[447] Most of the above investigations were carried out with systems where R′ is alkyl, but a radical-pair mechanism has also been suggested for the case where R′ is aryl.[448] When R′ is allylic a concerted mechanism can operate (Reaction **18-35**).

When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde[449]:

$$CH_2{=}CH{-}CH_2{-}OR' \longrightarrow R'CH_2{-}CH{=}CH{-}OLi \longrightarrow R'CH_2CH_2CHO$$

[437] See Bailey, W.F.; England, M.D.; Mealy, M.J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* ***2000****, 2,* 489.
[438] For migration of vinyl, see Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* ***1974****, 96*, 2576. For rearrangment of an α-trimethylsilyl allyl ether see Maleczka, Jr., R.E.; Geng, F. *Org. Lett.* ***1999****, 1*, 1115.
[439] Wittig, G. *Angew. Chem.* ***1954****, 66*, 10; Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Chem. Soc., Chem. Commun.* ***1987****, 23,* 1232.
[440] Maleczka Jr., R.E.; Geng, F. *J. Am. Chem. Soc.* ***1998****, 120*, 8551.
[441] See Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1970****, 9,* 763.
[442] See Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* ***1968***, 2809.
[443] See Cast, J.; Stevens, T.S.; Holmes, J. *J. Chem. Soc.* ***1960***, 3521.
[444] Hebert, E.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* ***1980***, 1035; *Nouv. J. Chim.* ***1981****, 5,* 327.
[445] Lansbury, P.T.; Pattison, V.A. *J. Org. Chem.* ***1962****, 27*, 1933; *J. Am. Chem. Soc.* ***1962****, 84,* 4295.
[446] Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1973****, 95*, 6870.
[447] Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1976****, 98*, 1526. For evidence against this, see Hebert, E.; Welvart, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* ***1983****, 24*, 1381.
[448] Eisch, J.J.; Kovacs, C.A.; Rhee, S. *J. Organomet. Chem.* ***1974****, 65,* 289.
[449] Schlosser, M.; Strunk, S. *Tetrahedron* ***1989****, 45,* 2649.

An *aza-Wittig rearrangement* is also known.[450] Other [2,3]-rearrangements are discussed in Reaction **18-35.**

There are no OS references, but see OS **VIII**, 501, for a related reaction.

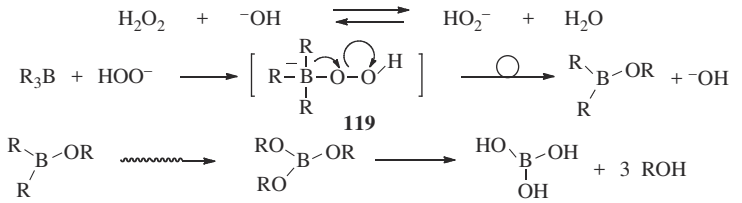
F. Boron-to-Carbon Migrations[451]

For another reaction involving boron-to-carbon migration, see **10-73**.

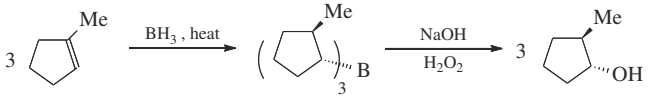
18-23 Conversion of Boranes to Alcohols

$$R_3B \xrightarrow[NaOH]{H_2O_2} R\text{-}OH + B(OH)_3$$

Oxidation of trialkylboranes (see Reaction **15-16**) uses NaOH and H_2O_2, which react to give the hydroperoxide anion, (HOO^-). Reaction of the organoborane with basic H_2O_2 (via HOO^-) leads to an ate-complex, and subsequent B → O rearrangement of an alkyl group on boron to a peroxy oxygen, with expulsion of hydroxide, leads to a borate, and then an alcohol after hydrolysis. The proposed mechanism[452] is shown in which a trialkylborane is converted to 3 molar equivalents of the alcohol, along with boric acid.



Using the hydroboration reaction in **15-16**, this procedure converts alkenes to an *anti-Markovnikov* borane, and oxidation leads to the *anti-Markovnikov alcohol*. An example is the conversion of methylcyclopentene to *trans*-2-methylcyclopentanol.[453] Formation of the organoborane proceeds via a cis-addition of B—H, placing the boron trans to the methyl group, and stereoselective oxidation and B → O rearrangement leads to retention of configuration in the alcohol, as shown.



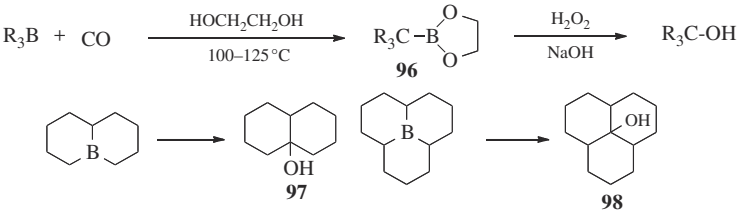
[450] Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. *J. Chem. Soc., Chem. Commun.* ***1995***, 1835; Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* ***1994,*** *116*, 9781.

[451] Matteson, D.S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1984***, pp. 307–409, pp. 346–387; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 256–301; Negishi, E.; Idacavage, M.J. *Org. React.* ***1985,*** *33,* 1; Suzuki, A. *Top. Curr. Chem.* ***1983,*** *112,* 67; Pelter, A. *Chem. Soc. Rev.* ***1982,*** *11*, 191; Cragg, G.M.L.; Koch, K.R. *Chem. Soc. Rev.* ***1977,*** *6,* 393; Weill-Raynal, J. *Synthesis* ***1976***, 633; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 249–300; Paetzold, P.I.; Grundke, H. *Synthesis* ***1973***, 635.

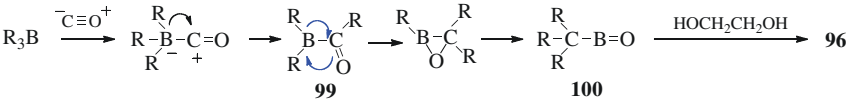
[452] Brown, H.C. *Hydroboration*, W.A. Benjamin, New York, ***1962***. See Kuivila, H.G. *J. Am. Chem. Soc.* ***1954,*** *76,* 870; ***1955,*** *77,* 4014; Kuivila, H.G.; Wiles, R.A. *J. Am. Chem. Soc.* ***1955,*** *77,* 4830; Kuivila, H.G.; Armour, A.G. *J. Am. Chem. Soc.* ***1957,*** *79,* 5659; Wechter, W.J. *Chem. & Ind. (London)* ***1959***, 294.

[453] Zweifel, G.; Brown, H.C. *Org. React.* ***1964,*** *13,* 1.

Trialkylboranes can be prepared from alkenes by Reaction **15-16**, and they react with carbon monoxide[454] at 100–125 °C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes (**96**), which are easily oxidized (Reaction **12-27**) to tertiary alcohols.[455] The R groups may be primary, secondary, or tertiary, and may be the same or different.[456] Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols (e.g., tricyclohexylcarbinol, **97** and tri-2-norbornylcarbinol, **98**), which are difficult to prepare by Reaction **16-24**. Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.[457] The preparation of such heterocyclic boranes was discussed at Reaction **15-16**. The overall conversion of a diene or triene to a cyclic alcohol has been described by H.C. Brown as "stitching" with boron and "riveting" with carbon.



The mechanism has been shown to be intramolecular by the failure to find cross-over products when mixtures of boranes are used.[458] The following scheme, involving three boron-to-carbon migrations, to **99** and then to **100** has been suggested.



The purpose of the ethylene glycol is to intercept the boronic anhydride (**100**), which otherwise forms polymers that are difficult to oxidize. As will be seen in Reaction **18-23** and **18-24**, it is possible to stop the reaction after only one or two migrations have taken place.

$$\text{Method 1} \quad R_3B + CHCl_2OMe \xrightarrow[\text{2. } H_2O_2-NaOH]{\text{1. } LiOCEt_3-THF} R_3COH$$

$$\text{Method 2} \quad R_3B + {}^-CN \xrightarrow{THF} \underset{\mathbf{101}}{R_3B{-}CN} \xrightarrow[\text{2. } NaOH-H_2O_2]{\text{1. excess } (CF_3CO)_2O} R_3COH$$

There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (1) treatment with α,α-dichloromethyl methyl ether and the base lithium triethylcarboxide[459] (2) treatment with a suspension of sodium cyanide in THF

[454] See Negishi, E. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 81; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 343–371; *Acc. Chem. Res.* ***1969***, *2*, 65.
[455] See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.
[456] Negishi, E.; Brown, H.C. *Synthesis* ***1972***, 197.
[457] Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520, and references cited therein.
[458] Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4528.
[459] Brown, H.C.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 2422; Brown, H.C.; Katz, J.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 3968.

followed by reaction of the resulting trialkylcyanoborate (**101**) with an excess (>2 equiv) of trifluoroacetic anhydride.[460] All the above migrations take place with retention of configuration at the migrating carbon.[461]

Several other methods for the conversion of boranes to tertiary alcohols are also known.[462]

If the reaction between trialkylboranes and carbon monoxide (**18-23**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.[463] Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,[464] although if they are in the α or β position relative to the boron atom, difficulties

$$\underset{\textbf{101}}{R_3B^{-}\!-\!CN} \xrightarrow[2.\ H_2O_2\text{-}OH^-]{1.\ (CF_3CO)_2O} RCOR$$

may be encountered. The use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[465] By this procedure thexylboranes ($RR'R^2B$, where R^2 = thexyl) can be converted to unsymmetrical ketones (RCOR′).[466] Variations of this methodology have been used to prepare optically active alcohols.[467] For another conversion of trialkylboranes to ketones see Reaction **18-26**.[468]

OS **VII**, 427. Also see, OS **VI**, 137.

18-24 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids

$$R_3B + CO \xrightarrow[2.\ H_2O_2-OH]{1.\ LiBH_4} RCH_2OH$$

$$R_3B + CO \xrightarrow[2.\ H_2O_2-NaH_2PO_4-Na_2PHO_4]{1.\ LiAlH(OMe)_3} RCHO$$

When the reaction between a trialkylborane and carbon monoxide (**18-23**) is carried out in the presence of a reducing agent (e.g., lithium borohydride or potassium triisopropoxyborohydride), the reduction agent intercepts the intermediate (**99**), so that only one boron→carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[469] This procedure wastes two of the three R groups, but this problem can be avoided by the use of B-alkyl-9-BBN derivatives (see Reaction **15-16**).

[460] Pelter, A.; Hutchings, M.G.; Smith, K.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 145, and references cited therein.

[461] See, however, Pelter, A.; Maddocks, P.J.; Smith, K. *J. Chem. Soc., Chem. Commun.* ***1978***, 805.

[462] See Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985****, 285,* 65; Junchai, B.; Hongxun, D. *J. Chem. Soc., Chem. Commun.* ***1990***, 323.

[463] Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967****, 89,* 2738.

[464] Brown, H.C.; Kabalka, G.W.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967****, 89*, 4530.

[465] Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 129; See also, Mallison, P.R.; White, D.N.J.; Pelter, A.; Rowe, K.; Smith, K. *J. Chem. Res. (S),* ***1978***, 234. See also, Ref. 460.

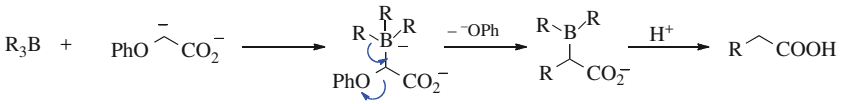
[466] See Brown, H.C.; Bakshi, R.K.; Singaram, B. *J. Am. Chem. Soc.* ***1988****, 110,* 1529.

[467] See Matteson, D.S. *Mol. Struct. Energ.* ***1988****, 5,* 343; *Acc. Chem. Res.* ***1988****, 21*, 294; *Synthesis* ***1986***, 973, pp. 980–983.

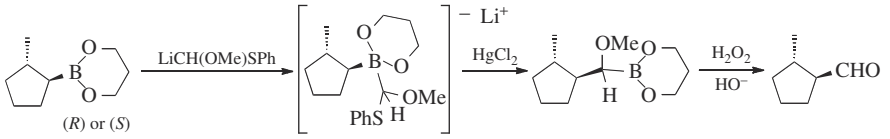
[468] See Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985****, 285*, 65; Brown. H.C.; Bhat, N.G.; Basavaiah, D. *Synthesis* ***1983***, 885; Narayana, C.; Periasamy, M. *Tetrahedron Lett.* ***1985***, *26*, 6361.

[469] Brown, H.C.; Hubbard, J.L.; Smith, K. *Synthesis* ***1979***, 701, and references cited therein. See Hubbard, J.L.; Smith, K. *J. Organomet. Chem.* ***1984****, 276,* C41.

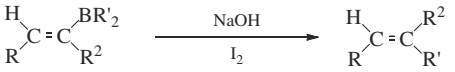
Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[470] When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*tert*-butoxyaluminum hydride,[471] other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.[472] Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.[473]



Boronic esters [$RB(OR')_2$] react with methoxy(phenylthio)methyllithium [LiCH(OMe)SPh] to give salts, which, after treatment with $HgCl_2$, and then H_2O_2, yield aldehydes.[474] This synthesis has been made enantioselective, with high ee values (>99%), by the use of an optically pure boronic ester,[475] for example:

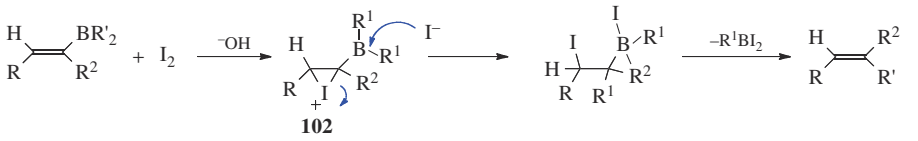


18-25 Conversion of Vinylic Boranes to Alkenes

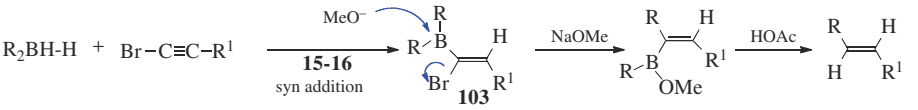


The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at **12-31**. When the substrate contains a vinylic group, the reaction takes a different course,[476] with one of the R′ groups migrating to the carbon, to give alkenes.[477] The reaction is stereospecific in two senses: (1) if the groups R and R″ are cis in the starting compound, they will be trans in the product; (2) there is retention of configuration within the migrating group R′.[478] Since vinylic boranes can be prepared from alkynes (Reaction **15-16**), this is a method for the addition of R′ and H to a triple bond. If $R^2 = H$, the product is a (*Z*)-alkene. The mechanism is believed to involve an iodonium intermediate, (e.g., **102**) and attack by iodide on boron. When R′ is vinylic, the product is a conjugated diene.[479]

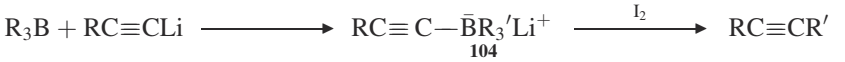
[470] Brown, H.C.; Knights, E.F.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969****, 91*, 2144.
[471] Brown, H.C.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969****, 91,* 4606.
[472] See Negishi, E.; Yoshida, T.; Silveira, Jr., A.; Chiou, B.L. *J. Org. Chem.* ***1975****, 40,* 814.
[473] Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R.S. *J. Org. Chem.* ***1990****, 55*, 6356. See also, Brown, H.C.; Imai, T. *J. Org. Chem.* ***1984****, 49*, 892.
[474] Brown, H.C.; Imai, T. *J. Am. Chem. Soc.* ***1983****, 105,* 6285. For a related method that produces primary alcohols, see Brown, H.C.; Imai, T.; Perumal, P.T.; Singaram, B. *J. Org. Chem.* ***1985****, 50,* 4032.
[475] Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* ***1985****, 107,* 4980.
[476] Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *J. Org. Chem.* ***1988****, 53,* 239.
[477] For a list of methods of preparing alkenes using boron reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley–VCH, NY, ***1999***, pp. 421–427.
[478] Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. *J. Am. Chem. Soc.* ***1971****, 93,* 6309.
[479] Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1986****, 27,* 977.



In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halo vinylic borane (**103**).[480] Treatment of **103** with NaOMe gives the rearrangement shown, and protonolysis of the product produces the (*E*)-alkene.[478] If R is a vinylic group, the product is a 1,3-diene.[481] If one of the groups is thexyl, the other migrates.[482] A combination of both of the procedures described above results in the preparation of trisubstituted alkenes.[483]

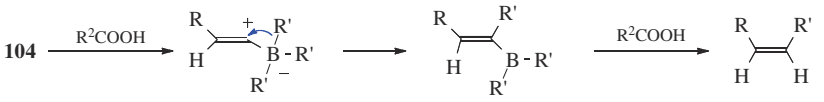


18-26 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides

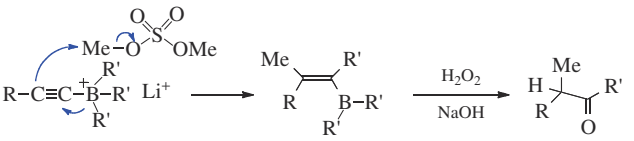


A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate (**104**) with iodine.[484] The R′ group may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older Reaction **10-74**.[485] The R group may be alkyl, aryl, or hydrogen, although in the last-mentioned case satisfactory yields are obtained only if lithium acetylide-ethylenediamine is used as the starting compound.[486] Optically active alkynes can be prepared by using optically active thexylborinates (RR^2BOR', R^2 = thexyl, where R is chiral) and $LiC{\equiv}CSiMe_3$.[487] The reaction can be adapted to the preparation of alkenes[488] by treatment of **104** with an electrophile (e.g., propanoic acid[489] or tributyltin chloride).[490] The reaction with Bu_3SnCl produces the (*Z*)-alkene stereoselectively.

[480] For improvements in this method, see Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Lee, H.D.; Negishi, E.; Katz, J. *J. Org. Chem.* ***1986****, 51,* 5270.
[481] Negishi, E.; Yoshida, T. *J. Chem. Soc. Chem.Commun.* ***1973***, 606; See also, Negishi, E.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R.H. *Tetrahedron* ***1991***, *47*, 343.
[482] Corey, E.J.; Ravindranathan, T. *J. Am. Chem. Soc.* ***1972****, 94,* 4013; Negishi, E.; Katz, J.; Brown, H.C. *Synthesis* ***1972***, 555.
[483] Zweifel, G.; Fisher, R.P. *Synthesis* ***1972***, 557.
[484] Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H.C.; Sinclair, J.A.; Midland, M.M. *J. Org. Chem.* ***1986****, 51,* 4507; Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. *J. Org. Chem.* ***1986****, 51*, 4521. For a review of reactions of organoborates, see Suzuki, A. *Acc. Chem. Res.* ***1982****, 15,* 178.
[485] For a study of the relative migratory aptitudes of R', see Slayden, S.W. *J. Org. Chem.* ***1981****, 46,* 2311.
[486] Midland, M.M.; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1974****, 39*, 731.
[487] Brown, H.C.; Mahindroo, V.K.; Bhat, N.G.; Singaram, B. *J. Org. Chem.* ***1991****, 56,* 1500.
[488] See Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley–VCH, NY, ***1999***, pp. 218–222.
[489] Pelter, A.; Gould, K.J.; Harrison, C.R. *Tetrahedron Lett.* ***1975***, 3327.
[490] Wang, K.K.; Chu, K. *J. Org. Chem.* ***1984****, 49,* 5175.



Treatment of **104** with electrophiles (e.g., methyl sulfate, allyl bromide, or triethyloxonium borofluoride), followed by oxidation of the resulting vinylic borane, gives a ketone (illustrated for methyl sulfate)[491]:



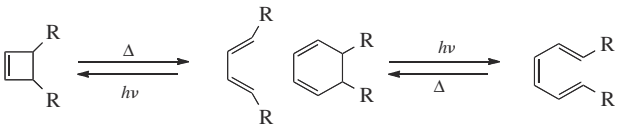
Note that there are reactions that involve N → O rearrangements, including those mediated by silicon.[492]

18.F.ii. Non-1,2 Rearrangements

A. Electrocyclic Rearrangements

18-27 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

(4) *seco*-1/4/Detachment; (4) *cyclo*-1/4/Attachment
(6) *seco*-1,6/Detachment; (6) *cyclo*-1/6/Attachment

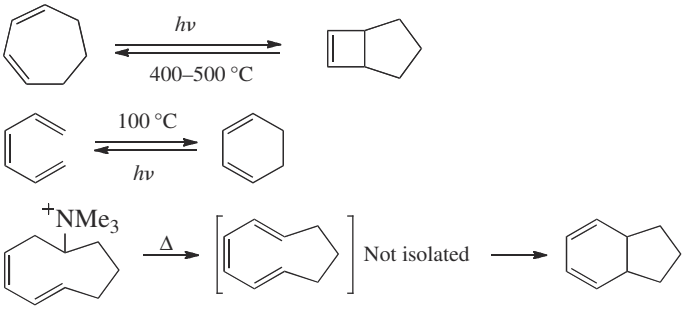


Cyclobutenes and 1,3-dienes can be interconverted by treatment with UV light or with heat.[493] These are 4π-electrocyclizations. The thermal reaction is generally not reversible (although exceptions[494] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200 °C.[495] Benzocyclobutenes also undergo electrocyclic ring opening,[496] as do benzocyclobutanones.[497] The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.[498] In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, but exceptions are known in both

[491] Pelter, A.; Drake, R.A. *Tetrahedron Lett.* ***1988****, 29,* 4181.
[492] Talami, S.; Stirling, C.J.M. *Can. J. Chem.* ***1999****, 77*, 1105.
[493] See Dolbier, Jr., W.R.; Koroniak, H.; Houk, K.N.; Sheu, C. *Acc. Chem. Res.* ***1996****, 29*, 471; Niwayama, S.; Kallel, E.A.; Spellmeyer, D.C.; Sheu, C.; Houk, K.N. *J. Org. Chem.* ***1996****, 61*, 2813. The effect of pressure on this reaction has been discussed, see Jenner, G. *Tetrahedron* ***1998****, 54*, 2771.
[494] See Steiner, R.P.; Michl, J. *J. Am. Chem. Soc.* ***1978****, 100,* 6413 and references cited therein.
[495] See Um, J.M.; Xu, H.; Houk, K.N.; Tang, W. *J. Am. Chem. Soc.* ***2009****, 131,* 6664.
[496] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* ***2006****, 128,* 412.
[497] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* ***2006****, 128,* 13072.
[498] See Dauben, W.G.; Haubrich, J.E. *J. Org. Chem.* ***1988***, *53*, 600.

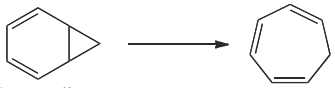
directions.[499] Substituent effects can lead to acceleration of the electrocyclization process.[500] *Torquoselectivity* in cyclobutene ring-opening reaction has been examined.[501]

Examples of these types of reactions include:



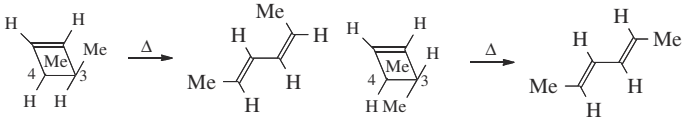
Ref. 502

An interesting example of 1,3-cyclohexadiene→1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.[503] This is a 6π-electrocyclization, and it has been catalyzed by Lewis acids.[504] Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see Reaction **18-32**) that they cannot generally be isolated, though some exceptions are known[505] (see also, **15-64**).



Norcaradiene

These reactions, called *electrocyclic rearrangements*,[506] take place by pericyclic mechanisms. The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis*,*trans*-2,4-hexadiene, while the trans isomer gave only the *trans*–*trans*-diene[507]:



[499] See Dauben, W.G.; McInnis, E.L.; Michno, D.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 91–129. For an *ab initio* study see Rodríguez-Otero, J. *J. Org. Chem.* ***1999***, *64*, 6842.

[500] Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* ***2001***, *66*, 3099. See Beaudry, C.M.; Malerich, J.P.; Trauner, D. *Chem. Rev.* ***2005***, *105*, 4757.

[501] Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 7246.

[502] Chapman, O.L.; Pasto, D.J.; Borden, G.W.; Griswold, A.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1220.

[503] See Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237.

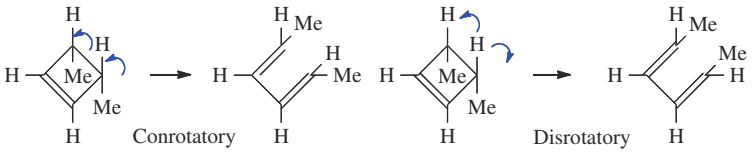
[504] Bishop, L.M.; Barbarow, J.E.; Bergman, R.G.; Trauner, D. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8100.

[505] See Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

[506] See Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***; Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, ***1980***; Laarhoven, W.H. *Org. Photochem.* ***1987***, *9*, 129; George, M. V.; Mitra, A.; Sukumaran, K.B. *Angew. Chem. Int. Ed.* ***1980***, *19*, 973; Jutz, J.C. *Top. Curr. Chem.* ***1978***, *73*, 125; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, ***1972***, pp. 48–72; Criegee, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 559. See Schultz, A.G.; Motyka, L. *Org. Photochem.* ***1983***, *6*, 1.

[507] Winter, R.E.K. *Tetrahedron Lett.* ***1965***, 1207; Criegee, R.; Noll, K. *Liebigs Ann. Chem.* ***1959***, *627*, 1.

This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3–C-4 bond.[508] It is called conrotatory because both movements are clockwise (or both counterclockwise). Because both rotate in the same direction, the cis isomer gives the *cis–trans*-diene.[509] The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the cis isomer would have given the *cis–cis*-diene (shown) or the *trans–trans*-diene. If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse



reaction is also conrotatory. In contrast, the photochemical cyclobutene: 1,3-diene interconversion is *disrotatory* in either direction.[510] On the other hand, the cyclohexadiene: 1,3,5-triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Section **15-60**, the FOM.[511] As in the case of cycloaddition reactions, we will use the FOM and *Möbius–Hückel* approaches.[512]

The Frontier Orbital Method (FOM)[513]

As applied to these reactions, the FOM may be expressed: *A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product*. In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the χ_2 orbital (Fig. 18.1). Therefore, in a thermal process, the cyclobutene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Fig. 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Fig. 18.1), and in order for the *p* orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

This reaction may be considered from the opposite direction (ring closing). For this direction, the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion

[508] Baldwin, J.E.; Gallagher, S.S.; Leber, P.A.; Raghavan, A.S.; Shukla, R. *J. Org. Chem.* ***2004****, 69,* 7212.
[509] See Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965****, 87,* 395.
[510] See Leigh, W.J.; Zheng, K. *J. Am. Chem. Soc.* ***1991****, 113,* 4019; Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H.; Ma, J. *J. Am. Chem. Soc.* ***1991****, 113,* 4993, and references cited therein.
[511] Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965****, 87*, 395. Also see, Longuet-Higgins, H.C.; Abrahamson, E.W. *J. Am. Chem. Soc.* ***1965****, 87,* 2045; Fukui, K. *Tetrahedron Lett.* ***1965***, 2009.
[512] See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–359; Yates, K. *Hückel Molecular Orbital Theory,* Academic Press, NY, ***1978***, pp. 250–263. Also see, Zimmerman, H.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971****, 4,* 272; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971****, 10*, 761; Jefford, C. W.; Burger, U. *Chimia* ***1971****, 25,* 297; Herndon, W.C. *J. Chem. Educ.* ***1981****, 58,* 371.
[513] Fukui, K. *Fortschr. Acc. Chem. Res.* ***1971***, *4,* 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645; Fleming, I. *Pericyclic Reactions*, Oxford Univ. Press, Oxford, ***1999***; Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 181–271.

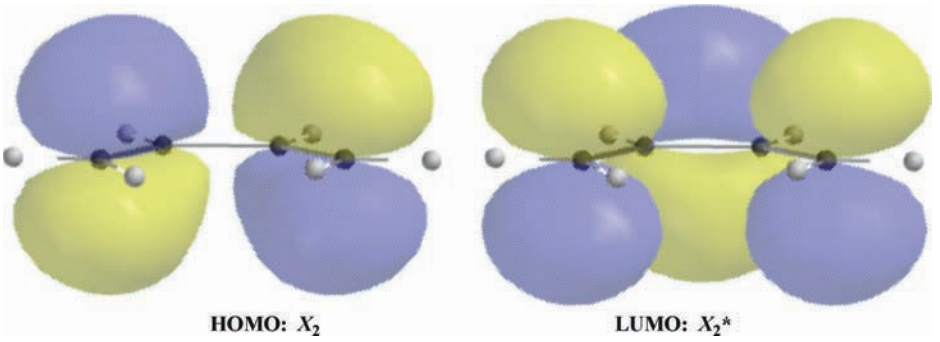


FIG. 18.1. Symmetries of the X_2 and X_3^* orbitals of a conjugated diene

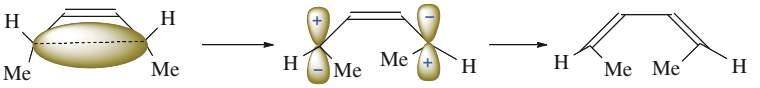


FIG. 18.2. Thermal opening of 1,2-diethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting *p*-orbitals have the symmetry of the HOMO of the diene.

(Fig. 18.3). In the photochemical process, the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius–Hückel Method

As seen in Reaction **15-60**, the *Möbius–Hückel Method*, a basis set of *p* orbitals is chosen and inspected for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Fig. 18.4*a*) results in overlap of plus lobes only, while in conrotatory closing (Fig. 18.4*b*) there is one overlap of a plus with a minus lobe. In the first case, there are zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a *Hückel system,* and so is allowed thermally only if the total number of electrons is $4n + 2$ (Sec. **15-60**, the *Möbius–Hückel Method*). Since the total here is 4, the disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a *Möbius*

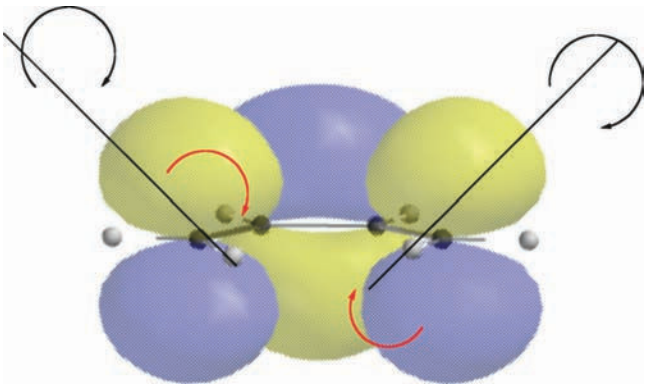


FIG. 18.3. Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

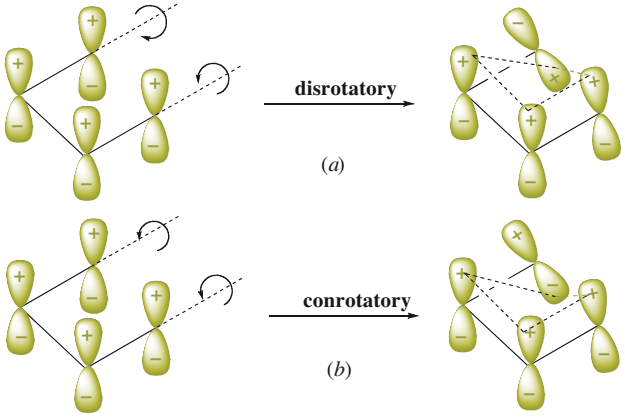
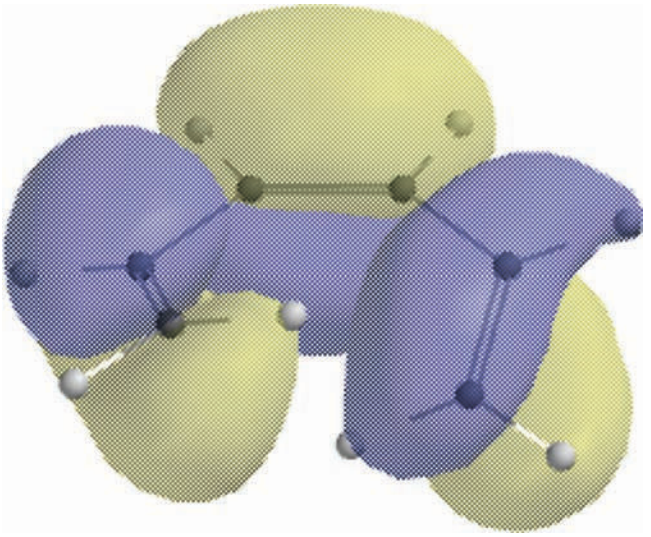


FIG. 18.4. The 1,3-diene–cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversion. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversion, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

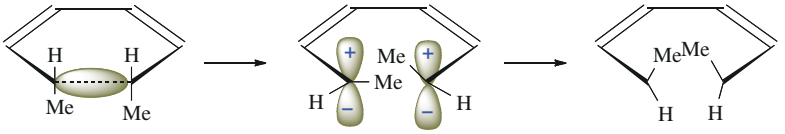
system, which is thermally allowed if the total number is 4*n*. The conrotatory process is therefore allowed thermally. For the photochemical reactions, the rules are reversed: A reaction with 4*n* electrons requires a *Hückel* system, so only the disrotatory process is allowed.

Both the FOM and the *Möbius–Hückel* methods can also be applied to the cyclohexadiene: 1,3,5-triene reaction[514]; in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for 1,3,5-hexatriene, the symmetry of the HOMO is

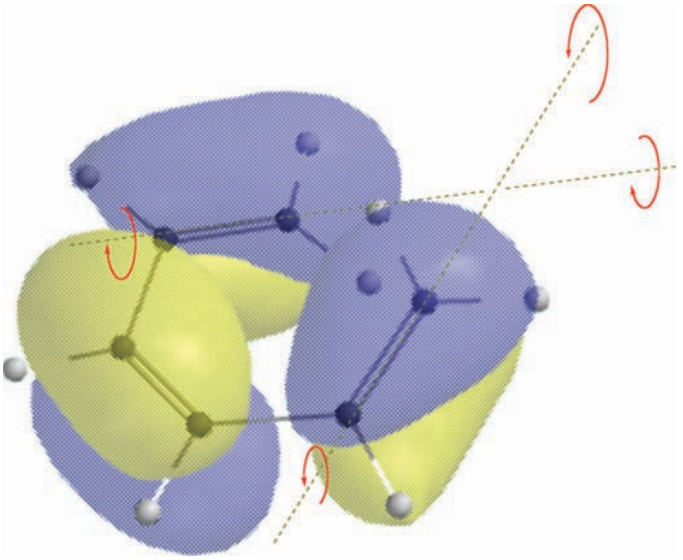


[514] For a discussion of the transition structures and energy, see Zora, M. *J. Org. Chem.* ***2004****, 69*, 1940.

In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



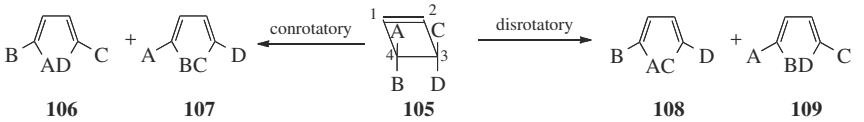
Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals that overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the *Möbius–Hückel* approach, diagrams similar to Fig. 18.4 can be drawn for this case. Here too, the disrotatory pathway is a *Hückel* system and the conrotatory pathway a *Möbius* system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction the *Möbius* pathway.

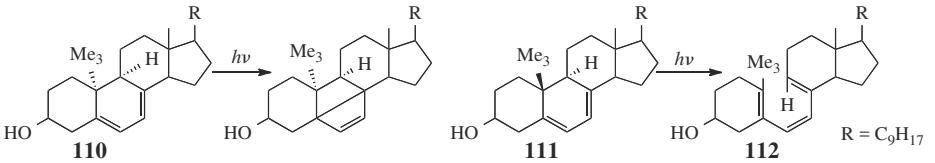
In the most general case, four possible products can arise from a given cyclobutene or cyclohexadiene: two from the conrotatory and two from the disrotatory pathway. For example, conrotatory ring opening of **105** gives either **106** or **107**, while disrotatory opening gives either **108** or **109**. The orbital-symmetry rules indicate when a given reaction will operate by the conrotatory and when by the disrotatory mode, but not which of the two possible conrotatory or disrotatory pathways will be followed. Often, however, it is possible to make such



106 **107** **105** **108** **109**

predictions on steric grounds. For example, in the opening of **105** by the disrotatory pathway, **108** arises when groups A and C swing in toward each other (clockwise motion around C-4,

counterclockwise around C-3), while **109** is formed when groups B and D swing in and A and C swing out (clockwise motion around C-3, counterclockwise around C-4). This observation leads to a prediction that when A and C are larger than B and D, the predominant or exclusive product will be **109** rather than **108**. Predictions of this kind have largely been borne out.[515] There is evidence, however, that steric effects[516] are not the only factor, and that electronic effects also play a role, and their role may be even greater.[517] An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.[518] The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO (an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.[519]

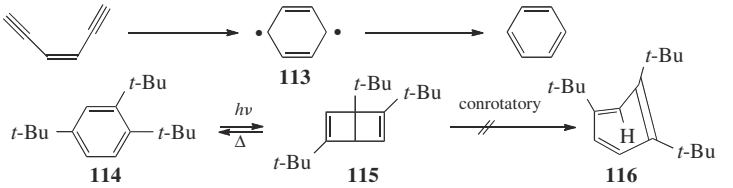


Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.[520] An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer (**110**) (or of the other syn isomer, not shown) leads to the corresponding cyclobutene,[521] while photolysis of the anti isomers (one of them is **111**) gives the ring-opened 1,3,5-triene (**112**). This difference in behavior is at first sight remarkable, but is easily explained by the orbital-symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **110** were to react by this pathway, the product would be the triene **112**, but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **111** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (Sec. 4.K.iii), but are very strained. Stable *trans*-cyclohexenes are unknown (Sec. 4.Q.iii). Thus, **110** and **111** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

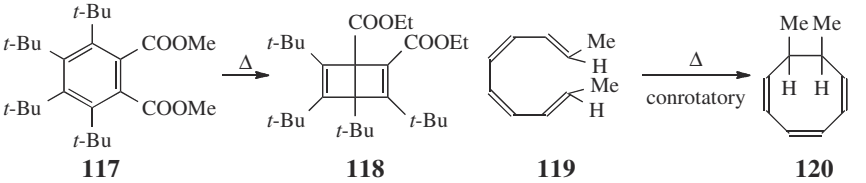
A related process is the *Bergmann cyclization*,[522] where an ene–diyne cyclizes to a biradical (**103**) and then aromatizes as shown. Simply heating the en–diyne will usually lead to aromatization via this pathway.[523] Quinones can be formed via *Bergman*

[515] See Gesche, P.; Klinger, F.; Riesen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* ***1987****, 70,* 2087.
[516] Leigh, W.J.; Postigo, J.A. *J. Am. Chem. Soc.* ***1995****, 117*, 1688.
[517] Dolbier Jr., W.R.; Gray, T.A.; Keaffaber, J.J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* ***1990****, 112,* 363; Hayes, R.; Ingham, S.; Saengchantara, S.T.; Wallace, T.W. *Tetrahedron Lett.* ***1991****, 32,* 2953.
[518] See Kallel, E.A.; Wang, Y.; Spellmeyer, D.C.; Houk, K.N. *J. Am. Chem. Soc.* ***1990****, 112,* 6759.
[519] Piers, E.; Lu, Y.-F. *J. Org. Chem.* ***1989****, 54,* 2267.
[520] See Dauben, W.G.; Kellogg, M.S.; Seeman, J.I.; Vietmeyer, N.D.; Wendschuh, P.H. *Pure Appl. Chem.* ***1973****, 33,* 197.
[521] Dauben, W.G.; Fonken, G.J. *J. Am. Chem. Soc.* ***1959****, 81,* 4060.
[522] Bergman, R.G. *Accts. Chem. Res.* ***1973****, 6*, 25; Adam, W.; Krebs, O. *Chem. Rev.* ***2003****, 103*, 4131. See Lewis, K.D.; Matzger, A.J. *J. Am. Chem. Soc.* ***2005****, 127*, 9968; Zeidan, T.A; Manoharan, M.; Alabugin, I.V. *J. Org. Chem.* ***2006****, 71,* 954; Zeidan, T.A.; Kovalenko, S.V.; Manoharan, M.; Alabugin, I.V. *J. Org. Chem* ***2006****, 71,* 962.
[523] See Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* ***1997***, 381.

cyclization[524] and there are other synthetic applications.[525] The role of vinyl substitution has been examined.[526] An *aza-Bergman cyclization* is known.[527]



The 1,3-diene-cyclobutene interconversion can even be applied to benzene rings. For example,[528] photolysis of 1,2,4-tri-*tert*-butylbenzene (**114**) gives 1,2,5-tri-*tert*-butyl [2.2.0]hexadiene (**115**, a *Dewar benzene)*.[529] The reaction owes its success to the fact that once **115** is formed, it cannot, under the conditions used, revert to **114** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **115** to **114** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **115** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**116**), which is of course too strained to exist. Compound **115** cannot revert to **114** by a photochemical pathway either, because light of the frequency used to excite **114** would not be absorbed by **115**. This is another example of a molecule that owes its stability to the orbital-symmetry rules (see Reaction **15-63**). Pyrolysis of **115** does give **114**, probably by a diradical mechanism.[530] In the case of **117** and **118**, the *Dewar benzene* is actually more stable than the benzene. Compound **117** rearranges to **118** in 90% yield at 120 °C.[531] In this case, thermolysis of the benzene gives the *Dewar benzene* (rather than the reverse), because of the strain of four adjacent *tert*-butyl groups on the ring.



A number of electrocyclic reactions have been carried out with systems of other sizes, [(e.g., conversion of the 1,3,5,7-octatetraene (**119**) to the cyclooctatriene (**120**)].[532] The

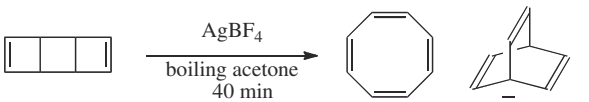
[524] Jones, G.B.; Warner, P.M. *J. Org. Chem.* ***2001****, 66*, 8669.
[525] Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron* ***2001****, 57*, 3753.
[526] Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* ***2001****, 123*, 2134.
[527] Feng, L.; Kumar, D.; Kerwin, S.M. *J. Org. Chem.* ***2003****, 68*, 2234.
[528] See Ward, H.R.; Wishnok, J.S. *J. Am. Chem. Soc.* ***1968****, 90*, 1085; Bryce-Smith, D.; Gilbert, A.; Robinson, D.A. *Angew. Chem. Int. Ed.* ***1971****, 10*, 745. Also see Barlow, M.G.; Haszeldine, R.N.; Hubbard, R. *Chem. Commun.* ***1969***, 202; Lemal, D.M.; Staros, J.V.; Austel, V. *J. Am. Chem. Soc.* ***1969****, 91,* 3373.
[529] van Tamelen, E.E. *Acc. Chem. Res.* ***1972****, 5,* 186. See Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967****, 6,* 78), *Dewar benzenes* can be photolyzed further to give prismanes.
[530] See Wingert, H.; Irngartinger, H.; Kallfass, D.; Regitz, M. *Chem. Ber.* ***1987****, 120,* 825.
[531] Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980****, 19*, 1022. See also, Wingert, H.; Maas, G.; Regitz, M. *Tetrahedron* ***1986****, 42,* 5341.
[532] Marvell, E.N.; Seubert, J. *J. Am. Chem. Soc.* ***1967****, 89,* 3377; Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* ***1969***, 1461; Dahmen, A.; Huber, H. *Tetrahedron Lett.* ***1969***, 1465.

stereochemistry of these reactions can be predicted in a similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n+2$ (where n is any integer including zero).

	Thermal Reaction	Photochemical Reaction
$4n$	Conrotatory	Disrotatory
$4n+2$	Disrotatory	Conrotatory

Although the orbital-symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (Reaction **15-60**, the *Möbius–Hückel* Method) that they only say what is allowed and what is forbidden, but t*he fact that a reaction is allowed does not necessarily mean that the reaction takes plac*e, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.[533] Furthermore, a "forbidden" reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene–butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis*,*cis*- and *trans*,*trans*-1,4-dichloro-1,3-butadienes, as well as the allowed cis, trans isomer) by the use of IR laser light.[534] This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (Sec. 7.A.i), but not to a higher electronic state.

As is the case for $[2+2]$-cycloaddition reactions (**15-63**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[535] An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene to cyclooctatetraene[536]:



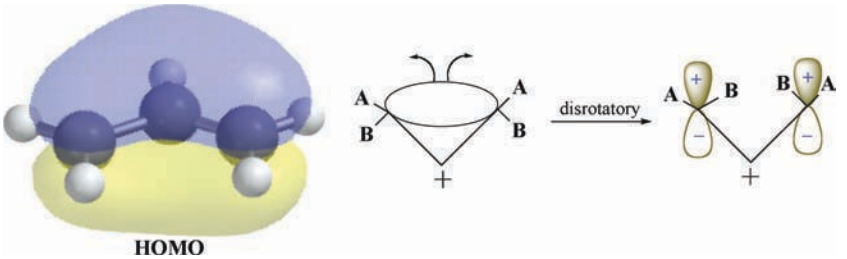
Barrelene anion

This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.[537] In another example, the major thermal product from the barrelene anion is a rearranged allyl anion that is formed by disrotatory cleavage of the cyclopropyl ring, a formally *Woodward–Hoffmann*-forbidden process.[538]

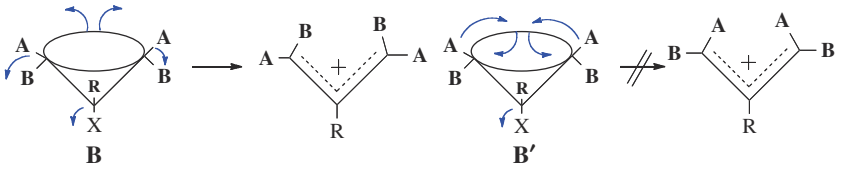
The ring opening of cyclopropyl cations (Sec. 10.G.i, category 7 and Reaction **18-3**) is an electrocyclic reaction and is governed by the orbital symmetry rules.[539] For this case, the

[533] See Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972****, 5,* 402.
[534] Mao, C.; Presser, N.; John, L.; Moriarty, R.M.; Gordon, R.J. *J. Am. Chem. Soc.* ***1981****, 103,* 2105.
[535] Pettit, R.; Sugahara, H.; Wristers, J.; Merk, W. *Discuss. Faraday Soc.* ***1969****, 47*, 71. See also, Labunskaya, V.I.; Shebaldova, A.D.; Khidekel, M.L. *Russ. Chem. Rev.* ***1974****, 43,* 1; Mango, F.D. *Top. Curr. Chem.* ***1974****, 45,* 39; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971****, 93,* 1123.
[536] Merk, W.; Pettit, R. *J. Am. Chem. Soc.* ***1967****, 89*, 4788.
[537] See Pinhas, A.R.; Carpenter, B.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 15.
[538] Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* ***2003****, 5,* 3407.
[539] See DePuy, C.H. *Acc. Chem. Res.* ***1968****, 1*, 33; Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968****, 7,* 588.

rule is invoked that the σ bond opens in such a way that the resulting *p* orbitals have the symmetry of the highest occupied orbital of the product, in this case,



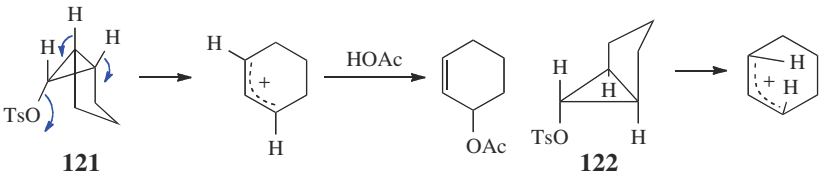
an allylic cation. Recall that an allylic system has three molecular orbitals (Sec. 2.C, category 3). For the cation, with only two electrons, the highest occupied orbital is the one of lowest energy (**HOMO**). Thus, the cyclopropyl cation must undergo a disrotatory ring opening in order to maintain the symmetry. Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,[540] since in this case it is the next orbital of the allylic system that is the highest occupied, and this has the opposite symmetry.[541] However, it is difficult to generate a free cyclopropyl cation (Sec. 10.G.i, category 7), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This, of course, means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2 type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital-symmetry rules require that the ring opening is disrotatory, but as seen above, there are two disrotatory pathways and the rules do not indicate which is preferred. But the fact that the σ orbital provides assistance from the backside means that the two substituents that are trans to the leaving group must move *outward*, not inward.[542] Thus, the disrotatory pathway that is followed is the one shown in **B**, not the one shown in **B′**, because the former puts the electrons of the σ bond on the side opposite



that of the leaving group.[543] Strong confirmation of this picture[544] comes from acetolysis of *endo*- (**121**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**112**). The groups trans to the tosylate must move outward. For **121,** this means that the two hydrogen atoms can go outside the

[540] See Boche, G. *Top. Curr. Chem.* ***1988****, 146,* 1.
[541] See Coates, R.M.; Last, L.A. *J. Am. Chem. Soc.* ***1983****, 105,* 7322. For a review of the analogous ring opening of epoxides, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1977****, 16,* 572.
[542] DePuy, C.H.; Schnack, L.G.; Hausser, J.W.; Wiedemann, W. *J. Am. Chem. Soc.* ***1965****, 87,* 4006.
[543] It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser, J.W.; Grubber, M.J. *J. Org. Chem.* ***1972****, 37*, 2648; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972****, 37,* 4087.
[544] Also see Reese, C.B.; Shaw, A. *J. Am. Chem. Soc.* ***1970****, 92,* 2566; Dolbier, Jr., W.R.; Phanstiel, O. *Tetrahedron Lett.* ***1988****, 29,* 53, and references cited therein.

framework of the six-membered ring, but for **122** they

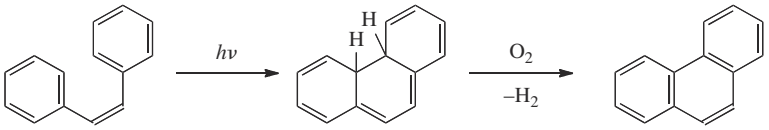


are forced to go inside. Consequently, it is not surprising that the rate ratio for solvolysis of **121/122** was found to be $>2.5 \times 10^6$ and that at 150 °C, **122** did not solvolyze at all.[545] This evidence is kinetic. Unlike the cases of the cyclobutene (1,3-diene and cyclohexadiene) 1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in superacids (Sec. 5.A.ii), where it is possible to keep the cations intact and to study their structures by NMR, that in all cases studied the cation that is predicted by these rules is in fact formed.[546]

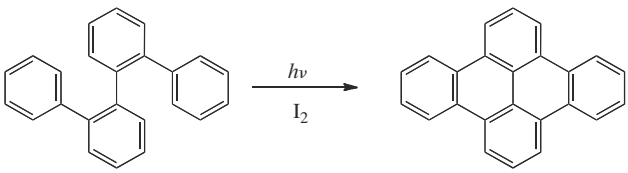
OS **V**, 235, 277, 467; **VI**, 39, 145, 196, 422, 427, 862; **IX**, 180.

18-28 Conversion of One Aromatic Compound to Another

(6) *cyclo*-de-hydrogen-coupling (Overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with UV light[547] in the presence of an oxidizing agent, (e.g., dissolved molecular oxygen, $FeCl_3$, or iodine).[548] The reaction is a photochemically allowed conrotatory[549] conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.[550] The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the cis isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, for example[551]:

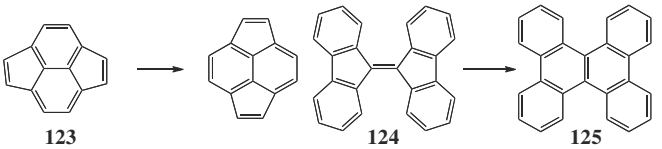


[545] Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P.v.R.; Su, T.M.; Van Dine, G.W. *Tetrahedron Lett.* ***1967***, 3639.
[546] Schleyer, P.v.R.; Su, T.M.; Saunders, M.; Rosenfeld, J.C. *J. Am. Chem. Soc.* ***1969***, *91,* 5174.
[547] Mallory, F.B.; Mallory, C.W. *Org. React.* ***1984***, *30,* 1; Blackburn, E.V.; Timmons, C.J. *Q. Rev. Chem. Soc.* ***1969***, *23,* 482. See Laarhoven, W.H. *Org. Photochem.* ***1989***, *10,* 163.
[548] See Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* ***1991***, *56*, 3769.
[549] Cuppen, T.J.H.M.; Laarhoven, W.H. *J. Am. Chem. Soc.* ***1972***, *94,* 5914.
[550] Doyle, T.D.; Benson, W.R.; Filipescu, N. *J. Am. Chem. Soc.* ***1976***, *98,* 3262.
[551] Sato, T.; Shimada, S.; Hata, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2484.

though not all such systems give a reaction.[552] The use of substrates containing heteroatoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems.

Isomerization of biphenylene to benzo[*a*]pentalene[553] is a well-known benzene ring contraction rearrangement,[554] driven by relief of strain in the four-membered ring. Related to this process is the flash vacuum pyrolysis (FVP) of the alternant polycyclic aromatic hydrocarbon benzo[*b*]biphenylene at 1100 °C, which gives fluoranthene, a nonalternant polycyclic aromatic hydrocarbon, as the major product at 1100 °C in the gas phase.[555] The mechanism used explain that this isomerization involves equilibrating diradicals of 2-phenylnaphthalene, which rearrange by the net migration of a phenyl group to give equilibrating diradicals of 1-phenylnaphthalene, one isomer of which then cyclizes to fluoranthene.

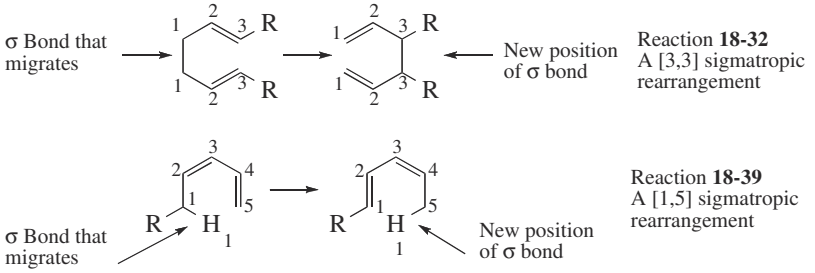
Another transformation of one aromatic compound to another is the *Stone–Wales rearrangement* of pyracyclene (**123**),[556] which is a bond-switching reaction. The rearrangement of bifluorenylidene (**124**) to dibenzo[*g,p*]chrysene (**125**) occurs at temperatures as low as 400 °C and is accelerated in the presence of decomposing iodomethane, a convenient source of methyl radicals.[557] This result suggested a radical rearrangement. This rearrangement is believed to occur by a radical-promoted mechanism consisting of a sequence of homoallyl-cyclopropylcarbinyl rearrangement steps.[558]



123 **124** **125**

B. Sigmatropic Rearrangements

A sigmatropic rearrangement is defined[559] as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



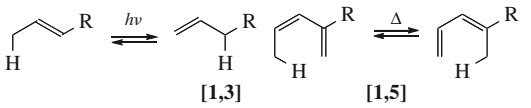
The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i,j*]. These numbers can be determined by counting the atoms over which each end of the

[552] See Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983****, 102*, 185, pp. 185–204.
[553] Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1993****, 34,* 6615; Brown, R.F.C.; Choi, N.; Coulston, K.J.; Eastwood, F.W.; Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1994****, 35,* 4405.
[554] See Brown, R F.C.; Eastwood, F.W.; Wong, N.R. *Tetrahedron Lett.* ***1993****, 34*, 3607.
[555] Preda, D.V.; Scott, L.T. *Org. Lett.* ***2000****, 2,* 1489.
[556] Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* ***1986****, 128*, 501.
[557] Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 712
[558] Alder, R. W.; Harvey, J. N. *J. Am. Chem. Soc.* ***2004****, 126*, 2490.
[559] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 114.

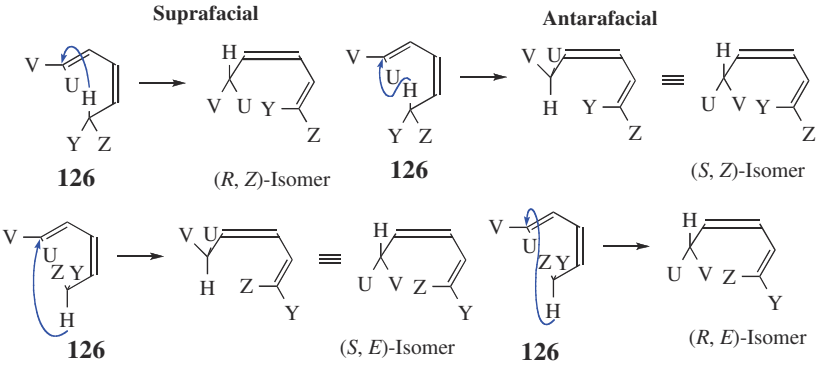
σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has migrated from C-1 to C-3, so the order is [3,3]. In the second example, the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

18-29 [1,j]-Sigmatropic Migrations of Hydrogen

1/→3/Hydrogen-migration; 1/→5/Hydrogen-migration

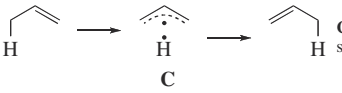


Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,[560] although the reaction is subject to geometrical constraints. Isotope effects play a role in sigmatropic rearrangements, and there is evidence for a kinetic silicon isotope effect.[561] Pericyclic mechanisms are involved,[562] and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, illustrated for the case of a [1,5]-sigmatropic rearrangement,[563] starting with a substrate of the form **126**, where the migration origin is an asymmetric carbon atom and U ≠ V. In one of the two pathways, the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **126** (different rotamers) can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the (*R*,*Z*)-isomer, or it can rotate 180° and move across the bottom of the π system to give the (*S*,*E*)- isomer.[564] The antarafacial migration can similarly lead to two diastereomers, in this case the (*S*,*Z*)- and (*R*,*E*)-isomers.



[560] Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***; Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981****, 50*, 666; Spangler, C.W. *Chem. Rev.* ***1976****, 76,* 187.
[561] Lin, Y.-L.; Turos, E. *J. Am. Chem. Soc.* ***1999****, 121*, 856.
[562] Moss, S.; King, B.T.; de Meijere, A.; Kozhushkov, S.I.; Eaton, P.E.; Michl, J. *Org. Lett.* ***2001****, 3*, 2375.
[563] Note that a [1,5]-sigmatropic rearrangement of hydrogen is also an internal ene synthesis (Reaction **15-20**).
[564] The designations U, V, Y, and Z are arbitrary, so which isomer is(*R*,*Z*) and which is (*S*,*E*) is arbitrary.

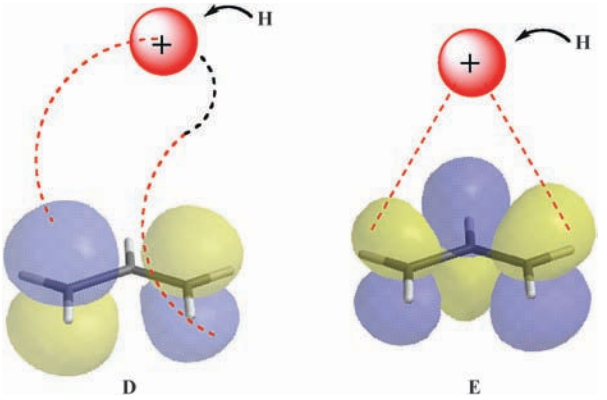
In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital-symmetry rules; the other is forbidden. To analyze this situation, first use a modified frontier orbital approach.[565] Imagine that in the transition state **C**, the migrating H atom breaks away from the rest of the system, which is treated as if it were a free radical.



C

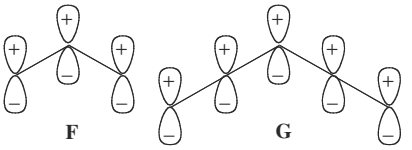
C is an imaginary transition state for a [1,3]-sigmatropic rearrangement

Note that this is not what actually takes place; it is *imagined* in order to analyze the process. In a [1,3]-sigmatropic rearrangement, the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (Sec. 2.C, category 3) has three π orbitals, but the only one that is of concern, the HOMO, which, in a thermal rearrangement is **D**. The electron of the hydrogen atom is of course in a 1*s* orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus lobe, of the HOMO; it cannot move to a lobe of opposite sign.*[566] The only way this can happen in a thermal [1,3]-sigmatropic rearrangement is by an antarafacial migration. Consequently, the rule predicts that antarafacial thermal [1,3]-sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway is forbidden.



D **E**

A similar analysis of [1,5]-sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered *j*, [1,*j*]-suprafacial migrations are allowed thermally when *j* is of the form $4n + 1$, and photochemically when *j* has the form $4n - 1$; the opposite is true for antarafacial migrations.



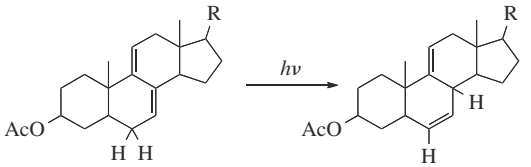
F **G**

[565] See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140.

[566] This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

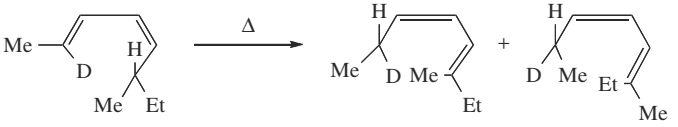
As expected, the *Möbius–Hückel* method leads to the same predictions. Here, examine the basis set of orbitals shown in **F** and **G** for [1,3]- and [1,5]-rearrangements, respectively. A [1,3]-shift involves four electrons, so an allowed thermal pericyclic reaction must be a *Möbius* system (**15-60**, the *Möbius–Hückel* Method) with one or an odd number of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5]-shift, with six electrons, is allowed thermally only when it is a *Hückel* system with zero or an even number of sign inversions; hence it requires a suprafacial migration.[567]

The actual reported results bear out this analysis. Thus a thermal [1,3]-migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3]-sigmatropic migrations of hydrogen are unknown.[568] On the other hand, the photochemical pathway allows suprafacial [1,3]-shifts, and a few such reactions are known, an example being the photochemical rearrangement of **127** to **128**.[569] Substituents influence the efficacy of the [1,3]-hydrogen shift.[570]

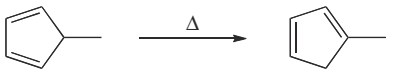


127 **128**

The situation is reversed for [1,5]-hydrogen shifts. In this case, the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.[571] Two examples of the thermal reaction are



Ref. 572



Ref. 573

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*,[574] and such migrations

[567] See Kless, A.; Nendel, M.; Wilsey, S.; Houk, K.N. *J. Am. Chem. Soc.* ***1999****, 121*, 4524.

[568] See, however, Yeh, M.; Linder, L.; Hoffman, D.K.; Barton, T.J. *J. Am. Chem. Soc.* ***1986****, 108*, 7849. See also, Pasto, D.J.; Brophy, J.E. *J. Org. Chem.* ***1991****, 56*, 4554.

[569] Dauben, W.G.; Wipke, W.T. *Pure Appl. Chem.* ***1964****, 9,* 539, p. 546. See Kropp, P.J.; Fravel, Jr., H.G.; Fields, T.R. *J. Am. Chem. Soc.* ***1976****, 98,* 840.

[570] Hudson, C.E.; McAdoo, D.J. *J. Org. Chem.* ***2003****, 68*, 2735.

[571] See Kiefer, E.F.; Tanna, C.H. *J. Am. Chem. Soc.* ***1969****, 91*, 4478; Dauben, W.G.; Poulter, C.D.; Suter, C. *J. Am. Chem. Soc.* ***1970****, 92*, 7408.

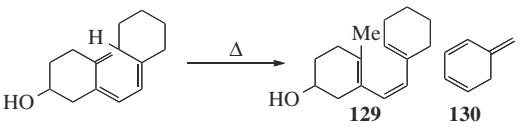
[572] Roth, W.R.; König, J.; Stein, K. *Chem. Ber.* ***1970****, 103,* 426.

[573] See Klärner, F. *Top. Stereochem.* ***1984****, 15,* 1; Hess, Jr., B.A.; Baldwin, J.E. *J. Org. Chem.* ***2002****, 67*, 6025.

[574] Childs, R.F. *Tetrahedron* ***1982****, 38*, 567. See also, Minkin, V.I.; Mikhailov, I.E.; Dushenko, G.A.; Yudilevich, J.A.; Minyaev, R.M.; Zschunke, A.; Mügge, K. *J. Phys. Org. Chem.* ***1991****, 4,* 31. For a study of [1,5]-sigmatropic shiftamers, see Tantillo, D.J.; Hoffmann, R. *Acc. Chem. Res.* ***2006****, 39,* 477.

are known for cyclopentadiene,[575] pyrrole, and phosphole derivatives.[576] Geminal bond participation has been observed in pentadienes,[577] the effects of phenyl substituents have been studied,[578] and the kinetics and activation parameters of [1,5]-hydrogen shifts have been examined.[579] The [1,5]-hydrogen shifts are also known with vinyl aziridines.[580] A Ru catalyzed cycloisomerization of en-1-ynes leads to cyclic dienes.[581]

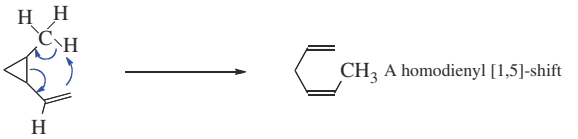
The rare [1,4]-hydrogen transfer has been observed in radical cyclizations.[582] With respect to [1,7]-hydrogen shifts, the rules predict the thermal reaction to be antarafacial.[583] Unlike the case of [1,3]-shifts, the transition state is not too greatly strained, and an example of such rearrangements is the formation of **129** and **130**.[584] Photochemical [1,7]-shifts are suprafacial and, not surprisingly, many of these have been observed.[585]



129 **130**

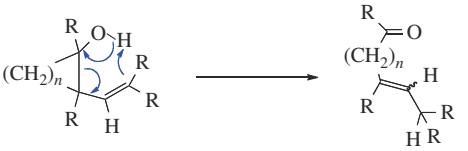
The orbital symmetry rules also help to explain the unexpected stability of certain compounds (see Reaction **15-63**, preceding Reaction **15-64** and **18-27**, the *Möbius–Hückel* Method). Thus, **130** could, by a thermal [1,3]-sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet **130** has been prepared and is stable at dry ice temperature and in dilute solutions.[586]

Analogues of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, for example,[587]



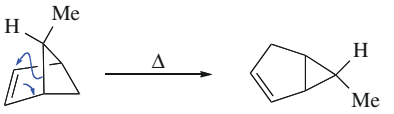
The reverse reaction has also been reported.[588] 2-Vinylcycloalkanols[589] undergo an analogous reaction, as do cyclopropyl ketones (see **18-33**, preceding **18-34** for this reaction).

[575] Shelton, G.R.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2007****, 129,* 164.
[576] Bachrach, S.M. *J. Org. Chem.* ***1993****, 58*, 5414.
[577] Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* ***2001***, 166.
[578] Hayase, S.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2004****, 126*, 10028.
[579] Baldwin, J.E.; Raghavan, A.S.; Hess, Jr., B.A.; Smentek, L. *J. Am. Chem. Soc.* ***2006****, 128*, 14854; Baldwin, J.E.; Chapman, B.R. *J. Org. Chem.* ***2005****, 70,* 377. See also von E. Doering, W.; Keliher, E.J. *J. Am. Chem. Soc.* ***2007****, 129,* 2488; Peles, D.N.; Thoburn, J.D. *J. Org. Chem.* ***2008****, 73,* 3135.
[580] Somfai, P.; Åhman, J. *Tetrahedron Lett.* ***1995****, 36*, 1953.
[581] Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* ***2005****, 127*, 11606.
[582] Journet, M.; Malacria, M. *Tetrahedron Lett.* ***1992****, 33*, 1893.
[583] See Hess Jr., B.A. *J. Org. Chem.* ***2001****, 66,* 5897.
[584] Gurskii, M.E.; Gridnev, I.D.; Il'ichev, Y.V.; Ignatenko, A.V.; Bubnov, Y.N. *Angew. Chem. Int. Ed.* ***1992****, 31*, 781; Baldwin, J.E.; Reddy, V.P. *J. Am. Chem. Soc.* ***1988****, 110,* 8223.
[585] See ter Borg, A.P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1969****, 88*, 266; Tezuka, T.; Kimura, M.; Sato, A.; Mukai, T. *Bull. Chem. Soc. Jpn.* ***1970****, 43*, 1120.
[586] Bailey, W.J.; Baylouny, R.A. *J. Org. Chem.* ***1962****, 27,* 3476.
[587] See Parziale, P.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990****, 112,* 1650; Pegg, G.G.; Meehan, G.V. *Aust. J. Chem.* ***1990****, 43,* 1009, 1071.
[588] Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965****, 688*, 28. See, Grimme, W. *Chem. Ber.* ***1965****, 98*, 756.
[589] Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1960****, 82*, 4918; Leriverend, P.; Conia, J.M. *Tetrahedron Lett.* ***1969***, 2681; Conia, J.M.; Barnier, J.P. *Tetrahedron Lett.* ***1969***, 2679.



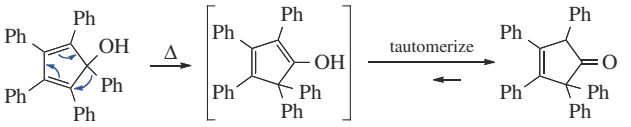
18-30 [1,j]-Sigmatropic Migrations of Carbon

[1,3] migration of alkyl



Ref. 590

[1,5] migration of phenyl



Ref. 591

Sigmatropic migrations of alkyl or aryl groups[592] are less common than the corresponding hydrogen migrations.[593] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1*s* orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if the imaginary transition states for this case are drawn (see above), a thermal suprafacial [1,5]-process (Fig. 18.5) is observed, and symmetry can be conserved only if the migrating carbon moves in such a way that the lobe that was originally attached to the π system remains attached to the π system.

This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3]-migration (Fig. 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C—C bond. Thus, configuration in the migrating group will be *inverted*. From these considerations, suprafacial [1,*j*]-sigmatropic rearrangements in which carbon is the migrating group should always be allowed, both thermally and photochemically, but thermal [1,3]-migrations[594] will proceed with inversion and thermal [1,5]-migrations with retention of configuration within the migrating group. More generally, suprafacial [1, *j*]-migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.

[590] Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607.
[591] Youssef, A.K.; Ogliaruso, M.A. *J. Org. Chem.* ***1972***, *37*, 2601.
[592] See Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187.
[593] See Shen, K.; McEwen, W.E.; Wolf, A.P. *Tetrahedron Lett.* ***1969***, 827; Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1578.
[594] See Baldwin, J.E.; Leber, P.A. *Org. Biomol. Chem.* ***2008***, *6*, 35.

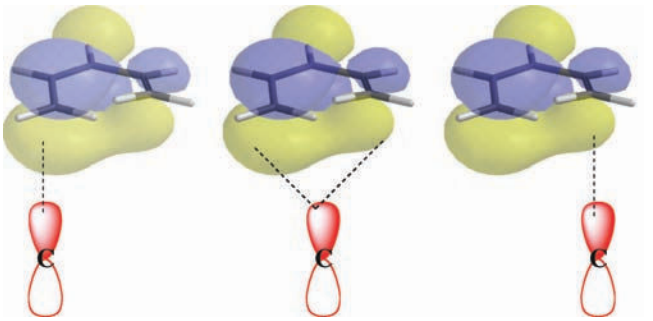


FIG. 18.5. Hypothetical orbital movement for a thermal [1,5]-sigmatropic migration of carbon. To move from one negative lobe, the migrating carbon uses only its own negative lobe, retaining its configuration.

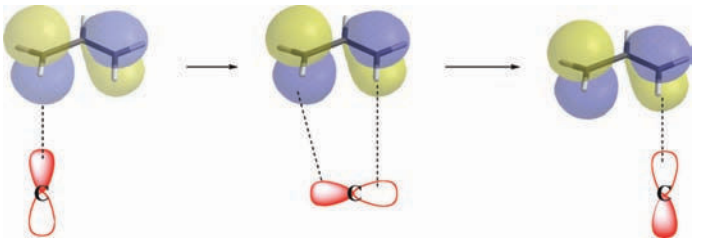
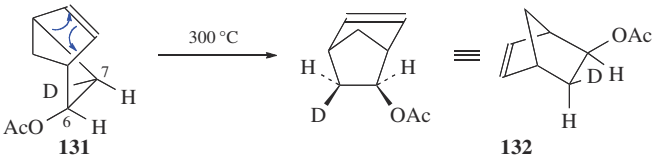


FIG. 18.6. Hypothetical orbital movement for a thermal [1,3]-sigmatropic migration of carbon. The migrating carbon moves a negative to a positive lobe, requiring it to switch its own bonding lobe from negative to positive, inverting its configuration.

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (**131**), which gave the *exo*-deuterio-*exo*-norbornyl acetate (**132**).[595] Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3]-sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.[596] However, similar studies of the pyrolysis of the parent hydrocarbon of **131**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11–29%) was formed with retention.[597] Other cases of lack of complete inversion are also known.[598] A diradical mechanism has been invoked to explain such cases.[599] There is strong evidence for a radical mechanism for some [1,3]-sigmatropic rearrangements.[600]

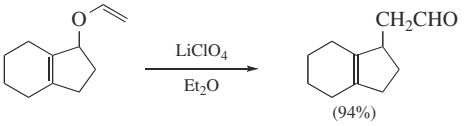
[595] Berson, J.A. *Acc. Chem. Res.* ***1968,*** *1*, 152.
[596] See Berson, J.A. *Acc. Chem. Res.* ***1972,*** *5*, 406; Klärner, F.; Adamsky, F. *Angew. Chem. Int. Ed.* ***1979,*** *18,* 674.
[597] Baldwin, J.E.; Belfield, K.D. *J. Am. Chem. Soc.* ***1988,*** *110*, 296; Klärner, F.; Drewes, R.; Hasselmann, D. *J. Am. Chem. Soc.* ***1988,*** *110,* 297.
[598] See Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988,*** *110,* 8500.
[599] See Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988,*** *110*, 8500. See also, Berson, J.A. *Chemtracts: Org. Chem.* ***1989,*** *2,* 213.
[600] See Dolbier, W.B.; Phanstiel IV, O. *J. Am. Chem. Soc.* ***1989,*** *111,* 4907.

Photochemical suprafacial [1,3]-migrations of carbon have been shown to proceed with retention, as predicted.[601]



131 **132**

Although allylic vinylic ethers generally undergo [3,3]-sigmatropic rearrangements (Reaction **18-33**), they can be made to give the [1,3] kind, to give aldehydes, for example,

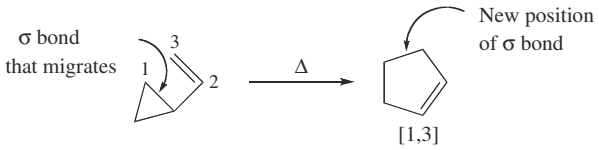


by treatment with $LiClO_4$ in diethyl ether.[602] In this case, the C—O bond undergoes a 1,3-migration from the O to the end vinylic carbon. When the vinylic ether is of the type $ROCR'{=}CH_2$, ketones (RCH_2COR') are formed. There is evidence that this [1,3]-sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.[602]

Thermal suprafacial [1,5]-migrations of carbon have been found to take place with retention,[603] but also with inversion.[604] A diradical mechanism has been suggested for the latter case.[604]

Simple nucleophilic, electrophilic, and free radical 1,2-shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2]-rearrangements). As previously discussed (see discussion in introductory section preceding 18.A) similar principles applied to such rearrangements show that nucleophilic 1,2-shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair. The mechanism of the forbidden [3*s*,5*s*]-sigmatropic shift has been examined.[605]

18-31 Conversion of Vinylcyclopropanes to Cyclopentenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring[606] is a special case of a [1,3]-sigmatropic migration of carbon, although it can also be considered an internal

[601] Cookson, R.C.; Hudec, J.; Sharma, M. *Chem. Commun.* ***1971***, 107, 108.

[602] Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *J. Am. Chem. Soc.* ***1991****, 113*, 5488; Palani, N.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1995****, 36*, 9527.

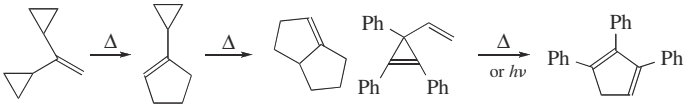
[603] Boersma, M.A.M.; de Haan, J.W.; Kloosterziel, H.; van de Ven, L.J.M. *Chem. Commun.* ***1970***, 1168.

[604] See Gajewski, J.J.; Gortva, A.M.; Borden, J.E. *J. Am. Chem. Soc.* ***1986****, 108*, 1083; Baldwin, J.E.; Broline, B.M. *J. Am. Chem. Soc.* ***1982****, 104*, 2857.

[605] Leach, A.G.; Catak, S.; Houk, K.N. *Chem. Eur. J.* ***2002****, 8*, 1290.

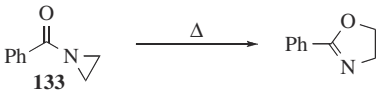
[606] See Baldwin, J.E. *Chem. Rev.* ***2003****, 103*, 1197; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989****, 89*, 165, pp. 169–172; Hudlicky, T.; Kutchan, T.M.; Naqvi, S.M. *Org. React.* ***1985****, 33*, 247; Hudlicky, T.; Reed, J.W. *Angew. Chem. Int. Ed.* ***2010****, 49*, 4864. See Tanko, J.M.; Li, X.; Chahma, M.; Jackson, W.F.; Spencer, J.N. *J. Am. Chem. Soc.* ***2007****, 129,* 4181.

[$_{\pi}2 + _{\sigma}2$]-cycloaddition reaction (see **15-63**). It is known as a *vinylcyclopropane rearrangement*.[607] The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring[608] or on the vinyl group and has been extended to 1,1-dicyclopropylethene[609] and (both thermally[610] and photochemically[611]) to vinylcyclopropenes. This



rearrangement can be catalyzed by Rh and Ag compounds, and has been used to form rings.[612] Two competing reactions are the homodienyl [1,5]-shift (if a suitable H is available, see **18-29**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **18-3**).

Flash vacuum pyrolysis of the trimethylsilyl ether of cyclopropylcarbinyl alcohols gives ring expanded ketones.[613] Various heterocyclic analogues[614] are also known, as in the rearrangement of aziridinyl amides (**133**).[615] Cyclopropyl ketones can be treated with tosylamine and a Zr catalyst, which converts the imine formed *in situ* to a pyrroline.[616] *N*-Cyclopropylimines undergo rearrangement to cyclic imines (pyrrolines) under photochemical conditions.[617] *P*-Vinyl phosphiranes (the P analogue of cyclopropanes with P in the ring) under a similar rearrangement, and the mechanism has been studied.[618]



133

Vinylcyclobutanes can be converted to cyclohexenes,[619] but larger ring compounds do not generally give the reaction.[620] Tricyclo[4.1.0.0^{2,5}]heptanes rearrange to give nonconjugated cycloheptadienes.[621] The bicyclo[2.1.0]pentane derivatives undergo this reaction.

[607] See Armesto, D.; Ramos, A.; Mayoral, E.P.; Ortiz, M.J.; Agarrabeitia, A.R. *Org. Lett.* ***2000****, 2*, 183.
[608] For a study of substituent effects, see McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3559.
[609] Ketley, A.D. *Tetrahedron Lett.* ***1964***, 1687; Branton, G.R.; Frey, H.M. *J. Chem. Soc. A* ***1966***, 1342.
[610] Small, A.; Breslow, R. cited in Breslow, R. in de Mayo, P. *Molecular Rearrangments,* Vol. 1, Wiley, NY, ***1963***, p. 236.
[611] Zimmerman, H.E.; Kreil, D.J. *J. Org. Chem.* ***1982****, 47*, 2060.
[612] Wender, P.A.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1998****, 120*, 1940.
[613] Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004****, 6*, 2989.
[614] See Boeckman Jr., R.K.; Walters, M.A. *Adv. Heterocycl. Nat. Prod. Synth.* ***1990****, 1,* 1.
[615] Heine, H.W. *Mech. Mol. Migr.* ***1971****, 3,* 145; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 282–290. See also, Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989****, 89*, 165, pp. 190–192.
[616] Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* ***2004***, 1622.
[617] Campos, P.J.; Soldevilla, A.; Sampedro, D.; Rodrguez, M.A. *Org. Lett.* ***2001****, 3,* 4087.
[618] Mátrai, J.; Dransfeld, A.; Veszprém, T.; Nguyen, M.T. *J. Org. Chem.* ***2001****, 66*, 5671.
[619] See Baldwin, J.E.; Fedé, J.-M. *J. Am. Chem. Soc.* ***2006****, 128,* 5608; Northrop, B.H.; Houk, K.N. *J. Org. Chem.* ***2006****, 71,* 3; Leber, P.A.; Baldwin, J.E. *Acc. Chem. Res.* ***2002****, 35*, 279.
[620] See Thies, R.W. *J. Am. Chem. Soc.* ***1972****, 94*, 7074.
[621] Deak, H.L.; Stokes, S.S.; Snapper, M.L. *J.. Am. Chem. Soc.* ***2001****, 123*, 5152.

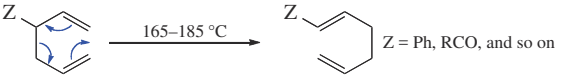
The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate ($Ar_3N\bullet^+$ SbF_6^-, Ar = *p*-bromophenyl).[622] This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.[623]

The mechanisms of these ring expansions are not certain. Both concerted[624] and diradical[625] pathways have been proposed,[626] and it is possible that both pathways operate, in different systems.

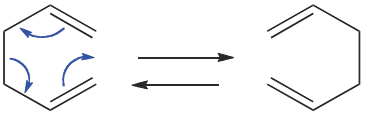
For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS **68**, 220.

18-32 The Cope Rearrangement

(3/4/)→(1/6/)-*sigma*-Migration



When 1,5-dienes are heated, a [3,3]-sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the *Cope elimination* Reaction, **17-9**) occurs to generate an isomeric 1,5-diene.[627] When the diene is symmetrical about the 3,4-bond, the reaction gives a product identical with the starting material[628]:



Therefore, a *Cope rearrangement* can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300 °C gives 1,5-heptadiene.[629] However, the reaction takes place more easily (lower temperature required) when there is a group on the C-3 or C-4 with leads to the new double bond being substituted. The reaction is reversible[630] and produces an equilibrium mixture of the two 1,5-dienes, which is *richer in the thermodynamically*

[622] Dinnocenzo, J.P.; Conlan, D.A. *J. Am. Chem. Soc.* ***1988****, 110,* 2324.

[623] See Bauld, N.L. *Tetrahedron* ***1989****, 45,* 5307. For a rearrangement of a housane cation radical, see Gerken, J.B.; Wang, S.C.; Preciado, A.B.; Park, Y.S.; Nishiguchi, G.; Tantillo, D.J.; Little, R.D. *J. Org. Chem.* ***2005****, 70*, 4598.

[624] See Gajewski, J.J.; Olson, L.P. *J. Am. Chem. Soc.* ***1991****, 113*, 7432.

[625] See Zimmerman, H.E.; Fleming, S.A. *J. Am. Chem. Soc.* ***1983****, 105,* 622; Klumpp, G.W.; Schakel, M. *Tetrahedron Lett.* ***1983****, 24,* 4595; McGaffin, G.; de Meijere, A.; Walsh, R. *Chem. Ber.* ***1991****, 124,* 939. See Roth, W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. *J. Am. Chem. Soc.* ***1990****, 112,* 1722 and references cited therein.

[626] See Gajewski, J.J.; Olson, L.P.; Willcott III, M.R. *J. Am. Chem. Soc.* ***1996****, 118*, 299. For a discussion of the mechanism of this reaction, see Su, M.-D. *Tetrahedron* ***1995****, 51*, 5871.

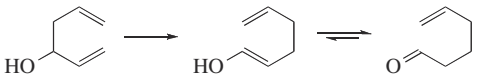
[627] Bartlett, P.A. *Tetrahedron* ***1980****, 36,* 2, pp. 28–39; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975****, 22,* 1; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971****, 8*, 75, pp. 153–201; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 455–461.

[628] Note that the same holds true for [1,*j*]-sigmatropic reactions of symmetrical substrates (**18-28** and **18-29**).

[629] Levy, H.; Cope, A.C. *J. Am. Chem. Soc.* ***1944****, 66,* 1684.

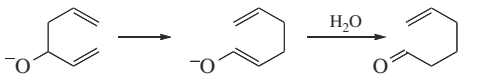
[630] See Cooper, N.J.; Knight, D.W. *Tetrahedron* ***2004****, 60,* 243.

more stable isomer. However, the equilibrium can be shifted to the right for 3-hydroxy-1,5-dienes,[631] because the product tautomerizes to the ketone or aldehyde:



Oxy-Cope

This reaction of 3-hydroxy-1,5-dienes is called the *oxy-Cope rearrangement*,[632] and has proved highly useful in synthesis.[633] The *oxy-Cope rearrangement* is greatly accelerated (by factors of 10^{10}–10^{17}) if the alkoxide is used rather than the alcohol (the *anionic oxy-Cope rearrangement*),[634] where the direct product is the enolate ion, which is hydrolyzed to the ketone. A metal-free reaction using a phosphazene base has been reported.[635] The silyloxy-*Cope rearrangement* has proven to be quite useful.[636] An antibody-catalyzed *oxy-Cope reaction* is known,[637] and the mechanism and origins of catalysis for this reaction have been studied.[638] Sulfur substituents also lead to rate enhancement of the *oxy-Cope rearrangement*.[639] Note that *2-oxonia Cope rearrangements* have been implicated in *Prins cyclization* reactions (**16-54**).[640] A highly diastereoselective *oxonia-Cope rearrangement* proceeded using a chiral aldehyde with a chiral conjugated ester.[641]



Anionic-oxy-Cope

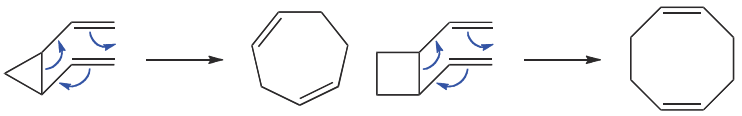
aza-Cope rearrangements are also known.[642] There is an enantioselective *aza-Cope rearrangement*.[643] There is also a 1,2-*oxaza-Cope rearrangement*. Involving esters and alkyl nitrites.[644] In *amino-Cope rearrangements*, the solvent plays a role in the regioselectivity of the reaction.[645] It has been suggested that this latter reaction does not proceed solely by a concerted [3.3]-sigmatropic rearrangement.[646]

[631] See Elmore, S.W.; Paquette, L.A. *Tetrahedron Lett.* ***1991****, 32,* 319.
[632] Paquette, L.A. *Angew. Chem. Int. Ed.* ***1990****, 29*, 609; Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 738–743; Warrington, J.M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* ***2000****, 2,* 663; Ovaska, T.V.; Roses, J.B. *Org. Lett.* ***2000****, 2*, 2361; Jung, M.E.; Nishimura, N.; Novack, A.R. *J. Am. Chem. Soc.* ***2005****, 127*, 11206.
[633] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1306–1307.
[634] See Gajewski, J.J.; Gee, K.R. *J. Am. Chem. Soc.* ***1991****, 113*, 967. See also, Wender, P.A.; Ternansky, R.J.; Sieburth, S.M. *Tetrahedron Lett.* ***1985****, 26,* 4319. Also see Schulze, S.M.; Santella, N.; Grabowski, J.J.; Lee, J.K. *J. Org. Chem.* ***2001****, 66*, 7247.
[635] Mamdani, H.T.; Hartley, R.C. *Tetrahedron Lett.* ***2000****, 41,* 747.
[636] For a review, see Schneider, C. *Synlett* ***2001***, 1079.
[637] Braisted, A.C.; Schultz, P.G. *J. Am. Chem. Soc.* ***1994****, 116,* 2211.
[638] Black, K.A.; Leach, A.G.; Kalani, Y.S.; Houk, K.N. *J. Am. Chem. Soc.* ***2004****, 126*, 9695.
[639] Paquette, L.A.; Reddy, Y.R.; Vayner, G.; Houk, K.N. *J. Am. Chem. Soc.* ***2000****, 122*, 10788.
[640] See Jasti, R.; Anderson, C.D.; Rychnovsky, S.D. *J. Am. Chem. Soc.* ***2005****, 127*, 9939.
[641] Chen, Y.-H.; McDonald, F.E. J. *Am. Chem. Soc.* ***2006****, 128,* 4568.
[642] Beholz, L.G.; Stille, J.R. *J. Org. Chem.* ***1993****, 58*, 5095; Sprules, T.J.; Galpin, J.D.; Macdonald, D. *Tetrahedron Lett.* ***1993****, 34*, 247; Yadav, J.S.; Reddy, B.V.S.; Rasheed, M.A.; Kumar, H.M.S. *Synlett* ***2000***, 487.
[643] Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* ***2008****, 47,* 10090.
[644] Zakarian, A.; Lu, C.-D. *J. Am. Chem. Soc.* ***2006****, 128,* 5356.
[645] Dobson, H.K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T.R.; Macdonald, D. *Tetrahedron Lett.* ***1999****, 40*, 3119.
[646] Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.* ***1999****, 40*, 3801.

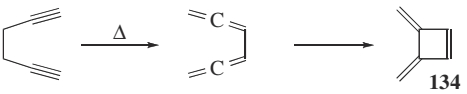
The 1,5-diene system may be inside a ring or part of an allenic system[647] (the example shown illustrates both of these situations).[648] However, the reaction does not take place when one of the double bonds is part of



an aromatic system (e.g., 4-phenyl-1-butene).[649] When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and divinylcyclobutanes, as shown.[650] Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly



that they generally cannot be isolated at room temperature,[651] but exceptions are known.[652] Note that divinyloxiranes, divinylphosphiranes, and divinylthiiranes undergo similar rearrangements.[653] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes (**134**).[654] A rate-determining *Cope rearrangement* is followed by a very rapid electrocyclic (**18-27**) reaction.

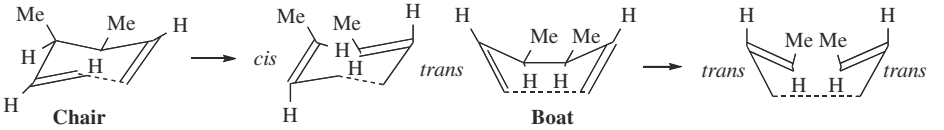


134

The interconversion of 1,3,5-trienes and cyclohexadienes (in Reaction **18-27**) is very similar to the *Cope rearrangement*, but in **18-27**, the 3,4-bond goes from a double to a single bond rather than from a single bond to no bond. Like [2 + 2]-cycloadditions (Reaction **15-63**), *Cope rearrangements* of simple 1,5-dienes can be catalyzed by certain transition metal compounds. For example, the addition of a Pd catalyst causes the reaction to take place at room temperature.[655]

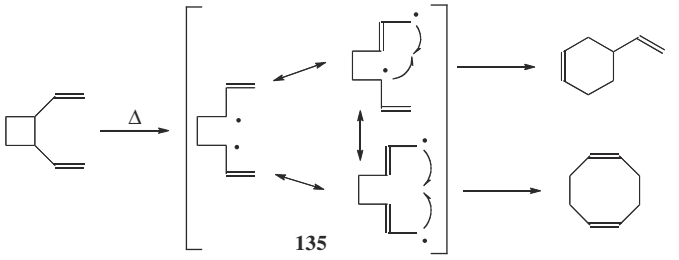
[647] Duncan, J.A.; Azar, J.K.; Beatle, J.C.; Kennedy, S.R.; Wulf, C.M. *J. Am. Chem. Soc.* ***1999****, 121*, 12029.
[648] Harris, Jr., J.F. *Tetrahedron Lett.* ***1965***, 1359.
[649] See Newcomb, M.; Vieta, R.S. *J. Org. Chem.* ***1980****, 45,* 4793. Also see Jung, M.E.; Hudspeth, J.P. *J. Am. Chem. Soc.* ***1978****, 100*, 4309; Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* ***1980****, 45,* 2368.
[650] Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989****, 89*, 165, see pp. 172–174; Mil'vitskaya, E.M; Tarakanova, A.V.; Plate, A.F. *Russ. Chem. Rev.* ***1976****, 45*, 469, see pp. 475–476.
[651] See Schneider, M.P.; Rebell, J. *J. Chem. Soc., Chem. Commun.* ***1975***, 283.
[652] See Schneider, M.P.; Rau, A. *J. Am. Chem. Soc.* ***1979****, 101,* 4426.
[653] Zora, M. *J. Org. Chem.* ***2005****, 70,* 6018.
[654] Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981****, 37,* 3765; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445, pp. 428–430; Huntsman, W.D. *Intra-Sci. Chem. Rep.,* ***1972****, 6*, 151.
[655] Siebert, M.R.; Tantillo, D.J. *J. Am. Chem. Soc.* ***2007****, 129,* 8686. Overman, L.E. *Angew. Chem. Int. Ed.* ***1984****, 23,* 579; Lutz, R.P. *Chem. Rev.* ***1984****, 84,* 205. See Overman, L.E.; Renaldo, A.F. *J. Am. Chem. Soc.* ***1990****, 112,* 3945.

As indicated with the arrows, the mechanism of the uncatalyzed *Cope rearrangement* is a simple six-centered pericyclic process.[656] Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.[657] For the case of 3,4-dimethyl-1,5-hexadiene, it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the cis–trans product, while the (±) diastereomer gave the *trans–trans*-diene.[658] If the transition state is in the chair form (taking the meso isomer, e.g.), one methyl must be "axial" and the other "equatorial" and the product must be the



cis–trans-alkene. There are two possible boat forms for the transition state of the meso isomer. One leads to a trans–trans product; the other to a *cis–cis*-alkene. For the (±) pair, the predictions are just the opposite: There is just one boat form, and it leads to the *cis–trans*-alkene, while one chair form ("diaxial" methyls) leads to the cis–cis product and the other ("diequatorial" methyls) predicts the trans–trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[659] While 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), other compounds are not so free. Thus 1,2-divinylcyclopropane (see above) can react *only* in the boat form, demonstrating that such reactions are possible.[660]

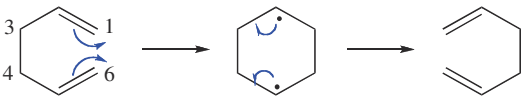
Because of the nature of the transition state[661] in the pericyclic mechanism, optically active substrates with a stereogenic carbon at C-3 or C-4 transfer the chirality to the product (see Reaction **18-33** for an example in the mechanistically similar *Claisen rearrangement*).[662] There are many examples of asymmetric [3,3]-sigmatropic rearrangements.[663]



[656] See Poupko, R.; Zimmermann, H.; Müller, K.; Luz, Z. *J. Am. Chem. Soc.* ***1996****, 118*, 7995.
[657] See Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. *J. Am. Chem. Soc,* ***1992****, 114*, 2635. See also, Tantillo, D.J.; Hoffmann, R. *J. Org. Chem.* ***2002****, 67*, 1419.
[658] Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1962****, 18*, 67. See also, Gajewski, J.J.; Benner, C.W.; Hawkins, C. M. *J. Org. Chem.* ***1987****, 52,* 5198; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988****, 110*, 890.
[659] See Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965****, 87*, 4389; Fukui, K.; Fujimoto, H. *Tetrahedron Lett.* ***1966***, 251.
[660] See Gajewski, J.J.; Jimenez, J.L. *J. Am. Chem. Soc.* ***1986****, 108*, 468.
[661] See Özkan, I.; Zora, M. *J. Org. Chem.* ***2003****, 68*, 9635.
[662] See Hill, R.K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 503–572, 503–545.
[663] For a review, see Nubbemeyer, U. *Synthesis* ***2003***, 961.

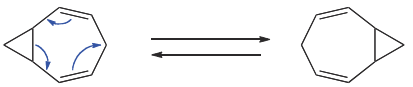
Not all *Cope rearrangements* proceed by the cyclic six-centered mechanism.[664] Thus *cis*-1,2-divinylcyclobutane (see above) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from Reaction **18-31**). This reaction can be rationalized as proceeding by a diradical mechanism (see **135**),[665] although it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by *Cope rearrangement* of the latter.[666]

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[667] Indeed, a nonconcerted *Cope rearrangement* has been reported.[668] In this pathway,[669] the 1,6-bond is formed before the 3,4-bond breaks:



This is related to the *Bergman cyclization* that was introduced in Reaction **18-27**.

It was pointed out earlier that a *Cope rearrangement* of the symmetrical 1,5-hexadiene gives 1,5-hexadiene. This is a *degenerate Cope rearrangement* (Sec. 18.A.ii). Bicyclo[5.1.0]octadiene (**136**) undergoes a similar rearrangement.[670] At room temperature, the NMR spectrum of this compound is in accord with the structure shown on the left. At 180 °C, it is converted by a *Cope reaction* to a compound equivalent to itself. The interesting thing is that at 180 °C the NMR spectrum shows that what exists is an equilibrium mixture of the two



136 **136**

structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift[671] (see Sec. 2.N for other types of tautomerism). The positions of the nuclei are not the same in the two structures. Molecules like **136** that exhibit valence tautomerism (in this case, at

[664] See Navarro-Vázquez, A.; Prall, M.; Schreiner, P.R. *Org. Lett.* ***2004****, 6*, 2981.

[665] Hammond, G.S.; De Boer, C.D. *J. Am. Chem. Soc.* ***1964****, 86*, 899; Trecker, D.J.; Henry, J.P. *J. Am. Chem. Soc.* ***1964****, 86*, 902. Also see, Kessler, H.; Ott, W. *J. Am. Chem. Soc.* ***1976****, 98*, 5014. Also see Berson, J.A. in de Mayo, P. *Rearrangements in Ground and Excited States,* Academic Press, NY, ***1980***, pp. 358–372.

[666] See Baldwin, J.E.; Gilbert, K.E. *J. Am. Chem. Soc.* ***1976****, 98*, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin, J.E.; Ullenius, C. *J. Am. Chem. Soc.* ***1984****, 96,* 1542.

[667] Kaufmann, D.; de Meijere, A. *Chem. Ber.* ***1984****, 117,* 1128; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1987****, 109,* 5893; *J. Chem. Soc., Chem. Commun.* ***1989***, 98. For evidence against this view, see Halevi, E.A.; Rom, R. *Isr. J. Chem.* ***1989****, 29*, 311; Owens, K.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990****, 112,* 5973.

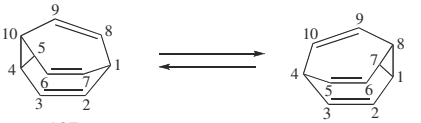
[668] Roth, W.R.; Gleiter, R.; Paschmann, V.; Hackler, U.E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* ***1998***, 961; Roth, W.R.; Schaffers, T.; Heiber, M. *Chem. Ber.* ***1992****, 125*, 739.

[669] For a report of still another mechanism, see Gompper, R.; Ulrich, W. *Angew. Chem. Int. Ed.* ***1976****, 15,* 299. See McGuire, M.J.; Piecuch, P. *J. Am. Chem. Soc.* ***2005****, 127,* 2608.

[670] Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1963****, 19*, 715.

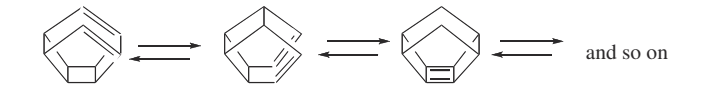
[671] See Decock-Le Révérend, B.; Goudmand, P. *Bull. Soc. Chim. Fr.* ***1973***, 389; Gajewski, J.J. *Mech. Mol. Migr.* ***1971****, 4,* 1, see pp. 32–49; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1971****, 10,* 11; Schröder, G.; Oth, J.F.M.; Merényi, R. *Angew. Chem. Int. Ed.* ***1965****, 4,* 752.

180 °C) are said to have *fluxional* structures. It may be recalled that *cis*-1,2-divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (see above), but in **136** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**137**) is especially interesting. The *Cope rearrangement* shown for **137** changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several *Cope*



137

rearrangements. In all, there are $\frac{10!}{3}$ or >1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate *Cope rearrangement*. Bullvalene has been synthesized and its ^{1}H NMR spectrum was determined.[672] At −25 °C, there are two peaks with an area ratio of 6 : 4. This is in accord with a single nontautomeric structure. The six protons are the vinylic protons and the four protons are the allylic ones. But at 100 °C, the compound shows only one NMR peak, indicating that the compound rapidly interchanges its structure among 1.2 million equivalent forms.[673] The ^{13}C NMR spectrum of bullvalene also shows only one peak at 100 °C.[674]



138



139 **140**

Another compound for which degenerate *Cope rearrangements* result in equivalence for all the carbons is *hypostrophene* (**138**).[675] In the case of the compound *barbaralane* (**139**)[676] (bullvalene in which one CH=CH has been replaced by a CH_2), there are only 2 equiv tautomers.[677] However, NMR spectra indicate that even at room temperature a rapid interchange of both tautomers is present, although by about −100 °C this has slowed

[672] Schröder, G. *Chem. Ber.* ***1964****, 97,* 3140; Merényi, R.; Oth, J.F.M.; Schröder, G. *Chem. Ber.* ***1964****, 97,* 3150. For a review of bullvalenes, see Schröder, G.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1967****, 6,* 414.

[673] See Paquette, L.A.; Malpass, J.R.; Krow, G.R.; Barton, T.J. *J. Am. Chem. Soc.* ***1969****, 91*, 5296.

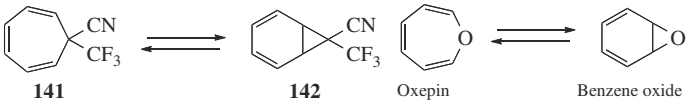
[674] Oth, J.F.M.; Müllen, K.; Gilles, J.; Schröder, G. *Helv. Chim. Acta* ***1974****, 57,* 1415; Nakanishi, H.; Yamamoto, O. *Tetrahedron Lett.* ***1974***, 1803; Günther, H.; Ulmen, J. *Tetrahedron* ***1974****, 30,* 3781. See Luger, P.; Buschmann, J.; McMullan, R.K.; Ruble, J.R.; Matias, P.; Jeffrey, G.A. *J. Am. Chem. Soc.* ***1986****, 108,* 7825.

[675] McKennis, J.S.; Brener, L.; Ward, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1971****, 93,* 4957; Paquette, L.A.; Davis, R.F.; James, D.R. *Tetrahedron Lett.* ***1974***, 1615.

[676] For a study of sigmatropic shiftamers in extended barbaralanes, see Tantillo, D.J.; Hoffmann, R.; Houk, K.N.; Warner, P.M.; Brown, E.C.; Henze, D.K. *J. Am. Chem. Soc.* ***2004****, 126*, 4256.

[677] Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem. Int. Ed.* ***1967****, 6,* 176; Doering, W. von E.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones, Jr., M.; Klumpp, G.W.; Rubin, R.M.; Saunders, M. *Tetrahedron* ***1967****, 23,* 3943; Henkel, J.G.; Hane, J.T. *J. Org. Chem.* ***1983****, 48,* 3858.

to the point where the spectrum is in accord with a single structure. In the case of *semibullvalene* (**140**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at −110 °C.[678] Compound **140** has the lowest energy barrier of any known compound capable of undergoing the *Cope rearrangement*.[679]

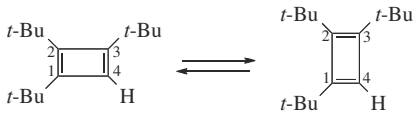


141 **142** Oxepin Benzene oxide

The molecules taking part in a valence tautomerization need not be equivalent. Thus, NMR spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene (**141**) and the norcaradiene (**142**).[680] In this case, one isomer (**142**) has the *cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide[681] and oxepin exist in a tautomeric equilibrium at room temperature.[682]

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[683] Many other members of this group are known. Similar groups of $(CH)_n$ compounds exist for other even-numbered values of "*n*".[685] For example, there are 20 possible $(CH)_8$[684] compounds,[685] and five possible $(CH)_6$ compounds,[686] all of which are known: benzene, prismane (Sec. 4.Q.i), Dewar benzene (see Reaction **18-27**, the *Möbius–Hückel Method*), bicyclopropenyl,[687] and benzvalene.[688]

An interesting example of valence tautomerism is the case of 1,2,3-tri-*tert*-butylcyclobutadiene (Sec. 2.K.ii). There are two isomers, both rectangular, and ^{13}C NMR spectra show that they exist in a dynamic equilibrium, even at −185 °C.[689]



[678] Meinwald, J.; Schmidt, D. *J. Am. Chem. Soc.* ***1969****, 91,* 5877; Zimmerman, H.E.; Binkley, R.W.; Givens, R.S.; Grunewald, G.L.; Sherwin, M.A. *J. Am. Chem. Soc.* ***1969****, 91*, 3316. See Seefelder, M.; Heubes, M.; Quast, H.; Edwards, W.D.; Armantrout, J.R.; Williams, R.V.; Cramer, C.J.; Goren, A.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***2005****, 70,* 3437.

[679] Moskau, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L.S.; Grohmann, K. *Chem. Ber.* ***1989****, 122,* 925. Are semibullvalenes homoaromatic? See Williams, R.V.; Gadgil, V.R.; Chauhan, K.; Jackman, L.M.; Fernandes, E. *J. Org. Chem.* ***1998****, 63*, 3302.

[680] Ciganek, E. *J. Am. Chem. Soc.* ***1965****, 87,* 1149. See Neidlein, R.; Radke, C.M. *Helv. Chim. Acta* ***1983****, 66,* 2626; Takeuchi, K.; Kitagawa, T.; Ueda, A.; Senzaki, Y.; Okamoto, K. *Tetrahedron* ***1985****, 41*, 5455.

[681] See Shirwaiker, G.S.; Bhatt, M.V. *Adv. Heterocycl. Chem.* ***1984****, 37,* 67.

[682] Vogel, E. *Pure Appl. Chem.* ***1969****, 20,* 237. See also, Boyd, D.R.; Stubbs, M.E. *J. Am. Chem. Soc.* ***1983****, 105*, 2554.

[683] See Balaban, A.T.; Banciu, M. *J. Chem. Educ.* ***1984****, 61,* 766; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 203–215; Scott, L.T.; Jones, Jr., M. *Chem. Rev.* ***1972****, 72*, 181. See also, Maier, G.; Wiegand, N.H.; Baum, S.; Wüllner, R. *Chem. Ber.* ***1989****, 122*, 781.

[684] See Hassenrück, K.; Martin, H.; Walsh, R. *Chem. Rev.* ***1989****, 89,* 1125.

[685] See Balaban, A.T; Banziu, M. *J. Chem. Educ.* ***1984****, 61*, 766; Banciu, M.; Popa, C.; Balaban, A.T. *Chem. Scr.,* ***1984****, 24,* 28.

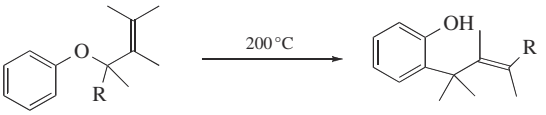
[686] Kobayashi, Y.; Kumadaki, I. *Top. Curr. Chem.* ***1984****, 123,* 103; Bickelhaupt, F.; de Wolf, W.H. *Recl. Trav. Chim. Pays-Bas* ***1988****, 107,* 459.

[687] See Davis, J.H.; Shea, K.J.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977****, 99*, 1499.

[688] See Christl, M. *Angew. Chem. Int. Ed.* ***1981****, 20,* 529; Burger, U. *Chimia,* ***1979***, 147.

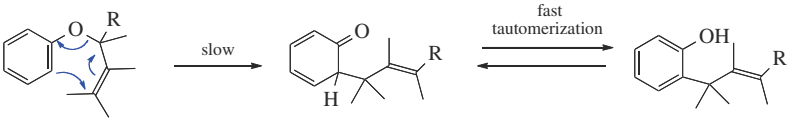
[689] Maier, G.; Kalinowski, H.; Euler, K. *Angew. Chem. Int. Ed.* ***1982****, 21*, 693.

18-33 The Claisen Rearrangement[690]



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[691] If both ortho positions are filled, the allylic group migrates to the para position (this is often called the *para-Claisen rearrangement*).[692] There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration, the allylic group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: The allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3]-sigmatropic rearrangement[693] and accounts for all these facts. For the ortho rearrangement,



Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of cross-over products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ^{14}C labeling, even when no substituents are present. Studies of the transition state geometry have shown that, like the *Cope rearrangement*, the *Claisen rearrangement* usually prefers a chair-like transition state.[694] A *retro-Claisen rearrangement* is known and its mechanism has been examined.[695]

[690] Castro, A.M.M. *Chem. Rev.* ***2004****, 104*, 2939; Hiersemann, M.; Nubbemeyer, U *The Claisen Rearrangement: Methods and Applications.* Wiley–VCH, **2007**.

[691] Fleming, I. *Pericyclic Reactions,* Oxford University Press, Oxford, ***1999***, pp. 71–83; Moody, C.J. *Adv. Heterocycl. Chem.* ***1987****, 42*, 203; Bartlett, P.A. *Tetrahedron* ***1980****, 36*, 2, see pp. 28–39; Ziegler, F.E. *Acc. Chem. Res.* ***1977****, 10,* 227; Bennett, G.B. *Synthesis* ***1977***, 589; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975****, 22*, 1; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 89–120; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971****, 8,* 75, pp. 153–201; Hansen, H.; Schmid, H. *Chimia,* ***1970****, 24*, 89; Jefferson, A.; Scheinmann, F. *Q. Rev. Chem. Soc.* ***1968****, 22,* 391.

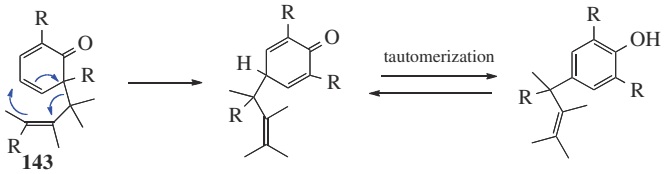
[692] See Gozzo, F.C.; Fernandes, S.A.; Rodrigues, D.C.; Eberlin, M.N.; Marsaioli, A.J. *J. Org. Chem.* ***2003****, 68*, 5493.

[693] See Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J. *J. Am. Chem. Soc.* ***1988****, 110*, 7153.

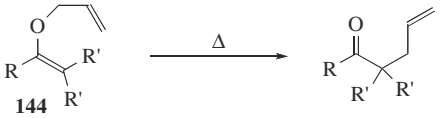
[694] Copley, S.D.; Knowles, J.R. *J. Am. Chem. Soc.* ***1985****, 107,* 5306. Also see, Yoo, H.Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1994****, 116*, 12047.

[695] Boeckman, Jr., R.K.; Shair, M.D.; Vargas, J.R.; Stolz, L.A. *J. Org. Chem.* ***1993****, 58*, 1295.

When the ortho positions have no hydrogen, a second [3,3]-sigmatropic migration (a *Cope reaction*) follows:



and the migrating group is restored to its original structure. Intermediates of structure **143** have been trapped by means of a *Diels–Alder reaction* (**15-60**).[696] The rearrangement of aryl allyl ethers is facilitated by Ag–KI in hot acetic acid,[697] and by $AlMe_3$ in water.[698] A solid-phase reaction of polymer-bound substrate undergoes the *Claisen rearrangement* with microwave irradiation.[699]



Allylic ethers of enols (allylic vinylic ethers, **144**) also undergo the *Claisen rearrangement*[700]; in fact, it was discovered with these compounds first.[701] In these cases of course, the final tautomerization does not take place even when $R' = H$, since there is no aromaticity to restore, and ketones are more stable than enols.[702] Catalytic *Claisen rearrangements* of allyl vinyl ethers are well known.[703] The use of water as solvent accelerates the reaction.[704] Microwave induced reactions on silica gel[705] and in ionic liquids[706] are known The mechanism is similar to that with allylic aryl ethers.[707] In the presence of a chiral Cu complex, *Claisen rearrangements* proceed with good enantioselectivity.[708] *N*-Heterocyclic carbenes catalyzed an enantioselective *Claisen rearrangement*.[709] A chiral hydrogen-bond donor has been used for enantioselective *Claisen rearrangements*.[710] A chiral allylic ether gave an enantioselective *Claisen rearrangement* with an Ir catalyst.[711]

[696] Conroy, H.; Firestone, R.A. *J. Am. Chem. Soc.* ***1956****, 78,* 2290.
[697] Sharghi, H.; Aghapour, G. *J. Org. Chem.* ***2000****, 65*, 2813.
[698] Wipf, P.; Ribe, S. *Org. Lett.* ***2001****, 3*, 1503.
[699] Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.C. *Synlett* ***2000***, 1129.
[700] See Ziegler, F.E. *Chem. Rev.* ***1988****, 88*, 1423.
[701] Claisen, L. *Ber.* ***1912****, 45,* 3157.
[702] See Boeckman, Jr., R.K.; Flann, C.J.; Poss, K.M. *J. Am. Chem. Soc.* ***1985****, 107,* 4359.
[703] For reviews, see Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* ***2002***, 1461; Majumdar, K.C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* ***2008****, 64,* 597.
[704] Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J. Org. Chem.* ***1989****, 54,* 5849. See Guest, J.M.; Craw, J. S.; Vincent, M.A.; Hillier, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 71; Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* ***1995****, 117*, 11337.
[705] Kotha, S.; Mandal, K.; Deb, A.C.; Banerjee, S. *Tetrahedron Lett.* ***2004****, 45*, 9603.
[706] Lin, Y.-L.; Cheng, J.-Y.; Chu, Y.-H. *Tetrahedron* ***2007****, 63*, 10949.
[707] See Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1989****, 111*, 511.
[708] Balta, B.; Öztürk, C.; Aviyente, V.; Vincent, M.A.; Hillier, I.H. *J. Org. Chem.* ***2008****, 73,* 4800.
[709] Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J.W. *J. Am. Chem. Soc.* ***2010****, 132,* 8810.
[710] Uyeda, C.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2008****, 130*, 9228.
[711] Nelson, S.G.; Kan Wang, K. *J. Am. Chem. Soc.* ***2006****, 128*, 4232.

Since the *Claisen rearrangement* mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring.[712] This is the case. Electron-donating groups increase the rate and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only ~10–20 times faster than the *p*-nitro compound.[713] However, solvent effects[714] are greater: Rates varied over a 300-fold range when the reaction was run in 17 different solvents.[715] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[716] Most *Claisen rearrangements* are performed without a catalyst, but $AlCl_3$ or BF_3 are sometimes used.[717] In this case, it may become a *Friedel–Crafts reaction*, with the mechanism no longer cyclic,[718] and ortho, meta, and para products may be obtained.

Allyl allene ethers undergo a *Claisen rearrangement* when heated in DMF to give the expected diene with a conjugated aldehyde unit.[719] Butenolides with a β-allylic ether unit undergo *Claisen rearrangement–Conia reaction*[720] cascade to give an oxaspiroheptane with β-keto lactone comprising the five-membered ring.[721] Allylic esters of β-keto acids undergo a *Claisen rearrangement* in what is known as the *Carroll rearrangement*[722] (also called the *Kimel–Cope rearrangement*[723]), and the reaction can be catalyzed by a Ru complex.[724] An asymmetric *Carroll rearrangement* was catalyzed by a chiral Pd complex.[725]

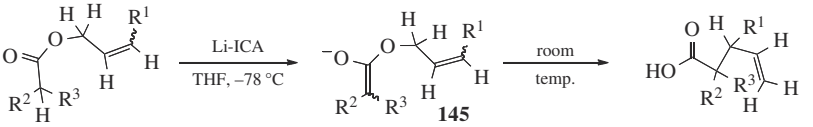
Heating an allylic alcohol with *N,N*-dimethylacetamide dimethyl acetal yields a transient intermediate, and subsequent *Claisen rearrangement* gives an amide in a sequence that is known as the *Eschenmoser variant* or the *Eschenmoser–Claisen rearrangement*.[726] This reaction has also been called the *Meerwein–Eschenmoser Claisen rearrangement*.[727] An enantioselective version has been reported using a chiral Pd complex.[728]

The enolate anions (**145**) of allylic esters (formed by treatment of the esters with LICA) rearrange to γ,δ-unsaturated acids.[729] Alternatively, the silylketene acetal $[R^3R^2C{=}C(OSiR_3)OCH_2CH{=}CHR^1]$ may be used instead of **145**.[730] This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland–*

[712] There are substituent effects, see Aviyente, V.; Yoo, H.Y.; Houk, K.N. *J. Org. Chem.* ***1997****, 62*, 6121.
[713] White, W.N.; Slater, C.D. *J. Org. Chem.* ***1962****, 27,* 2908; Zahl, G.; Kosbahn, W.; Kresze, G. *Liebigs Ann. Chem.* ***1975***, 1733. See also, Desimoni, G.; Faita, G.; Gamba, A.; Righetti, P.P.; Tacconi, G.; Toma, L. *Tetrahedron* ***1990****, 46*, 2165; Gajewski, J.J.; Gee, K.R.; Jurayj, J. *J. Org. Chem.* ***1990****, 55,* 1813.
[714] See Gajewski, J.J. *Accts. Chem. Res.* ***1997****, 30*, 219.
[715] White, W.N.; Wolfarth, E.F. *J. Org. Chem.* ***1970****, 35*, 2196. See also, Brandes, E.; Greico, P.A.; Gajewski, J.J. *J. Org. Chem.* ***1989****, 54*, 515.
[716] Svanholm, U.; Parker, V.D. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 169.
[717] See Lutz, R.P. *Chem. Rev.* ***1984****, 84*, 205.
[718] See Yagodin, V.G.; Bunina-Krivorukova, L.I.; Bal'yan, Kh.V. *J. Org. Chem. USSR* ***1971****, 7,* 1491.
[719] Parsons, P.J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.* ***2000****, 2*, 571.
[720] For a review of the *Conia-ene reaction*, see Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1.
[721] Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* ***2001***, 1951.
[722] Carroll, M.F. *J. Chem. Soc.* ***1941***, 507; Ziegler, F.E. *Chem. Rev.* ***1988****, 88*, 1423.
[723] Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* ***1943****, 65*, 1992.
[724] Burger, E.C.; Tunge, J.A. *Org. Lett.* ***2004****, 6,* 2603.
[725] Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* ***2005***, 3951.
[726] Felix, D.; Gschwend-Steen, K.; Wick, A.E.; Eschenmoser, A. *Helv. Chim. Acta* ***1969****, 52*, 1030.
[727] Gradl, S. N.; Trauner, D. in *The Meerwein–Eschenmoser–Claisen Rearrangement. In The Claisen Rearrangement*, Hiersemann, M.; Nubbemeyer, U., Eds., Wiley–VCH, Weinheim, ***2007***, pp 367–396.
[728] Linton, E.C.; Kozlowski, M.C. *J. Am. Chem. Soc.* ***2008****, 130,* 16162.
[729] Gajewski, J.J.; Emrani, J. *J. Am. Chem. Soc.* ***1984****, 106,* 5733; Cameron A.G.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 161. See Wilcox, C.S.; Babston, R.E. *J. Am. Chem. Soc.* ***1986****, 108*, 6636.
[730] Ireland, R.E.; Wipf, P.; Armstrong, III, J.D. *J. Org. Chem.* ***1991****, 56,* 650. See also Ref. 714.

Claisen rearrangement.[731] Note the presence of the negative charge in **145**. As with the *oxy-Cope rearrangement* (in Reaction **18-34**), negative charges generally accelerate the *Claisen reaction*,[732] although the extent of the acceleration can depend on the identity of the positive counterion.[733] The reaction proceeds with good syn selectivity in many cases.[734] The *Ireland–Claisen rearrangement* has been made enantioselective by converting **145** to an enol borinate in which the boron is attached to a chiral group.[735] The *Ireland–Claisen rearrangement* can be done with amide derivatives also.[736]

As just mentioned, asymmetric *Claisen rearrangement* reactions are well known.[737] Chiral Lewis acids have been designed for this purpose.[738] In general, asymmetric [3,3]-sigmatropic rearrangements are well known.[739]



145

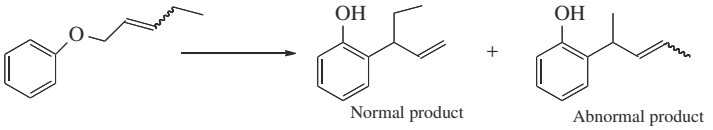
A number of analogues of the *Claisen rearrangement* are known, for example, rearrangement of $ArNHCH_2CH{=}CH_2$,[740] of *N*-allylic enamines $(R_2C{=}CRNRCR_2CR{=}CR_2)$[741] of allylic imino esters $[RC(OCH_2CH{=}CH_2){=}NR]$[742] (these have often been rearranged with transition metal catalysts[743]), and of $RCH{=}NRCHRCH_2CH{=}CH_2$. These rearrangements of nitrogen-containing compounds can be called *aza-Claisen rearrangements,*[744] but are sometimes called *aza-Cope rearrangements*,[745] as described in Reaction **18-32**. A Pd catalyzed *aza-Claisen* has been reported.[746] An important contribution to this variation is the rearrangement of

[731] See Chai, Y.; Hong, S.-p.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* ***2002****, 58*, 2905.
[732] See Denmark, S.E.; Harmata, M.A.; White, K.S. *J. Am. Chem. Soc.* ***1989****, 111*, 8878.
[733] Koreeda, M.; Luengo, J.I. *J. Am. Chem. Soc.* ***1985****, 107,* 5572; Kirchner, J.J.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* ***1988****, 29,* 4229.
[734] Mohamed, M.; Brook, M.A. *Tetrahedron Lett.* ***2001****, 42*, 191. See Khaledy, M.M.; Kalani, M.Y.S.; Khuong, K.S.; Houk, K.N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* ***2003****, 68*, 572.
[735] Corey, E.J.; Lee, D. *J. Am. Chem. Soc.* ***1991****, 113,* 4026.
[736] Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* ***1993****, 34*, 3297; Walters, M.A.; Hoem, A.B.; Arcand, H.R.; Hegeman, A.D.; McDonough, C.S. *Tetrahedron Lett.* ***1993****, 34*, 1453.
[737] See Zumpe, F.L.; Kazmaier, U. *Synlett* ***1998***, 434; Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* ***1997****, 38*, 4815; Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed.* ***1995****, 34*, 2012. For asymmetric induction in the thio-Claisen rearrangement, see Reddy, K.V.; Rajappa, S. *Tetrahedron Lett.* ***1992****, 33*, 7957.
[738] Maruoka, K.; Saito, S.; Yamamoto, J. *J. Am. Chem. Soc.* ***1995****, 117*, 1165. See Hiersemann, M.; Abraham, L. *Org. Lett.* ***2001****, 3*, 49; Miller, S.P.; Morken, J.P. *Org. Lett.* ***2002****, 4*, 2743.
[739] For a review, see Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron Asymmetry,* ***1996****, 7*, 1847.
[740] Jolidon, S.; Hansen, H. *Helv. Chim. Acta* ***1977****, 60,* 978.
[741] Anderson, J.C.; Flaherty, A.; Swarbrick, M.E. *J. Org. Chem.* ***2000****, 65*, 9152. See Wu, P.; Fowler, F.W. *J. Org. Chem.* ***1988****, 53,* 5998.
[742] See Metz, P.; Mues, C. *Tetrahedron* ***1988****, 44*, 6841. Also see Gradl, S.N.; Kennedy-Smith, J.J.; Kim, J.; Trauner, D. *Synlett* ***2002***, 411.
[743] See Schenck, T.G.; Bosnich, B. *J. Am. Chem. Soc.* ***1985****, 107,* 2058, and references cited therein; Anderson, C.E.; Overman, L.E. *J. Am. Chem. Soc.* ***2003****, 125*, 12412.
[744] See Kirsch, S.F.; Overman, L.F.; Watson, M.P. *J. Org. Chem.* ***2004****, 69*, 8101. For a review, see Majumdar, K.C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* ***2009***, 2117. See also, Forte, L.; Lafortune, M.C.; Bierzynski, I.R.; Duncan, J.A. *J. Am. Chem. Soc.* ***2010****, 132*, 2196.
[745] Blechert, S. *Synthesis* ***1989***, 71; Heimgartner, H.; Hansen, H.; Schmid, H. *Adv. Org. Chem.* ***1979****, 9,* pt. 2, 655.
[746] Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron Asymmetry,* ***1998****, 9*, 1065. See Gilbert, J.C.; Cousins, K.R. *Tetrahedron* ***1994****, 50*, 10671.

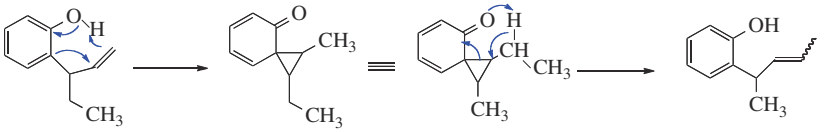
trichloroacetimidate derivatives of prochiral (*Z*)-2-alken-1-ols, usually with a Pd catalyst, to give chiral allylic esters.[747] There is a catalytic enantioselective *aza-Cope rearrangement*.[748] A so-called *amine-Claisen rearrangement* was reported for *N*-allyl indoles, when heated in the presence of $BF_3{\bullet}OEt_2$.[749] An *azo-Cope* rearrangement, $CH_2{=}CHCR_2'){CR_2}'N{=}NAr \rightarrow R_2'C{=}CHCH_2NArN{=}CR_2{}^2$, has been reported.[750] In a related reaction, allylic phorphorimidates undergo [3,3]-sigmatropic rearrangement.[751]

The conversion of allylic aryl thioethers, ($ArSCH_2CH{=}CH_2$) to *o*-allylic thiophenols is not feasible, because the latter are not stable,[752] but react to give bicyclic compounds.[753] However, many allylic vinylic sulfides do give the rearrangement (the *thio-Claisen rearrangement*).[754] Allylic vinylic sulfones (e.g., $H_2C{=}CRCH_2{-}SO_2{-}CH{=}CH_2$) rearrange, when heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts ($CH_2{=}CRCH_2CH_2CH_2SO_3^-$), produced by reaction of the reagents with the unstable sulfene intermediates $CH_2{=}CRCH_2CH_2CH{=}SO_2$.[755] Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.[756] Chiral vinyl sulfoxides undergo *Claisen rearrangement* with good enantioselectivity.[757]

Ethers with an alkyl group in the γ position (ArO—C—C=C—R systems) sometimes give abnormal products, with the β carbon becoming attached to the ring[758]:

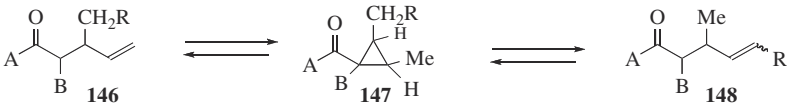


It has been established that these abnormal products do not arise directly from the starting ether, but are formed by a further rearrangement of the normal product[759]:



[747] Kirsch, S.F.; Overman, L.E. *J. Am. Chem. Soc.* ***2005****, 127,* 2866; Watson, M.P.; Overman, L.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***2007****, 129,* 5031.
[748] Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* ***2008****, 47*, 10090.
[749] Anderson, W.K.; Lai, G. *Synthesis* ***1995***, 1287.
[750] Mitsuhashi, T. *J. Am. Chem. Soc.* ***1986****, 108,* 2400.
[751] Chen, B.; Mapp, A.K. *J. Am. Chem. Soc.* ***2005****, 127*, 6712.
[752] They have been trapped: See, for example, Mortensen, J.Z.; Hedegaard, B.; Lawesson, S. *Tetrahedron* ***1971****, 27,* 3831; Kwart, H.; Schwartz, J.L. *J. Org. Chem.* ***1974****, 39,* 1575.
[753] Kwart, H.; Cohen, M.H. *J. Org. Chem.* ***1967****, 32*, 3135; *Chem. Commun.* ***1968***, 319; Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* ***1969***, 1971, 2449.
[754] For a review, see Majumdar, K.C.; Ghosh, S.; Ghosh, M. *Tetrahedron* ***2003****, 59,* 7251.
[755] King, J.F.; Harding, D.R.K. *J. Am. Chem. Soc.* ***1976****, 98*, 3312.
[756] Block, E.; Ahmad, S. *J. Am. Chem. Soc.* ***1985****, 107*, 6731.
[757] de la Pradilla, R.F.; Montero, C.; Tortosa, M.; Viso, A. *Chemistry: Eur. J.* ***2009****, 15,* 697.
[758] For abnormal *Claisen rearrangements*, see Hansen, H. *Mech. Mol. Migr.* ***1971****, 3,* 177; Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 743–750.
[759] Lauer, W.M.; Johnson, T.A. *J. Org. Chem.* ***1963****, 28*, 2913; Fráter, G.; Schmid, H. *Helv. Chim. Acta* ***1966****, 49*, 1957; Marvell, E.N.; Schatz, B. *Tetrahedron Lett.* ***1967***, 67.

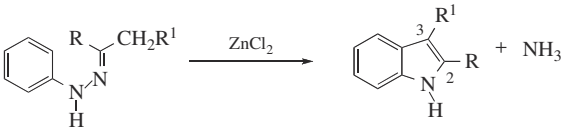
This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5]-*sigmatropic hydrogen shift* (see Reaction **18-29**), and a [1,5]-*homosigmatropic rearrangement*, involves a shift of three electron pairs over *seven* atoms. It has been found that this "abnormal" *Claisen rearrangement* is general and can interconvert the enol forms of systems of the types **146** and **147** through the cyclopropane intermediate (**148**).[760]



A = H, R, Ar, OR, and so on B = H, R, Ar, COR, COAr, COOR, and so on

OS **III**, 418; **V**, 25; **VI**, 298, 491, 507, 584, 606; **VII**, 177; **VIII**, 251, 536.

18-34 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in the *Fischer indole synthesis*.[761] Zinc chloride is a commonly used catalyst, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition metals have also been used. Microwave irradiation has been used to facilitate this reaction.[762] The reaction has been done using an $AlCl_3$ complex as an ionic liquid,[763] and solid-phase *Fischer indole syntheses* are known.[764] Aniline derivatives react with α-diazoketones, in the presence of a Rh catalyst, to give indoles as well.[765] Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (Reaction **16-2**) or by aliphatic diazonium coupling (Reaction **12-7**). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). Vinyl ethers (e.g., dihydrofuran) serve as an aldehyde surrogate when treated with phenylhydrazine and a catalytic amount of aq H_2SO_4 to give an 3-substituted indole.[766]

[760] Watson, J.M.; Irvine, J.L.; Roberts, R.M. *J. Am. Chem. Soc.* ***1973****, 95,* 3348.

[761] Robinson, B. *The Fischer Indole Synthesis*, Wiley, NY, ***1983***; Grandberg, I.I.; Sorokin, V.I. *Russ. Chem. Rev.* ***1974****, 43*, 115; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 190–207; Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, NY, ***1970***, pp. 142–163; Robinson, B. *Chem. Rev.* ***1969****, 69*, 227. For reviews of so-called abnormal *Fischer indole syntheses*, see Ishii, H. *Acc. Chem. Res.* ***1981****, 14*, 275; Fusco, R.; Sannicolo, F. *Tetrahedron* ***1980****, 36,* 161.

[762] Lipinska, T.; Guibé-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* ***1999****, 29*, 1349.

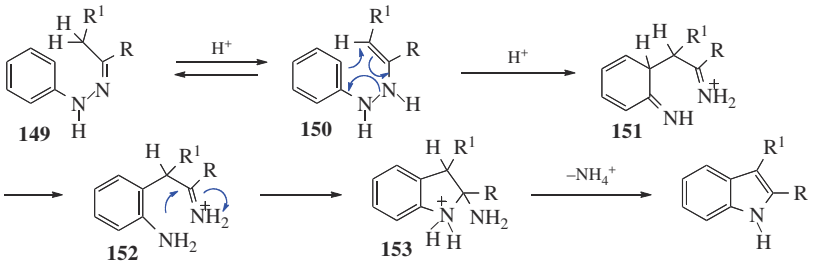
[763] Rebeiro, G.LO.; Khadilkar, B.M. *Synthesis* ***2001***, 370.

[764] Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun.* ***2003***, 1822.

[765] Moody, C.J.; Swann, E. *Synlett* ***1998***, 135.

[766] Campos, K.R.; Woo, J.C.S.; Lee, S.; Tillyer, R.D. *Org. Lett.* ***2004****, 6*, 79.

At first glance, the reaction does not seem to be a rearrangement. However, the key step of the mechanism[767] is a [3,3]-sigmatropic rearrangement[768]:

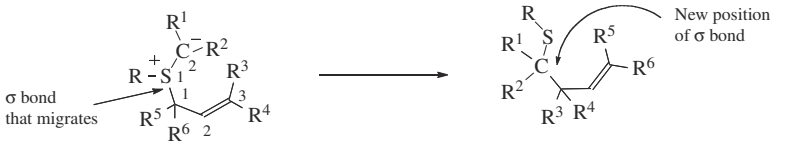


There is much evidence for this mechanism, for example, (1) the isolation of **153**,[769] (2) the detection of **152** by ^{13}C and ^{15}N NMR,[770] (3) the isolation of side products that could only have come from **151**,[771] and (4) ^{15}N-labeling experiments showing that it was the nitrogen farther from the ring that is eliminated as ammonia.[772] The main function of the catalyst seems to be to speed the conversion of **149** to **150**. The reaction can be performed without a catalyst.

OS **III**, 725; **IV**, 884. Also see, OS **IV**, 657.

18-35 [2,3]-Sigmatropic Rearrangements

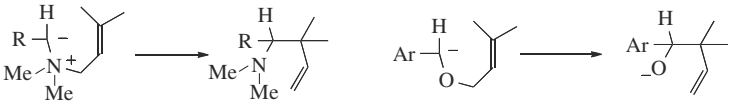
(2/*S*-3/)→(1/5/)-*sigma*-Migration



Sulfur ylids bearing an allylic group are converted to unsaturated sulfides on heating.[773] This is a concerted [2,3]-sigmatropic rearrangement[774] and has also been demonstrated for the analogous cases of nitrogen ylids[775] and the conjugate bases of allylic ethers (in the last case it is called a *[2,3]-Wittig rearrangement*).[776] It has been argued that the *[2,3]-Wittig rearrangement* demands severe deformation of the molecule in order to proceed.[777] It has been shown that SmI_2 induces a *[2,3]-Wittig rearrangement*.[778] The reaction has been

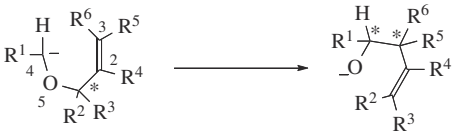
[767] For a mechanistic study, see Hughes, D.L.; Zhao, D. *J. Org. Chem.* ***1993****, 58*, 228.
[768] This mechanism was proposed by Robinson, G.M.; Robinson, R. *J. Chem. Soc.* ***1918****, 113,* 639.
[769] See Forrest, T.P.; Chen, F.M.F. *J. Chem. Soc., Chem. Commun.* ***1972***, 1067.
[770] Douglas, A.W. *J. Am. Chem. Soc.* ***1978****, 100*, 6463; ***1979****, 101*, 5676.
[771] Bajwa, G.S.; Brown, R.K. *Can. J. Chem.* ***1969****, 47,* 785; ***1970****, 48*, 2293 and references cited therein.
[772] Clausius, K.; Weisser, H.R. *Helv. Chim. Acta* ***1952****, 35,* 400.
[773] See Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* ***2005****, 127,* 15106. For a review as applied to ring expansions, see Vedejs, E. *Acc. Chem. Res.* ***1984****, 17,* 358.
[774] See Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1979****, 18,* 563.
[775] See Mander, L.N.; Turner, J.V. *J. Org. Chem.* ***1973****, 38*, 2915; Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* ***1990****, 112*, 1999.
[776] Nakai, T.; Mikami, K. *Chem. Rev.* ***1986****, 86,* 885. See Schöllkopf, U.; Fellenberger, K.; Rizk, M. *Liebigs Ann. Chem.* ***1970****, 734,* 106; Rautenstrauch, V. *Chem. Commun.* ***1970***, 4. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1063–1067.
[777] You, Z.; Koreeda, M. *Tetrahedron Lett.* ***1993****, 34*, 2597.
[778] Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* ***1997****, 62*, 7542. Also see, Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***1998****, 39*, 5229. For an enantioselective *[2,3]-Wittig rearrangement*, see Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* ***1994****, 35*, 5019.

extended to certain other systems,[779] even to an all-carbon system.[780]



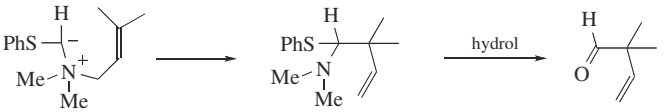
Treatment of an α-(*N*-allylic amino) ketone with NaH led to 2-allylic α-amino ketones via a [2,3]-rearrangement.[781] In the presence of a chiral ligand on nitrogen,[781] or with a chiral additive,[782] good asymmetric induction is possible. Vinylaziridines undergo [2.3]-sigmatropic rearrangement.[783]

Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the *Stevens or Wittig rearrangements* (**18-21** and **18-22**). However, in this case the migrating group *must* be allylic (in **18-21** and **18-22** other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (1) the radical-ion or ion-pair mechanisms (**18-21** and **18-22**) and (2) the concerted pericyclic [2,3]-sigmatropic rearrangement. These are easily distinguished since the latter always involves an allylic shift (as in the *Claisen rearrangemen*t), while the former pathway does not.



Of these reactions, the *[2,3]-Wittig rearrangement* in particular has often been used as a means of transferring chirality. The product of this reaction has potential stereogenic centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a stereogenic center at C-1, the product may be optically active as well. Many examples are known in which optically active ethers were converted to a product that was optically active because of chirality at C-3, C-4, or both.[784] If a suitable stereogenic center is present in R^1 (or if a functional group in R^1 can be so converted), then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of β,γ-unsaturated aldehydes, because the product is easily hydrolyzed.[785]



[779] See Murata, Y.; Nakai, T. *Chem. Lett.* ***1990***, 2069. Also see Reich, H.J. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 365–393; Reich, H.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 102–111.

[780] Baldwin, J.E.; Urban, F.J. *Chem. Commun.* ***1970***, 165.

[781] Workman, J.A.; Garrido, N.P.; Sançon, J.; Roberts, E.; Wessel, H.P.; Sweeney, J.B. *J. Am. Chem. Soc.* ***2005***, *127,* 1066.

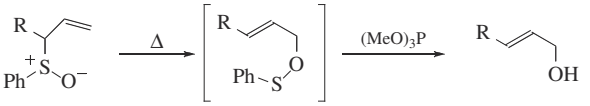
[782] Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* ***2005***, *127,* 9352.

[783] Somfai, P.; Panknin, O. *Synlett* ***2007***, 1190.

[784] Mikami, K.; Nakai, T. *Synthesis* ***1991***, 594; Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885, pp. 888–895. See also, Scheuplein, S.W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* ***1990***, *123,* 917; Wu, Y.; Houk, K.N.; Marshall, J.A. *J. Org. Chem.* ***1990***, *55,* 1421; Marshall, J.A.; Wang, X. *J. Org. Chem.* ***1990***, *55,* 2995.

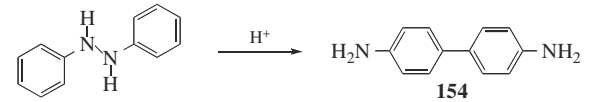
[785] Huynh, C.; Julia, S.; Lorne, R.; Michelot, D. *Bull. Soc. Chim. Fr.* ***1972***, 4057.

Another [2,3]-sigmatropic rearrangement converts allylic sulfoxides to rearranged allylic alcohols by treatment with a thiophilic reagent (e.g., trimethyl phosphite).[786] This is the *Mislow–Evans rearrangement*. In this case, the migration is from sulfur to oxygen. [2,3]-Oxygen-to-sulfur migrations are also known.[787] The *Sommelet–Hauser rearrangement* discussed in Reaction **13-31** is also a [2,3]-sigmatropic rearrangement.



OS **VIII**, 427.

18-36 The Benzidine Rearrangement



Hydrazobenzene **154**

When hydrazobenzene is treated with acids, it rearranges to give ~70% 4,4′-diaminobiphenyl (**154**, benzidine) and ~30% 2,4′-diaminobiphenyl. This reaction is called the *benzidine rearrangement* and is general for *N,N*′-diarylhydrazines.[788] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced: the 2,4′-diaminobiaryl, already referred to, the 2,2′-diaminobiaryl, and the *o*- and *p*-arylaminoanilines (called *semidines*). The 2,2′- and *p*-arylaminoaniline compounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4′-diaminobiaryl predominates, except when one or both para positions of the diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced even if the para positions are occupied. If SO_3H, CO_2H, or Cl (but not R, Ar, or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′ isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN=NAr. For example, *p,p*′-$PhC_6H_4NHNHC_6H_4Ph$ gives 88% disproportionation products at 25 °C.[789]

The mechanism has been exhaustively studied and several mechanisms have been proposed.[790] At one time, it was believed that NHAr broke away from ArNHNHAr and became attached to the para position to give the semidine, which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (Reaction **11-28**–**11-32**). However, this theory was proved incorrect when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two

[786] Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* ***1974****, 7,* 147; Hoffmann, R.W. *Angew. Chemie. Int. Ed., Engl.,* ***1979****, 18,* 563; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* ***1989****, 54,* 2779.

[787] See Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. *J. Org. Chem.* ***1990****, 55,* 1823.

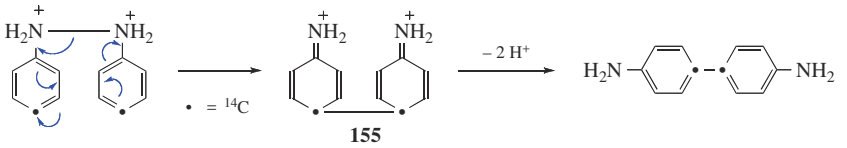
[788] Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, the reviews by Cox, R.A.; Buncel, E. pp. 775–807; Koga, G.; Koga, N.; Anselme, J. pp. 914–921; Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, Vol. 13, 1972, pp. 437–448; Shine, H.J. *Mech. Mol. Migr.* ***1969****, 2,* 191; Banthorpe, D.V. *Top. Carbocyclic Chem.* ***1969****, 1*, 1.

[789] Shine, H.J.; Stanley, J.P. *J. Org. Chem.* ***1967****, 32,* 905. For investigations of the mechanism of the disproportionation reactions, see Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986****, 108,* 1000; ***1987****, 109,* 5052.

[790] For a history, see Shine, H.J. *J. Phys. Org. Chem.* ***1989****, 2,* 491.

independent pieces (either ions or radicals) has been ruled out by many types of cross-over experiments, which always showed that the two rings of the starting material are in the product; that is, ArNHNHAr′ gives no molecules (of any of the five products) containing two Ar groups or two Ar′ groups, and mixtures of ArNHNHAr and Ar′NHNHAr′ give no molecules containing both Ar and Ar′. An important discovery was the fact that, although the reaction is always first order in substrate, it can be either first[791] or second[792] order in $[H^+]$. With some substrates the reaction is entirely first order in $[H^+]$, while with others it is entirely second order in $[H^+]$, regardless of the acidity. With still other substrates, the reaction is first order in $[H^+]$ at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,[793] because at intermediate acidities, both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate $ArNHNH_2Ar$ or the diprotonated $ArNH_2NH_2Ar$.

Most of the proposed mechanisms[794] attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products are formed in entirely different ways, as shown by isotope-effect studies.[795] When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of **154**, but 1.063 for formation of 2,4′-diaminobiphenyl. This showed that the N—N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a para position, there was an isotope effect of 1.028 for formation of **154**, but essentially no isotope effect (1.001) for formation of 2,4′-diaminobiphenyl. This can only mean that for **154** formation of the new C—C bond *and* breaking of the N—N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5.5]-sigmatropic rearrangement accounts for this[796]:



The diion **155** was obtained as a stable species in superacid solution at −78 °C by treatment of hydrazobenzene with $FSO_3H—SO_2$ (SO_2ClF).[797] Although the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5]-sigmatropic mechanism.[798]

[791] Shine, H.J.; Chamness, J.T. *J. Org. Chem.* ***1963****, 28,* 1232; Banthorpe, D.V.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 627.
[792] Banthorpe, D.V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* ***1971***, 2054.
[793] Banthorpe, D.V.; Ingold, C.K.; Roy, J. *J. Chem. Soc. B* ***1968***, 64; Banthorpe, D.V.; Ingold, C.K.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 624.
[794] Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1964***, 2864; Dewar, M.J.S. in de Mayo, P. *Molecular Rearrangments,* Vol. 1, Wiley, NY, ***1963***, pp. 323–344.
[795] Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982****, 104*, 2501.
[796] This step was also part of the "polar-transition-state mechanism". See also Ref. 793.
[797] Olah, G.A.; Dunne, K.; Kelly, D.P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1972****, 94,* 7438.
[798] Shine, H.J.; Park, K.H.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984****, 106,* 7077.

Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine takes place by a [1,5]-sigmatropic rearrangement,[799] and the conversion of 2,2′-hydrazonaphthalene to 2,2′-diamino-1,1′-binaphthyl by a [3,3] sigmatropic rearrangement.[800]

2,4′-Diaminobiphenyl is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N—N bond, but the C—C bond is not formed during this step.[801] The formation of the *o*-semidine also takes place by a nonconcerted pathway.[802] Under certain conditions, benzidine rearrangements have been found to go through radical cations.[803]

C. Other Cyclic Rearrangements

18-37 Metathesis of Alkenes (Alkene or Olefin Metathesis)[804]

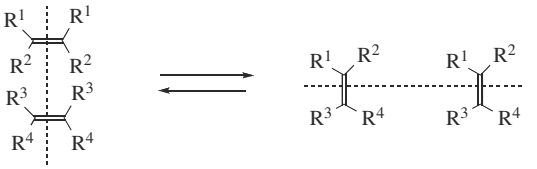
Alkene metathesis

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6-EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When alkenes are treated with certain catalysts they are converted to other alkenes in a reaction in which one set of alkylidene groups ($R^1R^2C{=}$) have become interchanged with other alkylidene groups ($R^3R^4C{=}$) by a process schematically illustrated by the equilibrium reaction shown below. In an early example shown above, 2-pentene (either cis, trans, or a cis–trans mixture) is converted to a mixture of ~50% 2-pentene, 25% 2-butene, and 25% 3-hexene. Nowadays, superior catalysts and experimental procedures have made this reaction synthetically useful (see below). The reaction is reversible[805] and the alkene starting material and products exist in equilibrium, so the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.[806] The reaction is called *metathesis* of alkenes or *alkene metathesis* (*olefin metathesis*).[807] In general, the reaction can be applied to a single unsymmetrical alkene, giving a mixture of itself and two other

[799] See Shine, H.J.; Zmuda, H.; Kwart, H.; Horgan, A.G.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982****, 104,* 5181.
[800] Shine, H.J.; Gruszecka, E.; Subotkowski, W.; Brownawell, M.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1985****, 107*, 3218.
[801] See Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986****, 108*, 1000; ***1987****, 109*, 5052.
[802] Rhee, E.S.; Shine, H.J. *J. Org. Chem.* ***1987****, 52*, 5633.
[803] See Nojima, M.; Ando, T.; Tokura, N. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 1504.
[804] Grubbs, R.H. *Tetrahedron* ***2004****, 60*, 7117; Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002****, 41*, 2403; Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003****, 42,* 4592. See Astruc, D. *New J. Chem.* ***2005****, 29*, 42; Chauvin, Y. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3740; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3748; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3760.
[805] Smith, III, A.B.; Adams, C.M.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2001****, 123*, 990.
[806] See Wang, J.; Menapace, H.R. *J. Org. Chem.* ***1968****, 33,* 3794; Hughes, W.B. *J. Am. Chem. Soc.* ***1970****, 92,* 532.
[807] Dragutn, V.; Balaban, A.T.; Dimonie, M. *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, Wiley, NY, ***1985***; Ivin, K.J. *Olefin Metathesis*, Academic Press, NY, ***1983***; Feast, W.J.; Gibson, V.C. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 5, Wiley, NY, 1989, pp. 199–228; Schrock, R.R. *J. Organomet. Chem.* ***1986****, 300*, 249; Grubbs, R.H. in Wilkinson, G *Comprehensive Organometallic Chemistry*, *Vol. 8,* Pergamon, Elmsford, NY, ***1982***, pp. 499–551; Basset, J.M.; Leconte, M. *CHEMTECH* ***1980***, 762; Banks, R.L. *Fortschr. Chem. Forsch.* ***1972****, 25,* 39; Calderon N.; Lawrence, J.P.; Ofstead, E.A. *Adv. Organomet. Chem.* ***1979****, 17,* 449; Grubbs, R.H. *Prog. Inorg. Chem.* ***1978****, 24,* 1; Calderon N. in Patai, S. *The Chemistry of Functional Groups: Supplement A* pt. 2, Wiley, NY, ***1977***, pp. 913–964; *Acc. Chem. Res.* ***1972****, 5,* 127; Katz, T.J. *Adv. Organomet. Chem.* ***1977****, 16,* 283; Haines, R.J.; Leigh, G.J. *Chem. Soc. Rev.* ***1975****, 4,* 155.

alkenes, or to a mixture of two alkenes, in which case the number of different molecules in the product depends on the symmetry of the reactants. In the example, a mixture of $R^1R^2C{=}CR^1R^2$ and $R^3R^4C{=}CR^3R^4$ gives rise to only one new alkene ($R^1R^2C{=}CR^3R^4$), while in the most general case, the reaction of two alkenes ($R^1R^2C{=}CR^3R^4$ and $R^5R^6C{=}CR^7R^8$) can give a mixture of 10 alkenes: the original $2 + 8$ new ones. In early work, W, Mo,[808] or Re complexes were used, and with simple alkenes the proportions of products are generally statistical,[809] which limited the synthetic utility of the reaction since the yield of any one product is low. In some cases, one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical in all cases.



It is possible to shift the equilibrium to favor certain products. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.[810] This example shows that it is possible to tailor the substrate to include two terminal alkenes that lead to ethylene as a product, whose escape from the reaction drives the equilibrium to product.

The development of better catalysts has revolutionized this reaction,[811] making it one of the most important methods available for modern synthesis. Both homogeneous[812] and heterogeneous[813] catalysts have been used for this reaction. Of the many homogeneous catalysts, Ru complexes are the most important,[814] and important heterogeneous catalysts include oxides of Mo, W, and Re deposited on alumina or silica gel.[815] The major breakthrough in these catalysts was the development of catalysts that are relatively air stable. Three important catalysts are metal carbene complexes **156**[816] and **157**[817] (*Grubbs catalyst I and II;* Mes = mesityl, respectively), and **158** (the *Shrock catalyst*).[818]

[808] See Crowe, W.E.; Zhang, Z.J. *J. Am. Chem. Soc.* ***1993****, 115*, 10998.; Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1993****, 115*, 3800.

[809] Calderon N.; Ofstead, E.A.; Ward, J.P.; Judy, W.A.; Scott, K.W. *J. Am. Chem. Soc.* ***1968****, 90*, 4133.

[810] Knoche, H. Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.,* ***1971****, 74*, 44118b]. See also, Ichikawa, K.; Fukuzumi, K. *J. Org. Chem.* ***1976****, 41,* 2633; Baker, R.; Crimmin, M.J. *Tetrahedron Lett.* ***1977***, 441.

[811] See Conrad, J.C.; Parnas, H.H.; Snelgrove, J.L.; Fogg, D.E. *J. Am. Chem. Soc.* ***2005****, 127*, 11882.

[812] Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327. See Hughes, W.B. *Organomet. Chem. Synth.* ***1972****, 1,* 341, see pp. 362–368.; Toreki, R.; Schrock, R.R. *J. Am. Chem. Soc.* ***1990****, 112,* 2448.

[813] Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.,* ***1964****, 3,* 170. See also, Banks, R.L. *CHEMTECH* ***1986***, 112.

[814] Gilbertson, S.R.; Hoge, G.S.; Genov, D.G. *J. Org. Chem.* ***1998****, 63*, 10077; Maier, M.E.; Bugl, M. *Synlett* ***1998***, 1390; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* ***1998****, 63*, 2808.

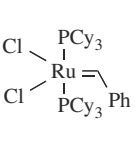
[815] See Banks, R.L. *Fortschr. Chem. Forsch.* ***1972****, 25*, 39, pp. 41–46.

[816] Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1996****, 118*, 100.

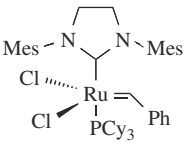
[817] Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* ***1999****, 1*, 953.

[818] Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc.* ***1991****, 113*, 6899, and references cited therein.

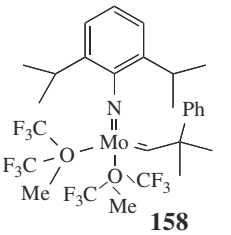
Catalyst **157** can be generated *in situ* from air stable precursors.[819]



156



157



158

The synthetic importance[820] of ring-closing and ring-opening metathesis reactions has, in part, led to the ongoing development of new catalysts.[821] Catalysts have been developed that are compatible with both water and methanol.[822] The reaction is compatible with the presence of other functional groups[823] (e.g., other alkene units,[824] carbonyl units,[825] the alkene unit of conjugated esters,[826] butenolides[827] and other lactones,[828] amines,[829] amides,[830] sulfones,[831] phosphine oxides,[832] sulfonate esters,[833] and sulfonamides,[834] see **149**).[835] Ether groups,[836] including vinyl ethers,[837] vinyl halides,[838] vinyl silanes,[839] vinyl sulfones,[840] allylic ethers,[841] and thioethers[842] are also compatible.

[819] Louie, J.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2001****, 40*, 247.
[820] See Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem. Int. Ed.* ***2005****, 44,* 4490; Donohoe, T.J.; Fishlock, L.P.; Procopiou, P.A. *Chemistry: European J.* ***2008****, 14,* 5716; Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* ***2006****, 45,* 6086.
[821] Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003*** *. 42*, 4592; Grela, K.; Kim, M. *Eur. J. Org. Chem.* ***2003***, 963; Zhang, W.; Kraft, S.; Moore, J.S. *J. Am. Chem. Soc.* ***2004****, 126*, 329; Iyer, K.; Rainier, J.D. *J. Am. Chem. Soc.* ***2007****, 129,* 12604; Vougioukalakis, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2008****, 130,* 2234; Matsugi, M.; Curran, D.P. *J. Org. Chem.* ***2005****, 70,* 1636; Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S.P.; Mauduit, M. *J. Org. Chem.* ***2008****, 73,* 4225; Katz, T.J. *Angew. Chem. Int. Ed.* ***2005****, 44,* 3010.
[822] Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem.* ***1998****, 63*, 9904.
[823] See Deiter, S.A.; Martin, S.F. *Chem. Rev.* ***2004****, 104*, 2199.
[824] Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* ***1994***, 2693.
[825] Schneider, M.F.; Junga, H.; Blechert, S. *Tetrahedron* ***1995****, 51*, 13003.
[826] Lee, C.W.; Grubbs, R.H. *J. Org. Chem.* ***2001****, 66*, 7155.
[827] Paquette, L.A.; Méndez-Andino, J. *Tetrahedron Lett.* ***1999****, 40*, 4301.
[828] Brimble, M.A.; Trzoss, M. *Tetrahedron* ***2004****, 60,* 5613.
[829] See Dolman, S.J.; Sattely, E.S.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* ***2002****, 124*, 6991.
[830] See Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* ***2004****, 69*, 6305.
[831] Yao, Q. *Org. Lett.* ***2002****, 4*, 427.
[832] Demchuk, O.M.; Pietrusiewicz, K.M.; Michrowska, A.; Grela, K. *Org. Lett.* ***2003****, 5*, 3217.
[833] LeFlohic, A.; Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* ***2003***, 667.
[834] See Kinderman, S.S.; Van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J.T. *Org. Lett.* ***2001****, 3*, 2045.
[835] Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P.H. *Chem. Commun.* ***1998***, 1315; Maier, M.E.; Lapeva, T. *Synlett* ***1998***, 891; Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* ***1998****, 63*, 6082; O'Mahony, D.J.R.; Belanger, D.B.; Livinghouse, T. *Synlett* ***1998***, 443.
[836] Edwards, S.D.; Lewis, T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1999****, 40*, 4267.
[837] See Rainier, J.D.; Cox, J.M.; Allwein, S.P. *Tetrahedron Lett.* ***2001****, 42,* 179.
[838] Chao, W.; Weinreb, S.M. *Org. Lett.* ***2003****, 5*, 2505.
[839] Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* ***2002****, 43*, 3513.
[840] Kim, S.; Lim, C.J. *Angew. Chem. Int. Ed.* ***2002****, 41*, 3265.
[841] Delgado, M.; Martín, J.D. *Tetrahedron Lett.* ***1997****, 38*, 6299; Miller, S.J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1995****, 117*, 2108.
[842] Leconte, M.; Pagano, S.; Mutch, A.; Lefebvre, F.; Basset, J.M. *Bull. Soc. Chim. Fr.* ***1995****, 132*, 1069.

Asymmetric ring-closing metathesis reactions have been reported,[843] and chiral metathesis catalysts are continually being developed.[844] The enantioselective synthesis of bicyclic lactams from dienyl lactams used a chiral Mo catalyst.[845] Asymmetric ring-opening metathesis has also been reported.[846]

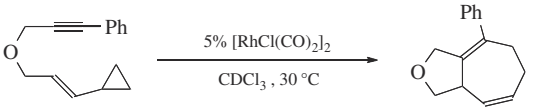
Recyclable catalysts have been developed,[847] and the reaction has been done in ionic liquids,[848] supercritical CO_2[849] (Sec. 9.D.ii), and in aqueous media.[850] Microwave-induced ring-closing metathesis[851] and also cross-metathesis reactions[852] are known. Polymer-bound Ru[853] and Mo catalysts[854] have been used, and catalyst **157** has been immobilized on PEG.[855] Efficient methods have been developed for the removal of Ru byproducts from metathesis reactions that include the use of a scavenger resin,[856] and removal by aqueous extraction.[857]

By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $CH_2{=}{>}RCH_2CH{=}{>}R_2CHCH{=}{>}R_2C{=}$.[858] Note that isomerization of the C=C unit can occur after metathesis,[859] but methods have been developed to prevent this, including addition of 2,6-dichlorobenzoquinone.[860] Cross-metathesis[861] (or symmetrical homo-metathesis[862]) of alkenes to give new alkenes can be accomplished. Monosubstituted alkenes react faster than disubstituted alkenes.[863] A double metathesis reaction of a diene (also called *domino*[864] or *tandem metathesis*[865]) with conjugated aldehydes has been

[843] Cefalo, D.R.; Kiely, A.F.; Wuchrer, M.; Jamieson, J.Y. ; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001****, 123*, 3139.
[844] See Funk, T.W.; Berlin, J.M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2006****, 128*, 1840.
[845] Sattely, E.S.; Cortez, G.A.; Moebius, D.C.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005****, 127,* 8526.
[846] Gillingham, D.G.; Kataoka, O.; Garber, S.B.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004****, 126*, 12288.
[847] Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus, Jr., P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999****, 121*, 791.
[848] Buijsman, R.C.; van Vuuren, E.; Sterrenburg, J.G. *Org. Lett.* ***2001****, 3*, 3785. See Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* ***2004***, 2282.
[849] Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* ***2001****, 123*, 9000.
[850] Binder, J.B.; Blank, J.J.; Raines, R.T. *Org. Lett.* ***2007****, 9,* 4885; Zaman, S.; Curnow, O.J.; Abell, A.D. *Austr. J. Chem.* ***2009****, 62*, 91; Burtscher, D.; Grela, K. *Angew. Chem. Int. Ed.* ***2009****, 48*, 442.
[851] See Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* ***2008***, 1125. For a solvent-free microwave-induced reaction, see Thanh, G.V.; Loupy, A. *Tetrahedron Lett.* ***2003****, 44*, 9091.
[852] Bargiggia, F.C.; Murray, W.V. *J. Org. Chem.* ***2005****, 70*, 9636.
[853] Yao, Q. *Angew. Chem. Int. Ed.* ***2000****, 39*, 3896; Schürer, S.C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem. Int. Ed.* ***2000****, 39,* 3898.
[854] Hultzsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2002****, 41*, 589.
[855] A recyclable catalyst, see Yao, Q.; Motta, A.R. *Tetrahedron Lett.* ***2004****, 45*, 2447.
[856] Ahn, Y.M.; Yang, K.; Georg, G.I. *Org. Lett.* ***2001****, 3*, 1411; Cho, J.H.; Kim, B.M. *Org. Lett.* ***2003****, 5*, 531. See Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* ***2004****, 45,* 3141.
[857] Hong, S.H.; Grubbs, R.H. *Org. Lett.* ***2007****, 9,* 1955.
[858] See Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2003,*** *125*, 11360.
[859] See Schmidt, B. *J. Org. Chem.* ***2004****, 69,* 7672; Sutton, A.E.; Seigal, B.A.; Finnegan, D.F.; Snapper, M.L. *J. Am. Chem. Soc.* ***2002****, 124,* 13390.
[860] Hong, S.H.; Sanders, D.P.; Lee, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2005****, 127,* 17160.
[861] See Stewart, I.C.; Douglas, C.J.; Grubbs, R.H. *Org. Lett.* ***2008****, 10,* 441; Lipshutz, B.H.; Aguinaldo, G.T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* ***2008****, 10,* 1325.
[862] Blanco, O.M.; Castedo, L. *Synlett* ***1999***, 557.
[863] See Lautens, M.; Maddess, M.L. *Org. Lett.* ***2004****, 6*, 1883.
[864] Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* ***2001****, 42*, 5245.
[865] Choi, T.-L.; Grubbs, R.H. *Chem. Commun.* ***2001****, 2*648.

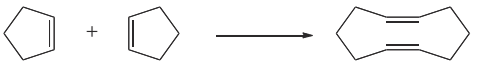
reported,[866] and a triple metathesis was reported to for a dihydropyran with two dihydropyran substituents.[867] Cross-metathesis of vinylcyclopropanes leads to an alkene with two cyclopropyl substituents.[868] Vinylcyclopropane-alkyne metathesis reactions have been reported.[869] Cyclic alkenes can be opened, usually with polymerization using metathesis catalysts. Ring-opening metathesis generates dienes from cyclic alkenes.[870] Allenes undergo a metathesis reaction to give symmetrical allenes.[871] An interesting variation reacts an α,ω-diene with a cyclic alkene. The combination of ring-opening metathesis and ring-closing cross-metathesis leads to ring expansion to give a macrocyclic nonconjugated diene.[872] Note that an alkane metathesis reaction is known.[873]

Dienes can react intermolecularly or intramolecularly.[874] Intramolecular reactions generate rings, including small rings,[875] usually alkenes or dienes. Alkene metathesis can be used to form very large rings, including 21-membered lactone rings.[876] Diynes undergo both cross-metathesis and ring-closing metathesis.[877] Diynes can also react intramolecularly to give large-ring alkynes.[878] Metathesis with vinyl-cyclopropyl-alkynes is also known, producing a ring-expanded product (see **159**).[879] Vinyl halides undergo metathesis reactions.[880]



159

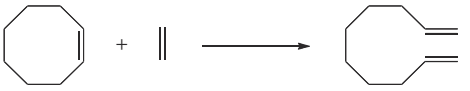
Two cyclic alkenes react to give dimeric dienes,[881] for example,



With many catalysts, the products can then react with additional monomers and with each other, so that polymers are produced, and the cyclic dienes are obtained only in low yield.

[866] BouzBouz, S.; Cossy, J. *Org. Lett.* ***2001****, 3,* 1451; van Otterlo, W.A.L.; Ngidi, E.L.; de Koning, C.D.; Fernandes, M.A. *Tetrahedron Lett.* ***2004****, 45*, 659.
[867] Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* ***2001****, 3,* 1973.
[868] Verbicky, C.A.; Zercher, C.K. *Tetrahedron Lett.* ***2000****, 41*, 8723.
[869] López, F.; Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2004****, 126*, 10262.
[870] See Randl, S.; Connon, S.J.; Blechert, S. *Chem. Commun.* ***2001***, 1796; Morgan, J.P.; Morrill, C.; Grubbs, R.H. *Org. Lett.* ***2002****, 4*, 67.
[871] Ahmed, M.; Arnauld, T.; Barrett, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. *Org. Lett.* ***2000****, 2*, 551.
[872] Lee, C.W.; Choi, T.-L.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2002****, 124*, 3224.
[873] Basset, J.-M.; Copret, C.; Soulivong, D.; Taoufik, M.; Cazat, J.T. *Acc. Chem. Res.* ***2010***, *43*, 323; Basset, J.-M.; Copéret, C.; Lefort, L.; Maunders, B.M.; Maury, O.; Le Roux, E.; Saggio, G.; Soignier, S.; Soulivong, D.; Sunley, G.J.; Taoufik, M.; Thivolle-Cazat, J. *J. Am. Chem. Soc.* ***2005****, 127,* 8604; Basset, J.-M.; Copéret, C.; Soulivong, D.; Taoufik, M.; Thivolle-Cazat, J. *Angew. Chem. Int. Ed.* ***2006****, 45,* 6082.
[874] See Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Accts. Chem. Res.* ***1995****, 28*, 446.
[875] Grela, K. *Angew. Chem. Int. Ed.* ***2008****, 47*, 5504.
[876] Fürstner, A.; Langemann, K. *J. Org. Chem.* ***1996****, 61*, 3942. Also see, Goldring, W.P.D.; Hodder, A.S.; Weiler, L. *Tetrahedron Lett.* ***1998****, 39*, 4955; Ghosh, A.K.; Hussain, K.A. *Tetrahedron Lett.* ***1998****, 39*, 1881.
[877] See Kim, M.; Miller, R.L.; Lee, D. *J. Am. Chem. Soc.* ***2005****, 127,* 12818.
[878] Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.
[879] Wender, P.A.; Sperandio, D. *J. Org.Chem.* ***1998****, 63*, 4164.
[880] Macnaughtan, M.L.; Johnson, M.J.A.; Kampf, J.W. *J. Am. Chem. Soc.* ***2007****, 129,* 7708.
[881] Calderon N.; Ofstead, E.A.; Judy, W.A. *J. Polym. Sci. Part A-1* ***1967****, 5*, 2209; Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968****, 90,* 3286; Wolovsky, R.; Nir, Z. *Synthesis* ***1972***, 134.

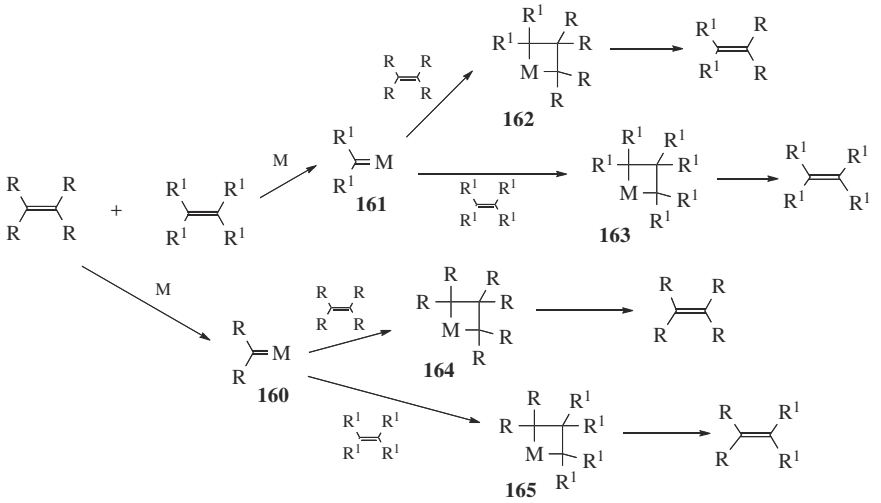
The reaction between a cyclic and a linear alkene can give a ring-opened diene[882]:



The reaction has also been applied to internal alkynes[883]:

$$2\,RC{\equiv}CR' \rightleftharpoons RC{\equiv}CR + R'C{\equiv}CR'$$

and some success has been reported for terminal triple bonds.[884] As noted above, molecules with a terminal alkene and a terminal alkyne react quite well (ene-yne metathesis).[885] Intramolecular reactions of a double bond with a triple bond are known[886] and a tetracyclic tetraene has been prepared from a poly-yne-diene.[887] Cross-metathesis of terminal alkynes and terminal alkenes (en-ynes)[888] to give a diene has also been reported.[889] Enyne metathesis generates 1,3-dienes.[890]



[882] Rossi, R.; Diversi, P.; Lucherini, A.; Porri, L. *Tetrahedron Lett.* ***1974***, 879; Lal, J.; Smith, R.R. *J. Org. Chem.* ***1975***, *40,* 775.

[883] See Weissman, H.; Plunkett, K.N.; Moore, J.S. *Angew. Chem. Int. Ed.* ***2006***, *45,* 585. For reviews, see Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* ***1992***, 539; Fürstner, A.; Davies, P.W. *Chem. Commun.* ***2005***, 2307.

[884] Couteliera, O.; Mortreux, A. *Adv. Synth. Catal.* ***2006***, *348*, 2038; Mortreux, A.; Petit, F.; Petit, M.; Szymanska-Buza, T. *J. Mol. Catal. A: Chemical* ***1995***, *96,* 95. However, see McCullough, L.G.; Listemann, M.L.; Schrock, R.R.; Churchill, M.R.; Ziller, J.W. *J. Am. Chem. Soc.* ***1983***, *105,* 6729.

[885] See Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* ***2000***, *2*, 543; Kitamura, T.; Mori, M. *Org. Lett.* ***2001***, *3*, 1161.

[886] See Gilbertson, S.R.; Hoge, G.S. *Tetrahedron Lett.* ***1998***, *39*, 2075.

[887] Zuercher, W.J.; Scholl, M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 4291.

[888] See Kang, B.; Lee, J.M.; Kwak, J.; Lee, Y.S.; Chang, S. *J. Org. Chem.* ***2004***, *69*, 7661. See Diver, S.T.; Giessert, A.J. *Chem. Rev.* ***2004***, *104*, 1317.

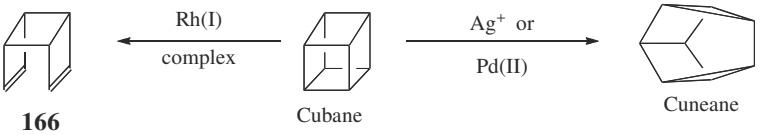
[889] Poulsen, C.S.; Madsen, R. *Synthesis* ***2003***, 1. See Lee, H.-Y.; Kim, B.G.; Snapper, M.L. *Org. Lett.* ***2003***, *5,* 1855; Giessert, A.J.; Brazis, N.J.; Diver, S.T. *Org. Lett.* ***2003***, *5,* 3819; Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* ***2004***, *126*, 10242. See also, Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* ***2003***, *5,* 3041.

[890] Hansen, E.C.; Lee, D. *Acc. Chem. Res.* ***2006***, *39,* 509; Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* ***2008***, *130,* 1562; Giessert, A.J.; Diver, S.T. *J. Org. Chem.* ***2005***, *70,* 1046. For a mechanistic study, see Galan, B.R.; Giessert, A.J.; Keister, J.B.; Diver, S.T. *J. Am. Chem. Soc.* ***2005***, *127,* 5762.

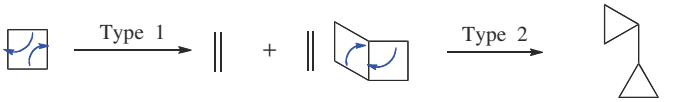
The generally accepted mechanism is a chain mechanism,[891] involving the intervention of a metal–carbene complex (**160** and **161**)[892] and a four-membered ring containing a metal[893] (**162**–**165**).[894] In the cross-metathesis reaction shown as an example, $R_2C{=}CR_2$ reacts with $R^1{}_2C{=}CR^1{}_2$ in the presence of a metal catalyst (M). Initial reaction with the catalyst leads to the two expected metal carbenes, (**160** and **161**). Metal carbene (**161**) can react with both alkenes to form metallocyclobutanes **162** and **163**. Each of these intermediates loses the metal to form the alkenes, the product of metathesis ($R_2C{=}CR^1{}_2$) and one of the original alkenes. In a likewise manner, **160** reacts with each alkene to form metallocyclobutanes **164** and **165**, which decomposes to $R_2C{=}CR_2$ and the metathesis product. It has been shown that the phosphine-containing methylidene complexes decompose to methylphosphonium salts,[895]

OS **80**, 85; **81**, 1.

18-38 Metal-Ion-Catalyzed σ-Bond Rearrangements



Many highly strained cage molecules undergo rearrangement when treated with metallic ions [e.g., Ag^+, Rh(I), or Pd(II)].[896] The bond rearrangements observed can be formally classified into two main types: (*Type 1*)



[2 + 2]-ring openings of cyclobutanes and (Type *2*) conversion of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type

[891] See Sanford, M.S.; Ulman, M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001****, 123*, 749; Sanford, M.S.; Love, J.A.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001****, 123*, 6543; Cavallo, L. *J. Am. Chem. Soc.* ***2002****, 124*, 8965; Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* ***2004****, 126,* 3496.

[892] See Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 244–267; Kingsbury, J.S.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005****, 127,* 4510; Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* ***2007****, 129,* 8207; Vyboishchikov, S.F.; Thiel, W. *Chemistry: European J.* ***2005****, 11,* 3921.

[893] See Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 459–520; Lindner, E. *Adv. Heterocycl. Chem.* ***1986****, 39,* 237. See Romero, P.E.; Piers, W.E. *J. Am. Chem. Soc.* ***2005****, 127*, 5032; Romero, P.E.; Piers, W.E. *J. Am. Chem. Soc.* ***2007****, 129,* 1698.

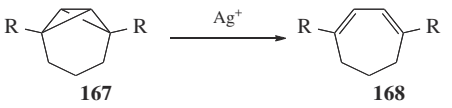
[894] See Grubbs, R.H. *Prog. Inorg. Chem.* ***1978****, 24*, 1; Katz, T.J. *Adv. Organomet. Chem.* ***1977****, 16*, 283; Calderon N.; Ofstead, E.A.; Judy, W.A. *Angew. Chem. Int. Ed.* ***1976****, 15,* 401. See also, Kress, J.; Osborn, J.A.; Greene, R.M. E.; Ivin, K.J.; Rooney, J.J. *J. Am. Chem. Soc.* ***1987****, 109,* 899; Feldman, J.; Davis, W.M.; Schrock, R.R. *Organometallics* ***1989****, 8,* 2266.

[895] Hong, S.H.; Wenzel, A.G.; Salguero, T.T.; Day, M.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2007****, 129,* 7961.

[896] Halpern, J. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 705–721; Bishop, III, K.C. *Chem. Rev.* ***1976****, 76,* 461; Cardin, D.J.; Cetinkaya, B.; Doyle, M.J.; Lappert, M.F. *Chem. Soc. Rev.* ***1973****, 2,* 99, pp. 132–139; Paquette, L.A. *Synthesis* ***1975***, 347; *Acc. Chem. Res.* ***1971****, 4,* 280.

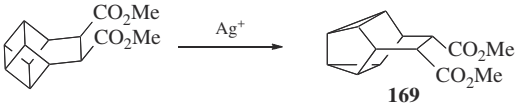
(see above). Treatment with Rh(I) complexes converts cubane to tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene (**166**),[897] an example of type 1, while Ag^+ or Pd(II) causes the second type of reaction, producing cuneane.[898] Other examples are the conversion of **167** to **168**, and formation of **159**, the 9,10-dicarbomethyoxy derivative of *snoutane* (pentacyclo[3.3.2.$0^{2,4}$.$0^{3,7}$.$0^{6,8}$]decane).

Type 1



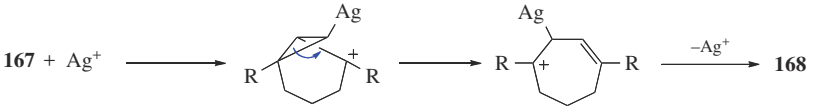
167 **168** Ref. 899

Type 2[900]

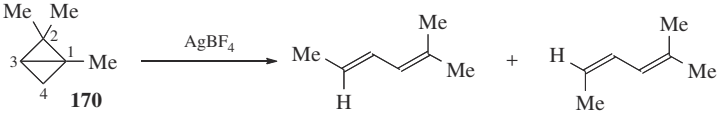


169 Ref. 901

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital-symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. Type 1 reactions are the reverse of the catalyzed [2 + 2] ring closures discussed at Reaction **15-63**. The following mechanism, in which Ag^+ attacks one of the edge bonds, has been suggested for the conversion of **167** to **168**.[902]



Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[903] For example, treatment of **170** with $AgBF_4$,[904]



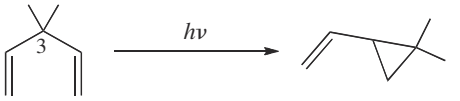
170

or [(π-allyl)PdCl]$_2$[905] gives a mixture of the two dienes shown, resulting from a formal cleavage of the C-1—C-3 and C-1—C-2 bonds (note that a hydride shift has taken place). Dienes can also be converted to bicyclobutanes under photochemical conditions.[906]

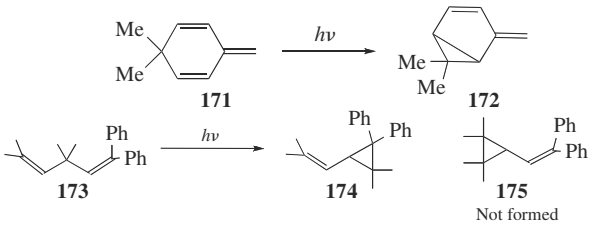
[897] Eaton, P.E.; Chakraborty, U.R. *J. Am. Chem. Soc.* ***1978****, 100,* 3634.
[898] Cassar, L.; Eaton, P.E.; Halpern, J. *J. Am. Chem. Soc.* ***1970****, 92,* 6336.
[899] Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972****, 93,* 4611; Paquette, L.A.; Wilson, S.E.; Henzel, R.P. *J. Am. Chem. Soc.* ***1972****, 94*, 7771.
[900] The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bishomo-, and trishomocubanes, see Marchand, A.P. *Chem. Rev.* ***1989****, 89,* 1011.
[901] See Paquette, L.A.; Beckley, R.S.; Farnham, W.B. *J. Am. Chem. Soc.* ***1975****, 97*, 1089.
[902] See Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972****, 93*, 4611.
[903] See Paquette, L.A.; Zon, G. *J. Am. Chem. Soc.* ***1974****, 96*, 203, 224.
[904] Paquette, L.A.; Henzel, R.P.; Wilson, S.E. *J. Am. Chem. Soc.* ***1971****, 93*, 2335.
[905] Gassman, P.G.; Meyer, R.G.; Williams, F.J. *Chem. Commun.* ***1971***, 842.
[906] Garavelli, M.; Frabboni, B.; Fato, M.; Celani, P.; Bernardi, F.; Robb, M.A.; Olivucci, M. *J. Am. Chem. Soc.* ***1999****, 121,* 1537.

18-39 The Di-π-methane and Related Rearrangements

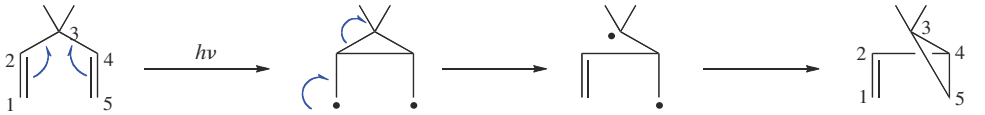
Di-π-methane rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3[907] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement*.[908] An example is conversion of **171** to **172**.[909] For most 1,4-dienes, it is only the singlet excited state that gives the reaction; triplet states generally take other pathways.[910] For unsymmetrical dienes, the reaction is regioselective. For example, **173** gave **174**, not **175**:[911]



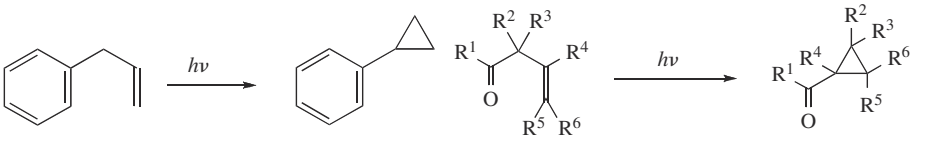
The mechanism can be described by the diradical pathway given[912] (the C-3 substituents act to stabilize the radical), although the species shown are not necessarily intermediates, but may represent transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.[913]



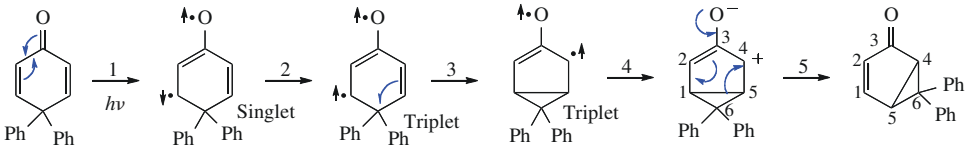
The reaction has been extended to allylic benzenes[914] (in this case C-3 substituents are not required), to β,γ-unsaturated ketones[915] (the latter reaction, which is called the *oxa-di-*

[907] Zimmerman, H.E.; Pincock, J.A. *J. Am. Chem. Soc.* ***1973****, 95,* 2957.
[908] Zimmerman, H.E. *Org. Photochem.* ***1991****, 11,* 1; Zimmerman, H.E. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 131–166; Hixson, S.S.; Mariano, P.S.; Zimmerman, H.E. *Chem. Rev.* ***1973****, 73,* 531. See also, Roth, W.R.; Wildt, H.; Schlemenat, A. *Eur. J. Org. Chem.* **2001**, 4081.
[909] Zimmerman, H.E.; Hackett, P.; Juers, D.F.; McCall, J.M.; Schröder, B. *J. Am. Chem. Soc.* ***1971****, 93*, 3653.
[910] However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, which is converted to semibullvalene) give the di-π-methane rearrangement only from triplet states.
[911] Zimmerman, H.E.; Baum, A.A. *J. Am. Chem. Soc.* ***1971****, 93*, 3646. See also, Paquette, L.A.; Bay, E.; Ku, A.Y.; Rondan, N.G.; Houk, K.N. *J. Org. Chem.* ***1982****, 47*, 422.
[912] See Zimmerman, H.E.; Boettcher, R.J.; Buehler, N.E.; Keck, G.E. *J. Am. Chem. Soc.* ***1975****, 97,* 5635. However, see Adam, W.; De Lucchi, O.; Dörr, M. *J. Am. Chem. Soc.* ***1989****, 111*, 5209.
[913] Zimmerman, H.E.; Robbins, J.D.; McKelvey, R.D.; Samuel, C.J.; Sousa, L.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.
[914] See Paquette, L.A.; Bay, E. *J. Am. Chem. Soc.* ***1984****, 106*, 6693; Zimmerman, H.E.; Swafford, R.L. *J. Org. Chem.* ***1984****, 49,* 3069.
[915] See Schuster, D.I. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 167–279; Houk, K.N. *Chem. Rev.* ***1976****, 76*, 1; Schaffner, K. *Tetrahedron* ***1976****, 32*, 641; Dauben, W.G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* ***1975****, 54,* 73.

π-methane rearrangement,[916] generally occurs only from the triplet state), to β,γ-unsaturated imines,[917] and to triple-bond systems.[918]



When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di-π-methane rearrangement.[919] In this reaction, photolysis of the substrate **176** gives the bicyclo[3.1.0]hexenone (**181**). Although the reaction is formally the same (note the conversion of **171** to **172**),

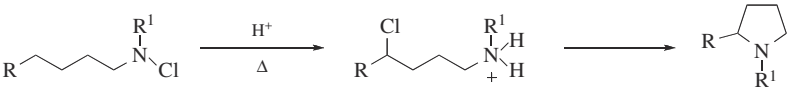


176 **177** **178** **179** **180** **181**

the mechanism is different from that of the di-π-methane rearrangement, because irradiation of a ketone can cause an $n \rightarrow \pi*$ transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism[920] in this case has been formulated as proceeding through the excited triplet states **178** and **179**. In step 1, the molecule undergoes an $n \rightarrow \pi*$ excitation to the singlet species **177**, which cross to the triplet **178**. Step 3 is a rearrangement from one excited state to another. Step 4 is a $\pi* \rightarrow n$ electron demotion (an intersystem crossing from $T_1 \rightarrow S_0$, see Sec. 7.A.vi, category 4). The conversion of **180** to **181** consists of two 1,2-alkyl migrations (a one-step process would be a 1,3-migration of alkyl to a carbocation center): The old C-6—C-5 bond becomes the new C-6—C-4 bond and the old C-6—C-1 bond becomes the new C-6—C-5 bond.[921]

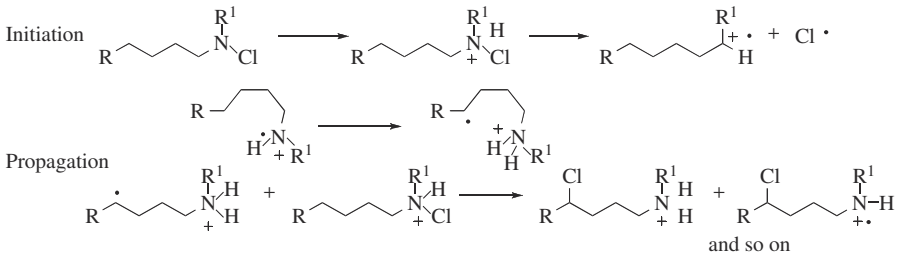
2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[922]

18-40 The Hofmann–Löffler and Related Reactions



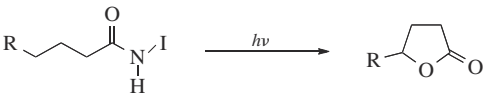
[916] For a review, see Demuth, M. *Org. Photochem.* ***1991****, 11,* 37.
[917] See Armesto, D.; Horspool, W.M.; Langa, F.; Ramos, A. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 223.
[918] See Griffin, G.W.; Chihal, D.M.; Perreten, J.; Bhacca, N.S. *J. Org. Chem.* ***1976****, 41,* 3931.
[919] See Schaffner, K.; Demuth, M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 281–348; Zimmerman, H.E. *Angew. Chem. Int. Ed.* ***1969****, 8,* 1; Kropp, P.J. *Org. Photochem.* ***1967****, 1,* 1; Schaffner, K. *Adv. Photochem.* ***1966****, 4,* 81; Schultz, A.G.; Lavieri, F.P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* ***1987****, 109,* 3991, and references cited therein.
[920] Schuster, D.I. *Acc. Chem. Res.* ***1978****, 11*, 65; Zimmerman, H.E.; Pasteris, R.J. *J. Org. Chem.* ***1980****, 45,* 4864, 4876; Schuster, D.I.; Liu, K. *Tetrahedron* ***1981****, 37,* 3329.
[921] Zimmerman, H.E.; Crumine, D.S.; Döpp, D.; Huyffer, P.S. *J. Am. Chem. Soc.* ***1969****, 91,* 434.
[922] Schaffner, K.; Demuth, M. in de Mayo, P. *Rearrangements in Ground and Excited States,* Vol. 3, Academic Press, NY, ***1980***, p. 281; Quinkert, G. *Angew. Chem. Int. Ed.* ***1972****, 11,* 1072; Kropp, P.J. *Org. Photochem.* ***1967****, 1,* 1.

A common feature of the reactions in this section[923] is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also, Reactions **19-2** and **19-17**). When *N*-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines, or piperidines are formed, in a reaction known as the *Hofmann–Löffler reaction* (also called the *Hofmann–Löffler–Freytag reaction*).[924] The R′ group is normally alkyl, but the reaction has been extended to R′ = H by the use of concentrated sulfuric



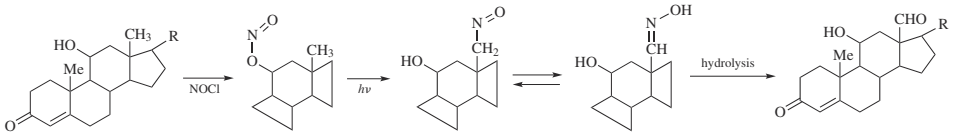
acid solution and ferrous salts.[925] The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (Reaction **10-31**), takes place. The reaction is most often induced by heat, but this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free radical type, with the main step involving an internal hydrogen abstraction.[926]

A similar reaction has been carried out on *N*-halo amides, which give γ-lactones[927]:

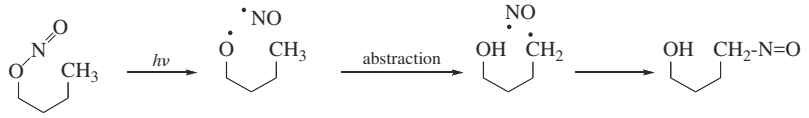


Another related reaction is the *Barton reaction*,[928] by which a methyl group in a unique position relative to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Formation of a radical and with the methyl group in the appropriate position, hydrogen-atom transfer via a six-center transition state leads to a nitrite. Hydrolysis of the oxime tautomer gives the aldehyde, for example[929]

[923] See Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 263–279.
[924] See Stella, L. *Angew. Chem. Int. Ed.* ***1983****, 22*, 337; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free Radical Chem.* ***1972****, 4,* 203, see pp. 249–259; Deno, N.C. *Methods Free-Radical Chem.* ***1972****, 3,* 135, see pp. 136–143.
[925] Schmitz, E.; Murawski, D. *Chem. Ber.* ***1966****, 99,* 1493.
[926] Wawzonek, S.; Thelan, P.J. *J. Am. Chem. Soc.* ***1950****, 72,* 2118.
[927] Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* ***1965***, 181; Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* ***1966****, 88,* 3051. See Neale, R.S. *Synthesis* ***1971***, 1.
[928] SeeHesse, R.H. *Adv. Free-Radical Chem.* ***1969***, *3*, 83; Barton, D.H.R. *Pure Appl. Chem.* ***1968***, *16*, 1; Saraiva, M.F.; Couri, M.R.C.; Le Hyaric, M.; de Almeida, M.V. *Tetrahedron* ***2009****, 65*, 3563.
[929] Barton, D.H.R.; Beaton, J.M. *J. Am. Chem. Soc.* ***1961****, 83*, 4083. Also see, Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Pechet, M.M. *J. Am. Chem. Soc.* ***1960****, 82,* 2640.



This reaction takes place only when the methyl group is in a favorable steric position.[930] The mechanism is similar to that of the *Hofmann–Löffler reaction*.[931]

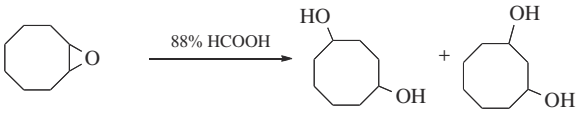


This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime R(C=NOH), which is hydrolyzable to a ketone, or to a nitroso dimer, while an R_2CH group gives a nitroso compound [$R_2C(NO)$]. With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.[932]

OS **III**, 159.

D. Noncyclic Rearrangements

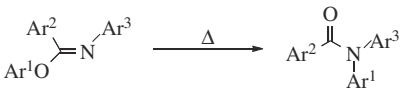
18-41 Hydride Shifts



The example shown is typical of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (**10-7**).[933] For a discussion of 1,3 and longer hydride shifts, see Sec. 18.B.

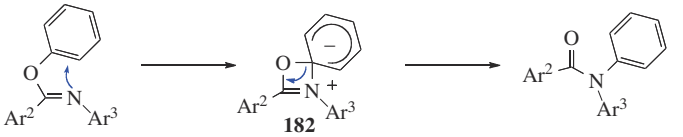
18-42 The Chapman Rearrangement

1/*O*→3/ *N*-Aryl-migration

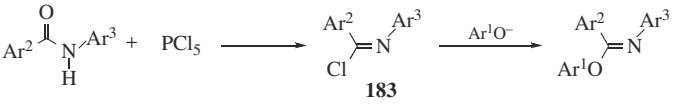


[930] See Burke, S.D.; Silks III, L.A.; Strickland, S.M.S. *Tetrahedron Lett.* ***1988****, 29*, 2761.
[931] See Green, M.M.; Boyle, B.A.; Vairamani, M.; Mukhopadhyay, T.; Saunders Jr., W.H.; Bowen, P.; Allinger, N.L. *J. Am. Chem. Soc.* ***1986****, 108,* 2381; Grossi, L. *Chemistry: European J.* ***2005****, 11*, 5419.
[932] See Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977****, 99,* 4518.
[933] Cope, A.C.; Fournier, Jr., A.; Simmons Jr., H.E. *J. Am. Chem. Soc.* ***1957****, 79*, 3905.

In the *Chapman rearrangement*, *N,N*-diaryl amides are formed when aryl imino esters are heated.[934] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[935] although the reaction can also be carried out without any solvent at all. Many groups may be present in the rings (e.g., alkyl, halo, OR, CN, and CO_2R). Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products can be hydrolyzed to

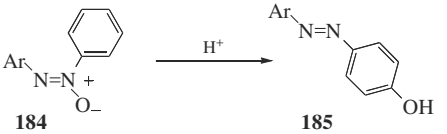


diarylamines, and this is a method for preparing these compounds. The mechanism probably involves an intramolecular[936] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift via a species (e.g., **182**). Aryl imino esters can be prepared from *N*-aryl amides by reaction with PCl_5, followed by treatment



of the resulting imino chloride (**183**) with an aroxide ion.[937] Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate.[938] The mechanism is different, involving an intermolecular process.[939] This is also true for derivatives for formamide ($Ar^2 = H$).

18-43 The Wallach Rearrangement



The conversion of azoxy compounds (e.g., **184**), upon acid treatment, to *p*-hydroxy azo compounds (e.g., **185**, or sometimes the *o*-hydroxy isomers[940]) is called the *Wallach rearrangement*.[941] When both para positions are occupied, the *o*-hydroxy product may be

[934] Schulenberg, J.W.; Archer, S. *Org. React.* ***1965****, 14,* 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 439–447; McCarty, C.G.; Garner, L.A. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 189–240. For a review of 1,3-migrations of R in general, see Landis, P.S. *Mech. Mol. Migr.* ***1969****, 2*, 43.

[935] Wheeler, O.H.; Roman, F.; Santiago, M.V.; Quiles, F. *Can. J. Chem.* ***1969****, 47,* 503.

[936] See Wheeler, O.H.; Roman, F.; Rosado, O. *J. Org. Chem.* ***1969****, 34,* 966; Kimura, M. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 205.

[937] See Bonnett, R. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 597–662.

[938] Landis, P.S. *Mech. Mol. Migr.* ***1969****, 2*, 43.

[939] See Challis, B.C.; Frenkel, A.D. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 192.

[940] See Yamamoto, J.; Nishigaki, Y.; Umezu, M.; Matsuura, T. *Tetrahedron* ***1980****, 36,* 3177.

[941] See Buncel, E. *Mech. Mol. Migr.* ***1968****, 1*, 61; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 272–284, 357–359; Cox, R.A.; Buncel, E. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 808–837.

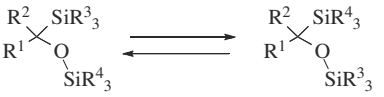
obtained, but ipso substitution at one of the para positions is also possible.[942] The following facts are known for the proposed mechanism[943]: (1) The para rearrangement is intermolecular.[944] (2) When the reaction was carried out with an azoxy compound in which the N—O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[945] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (3) Kinetic studies show that two protons are normally required for the reaction.[946] The following mechanism,[947] involving the symmetrical intermediate (**187**), has been proposed to explain the facts.[948] It has proved possible to obtain **186** and **187** as stable species in superacid solutions.[797] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[949]



A photochemical *Wallach rearrangement*[950] is also known: The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.[951]

18-44 Dyotropic Rearrangements

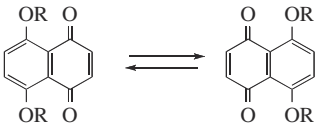
1/*C*-Trialkylsilyl,2/*O*-trialkylsilyl-interchange



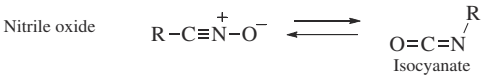
A *dyotropic rearrangement*[952] is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.[953] There are two types. The above is an example of type 1, which consists of reactions in which the two σ bonds interchange positions.

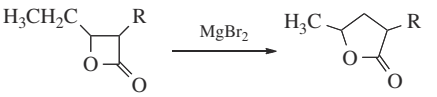
[942] See Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983,*** *56*, 643.
[943] Furin, G.G. *Russ. Chem. Rev.* ***1987,*** *56*, 532; Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* ***1980,*** *5,* 184; Buncel, E. *Acc. Chem. Res.* ***1975,*** *8,* 132.
[944] See Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963,*** *36*, 601.
[945] Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Chem. Ind. (London)* ***1958***, 755; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1960***, 808. Also see, Behr, L.C.; Hendley, E.C. *J. Org. Chem.* ***1966,*** *31,* 2715.
[946] See Cox, R.A. *J. Am. Chem. Soc.* ***1974,*** *96*, 1059.
[947] See Buncel, E.; Keum, S. *J. Chem. Soc., Chem. Commun.* ***1983***, 578.
[948] Also see Shemyakin, M.M.; Agadzhanyan, Ts.E.; Maimind, V.I.; Kudryavtsev, R.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1216; Hendley, E.C.; Duffey, D. *J. Org. Chem.* ***1970,*** *35*, 3579.
[949] Cox, R.A.; Dolenko, A.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 471; Cox, R.A.; Buncel, E. *J. Am. Chem. Soc.* ***1975,*** *97,* 1871.
[950] See Shimao, I.; Hashidzume, H. *Bull. Chem. Soc. Jpn.* ***1976,*** *49,* 754.
[951] See Shine, H.J.; Subotkowski, W.; Gruszecka, E. *Can. J. Chem.* ***1986,*** *64*, 1108.
[952] See Davis, R.L.; Tantillo, D.J. *J. Org. Chem.* ***2010,*** *75*, 1693.
[953] Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Yu.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co., Dordrecht, ***1988***, pp. 221–246; Minkin, V.I. *Sov. Sci. Rev. Sect. B* ***1985,*** *7,* 51; Reetz, M.T. *Adv. Organomet. Chem.* ***1977,*** *16*, 33. Also see, Mackenzie, K.; Gravaatt, E.C.; Gregory, R.J.; Howard, J.A.K.; Maher, J.P. *Tetrahedron Lett.* ***1992,*** *33*, 5629.

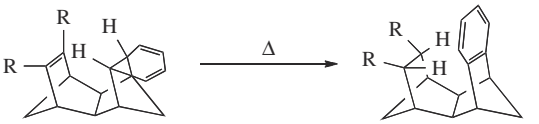
In type 2, the two σ bonds do not interchange positions. An example is



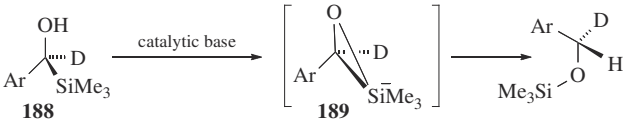
Some other examples are

Type 1  Ref. 954

Type 1  Ref. 955

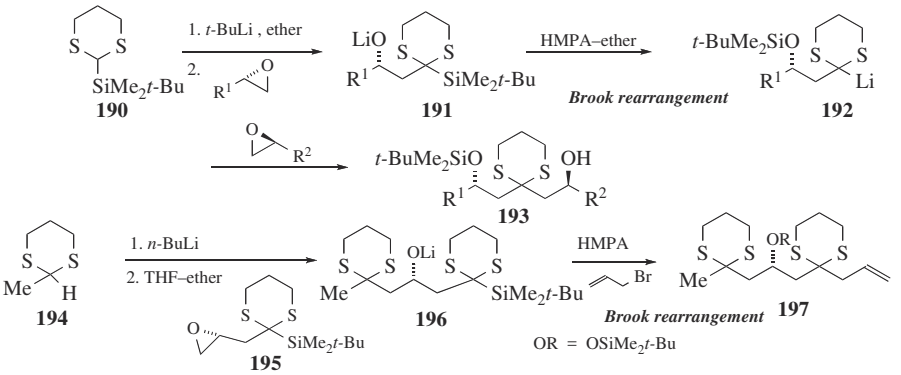
Type 2  Ref. 956

A useful type 1 example is the *Brook rearrangement*,[957] a stereospecific intramolecular migration of silicon from carbon to oxygen that occurs for (α-hydroxybenzyl)trialkylsilanes (**188**) in the presence of a catalytic amount of base.[958] Formation of a Si—O bond rather than the Si—C bond drives the rearrangement, which is believed to proceed via formation of **189**, and does proceed with inversion of configuration at carbon and retention of configuration at silicon.[959] A *reverse Brook rearrangement* is also known.[960] The reaction has been extended to other systems. A *homo-Brook rearrangement* has also been reported.[961] Another variation is the *aza-Brook rearrangement* of α-(silylallyl)amines.[962] The *Brook rearrangement* has been used in synthesis involving silyl dithianes.[963] A *Brook rearrangement* mediated [6 + 2]-annulation has been used for the construction of eight-membered carbocycles.[964]



[954] See Taylor, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1181.
[955] See Black, T.H.; Hall, J.A.; Sheu, R.G. *J. Org. Chem.* ***1988****, 53,* 2371; Black, T.H.; Fields, J.D. *Synth. Commun.* ***1988****, 18,* 125.
[956] See Mackenzie, K.; Proctor, G.; Woodnutt, D.J. *Tetrahedron* ***1987****, 43*, 5981, and cited references.
[957] For a review, see Moser, W.H. *Tetrahedron* ***2001****, 57*, 2065.
[958] Brook, A.G. *Acc. Chem. Res.* ***1974****, 7,* 77; Brook, A.G.; Bassendale, A.R. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 149–227.
[959] Brook, A. G.; Pascoe, J. D. *J . Am. Chem. Soc.* ***1971*** *93*, 6224.
[960] See Linderman, J.J.; Ghannam, A. *J. Am. Chem. Soc.* ***1990****, 112,* 2392.
[961] Wilson, S.R.; Georgiadis, G.M. *J. Org. Chem.* ***1983****, 48,* 4143.
[962] Honda, T.; Mori, M. *J. Org. Chem.* ***1996****, 61,* 1196.
[963] See Smith, III, A.B.; Adams, C. M. *Acc. Chem. Res.* ***2004****, 37,* 365; Smith, III, A.B.; Kim, D.-S. *Org. Lett.* ***2005****, 7,* 3247.
[964] Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* ***2004****, 6*, 2277.

The *Brook rearrangement* has been used in two important synthetic applications, a multicomponent coupling protocol initiated by a *Brook rearrangement* involving silyl dithianes as mentioned, and anion relay chemistry (ARC) involving a *Brook rearrangement*. An example of the former is the conversion of the 2-silyl dithiane (**190**) to the anion with *tert*-butyllithium followed by ring opening of an epoxide to give **191**.[965] Treatment with HMPA triggers a solvent-controlled *Brook rearrangement* that gives a new dithiane anion (**192**), which then reacts with a different epoxide to give the final product **193**. An example of the anion relay chemistry treats dithiane (**194**) with *n*-butyllithium, and then **195** to give **196**.[966] Subsequent treatment with a variety of electrophiles (e.g., allyl bromide, in HMPA), leads to **197** via a *Brook rearrangement*, and then alkylation of the resultant dithiane anion. This reaction can be initiated by nucleophiles other than dithiane anion.



[965] Smith, III, A.B.; Pitram, S.M.; Boldi, A.M.; Gaunt, M.J.; Sfouggatakis, C.; Moser, W.H. *J. Am. Chem. Soc.* ***2003****, 125,* 14435. See Smith, III, A.B.; Xian, M. *J. Am. Chem. Soc.* ***2006****, 128*, 66.
[966] Smith, III, A.B.; Xian, M. *J. Am. Chem. Soc.* ***2006****, 128*, 66.

CHAPTER 19

Oxidations and Reductions

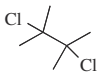
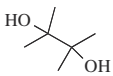
First, the terms oxidation and reduction must be clarified. Inorganic chemists define oxidation in two ways: loss of electrons and an increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions, and electrons are certainly transferred by making and breaking bonds, the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases (e.g., the oxidation number of carbon in CH_4 is -4), in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus carbon in propane has an oxidation number of -2.67 and in butane of -2.5, although organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. For the simple functional groups, this series is shown in Table 19.1.[1] Note that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we will find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. Note that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

Of course, there is no oxidation without a concurrent reduction. However, reactions are classified as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases, both the oxidant and reductant are organic; those reactions are treated separately at the end of the chapter.

[1] For more extensive tables, see Soloveichik, S.; Krakauer, H. *J. Chem. Educ.* ***1966****, 43,* 532.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

TABLE 19.1 Categories of Simple Functional Groups Arranged According to Oxidation State[a]

RH	 **ROH** **RCl** **RNH_2** . . . and so on	—C≡C—     . . . and so on	   . . . and so on	**CO_2** **CO_4**
Approximate Oxidation Number				
−4	−2	0	+2	+4

[a]Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations.

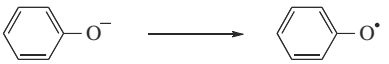
19.A. MECHANISMS

Note that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (Reaction **10-1**) and to methane with $LiAlH_4$ (Reaction **19-53**) have the same S_N2 mechanisms, but one is a reduction (according to our definition) and the other is not. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as done for the reactions considered in Chapters 10–18.[2] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, most reactions involved the bond change C=C → W—C—C—Y yet a relatively few mechanisms covered those reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction can vary greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents.

[2] See Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***; *Oxidation in Organic Chemistry,* Academic Press, NY, pt. A [Wiberg, K.B.], ***1965***, pts. B, C, and D [Trahanovsky, W.S.], ***1973, 1978, 1982***; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***; Stewart, R. *Oxidation Mechanisms*; W. A. Benjamin, NY, ***1964***. For a review, see Stewart, R. *Isot. Org. Chem.* ***1976****, 2,* 271.

Although oxidation and reduction mechanisms are not covered in the same way as other mechanisms, it is still possible to list a few broad mechanistic categories. The scheme of Wiberg is followed.[3]

1. *Direct Electron Transfer.*[4] Several reactions have been encountered in which the reduction is a direct gain of electrons or the oxidation is a direct loss of them. An example is the *Birch reduction* (Reaction **15-13**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones with a metal (**19-76**), where again it is a metal that supplies the electrons. This kind of mechanism is found largely in three types of reaction:[5] (a) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion), (b) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical, and (c) electrolytic oxidations or reductions (an example is the *Kolbe reaction*, **14-29**). An important example of (b) is oxidation of phenolate ions:



These reactions occur easily because of the relative stability of the radicals involved.[6] The (SET) mechanism, which has been seen several times (see Sec. 10.B) is an important case.

2. *Hydride Transfer.*[7] In some reactions, a hydride ion is transferred to or from the substrate. The reduction of epoxides with $LiAlH_4$ is an example (**19-35**). Another is the *Cannizzaro reaction* (**19-81**). Reactions in which a hydride ion is transferred to a carbocation belong in this category:[8]

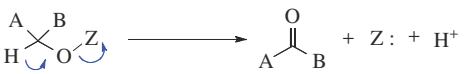
$$R^+ + R'H \longrightarrow RH + R'^+$$

3. *Hydrogen-Atom Transfer.* Many oxidation and reduction reactions are free radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of Reaction **14-1** involves abstraction of hydrogen:

$$RH + Cl\bullet \longrightarrow R\bullet + HCl$$

This is the case for many of the reactions of Chapter 14.

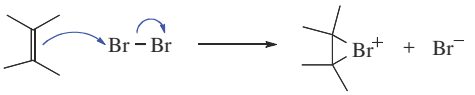
4. *Formation of Ester Intermediates.* A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:



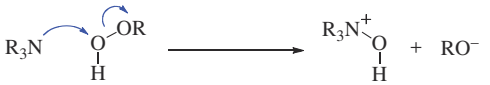
[3] Wiberg, K.B. *Surv. Prog. Chem.* ***1963***, *1*, 211.
[4] See Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer, NY, ***1987***; Eberson, L. *Adv. Phys. Org. Chem.* ***1982***, *18,* 79; Deuchert, K.; Hünig, S. *Angew. Chem. Int. Ed.* ***1978***, *17*, 875.
[5] Littler, J.S.; Sayce, I.G. *J. Chem. Soc.* ***1964***, 2545.
[6] See Mihailovic, M.Lj.; Cekovic, Z. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 505–592.
[7] For a review, see Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24,* 57.
[8] See Nenitzescu, C.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 463–520.

Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism will be seen in Reaction **19-23**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H. Another is the oxidation of a secondary alcohol to a ketone (Reaction **19-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (Reaction **19-7**), the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. Note that the cleavage shown is an example of an E2 elimination.

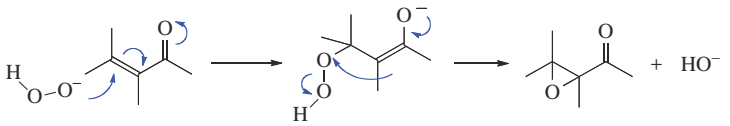
5. *Displacement Mechanisms.* In these reactions, the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an alkene (Reaction **15-39**).



An example from this chapter is found in Reaction **19-29**:



6. *Addition–Elimination Mechanisms.* In the reaction between α,β-unsaturated ketones and alkaline peroxide (**15-50**), the oxidizing agent adds to the substrate and then part of it is lost:



In this case, the oxygen of the oxidizing agent is in oxidation state −1 and the hydroxide ion departs with its oxygen in the −2 state, so it is reduced and the substrate is oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (Reaction **19-17**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

19.B. REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with other chapters.[9] This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent (e.g., acid dichromate or $LiAlH_4$; except for a discussion of selectivity of reducing agents Sec. 19.B.ii, A). Some oxidizing or reducing agents are fairly specific in their action,

[9] See Hudlicky, M. *J. Chem. Educ.* ***1977****, 54*, 100.

attacking only one or a few types of substrate. Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[10,11]

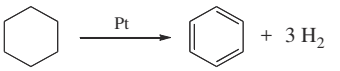
19.B.i. Oxidations[11]

In some cases, oxidations have been placed in another chapter. The oxidations of an alkene to a diol (Reaction **15-48**), and an aromatic compound to a diol (Reaction **15-49**), or oxidations to an epoxide (Reaction **15-50**) are placed in Chapter 15, for consistency with the concept of addition to a π bond. Diamination of an alkene (Reaction **15-53**) and formation of aziridines (Reaction **15-54**) are in Chapter 15 for the same reason. Most other oxidations have been placed here. The reactions in this section are classified into groups depending on the type of bond change involved. These groups are Section (A) eliminations of hydrogen, Section (B) oxidations involving cleavage of carbon–carbon bonds, Section (C) reactions involving replacement of hydrogen by oxygen, Section (D) reactions in which oxygen is added to the substrate, and Section (E) oxidative coupling.

A. Eliminations of Hydrogen

19-1 Aromatization of Six-Membered Rings

Hexahydro-terelimination



[10] See Mijs, W.J.; de Jonge, C.R.J.I. *Organic Synthesis by Oxidation with Metal Compounds*, Plenum, NY, ***1986***; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***; Arndt, D. *Manganese Compounds as Oxidizing Agents in Organic Chemistry*, Open Court Publishing Company, La Salle, IL, ***1981***; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court Publishing Company: La Salle, IL, ***1980***. For some reviews, see Curci, R. *Adv. Oxygenated Processes* ***1990***, *2*, 1 (dioxiranes); Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205 (dioxiranes); Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187(dioxiranes); Ley, S.V. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 163–206 (seleninic anhydrides and acids); Fatiadi, A.J. *Synthesis* ***1987***, 85 ($KMnO_4$); Rubottom, G.M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, pp. 1–145 (lead tetraacetate); Fatiadi, A.J. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 147–335; *Synthesis* ***1974***, 229 (HIO_4); Fatiadi, A.J. *Synthesis* ***1976***, 65, 133 (MnO_2); Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 143–174 (MnO_2); George, M.V.; Balachandran, K.S. *Chem. Rev.* ***1975***, 75, 491 (nickel peroxide); Courtney, J.L.; Swansborough, K.F. *Rev. Pure Appl. Chem.* ***1972***, *22*, 47 (ruthenium tetroxide); Ho, T.L. *Synthesis* ***1973***, 347 (ceric ion); Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971***, 25, 407 (lead tetraacetate); Sklarz, B. *Q. Rev. Chem. Soc.* ***1967***, 21, 3 (HIO_4); Korshunov, S.P.; Vereshchagin, L.I. *Russ. Chem. Rev.* ***1966***, *35*, 942 (MnO_2);. For reviews of the behavior of certain reducing agents, see Keefer, L.K.; Lunn, G. *Chem. Rev.* ***1989***, *89*, 459 (Ni-Al alloy); Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, 34, 1–317 (metal alkoxyaluminum hydrides); Caubère, P. *Angew. Chem. Int. Ed.* ***1983***, *22*, 599 (modified sodium hydride); Nagai, Y. *Org. Prep. Proced. Int.* ***1980***, *12*, 13 (hydrosilanes); Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294 ($LiAlH_4$); Winterfeldt, E. Synthesis ***1975***, 617 (diisobutylaluminum hydride and triisobutylaluminum); Hückel, W. *Fortschr. Chem. Forsch.* ***1966***, *6*, 197 (metals in ammonia or amines). See also Ref. 9.

[11] For books on oxidation reactions, see Hudlicky, M. *Oxidations in Organic Chemistry,* American Chemical Society, Washington, ***1990***; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, 2 vols., Academic Press, NY, ***1985, 1988*** [The first volume pertains to hydrocarbon substrates; the second mostly to oxygen- and nitrogen-containing substrates]; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***; Augustine, R.L.; Trecker, D.J. *Oxidation*, 2 Vols., Marcel Dekker, NY, ***1969, 1971***.

Six-membered alicyclic rings can be aromatized in a number of ways.[12] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: In such cases, one alkyl group often migrates or is eliminated, but more drastic conditions are usually required for this. In some cases, OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, although this is not the case for partially hydrogenated azulene systems, which are frequently found in nature; these are converted to azulenes.

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts[13] (e.g., Pt, Pd,[14] and Ni). Palladium trifluoroacetate also facilitates oxidative aromatization of cyclohexene.[15] In this case, the reaction is the reverse of double-bond hydrogenation (**15-11** and **15-15**), and presumably the mechanism is also the reverse, although not much is known.[16] Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.[17] The substrate is heated with the catalyst at ~300–350 °C. The reactions can often be carried out under milder conditions if a hydrogen acceptor (e.g., maleic acid, cyclohexene, or benzene) is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. Other transition metals can be used.[18] It has been reported that dehydrogenation of 1-methylcyclohexene-1-^{13}C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.[19] For polycyclic systems, heating with oxygen on activated carbon generates the aromatic compound, as in the conversion of dihydroanthracene to anthracene.[20]
2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H_2S and H_2Se. Little is known about this mechanism either.[21]

[12] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 16–22, 217–222; Fu, P.P.; Harvey, R.G. *Chem. Rev.* ***1978****, 78,* 317; Valenta, Z. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 1–76; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 34–44.

[13] See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 1–59.

[14] See Cossy, J.; Belotti, D. *Org. Lett.* ***2002****, 4*, 2557. See Cho, C.S.; Patel, D.B.; Shim, S.C. *Tetrahedron* ***2005****, 61*, 9490.

[15] Bercaw, J.E.; Hazari, N.; Labinger, J.A. *J. Org. Chem.* ***2008****, 73,* 8654.

[16] See Tsai, M.; Friend, C.M.; Muetterties, E.L. *J. Am. Chem. Soc.* ***1982****, 104,* 2539. See also, Augustine, R.L.; Thompson, M.M. *J. Org. Chem.* ***1987****, 52*, 1911.

[17] Land, D.P.; Pettiette-Hall, C.L.; McIver Jr., R.T.; Hemminger, J.C. *J. Am. Chem. Soc.* ***1989****, 111*, 5970.

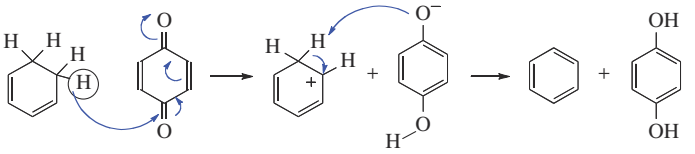
[18] Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* ***2002****, 43*, 2785.

[19] Marshall, J.L.; Miiller, D.E.; Ihrig, A.M. *Tetrahedron Lett.* ***1973***, 3491.

[20] Nakamichi, N.; Kawabata, H.; Hiyashi, M. *J. Org. Chem.* ***2003****, 68*, 8272.

[21] Silverwood, H.A.; Orchin, M. *J. Org. Chem.* ***1962****, 27*, 3401.

3. Quinones[22] become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[23] The latter is more reactive and can be used in cases where the substrate is difficult to dehydrogenate. It is likely that the mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion.[24]



Other reagents[25] have been used for aromatization of six-membered rings, including atmospheric oxygen, MnO_2,[26] SeO_2, H_2SO_4, and a Ru catalyst.[27] The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances, the hydrogen is not released as H_2 or transferred to an external oxidizing agent, but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and can be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

Heteroatom rings, as found in quinoline derivatives, for example, can be generated from amino-ketones with [hydroxy(tosyloxy)iodo]benzene and perchloric acid[28] or with $NaHSO_4$—$Na_2Cr_2O_7$ on wet silica.[29] Dihydropyridines are converted to pyridines with $NaNO_2$–oxalic acid and wet silica,[30] $BaMnO_4$,[31] $FeCl_3$–acetic acid,[32] or SeO_2.[33] *Hantzsch 1,4-dihydropyridines* (see Reactions **15-14** and **16-17**) are aromatized by treatment with ferric perchlorate in acetic acid.[34] Cyclic imines are converted to pyridine derivatives with NCS and then excess sodium methoxide.[35] Enamines are aromatized with Sn or Sb compounds.[36]

[22] Becker, H.; Turner, A.B. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1351–1384; Becker, H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 335–423.

[23] See Turner, A.B. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 193–225; Walker, D.; Hiebert, J.D. *Chem. Rev.* ***1967***, *67,* 153.

[24] Trost, B.M. *J. Am. Chem. Soc.* ***1967***, *89*, 1847. See also, Radtke, R.; Hintze, H.; Rösler, K.; Heesing, A. *Chem. Ber.* ***1990***, *123*, 627; Höfler, C.; Rüchardt, C. *Liebigs Ann. Chem.* ***1996***, 183. See also Ref. 22.

[25] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 187–191.

[26] See Leffingwell, J.C.; Bluhm, H.J. *Chem. Commun.* ***1969***, 1151.

[27] Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* ***2003***, 576.

[28] Varma, R.S.; Kumar, D. *Tetrahedron Lett.* ***1998***, *39*, 9113.

[29] Damavandi, J.A.; Zolfigol, M.A.; Karami, B. *Synth. Commun.* ***2001***, *31*, 3183.

[30] Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Comm.* ***2000***, *30*, 551.

[31] Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* ***2001***, *31*, 2241.

[32] Lu, J.; Bai, Y.; Wang, Z.; Yang, B.Q.; Li, W. *Synth. Commun.* ***2001***, *31*, 2625.

[33] Cai, X.-h.; Yang, H.-j.; Zhang, G.-l. *Can. J. Chem.* ***2005***, *83*, 273.

[34] Heravi, M.M.; Behbahani, F.K.; Oskooie, H.A.; Shoar, R.H. *Tetrahedron Lett.* ***2005***, *46,* 2775.

[35] DeKimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* ***1996***, 635.

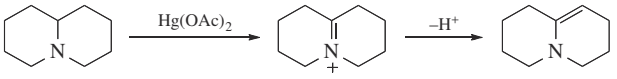
[36] Bigdeli, M.A.; Rahmati, A.; Abbasi-Ghadim, H.; Mahdavinia, G.H. *Tetrahedron Lett.* ***2007***, *48,* 4575.

Note that hydrogenolysis of cyclohexane leads to *n*-hexane with hydrogen and an Ir catalyst.[37]

OS **II**, 214, 423; **III**, 310, 358, 729, 807; **IV**, 536; **VI**, 731. Also see, OS **III**, 329.

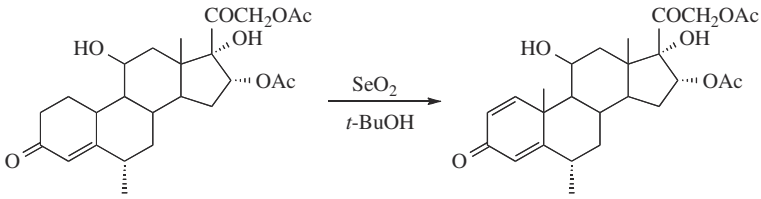
19-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds

Dihydro-elimination



1

Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, although industrially mixtures of alkenes are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions. Heating cyclooctane with an Ir catalyst leads to cyclooctene.[38] Treating alkenes that have an allylic hydrogen with $CrCl_2$ converts them to allenes.[39] It is not surprising, however, that most of the exceptions generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.[40] One example is the synthesis developed by Leonard and Musker,[41] in which tertiary amines give enamines (Reaction **10-69**) when treated with mercuric acetate[42] (see the example above). In this case, the initial product is the iminium ion (**1**) that loses a proton to give the enamine. Other transition metal catalysts convert amines to enamines, including Co compounds.[43] *Hünig's base* (diisopropylethylamine) was converted to the enamine *N,N*-diisopropyl-*N*-vinylamine by heating with an Ir catalyst.[44]



2 **3**

[37] Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001****, 123*, 1658.

[38] Göttker-Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* ***2004****, 126,* 1804.

[39] Takai, K.; Kokumai, R.; Toshikawa, S. *Synlett* ***2002***, 1164.

[40] See Haines, A.J. *Methods for the Oxidation of Organic Compounds,* Vol. 1, Academic Press, NY, ***1985***, pp. 6–16, 206–216. For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 251–256.

[41] See Leonard, N.J.; Musker, W.K. *J. Am. Chem. Soc.* ***1959****, 81,* 5631; ***1960****, 82,* 5148.

[42] See Haynes, L.W.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed. Marcel Dekker, NY, ***1988***, pp. 103–163; Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 102–107.

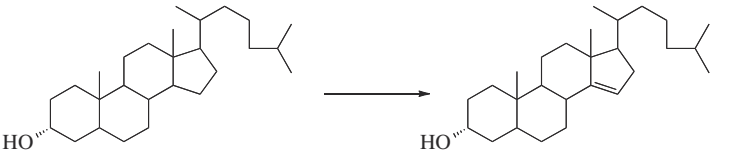
[43] Bolig, A.D.; Brookhart, M. *J. Am. Chem. Soc.* ***2007****, 129*, 14544.

[44] Zhang, X.; Fried, A.; Knapp, S.; Goldman, A.S. *Chem. Commun.* ***2003***, 2060.

The oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β-unsaturated carbonyl compound by removing H_2[45] (note that this reagent more often gives Reaction **19-17**). This reaction has been most often applied in the steroid series, an example being formation of **2** from **3**.[46] Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[47] and 1,2-diarylalkanes. These conversions can also be carried out by certain quinones, most notably DDQ (see Reaction **19-1**).[24] Molecular oxygen has been used to convert cyclic ketones to the conjugated ketone in the presence of a Pd catalyst.[48]

Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$,[49] by $FeCl_3$,[50] and by benzeneseleninic anhydride[51] (this reagent also dehydrogenates lactones in a similar manner), among other reagents. In an indirect method of achieving this conversion, the silyl enol ether of a simple ketone is treated with DDQ[52] or with triphenylmethyl cation[53] (for another indirect method, see Reaction **17-12**). Silyl enol ethers give the conjugated ketone upon treatment with ceric ammonium nitrate in DMF[54] or with $Pd(OAc)_2/NaOAc/O_2$.[55]

Simple linear alkanes have been converted to alkenes by treatment with certain transition metal compounds.[56]



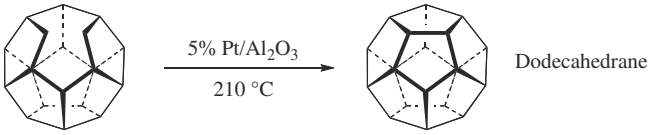
4 **5**

An entirely different approach (remote functionalization) allows specific dehydrogenation, as reported by R. Breslow[57] and by J.E. Baldwin et al.[58] 3α-Cholestanol (**4**) was converted to 5α-cholest-14-en-3α-ol (**5**), for example, thus introducing a double bond at a specific site remote from any functional group.[59]

[45] See Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2, Wiley, NY, ***1987***, pp. 91–213, 110–114; Jerussi, R.A. *Sel. Org. Transform.* ***1970****, 1,* 301, see pp. 315–321.
[46] Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* ***1960****, 82*, 1235.
[47] See Barnes, C.S.; Barton, D.H.R. *J. Chem. Soc.* ***1953***, 1419.
[48] Tokunaga, M.; Harada, S.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *Tetrahedron Lett.* ***2007****, 48,* 6860. For a review, see Muzart, J. *Eur. J. Org. Chem.* ***2010***, 3779.
[49] See Mukaiyama, T.; Ohshima, M.; Nakatsuka, T. *Chem. Lett.* ***1983***, 1207. See also, Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 103–110.
[50] Cardinale, G.; Laan, J.A.M.; Russell, S.W.; Ward, J.P. *Recl. Trav. Chim. Pays-Bas* ***1982****, 101,* 199.
[51] Barton, D.H.R.; Hui, R.A.H.F.; Ley, S.V.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1919; Barton, D.H.R.; Godfrey, C.R.A.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1947.
[52] Jung, M.E.; Pan, Y.; Rathke, M.W.; Sullivan, D.F.; Woodbury, R.P. *J. Org. Chem.* ***1977****, 42,* 3961.
[53] Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* ***1978***, 3455. Also see Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* ***1983****, 24*, 5635, 5639.
[54] Evans, P.A.; Longmire, J.M.; Modi, D.P. *Tetrahedron Lett.* ***1995****, 36*, 3985.
[55] Larock, R.C.; Hightower, T.R.; Kraus, G.A.; Hahn, P.; Zheng, O. *Tetrahedron Lett.* ***1995****, 36*, 2423.
[56] See Maguire, J.A.; Boese, W.T.; Goldman, A.S. *J. Am. Chem. Soc.* ***1989****, 111,* 7088; Sakakura, T.; Ishida, K.; Tanaka, M. *Chem. Lett.* ***1990***, 585, and references cited therein.
[57] See Breslow, R. *Chemtracts: Org. Chem.* ***1988****, 1*, 333; *Acc. Chem. Res.* ***1980****, 13*, 170; *Isr. J. Chem.* ***1979****, 18*, 187; *Chem. Soc. Rev.* ***1972****, 1,* 553.
[58] Baldwin, J.E.; Bhatnagar, A.K.; Harper, R.W. *Chem. Commun.* ***1970***, 659.
[59] See Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* ***1989****, 111*, 4561. See also, Bégué, J. *J. Org. Chem.* ***1982****, 47*, 4268; Nagata, R.; Saito, I. *Synlett* ***1990***, 291; Breslow, R.; Brandl, M.; Hunger, J.; Adams, A.D. *J. Am. Chem. Soc.* ***1987****, 109,* 3799; Batr, R.; Breslow, R. *Tetrahedron Lett.* ***1989****, 30*, 535; Orito, K.; Ohto, M.; Suginome, H. *J. Chem. Soc. Chem. Commun.* ***1990***, 1076.

Certain 1,2-diarylalkenes (ArCH=CHAr′) have been converted to the corresponding alkynes (ArC≡CAr′) by treatment with *t*-BuOK in DMF.[60] Dihydroindoles are converted to indoles with *N*,*N*′,*N*″-trichloro-1,3,5-triazin-2,4,6-trione and DBU.[61]

A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane[62]:



OS **V**, 428, **VII**, 4, 473.

19-3 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones

C,*O*-Dihydro-elimination

$$RCH_2OH \xrightarrow[\text{copper}]{\text{chromite}} RCHO \qquad RCHOHR' \xrightarrow[K_2Cr_2O_7]{H_2SO_4} RCOR'$$

Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in seven main ways:[63]

1. *With Chromium Reagents.*[64] Secondary alcohols are easily oxidized to ketones by dichromate in acidic media[65] at room temperature or slightly above. A solution of chromic and sulfuric acid in water is known as the *Jones reagent*.[66] Secondary alcohols are oxidized to ketones rapidly and in high yield without disturbing any double or triple bonds that may be present (see Reaction **19-10**) and without epimerizing an adjacent stereogenic center.[67] Mixing sodium dichromate with an alcohol, without solvent, provides a method for oxidation when the mixture is shaken.[68] Chromium trioxide (CrO_3)[69] has been used to oxidize primary and alcohols under solvent-free conditions. Chromium trioxide on silica gel, in supercritical CO_2,

[60] Akiyama, S.; Nakatsuji, S.; Nomura, K.; Matsuda, K.; Nakashima, K. *J. Chem. Soc. Chem. Commun.* ***1991***, 948.
[61] Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* ***2001***, *42*, 5385.
[62] Paquette, L.A.; Doherty, A.M. *Polyquinane Chemistry*, Springer, NY, ***1987***. See in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, the reviews by Paquette, L.A. pp. 313–352, and by Fessner, W.; Prinzbach, H. pp. 353–405; Paquette, L.A. *Chem. Rev.* ***1989***, *89*, 1051; in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Academic Press, NY, ***1984***, pp. 175–200.
[63] Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 114–126, 132–149; Haines, A.M. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 5–148, 326–390; Müller, P. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 469–538. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1234–1250.
[64] See Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 56–81; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 257–273.
[65] See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 118–216; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, ***1967***, pp. 142–147, 1059–1064, and subsequent volumes in this series.
[66] Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* ***1953***, 2548. Also see, Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 1389; Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 3383.
[67] See Djerassi, C.; Hart, P.A.; Warawa, E.J. *J. Am. Chem. Soc.* ***1964***, *86,* 78.
[68] Lou, J.-D.; Gao, C.-L.; Ma, Y.-C.; Huang, L.-H.; Li, L. *Tetrahedron Lett.* ***2006***, *47,* 311.
[69] Lou, J.-D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002***, *43*, 6095.

oxidizes alcohols to the corresponding carbonyl.[70] For acid-sensitive compounds, trimethylsilyl chromates[71] can be used. Chromium trioxide with aq *tert*-butylhydroperoxide oxidizes benzylic alcohols with microwave irradiation.[72] Phase-transfer catalysis is particularly useful,[73]especially when the substrates are generally insoluble in water (see Sec. 10.G.v). A catalytic amount of $Cr(acac)_3$ in conjunction with H_5IO_5 oxidizes benzylic alcohols to aldehydes.[74]

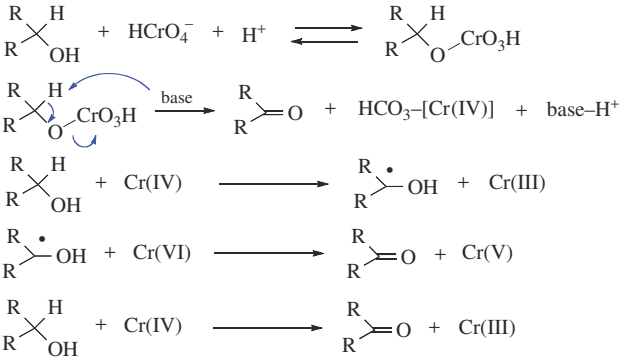
The Jones reagent can also oxidize primary allylic alcohols to the corresponding aldehydes,[75] although overoxidation to the carboxylic acid is a problem.[76] Oxidative cleavage of primary alcohols has been observed in the presence of molecular sieves 3 Å.[77] One way to mitigate overoxidation is to distil the aldehyde as it is formed, but this is not always possible. Due to these problems, other oxidizing conditions have been used to convert at least some primary alcohols to aldehydes.[78] Perhaps the three most commonly used Cr(VI) reagents used for the oxidation of allylic alcohols include[79] dipyridine Cr(VI) oxide (*Collins' reagent*),[80] pyridinium chlorochromate (PCC),[81] and pyridinium dichromate (PDC).[82] The PCC is somewhat acidic, and acid-catalyzed rearrangements have been observed.[83]

Analogous to the use of pyridine for PCC and PDC, a variety of amines and diamines have been converted to tetraalkylammonium halochromates or dichromates, including *N*-benzyl 1,4-diazabicyclo[2.2.2]octane ammonium dichromate with microwave irradiation,[84] γ-picolinium chlorochromate,[85] and quinolinium fluorochromate.[86] Benzyltriphenylphosphonium chlorochromate has been used in a similar manner.[87] Oxidizing agents have been supported on a polymer,[88]

[70] González-Núñez, M.E.; Mello, R.; Olmos, A.; Acerete, R.; Asensio, G. *J. Org. Chem.* ***2006****, 71*, 1039.
[71] Moiseenkov, A.M.; Cheskis, B.A.; Veselovskii, A.B.; Veselovskii, V.V.; Romanovich, A.Ya.; Chizhov, B.A. *J. Org. Chem. USSR* ***1987****, 23,* 1646.
[72] Singh, J.; Sharma, M.; Chhibber, M.; Kaur, J.; Kad, G.L. *Synth. Commun.* ***2000****, 30*, 3941. Also see Heravi, M.M.; Ajami, D.; Tabar-Hydar, K. *Synth. Commun.* ***1999****, 29*, 163; Mirza-Ayhayan, M.; Heravi, M.M. *Synth. Commun.* ***1999****, 29*, 785
[73] For a review, see Patel, S.; Mishra, B.K. *Tetrahedron* ***2007****, 63,* 4367.
[74] Xu, L.; Trudell, M.L. *Tetrahedron Lett.* ***2003****, 44*, 2553.
[75] Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* ***1975****, 40*, 1664.
[76] Though ketones are much less susceptible to further oxidation than aldehydes, such oxidation is possible (**19-8**), and care must be taken to avoid it, usually by controlling the temperature and/or the oxidizing agent.
[77] Fernandes, R.A.; Kumar, P. *Tetrahedron Lett.* ***2003****, 44*, 1275.
[78] Also see Nishiguchi, T.; Asano, F. *J. Org. Chem.* ***1989****, 54*, 1531; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1234–1250.
[79] See Warrener, R.N.; Lee, T.S.; Russell, R.A.; Paddon-Row, M.N. *Aust. J. Chem.* ***1978****, 31*, 1113.
[80] Collins, J.C.; Hess, W.W. *Org. Synth.* ***VI***, 644; Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* ***1975****, 97*, 5927.
[81] Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* ***1975***, 2647. See Luzzio, F.A.; Guziec, Jr., F.S. *Org. Prep. Proced. Int.* ***1988****, 20*, 533; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* ***1982***, 245; Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990****, 46,* 4417; Salehi, P.; Firouzabadi, H.; Farrokhi, A.; Gholizadeh, M. *Synthesis* ***2001***, 2273.
[82] See Czernecki, S.; Georgoulis, C.; Stevens, C.L.; Vijayakumaran, K. *Tetrahedron Lett.* ***1985****, 26,* 1699.
[83] See Ren, S.-K.; Wang, F.; Dou, H.-N.; Fan, C.-A.; He, L.; Song, Z.-L.; Xia, W.-J.; Li, D-R.; Jia, Y.-X.; Li, X.; Tu, Y.-Q. *Synthesis* ***2001***, 2384.
[84] Hajipour, A.R.; Mallakpour, S.E.; Khoee, S. *Synlett* ***2000***, 740.
[85] Khodaei, M.M.; Salehi, P.; Goodarzi, M. *Synth. Commun.* ***2001****, 31*, 1253.
[86] Rajkumar, G.A.; Arabindoo, B.; Murugesan, V. *Synth. Commun.* ***1999****, 29*, 2105.
[87] Hajipour, A.R.; Mallakpour, S.E.; Backnejad, H. *Synth. Commun.* ***2000****, 30*, 3855.
[88] For a review, see McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401. See also, Shirini, F.; Dabiri, M.; Dezyani, S.; Jalili, F. *Russ. J. Org. Chem.* ***2005****, 41*, 390.

including chromic acid,[89] as well as poly[vinyl(pyridinium fluorochromate)].[90] Triphenylmethylphosphonium dichromate is effective for selective oxidation of benzylic alcohols.[91]

Studies on the mechanism of oxidation with acid dichromate[92] led to the currently accepted mechanism as proposed by Westheimer[93] (cf. the first two steps with Sec. 19.A, category 4).



The base in the second step may be water, although it is also possible[94] that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygen atoms in which case the Cr(IV) species produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of ~6 found on use of MeCDOHMe, showing that the α hydrogen is removed in the rate-determining step.[95] Note that, as in Reaction **19-23** the substrate is oxidized by three different oxidation states of chromium.[96]



[89] Cainelli, G.; Cardillo, G.; Orena, M.; Sandri, S. *J. Am. Chem. Soc.* ***1976****, 98*, 6737; Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* ***1978***, 534. See also, San Filippo, Jr., J.; Chern, C. *J. Org. Chem.* ***1977****, 42,* 2182.

[90] Srinivasan, R.; Balasubramanian, K. *Synth. Commun.* ***2000****, 30*, 4397.

[91] Hajipour, A.R.; Safaei, S.; Ruoho, A.E. *Synth. Commun.* ***2009****, 39,* 3687.

[92] See Müller, P. *Chimia* ***1977****, 31*, 209; Wiberg, K.B. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 142–170; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 49–71; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 37–48; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1985****, 41*, 205.

[93] Westheimer, F.H. *Chem. Rev.* ***1949****, 45,* 419, see p. 434; Holloway, F.; Cohen, M.; Westheimer, F.H. *J. Am. Chem. Soc.* ***1951****, 73*, 65.

[94] Kwart, H.; Nickle, J.H. *J. Am. Chem. Soc.* ***1979****, 98,* 2881 and cited rererences; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1986****, 42,* 681. See also, Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990****, 46,* 1963.

[95] Westheimer, F.H.; Nicolaides, N. *J. Am. Chem. Soc.* ***1949****, 71,* 25. Also see Wiberg, K.B.; Schäfer, H. *J. Am. Chem. Soc.* ***1969****, 91*, 927, 933; Lee, D.G.; Raptis, M. *Tetrahedron* ***1973****, 29,* 1481.

[96] Doyle, M.P.; Swedo, R.J.; Rocek, J. *J. Am. Chem. Soc.* ***1973****, 95*, 8352; Wiberg, K.B.; Mukherjee, S.K. *J. Am. Chem. Soc.* ***1974****, 96*, 1884, 6647.

With other oxidizing agents discussed below, mechanisms are less clear.[97] It seems certain that some oxidizing agents operate by a hydride-shift mechanism,[98] for example, dehydrogenation with triphenylmethyl cation[99] and the *Oppenauer oxidation*, and some by a free radical mechanism (e.g., oxidation with $S_3O_8^{2-}$[100] and with VO_2^{+}[101]). A summary of many proposed mechanisms is given by Littler.[102]

2. *With Manganese and Other Metal Oxidizing Agents*. Potassium permanganate ($KMnO_4$) has been used for the oxidation of alcohols.[103] Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium permanganate ($KMnO_4$) under phase-transfer conditions.[104] Phase-transfer catalysis has also been used with chromic acid,[105] and ruthenium tetroxide.[106] Ultrasound has been used for $KMnO_4$ oxidations.[107] Permanganate supported on a polymer has been used.[108]

   Permanganate[109] is an important reagent for the selective oxidation of benzylic alcohols primary and benzylic alcohols, in preference to aliphatic substrates. [110]A variation oxidizes alcohols with $MnO_2/AlCl_3$.[111]

   An alternative to MnO_2 is the oxidation of allylic and benzylic alcohols with Me_3NO in the presence of $CHDFe(CO)_3$.[112] Similar oxidation occurs with $NaBrO_3$ in aq MeCN[113] or K_2FeO_4 on clay.[114] The reaction of AuCl with an anionic ligand leads to oxidation of primary alcohols to aldehydes.[115] The *Grubbs' catalyst,* $PhCH{=}Ru(PCy_3)_2Cl_2$, where Cy = cyclohetyl, (see **156** in Reaction **18-37**), in the presence of KOH, oxidized alcohols.[116]

[97] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 264–277.
[98] Barter, R.M.; Littler, J.S. *J. Chem. Soc. B* ***1967***, 205. See Moodie, R.B.; Richards, S.N. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1833; Ross, D.S.; Gu, C.; Hum, G.P.; Malhotra, R. *Int. J. Chem. Kinet.* ***1986****, 18,* 1277.
[99] Bonthrone, W.; Reid, D.H. *J. Chem. Soc.* ***1959***, 2773.
[100] Walling, C.; Camaioni, D.M. *J. Org. Chem.* ***1978****, 43,* 3266; Clerici, A.; Minisci, F.; Ogawa, K.; Surzur, J. *Tetrahedron Lett.* ***1978***, 1149; Beylerian, N.M.; Khachatrian, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1937.
[101] Littler, J.S.; Waters, W.A. *J. Chem. Soc.* ***1959***, 4046.
[102] Littler, J.S. *J. Chem. Soc.* ***1962***, 2190.
[103] See Takemoto, T.; Yasuda, K.; Ley, S.V. *Synlett* ***2001***, 1555. For oxidation in an ionic liquid, see Kumar, A.; Jain, N.; Chauhan, S.M.S. *Synth. Commun.* ***2004****, 34*, 2835.
[104] Kim, K.S.; Chung, S.; Cho, I.H.; Hahn, C.S. *Tetrahedron Lett.* ***1989****, 30,* 2559. See Lee, D.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry,* pt. D Academic Press, NY, ***1982***, pp. 147–206.
[105] See Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1979***, 134; Pletcher, D.; Tait, S.J.D. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 788.
[106] Morris Jr., P.E.; Kiely, D.E. *J. Org. Chem.* ***1987****, 52*, 1149.
[107] Yamawaki, J.; Sumi, S.; Ando, T.; Hanfusa, T. *Chem. Lett.* ***1983***, 379.
[108] See Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1981****, 22,* 4889. See also, Menger, F.M.; Lee, C. *J. Org. Chem.* ***1979****, 44,* 3446.
[109] Lou, J.D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002****, 43*, 6149.
[110] Taylor, R.J.K.; Reid, M.; Foot, J.; Raw, S.A. *Acc. Chem. Res.* ***2005****, 38* 851. See Varma, R.S.; Saini, R.K.; Dahiya, R. *Tetrahedron Lett.* ***1997****, 38*, 7823.
[111] Firouzabadi, H.; Etemadi, S.; Karimi, B.; Jarrahpour, A.A. *Synth. Commun.* ***1999****, 29*, 4333.
[112] Pearson, A.J.; Kwak, Y. *Tetrahedron Lett.* ***2005****, 46,* 5417.
[113] Shaabani, A.; Karimi, A.-R. *Synth. Commun.* ***2001****, 31*, 759.
[114] Tajbakhsh, M.; Heravi, M.M.; Habibzadeh, S.; Ghassemzadeh, M. *J. Chem. Res. (S)* ***2001***, 39.
[115] Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* ***2005****, 127*, 18004.
[116] Adair, G.R.A.; Williams, J.M.J. *Tetrahedron Lett.* ***2005****, 46*, 8233.

Tetrapropylammonium perruthenate (Pr_4N^+ RuO_4^-; also called TPAP; the *Ley reagent*)[117] is an important oxidizing agent that is compatible with the presence of other functionality in the molecule.[118] In the presence of molecular oxygen, oxidation of alcohols is catalytic in TPAP.[119] This reagent has been bound to a polymer.[120] Methods have been developed for recovery of the catalyst and reuse of TPAP.[121]

Many other oxidizing agents have been employed. Examples include ruthenium tetroxide,[122] $MeReO_3$,[123] HNO_3 with a $Yb(OTf)_3$ catalyst,[124] $FeBr_3$—H_2O_2,[125] ceric ammonium nitrate in an ionic liquid,[126] a Bi catalyst,[127] O_2 with transition metal catalysts,[128] and with RuO_2 and a zeolite catalyst.[129] Microwave induced oxidation of benzylic alcohols was reported using zeolite-supported ferric nitrate.[130]

Reagents that can be used specifically to oxidize a secondary OH group in the presence of a primary OH group[131] are H_2O_2–ammonium molybdate,[132] or urea–H_2O_2 with $MgBr_2$,[133] while $RuCl_2(PPh_3)_3$–benzene,[134] osmium tetroxide,[135] and

[117] Griffith, W.P.; Ley, S.V. *Aldrichimica Acta* ***1990****, 23,* 13; Chandler, W.D.; Wang, Z.; Lee, D.G. *Can. J. Chem.* ***2005****, 83,* 1212.
[118] With organotrifluoroborates: Molander, G.A.; Petrillo, D.E. *J. Am. Chem. Soc.* ***2006****, 128*, 9634.
[119] Lenz, R.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 3291.
[120] Hinzen, B.; Lenz, R.; Ley, S.V. *Synthesis* ***1998***, 977. Also see Brown, D.S.; Kerr, W.J.; Lindsay, D.M.; Pike, K.G.; Ratcliffe, P.D. *Synlett* ***2001***, 1257.
[121] Ley, S.V.; Ramarao, C.; Smith, M.D. *Chem. Commun.* ***2001***, 2278.
[122] See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, ***1973***, pp. 197–222.
[123] Divalentin, C.; Gandolfi, R.; Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* ***2001****, 123*, 2365; Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004****, 45*, 1233.
[124] Barrett, A.G.M.; Braddock, D.C.; McKinnell, R.M.; Waller, F.J. *Synlett* ***1999***, 1489.
[125] Martín, S.E.; Garrone, A. *Tetrahedron Lett.* ***2003****, 44*, 549.
[126] Mehdi, H.; Bodor, A.; Lantos, D.; Horváth, I.T.; De Vos, D.E.; Binnemans, K. *J. Org. Chem.* ***2007****, 72,* 517.
[127] Matano, Y.; Nomura, H. *J. Am. Chem. Soc.* ***2001****, 123,* 6443. With *tert*-butylhydroperoxide, see Malik, P.; Chakraborty, D. *Synthesis* ***2010***, 3736.
[128] See Schultz, M.J.; Sigman, M.S. *Tetrahedron* ***2006****, 62,* 8227; Lenoir, D. *Angew. Chem. Int. Ed.* ***2006****, 45,* 3206; Zhan, B.-Z.; Thompson, A. *Tetrahedron* ***2004****, 60*, 2917; Mallat, T.; Baiker, A. *Chem. Rev.* ***2004****, 104*, 3037; Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* ***2003****, 103,* 27. Catalysts of **Au:** Abad, A.; Almela, C.; Corma, A.; García, H. *Tetrahedron* ***2006****, 62,* 6666; Li, H.; Guan, B.; Wang, W.; Xing, D.; Fang, Z.; Wan, X.; Yang, L.; Shi, Z. *Tetrahedron* ***2007****, 63,* 8430; Miyamura, H.; Matsubara, R.; Miyazaki, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2007****, 46,* 4151; Abad, A.; Almela, C.; Corma, A.; García, H. *Chem. Commun.* ***2006***, 3178; Kim, S.; Bae, S.W.; Lee, J.S.; Park, J. *Tetrahedron* ***2009****, 65*, 1461. **Cu:** Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* ***2004****, 43*, 2228; Jiang, N.; Ragauskas, A.J. *Org. Lett.* ***2005****, 7,* 3689. **Co:** Jiang, N.; Ragauskas, A.J. *J. Org. Chem.* ***2006****, 71,* 7087. **Mo:** Velusamy, S.; Ahamed, M.; Punniyamurthy, T. *Org. Lett.* ***2004****, 6*, 4821. **Pd:** Nielsen, R.J.; Goddard III, W.A. *J. Am. Chem. Soc.* ***2006****, 128,* 9651; Steinhoff, B.A.; King, A.E.; Stahl, S.S. *J. Org. Chem.* ***2006****, 71,* 1861; Batt, F.; Bourcet, E.; Kassab, Y.; Fache, F. *Synlett* ***2007***, 1869. **Ru:** Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2002****, 41*, 4538. **V:** Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* ***2007****, 48,* 273.
[129] Zhan, B.-Z.; White, M.A.; Sham, T.-K.; Pincock, J.A.; Doucet, R.J.; Rao, K.V.R.; Robertson, K.N.; Cameron, T.S. *J. Am. Chem. Soc.* ***2003****, 125*, 2195.
[130] Heravi, M.M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *Chem. Commun.* ***1999***, 833.
[131] For a review, see Arterburn, J.B. *Tetrahedron* ***2001****, 57*, 9765.
[132] See Sakata, Y.; Ishii, Y. *J. Org. Chem.* ***1991****, 56,* 6233.
[133] Park, H.J.; Lee, J.C. *Synlett* ***2009***, 79.
[134] Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* ***1981****, 22,* 1605.
[135] Maione, A.M.; Romeo, A. *Synthesis* ***1984***, 955.

Br_2—$Ni(OBz)_2$[136] all oxidize primary OH groups in the presence of a secondary OH group.[137] Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.[138] α-Hydroxy ketones are oxidized to 1,2-diketones with $Bi(NO_3)_3$ and a $Cu(OAc)_2$ catalyst,[139] ferric chloride (solid state),[140] or O_2 and a V catalyst.[141] 1,2-Diols are oxidized to chiral α-hydroxy-ketones using NBS with a chiral Cu catalyst.[142]

3. *The Oppenauer Oxidation*. When a ketone in the presence of an aluminum alkoxide is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation*.[143] This is the reverse of the *Meerwein–Ponndorf–Verley reaction* (**19-36**) and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. A common base is aluminum *tert*-butoxide. The chief advantage of the method is its high selectivity. Although the method is most often used for the preparation of ketones, it has also been used for aldehydes. An Ir catalyst[144] has been developed for the *Oppenauer oxidation*, and also a water-soluble Ir catalyst.[145] Homogeneous water-soluble complexes catalyze the reaction.[146] An uncatalyzed reaction under supercritical conditions was reported.[147]
4. *DMSO Based Reagents*. The use of oxalyl chloride and DMSO at low temperature is called the *Swern oxidation*[148] and is widely used. A sulfonium salt is produced *in situ*, which reacts with the alcohol to generate the key intermediate required for oxidation.[149] Maintaining the low-reaction temperature is essential in this reaction, however, since the reagent generated *in situ* decomposes at temperatures significantly below ambient. Note that *Swern oxidation* of molecules having alcohol moieties, as well as a disulfide, leads to the ketone without oxidation of the sulfur.[150] Sulfoxides other than DMSO can be used in conjunction with oxalyl chloride for the oxidation of alcohols,[151] including fluorinated sulfoxides[152] and a polymer-bound sulfoxide.[153]

[136] Doyle, M.P.; Dow, R.L.; Bagheri, V.; Patrie, W.J. *J. Org. Chem.* ***1983****, 48,* 476.
[137] For a list of references, see Kulkarni, M.G.; Mathew T.S. *Tetrahedron Lett.* ***1990****, 31,* 4497.
[138] Nakano, T.; Terada, T.; Ishii, Y.; Ogawa, M. *Synthesis* ***1986***, 774.
[139] Tymonko, S.A; Nattier, B.A.; Mohan, R.S. *Tetrahedron Lett.* ***1999****, 40*, 7657.
[140] Zhou, Y.-M.; Ye, X.-R.; Xin, X.-Q. *Synth. Commun.* ***1999****, 29*, 2229.
[141] Kirahara, M.; Ochiai, Yy.; Takizawa, S.; Takahata, H.; Nemoto, H. *Chem. Commun.* ***1999***, 1387. See also, Sigman, M.S.; Jensen, D.R. *Acc. Chem. Res.* ***2006****, 39,* 221.
[142] Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* ***2007****, 48*, 8668.
[143] See Djerassi, C. *Org. React.* ***1951****, 6,* 207. See Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* ***2002***, 279; Graves, C.R.; Zeng, B.-S.; Nguyen. S.T. *J. Am. Chem. Soc.* ***2006****, 128,* 12596.
[144] Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* ***2003****, 68*, 1601.
[145] Ajjou, A.N. *Tetrahedron Lett.* ***2001****, 42*, 13.
[146] Ajjou, A.N.; Pinet, J.-L. *Can. J. Chem.* ***2005****, 83*, 702.
[147] Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A.; Hoz, S. *J. Org. Chem.* ***2004****, 69*, 1492.
[148] Omura, K.; Swern, D. *Tetrahedron* ***1978****, 34,* 1651. See Ohsugi, S.-i.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron* ***2003****, 59*, 8393.
[149] For a mechanism study, see Giagou T.; Meyer, M.P. *J. Org. Chem.* ***2010****, 75,* 8088.
[150] Fang, X.; Bandarage, U.K.; Wang, T.; Schroeder, J.D.; Garvey, D.S. *J. Org. Chem.* ***2001****, 66*, 4019.
[151] Nishida, K.; Ohsugi, S.-i.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* ***2002****, 43*, 5177.
[152] Crich, D.; Neelamkavil, S. *Tetrahedron* ***2002****, 58*, 3865.
[153] Choi, M.K.W.C.; Toy, P.H. *Tetrahedron* ***2003****, 59*, 7171.

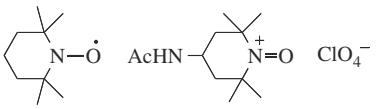
Similar oxidation of alcohols has been carried out with DMSO and other reagents[154] in place of DCC: acetic anhydride,[155] SO_3–pyridine–triethylamine,[156] trifluoroacetic anhydride,[157] pivaloyl chloride,[158] tosyl chloride,[159] $Ph_3P^+Br^-$,[160] trimethylamine *N*-oxide,[161] a Mo catalyst and O_2,[162] and methanesulfonic anhydride.[517] Dimethyl sulfoxide in 48% HBr oxidizes benzylic alcohols to aryl aldehydes.[163] An alcohol is treated with DMSO, DCC,[164] and anhydrous phosphoric acid[165] in what is called *Moffatt oxidation*. In this way, a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced. The strong acid conditions are sometimes a problem, and complete removal of the dicyclohexylurea byproduct can be difficult.

5. *TEMPO and Related Reagents*. The nitroxyl radical TEMPO (**6**) has been used in conjunction with coreagents, including mcpba,[166] O_2 with transition metal catalysts,[167] O_2 with HBr and *tert*-butylnitrite,[168] $CuBr_2$(bpy)–air (bpy = 2,2′-bipyridyl),[169] $CuBr{\cdot}SMe_2$ in perfluorous solvents,[170] bromohydantoins,[171] enzymes,[172] carbenes,[173] $NaNO_2$—HCl,[174] $NaIO_4$,[175] and H_5IO_6.[176] Silica-supported TEMPO,[177] polymer-bound TEMPO,[178] and PEG–TEMPO[179] have been used. The TEMPO derived ionic liquids,[180] or ionic liquid-supported TEMPO[181] have

[154] For a review, see Mancuso, A.J.; Swern, D. *Synthesis* ***1981***, 165.
[155] Albright, J.D.; Goldman, L. *J. Am. Chem. Soc.* ***1967****, 89,* 2416.
[156] Parikh, J.R.; Doering, W. von E. *J. Am. Chem. Soc.* ***1967****, 89,* 5507.
[157] Huang, S.L.; Omura, K.; Swern, D. *Synthesis* ***1978***, 297.
[158] Dubey. A.; Kandula, S.R.V.; Kumar, P. *Synth. Commun.* ***2008****, 38,* 746.
[159] Albright, J.D. *J. Org. Chem.* ***1974****, 39*, 1977.
[160] Bisai, A.; Chandrasekhar, M.; Singh, V.K. *Tetrahedron Lett.* ***2002****, 43*, 8355.
[161] Godfrey, A.G.; Ganem, B. *Tetrahedron Lett.* ***1990****, 31*, 4825.
[162] Khenkin, A.M.; Neumann, R. *J. Org. Chem.* ***2002****, 67*, 7075.
[163] Li, C.; Xu, Y.; Lu, M.; Zhao, Z.; Liu, L.; Zhao, Z.; Cui, Y.; Zheng, P.; Ji, X.; Gao, G. *Synlett* ***2002***, 2041.
[164] The DCC is converted to dicyclohexylurea, which in some cases is difficult to separate from the product. One way to avoid this problem is to use a carbodiimide linked to an insoluble polymer: Weinshenker, N.M.; Shen, C. *Tetrahedron Lett.* ***1972***, 3285.
[165] Fenselau, A.H.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1966****, 88*, 1762; Albright, J.D.; Goldman, L. *J. Org. Chem.* ***1965****, 30*, 1107.
[166] Rychnovsky, S.D.; Vaidyanathan, R. *J. Org. Chem.* ***1999****, 64*, 310.
[167] **Mn/Co:** Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001****, 42*, 6651. **Mo**: Ben-Daniel, R.; Alsteers, P.; Neumann, R. *J. Org. Chem.* ***2001****, 66*, 8650. **Ru**: Dijksman, A.; Marino-González, A.; Payeras, A.M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Am. Chem. Soc.* ***2001****, 123*, 6826.
[168] Xie, Y.; Mo, W.; Xu, D.; Shen, Z.; Sun, N.; Hu, B.; Hu, X. *J. Org. Chem.* ***2007****, 72,* 4288.
[169] Gamez, P.; Arends, I.W.C.E.; Reedijk, J.; Sheldon, R.A. *Chem. Commun.* ***2003***, 2414.
[170] Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* ***2000****, 41,* 4343.
[171] Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* ***2005****, 70,* 729.
[172] Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D. *Tetrahedron Lett.* ***2001****, 42*, 7551.
[173] Guin, J.; Sarkar, S.D.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* ***2008****, 47,* 8727.
[174] Wang, X.; Liu, R.; Jin, Y.; Liang, X. *Chemistry: European J.* ***2008****, 14,* 2679. For an Fe–TEMPO system, see Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun.* ***2005***, 5322.
[175] Lei, M.; Hu, R.-J.; Wang, Y.-G. *Tetrahedron* ***2006****, 62,* 8928.
[176] Kim, S.S.; Nehru, K. *Synlett* ***2002***, 616.
[177] Bolm, C.; Fey, T. *Chem. Commun.* ***1999***, 1795.
[178] Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* ***2002****, 66*, 8154.
[179] Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G. *Tetrahedron* ***2005****, 61,* 12058. See Miao, C.-X.; He, L.-N.; Wang, J.-Q.; Gao, J. *Synlett* ***2009***, 3291.
[180] Wu, X.-E.; Ma, L.; Ding, M.-X.; Gao, L.-X. *Synlett* ***2005***, 607.
[181] Fall, A.; Sene, M.; Gaye, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* ***2010****, 51*, 4501.

been used for the oxidation of alcohols. The TEMPO compound has also been used with a polymer-bound hypervalent iodine reagent.[182] A catalytic reaction using 5% TEMPO and 5% CuCl with O_2 in an ionic liquid oxidizes benzylic alcohols to the corresponding aldehyde.[183] Ion-supported TEMPO oxidation in water is possible.[184]

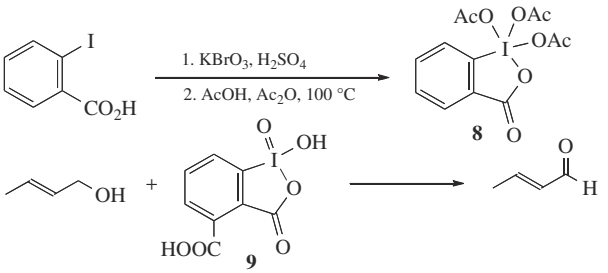
Other nitroxyl radical oxidizing agents are known.[185] A related oxidizing agent is oxoammonium salt **7** (*Bobbitt's reagent*), a stable and nonhygroscopic salt that oxidizes primary and secondary alcohols in dichloromethane.[186] The mechanism of oxidation for **7** has been examined.[187]



6 **7**

6. *With Hypervalent Iodine Reagents.*[188] Treatment of 2-iodobenzoic acid with $KBrO_3$ in H_2SO_4 and heating the resulting product to 100 °C with acetic anhydride and acetic acid[189] gives hypervalent iodine reagent (**8**), the so-called *Dess–Martin Periodinane*.[190] This reagent reacts with alcohols at ambient temperature to give the corresponding aldehyde or ketone.[191] The reaction is accelerated by water[192] and a water-soluble periodinane [*o*-iodoxybenzoic acid (**9**), IBX][193] has been prepared that oxidized allylic alcohols to conjugated aldehydes.[194] 2-Methyl-2-propanol has been used as a solvent.[195] The reagent has an indefinite shelf-life in a sealed container, but hydrolysis occurs upon long-term exposure to atmospheric moisture. A note of CAUTION! The *Dess–Martin reagent* can be shock sensitive under some conditions and explode ~200 °C.[196]

[182] Sakuratani, K.; Togo, H. *Synthesis* ***2003***, 21.
[183] Ansar, I.A.; Gree, R. *Org. Lett.* ***2002****, 4*, 1507.
[184] Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Tetrahedron* ***2006****, 62*, 556.
[185] de Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H. *Synthesis* ***1996***, 1153; Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* ***2005***, 1085.
[186] See Merbouh, N.; Bobbitt, J.M.; Brückner, C. *Org. Prep. Proceed. Int.* ***2004****, 36*, 1.
[187] Bailey, W.F.; Bobbitt, J.M.; Wiberg, K.B. *J. Org. Chem.* ***2007****, 72,* 4504.
[188] See Su, J.T.; Goddard, III, W.A. *J. Am. Chem. Soc.* ***2005****, 127,* 14146; Wirth, T. *Angew. Chem. Int. Ed.* ***2005****, 44*, 3656. See Duschek, A.; Kirsch, S.F. *Chemistry: Eur. J.* ***2009****, 15*, 10713.
[189] See Lin, C.-K.; Lu, T.-J. *Tetrahedron* ***2010****, 66,* 9688.
[190] Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* ***1991****, 113*, 7277. See Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* ***1999****, 64*, 4537.
[191] See Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* ***1994****, 35*, 8019.
[192] Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* ***1994****, 59*, 7549. In aqueous β–cyclodextrin–acetone solution, see Surendra, K.; Krishnaveni, N.S.; Reddy, M.A.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003****, 68*, 2058.
[193] Gallen, M.J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C.M. *Angew. Chem. Int. Ed.* ***2006****, 45*, 2929.
[194] Thottumkara, A.P.; Vinod, T.K. *Tetrahedron Lett.* ***2001****, 43*, 569.
[195] Van Arman, S.A. *Tetrahedron Lett.* ***2009****, 50*, 4693.
[196] Plumb, J.B.; Harper, D.J. *Chem. Eng. News,* ***1990***, July 16, p. 3. For an improved procedure, see Ireland, R.E.; Liu, L. *J. Org. Chem.* ***1993****, 58*, 2899.



Iodine has been used as a cocatalyst.[197] Other hypervalent iodine oxidizing reagents are known,[198] including $PhI(OAc)_2$/TEMPO,[199] $PhI(OAc)_2$–chromium salen,[200] $PhI(OAc)_2$ supported on alumina with microwave irradiation,[201] and an ion-supported hypervalent iodine(III) reagent.[202] Microwave irradiation of benzylic alcohols with PhI(OH)OTs gave the corresponding aldehyde.[203] Hypervalent iodine compounds have been used in ionic liquids.[204] Heating benzylic alcohols with *o*-iodoxybenzoic acid under solvent-free conditions gave the aldehyde.[205] 2-Iodobenzenesulfonic acid is a very active catalyst for oxidation of alcohols using Oxone.[206]

7. *By Catalytic Dehydrogenation.* For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the carboxylic acid is prevented. Copper chromite is often used, but other catalysts (e.g., Ag and Cu), have also been employed. Many ketones were prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, procedures using Cu(II) complexes,[207] Rh complexes,[208] Ru complexes,[209] Raney nickel,[210] and Pd complexes[211] (under phase transfer conditions)[212] have been reported. Allylic alcohols[213] are oxidized to the corresponding saturated aldehyde or ketone by heating with a Rh catalyst, and benzylic alcohols are converted to the aldehyde with a Rh

[197] Karade, N.N.; Tiwari, G.B.; Huple, D.B. *Synlett* ***2005***, 2039.
[198] Moriarty, R.M.; Prakash, O. *Accts. Chem. Res.* ***1986****, 19*, 244; Dohi, T.; Takenaga, N.; Fukushima, K.-i.; Uchiyama, T.; Kato, D.; Motoo, S.; Fujioka, H.; Kita, Y. *Chem. Commun.* ***2010***, 7697.
[199] DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997****, 62,* 6974.
[200] Adam, W.; Hajra, S.; Herderich, M.; Saha-Möller, C.R. *Org. Lett.* ***2000****, 2*, 2773.
[201] Varma, R.S.; Saini, R.K.; Dahiya, R. *J. Chem. Res. (S)* ***1998***, 120.
[202] Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem. Int. Ed.* ***2005****, 44*, 952.
[203] Lee, J.C.; Lee, J.Y.; Lee, S.J. *Tetrahedron Lett.* ***2004****, 45*, 4939.
[204] Liu, Z.; Chen, Z.-C.; Zheng, Q.-C. *Org. Lett.* ***2003****, 5*, 3321; Karthikeyan, G.; Perumal, P.T. *Synlett* ***2003***, 2249.
[205] Moorthy, J.N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.* ***2004****, 45*, 5419.
[206] Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* ***2009****, 131*, 251.
[207] Muldoon, J.; Brown, S.N. *Org. Lett.* ***2002****, 4*, 1043.
[208] Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* ***2003****, 44*, 9201.
[209] Meijer, R.H.; Ligthart, G.B.W.L.; Meuldijk, J.; Vekemans, J.A.J.M.; Hulshof, L.A.; Mills, A.M.; Kooijman, H.; Spek, A.L. *Tetrahedron* ***2004****, 60*, 1065.
[210] Krafft, M.E.; Zorc, B. *J. Org. Chem.* ***1986****, 51*, 5482.
[211] See Mandal, S.K.; Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Org. Chem.* ***2003****, 68*, 4600. See also, Mandal, S.K.; Sigman, M.S. *J. Org. Chem.* ***2003****, 68*, 7535; Guram, A.S.; Bei, X.; Turner, H.W. *Org. Lett.* ***2003****, 5*, 2485. For a review, see Muzart, J. *Tetrahedron* ***2003****, 59*, 5789.
[212] Choudary, B.M.; Reddy, N.P.; Kantam, M.L.; Jamil, Z. *Tetrahedron Lett.* ***1985****, 26,* 6257.
[213] Tanaka, K.; Fu, G.C. *J. Org. Chem.* ***2001****, 66*, 8177.

catalyst.[214] Propargylic alcohols are oxidized by heating with a V catalyst.[215] Secondary alcohols are oxidized with $Bi(NO_3)_3$ on Montmorillonite.[216] Biooxidation is possible as well via hydrogen transfer.[217]

8. *Miscellaneous Reagents.*[218] Nitric acid in dichloromethane oxidizes benzylic alcohols to the corresponding ketone.[219] Bromine is an effective oxidant, and iodine under photochemical conditions has been used.[220] Heating a 1,2-diol with NBS in CCl_4 gave the 1,2-diketone.[221] Iodine has been used in conjunction with DMSO and hydrazine.[222] Enzymatic oxidations have been reported.[223] Oxidation of alcohols in water is possible using I_2O_5.[224] Dimethyl dioxirane[225] oxidizes benzylic alcohols to the corresponding aldehyde,[226] and dioxirane reagents are sufficiently mild that an α,β-epoxy alcohol was oxidized to the corresponding ketone, without disturbing the epoxide, using methyl trifluoromethyl dioxirane.[227] Hydrogen peroxide with urea oxidizes aryl aldehydes in formic acid.[228] *tert*-Butylhydroperoxide with a Cu catalyst gives oxidation in an ionic liquid.[229] Potassium monoperoxysulfate in the presence of a chiral ketone oxidizes 1,2-diols to α-hydroxy ketones enantioselectively.[230] Potassium monoperoxysulfate also oxidizes secondary alcohols in the presence of O_2.[231] Air, in the presence of a zeolite oxidizes benzylic alcohols.[232] Periodic acid oxidizes aldehydes or ketones in the presence of a PCC catalyst.[233] Sodium hypochlorite in acetic acid[234] or in water with β-cyclodextrin[235] is a useful oxidizing agent. Calcium hypochlorite on moist alumina with microwave

[214] Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2001****, 42*, 7067; Csjernyik, G.; Ell, A.H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* ***2002****, 67*, 1657.

[215] Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Uemura, S. *Tetrahedron Lett.* ***2001****, 42*, 8877.

[216] Samajdar, S.; Becker, F.F.; Banik, B.K. *Synth. Commun.* ***2001****, 31*, 2691.

[217] See Orbegozo, T.; de Vries, J.G.; Kroutil, W. *Eur. J. Org. Chem.* ***2010***, 3445; Orbegozo, T.; Lavandera, I.; Fabian, W.M.F.; Mautner, B.; de Vries, J.G.; Kroutil, W. *Tetrahedron* ***2009****, 65*, 6805.

[218] See Sheldon, R.A.; Arends, I.W.C.E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* ***2002****, 35,* 774.

[219] Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* ***2003***, 526.

[220] Itoh, A.; Kodama, T.; Masaki, Y. *Chem. Lett.* ***2001***, 686.

[221] Khurana, J.M.; Kandpal, B.M. *Tetrahedron Lett.* ***2003****, 44*, 4909.

[222] Gogoi, P.; Sarmah, G.K.; Konwar, D. *J. Org. Chem.* ***2004****, 69*, 5153.

[223] *Bacilus stearothermophilus*: Fantin, G.; Fogagnolo, M.; Giovannini, P.P.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron Lett.* ***1995****, 36*, 441. *Chloroperoxidase*: Hu, S.; Dordick, J.S. *J. Org. Chem.* ***2002****, 67*, 314. *Gluconobaccter oxydans* DSM 2343: Villa, R.; Romano, A.; Gandolfi, R.; Gargo, J.V.S.; Molinari, F. *Tetrahedron Lett.* ***2002****, 43*, 6059.

[224] Liu, Z.-Q.; Zhao, Y.; Luo, H.; Chai, L.; Sheng, Q. *Tetrahedron Lett.* ***2007****, 48,* 3017.

[225] See Deubel, D.V. *J. Org. Chem.* ***2001****, 66*, 3790.

[226] Baumstark, A.L.; Kovac, F.; Vasquez, P.C. *Can. J. Chem.* ***1999****, 77*, 308. See Angelis, Y.S.; Hatzakis, N.S.; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* ***2001****, 42*, 3753.

[227] D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M.R.; Turteltaub, J.S.; Williard, P.G.; Curci, R. *J. Org. Chem.* ***2004****, 69*, 8510.

[228] Balicki, R. *Synth. Commun.* ***2001****, 31*, 2195.

[229] Liu, C.; Han, J.; Wang, J. *Synlett* ***2007***, 643.

[230] Adam, W.; Saha-Möller, C.R.; Zhao, C.-G. *J. Org. Chem.* ***1999****, 64*, 7492.

[231] Döbler, C.; Mehltretter, G.M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* ***2001****, 42*, 8447.

[232] Son, Y.-C.; Makwana, V.D.; Howell, A.R.; Suib, S.L. *Angew. Chem. Int. Ed.* ***2001****, 40*, 4280.

[233] Hunsen, M. *Tetrahedron Lett.* ***2005****, 46*, 1651. See also, Zhang, S.; Xu, L.; Trudell, M.L. *Synthesis* ***2005***, 1757.

[234] Stevens, R.V.; Chapman, K.T.; Weller, H.N. *J. Org. Chem.* ***1980****, 45,* 2030. See also, Mohrig, J.R.; Nienhuis, D.M.; Linck, C.F.; van Zoeren, C.; Fox, B.G.; Mahaffy, P.G. *J. Chem. Educ.* ***1985****, 62,* 519; Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* ***2004****, 45*, 2013.

[235] Ji, H.-B.; Shi, D.-P.; Shao, M.; Li, Z.; Wang, L.-F. *Tetrahedron Lett.* ***2005****, 46,* 2517.

irradiation has been used to oxidize benzylic alcohols.[236] Hydrogen bromide in aq H_2O_2 oxidizes secondary alcohols to ketones.[237] With ultrasound, DDQ selectively oxidizes a benzylic or allylic hydroxyl group of 1,2-diols with those substituents.[238] Photoxidation of alcohols is possible in the presence of a catalytic amount of NBS.[239] A mixture of I_2—KI—K_2CO_3—H_2O oxidizes alcohols to aldehydes or ketones under anaerobic conditions.[240] Similarly $KBrO_3/ZrClO_2 \cdot 8H_2O$ can be used to oxidize alcohols.[241] Oxone oxidizes alcohols, catalyzed by $AlCl_3$.[242]

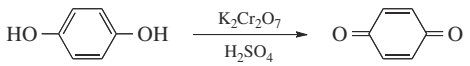
Tetrabutylammonium periodate[243] and benzyltriphenylphosphonium periodate.[244] oxidizes primary alcohols to aldehydes. On the other hand, *Fremy's salt* (see Reaction **19-4**) selectively oxidizes benzylic alcohols and not allylic or saturated ones.[245]

In a related reaction to the oxidation of alcohols, it is possible to oxidize ethers to aldehydes. Oxidation of trimethylsilyl ethers with O_2, a catalytic amount of *N*-hydroxyphthalimide and a Co catalyst, give an aldehyde.[246] Microwave irradiation with $BiCl_2$ oxidizes benzylic TMS ethers to the aldehyde.[247] Microwave irradiation on zeolite supported ferric nitrate has been used.[248] *O*-Tetrahydropyranyl ethers (*O*-THP) have been oxidized to the aldehyde with ferric nitrate on zeolites,[249] and the Pd catalyzed oxidation of allylic esters to conjugated ketones is known.[250] *N*-Bromosuccinimide with β-cyclodextrin oxidizes tetrahydropyranyl ethers in water.[251]

OS **I**, 87, 211, 241, 340; **II**, 139, 541; **III**, 37, 207; **IV**, 189, 192, 195, 467, 813, 838; **V**, 242, 310, 324, 692, 852, 866; **VI**, 218, 220, 373, 644, 1033; **VII**, 102, 112, 114, 177, 258, 297; **VIII**, 43, 367, 386; **IX**, 132, 432. Also see, OS **IV**, 283; **VIII**, 363, 501.

19-4 Oxidation of Phenols and Aromatic Amines to Quinones

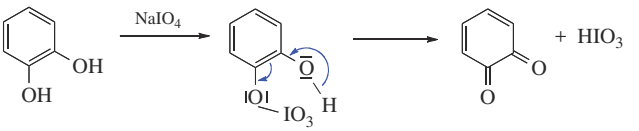
1/*O*,6/*O*-Dihydro-elimination



[236] Mojtahedi, M.M.; Saidi, M.R.; Bolourtchian, M.; Shirzi, J.S. *Monat. Chem.* ***2001****, 132*, 655.
[237] Sharma, V.B.; Jain, S.L.; Sain, B. *Synlett* ***2005***, 173.
[238] Peng, K.; Chen, F.; She, X.; Yang, C.; Cui, Y.; Pan, X. *Tetrahedron Lett.* ***2005****, 46,* 1217.
[239] Kuwabara, K.; Itoh, A. *Synthesis* ***2006***, 1949.
[240] Gogoi, P.; Konwar, D. *Org. Biomol. Chem.* ***2005****, 3*, 3473.
[241] Shirini, F.; Zolfigol, M.A.; Mollarazi, E. *Synth. Commun.* ***2005****, 35,* 1541.
[242] Wu, S.; Ma, H.; Le, Z. *Tetrahedron* ***2010****, 66,* 8641.
[243] Friedrich, H.B.; Khan, F.; Singh, N.; van Staden, M. *Synlett* ***2001***, 869.
[244] Hajipour, A.R.; Mallakpour, S.E.; Samimi, H.A. *Synlett* ***2001***, 1735.
[245] Morey, J.; Dzielenziak, A.; Saá, J.M. *Chem. Lett.* ***1985***, 263.
[246] Karimi, B.; Rajabi, J. *Org. Lett.* ***2004****, 6,* 2841.
[247] Hajipour, A.R.; Mallakpour, S.E.; Baltork, I.M.; Adibi, H. *Synth. Commun.* ***2001****, 31,* 1625.
[248] Heravi, M.M.; Ajami, D.; Ghassemzadeh, M.; Tabar-Hydar, K. *Synth. Commun.* ***2001****, 31*, 2097.
[249] Mohajerani, B.; Heravi, M.M.; Ajami, D. *Monat. Chem.* ***2001***, *132*, 871.
[250] Trost, B.M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* ***2006****, 128,* 2540.
[251] Narender, M.; Reddy, M.S.; Rao, K.R. *Synthesis* ***2004***, 1741. See Reddy, M.S.; Narender, M.; Nageswar, Y.V.D.; Rao, K.R. *Synthesis* ***2005***, 714.

Ortho and para diols are easily oxidized to o- and *p*-quinones, respectively.[252] Either or both OH groups can be replaced by NH_2 groups to give the same products, although for the preparation of o-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or NH_2; halogen, OR, Me, *t*-Bu, and even H, although yields are poor with the latter. Many oxidizing agents have been used: acid dichromate,[253] silver oxide, silver carbonate, lead tetraacetate, HIO_4, $NBS—H_2O—H_2SO_4$,[254] dimethyl dioxirane,[255] and atmospheric oxygen.[256] Oxidation has been done photochemically with O_2 and tetraphenylporphine.[257] A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N—O^{\bullet}$ (dipotassium nitrosodisulfonate; *Fremy's salt*), which is a stable free radical.[258] A mixture of 4-iodophenoxyacetic acid and Oxone is an effective catalyst for the oxidation of *p*-alkoxyphenols to *p*-quinones.[259] A supported iron phthalocyanine facilitates the aromatic oxidation of phenols.[260]

Less is known about the mechanism than is the case for oxidizing simple alcohols in Reaction **19-3**, and it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone.[261] Therefore the following mechanism[262] was proposed:



When catechol was oxidized with MnO_4^- under aprotic conditions, a semiquinone radical ion intermediate was involved.[263] For autoxidations[264] (i.e., with atmospheric O_2) a free radical mechanism is known to operate.[265]

OS **I**, 383, 482, 511; **II**, 175, 254, 430, 553; **III**, 663, 753; **IV**, 148; **VI**, 412, 480, 1010.

19-5 Dehydrogenation of Amines to Nitriles or Imines

1/1/*N*,2/2/*C*-Tetrahydro-bielimination

$$RCH_2NH_2 \longrightarrow RCN$$

[252] See Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 2, Academic Press, NY, ***1988***, pp. 305–323, 438–447; Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 247–276; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoiid Compounds,* Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 112–132.

[253] See Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 92–117.

[254] Kim, D.W.; Choi, H.Y.; Lee, K.Y.; Chi, D.Y. *Org. Lett.* ***2001***, *3*, 445.

[255] Adam, W.; Schönberger, A. *Tetrahedron Lett.* ***1992***, *33*, 53.

[256] See Hashemi, M.M.; Beni, Y.A. *J. Chem. Res. (S)* ***1998***, 138.

[257] Cossy, J.; Belotti, S. *Tetrahedron Lett.* ***2001***, *42,* 4329.

[258] See Zimmer, H.; Lankin, D.C.; Horgan, S.W. *Chem. Rev.* ***1971***, *71*, 229.

[259] Yakura, T.; Konishi, T. *Synlett* ***2007***, 765.

[260] Zalomaeva, O.V.; Sorokin, A.B. *New J. Chem.* ***2006***, *30,* 1768,

[261] Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* ***1962***, *16*, 529.

[262] This mechanism is an example of category 4 (Sec. 19.A).

[263] Bock, H.; Jaculi, D. *Angew. Chem. Int. Ed.* ***1984***, *23,* 305.

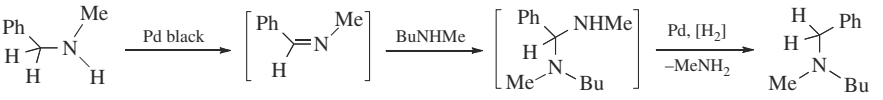
[264] For an example, see Rathore, R.; Bosch, E.; Kochi, J.K. *Tetrahedron Lett.* ***1994***, *35*, 1335.

[265] Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 368–381; Walling, C. *Free Radicals in Solution*, Wiley, NY, ***1957***, pp. 457–461.

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, I_2 in aq NH_3,[266] IBX see **19-3**, category 6),[267] NaOCl,[268] $Me_3N{-}O/OsO_4$,[269] $Ru/Al_2O_3/O2$,[270] and $CuCl/O_2$/pyridine.[271] Iodine and 1,3-diiodo-5,5-dimethylhydantoin in aq ammonia converted both amines and alcohols to nitriles.[272] Dehydrogenation of amines has been done in aq micelles.[273]

Several methods have been reported for the dehydrogenation of secondary amines to imines.[274] Among them[275] are treatment with (1) iodosylbenzene (PhIO) alone or in the presence of a Ru complex,[276] (2) DMSO and oxalyl chloride,[277] and (3) *t*-BuOOH and a Rh catalyst.[278] *N*-Tosyl aziridines are converted to *N*-tosyl imines when heated with a Pd catalyst.[279] An interesting variation treats pyrrolidine with iodobenzene and a Rh catalyst to give 2-phenylpyrroline.[280]

A reaction that involves dehydrogenation to an imine that then reacts further is the reaction of primary or secondary amines[281] with Pd black.[282] The imine initially formed by the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses NH_3 or RNH_2 to give a secondary or tertiary amine. An example is the reaction between *N*-methylbenzylamine and butylmethylamine, which produces 95% *N*-methyl-*N*-butylbenzylamine.



In a related reaction, alkyl azides react with BrF_3 to give the corresponding nitrile.[283]

19-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

1/*N*,2/*N*-Dihydro-elimination

$$\mathrm{Ar{-}NH{-}NH{-}Ar} \xrightarrow{\mathrm{NaOBr}} \mathrm{Ar{-}N{=}N{-}Ar}$$

[266] Iida, S.; Togo, H. *Synlett* ***2006***, 2633.
[267] Chiampanichayakul, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Kuhakarn, C. *Synthesis* ***2008***, 2045.
[268] Yamazaki, S. *Synth. Commun.* ***1997***, *27*, 3559; Jursic, B. *J. Chem. Res. (S)* ***1988***, 168.
[269] Gao, S.; Herzig, D.; Wang, B. *Synthesis* ***2001***, 544.
[270] Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1480.
[271] Capdevielle, P.; Lavigne, A.; Maumy, M. *Tetrahedron* ***1990***, 2835; Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N.K.; Maumy, M. *Tetrahedron Lett.* ***1990***, *31*, 3305.
[272] Iida, S.; Togo, H. *Tetrahedron* ***2007***, *63*, 8274.
[273] Biondini, D.; Brinchi, L.; Germani, R.; Goracci, L.; Savelli, G. *Eur. J. Org. Chem.* ***2005***, 3060.
[274] See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 117–124.
[275] See Cornejo, J.J.; Larson, K.D.; Mendenhall, G.D. *J. Org. Chem.* ***1985***, *50*, 5382; Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* ***1988***, *29*, 4115.
[276] Müller, P.; Gilabert, D.M. *Tetrahedron* ***1988***, *44*, 7171.
[277] Keirs, D.; Overton, K. *J. Chem. Soc. Chem. Commun.* ***1987***, 1660.
[278] Murahashi, S.; Naot, T.; Taki, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 613.
[279] Wolfe, J.P.; Ney, J.E. *Org. Lett.* ***2003***, *5*, 4607.
[280] Sezen, B.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 13244.
[281] See Larsen, J.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1213. Also see, Yamaguchi, J.; Takeda, T. *Chem. Lett.* ***1992***, 1933; Yamazaki, S. *Chem. Lett.* ***1992***, 823.
[282] Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* ***1983***, *105*, 5002. See also, Wilson, Jr., R.B.; Laine, R.M. *J. Am. Chem. Soc.* ***1985***, *107*, 361.
[283] Sasson, R.; Rozen, S. *Org. Lett.* ***2005***, *7*, 2177.

N,N′-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, $K_3Fe(CN)_6$ under phase-transfer conditions[284] $FeCl_3$,[285] MnO_2 (this reagent yields cis azobenzenes),[286] $CuCl_2$, and air and NaOH.[287] The reaction is also applicable to *N,N′*-dialkyl- and *N,N′*-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds,[288] but these are unstable and decompose to nitrogen and the hydrocarbon:

$$\mathrm{Ar{-}NH{-}NH_2} \longrightarrow [\mathrm{Ar{-}N{=}NH}] \longrightarrow \mathrm{ArH} + \mathrm{N_2}$$

Aniline derivatives are converted to azo compounds by heating with cetyltrimethylammonium dichromate in chloroform.[289] When hydrazones are oxidized with HgO, Ag_2O, MnO_2, PbO_4, or certain other oxidizing agents, diazo compounds ($R_2C{=}N{-}NH_2 \rightarrow R_2C{=}N^+{=}N^-$) are obtained[290]:

Hydrazones of the form $ArCH{=}NNH_2$ react with HgO in solvents, (e.g., diglyme or ethanol) to give nitriles (ArCN).[291] It is possible to oxidize dimethylhydrazones ($R{-}C{=}N{-}NMe_2$) to the corresponding nitrile ($R{-}C{\equiv}N$) with magnesium monoperoxyphthalate (MMPP),[292] or with dimethyl dioxirane.[293] Oxone on wet alumina also converts hydrazones to nitriles with microwave irradiation.[294] Oximes of aromatic aldehydes are converted to aryl nitriles with $InCl_3$[295] (ketoximes give a *Beckmann rearrangement*, Reaction **18-17**).

In a related reaction, primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2, lead tetraacetate, O_2 and a base, $BaMnO_4$,[296] and sodium perborate in acetic acid. *tert*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[297]

Nitrones [$C{=}N^+(R){-}O^-$] are generated by the oxidation of *N*-hydroxyl secondary amines with 5% aq NaOCl.[298] Secondary amines (e.g., dibenzylamine) can be converted to the corresponding nitrone by heating with cumyl hydroperoxide in the presence of a titanium catalyst.[299]

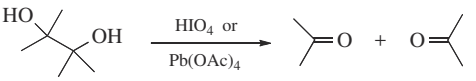
OS **II**, 496; **III**, 351, 356, 375, 668; **IV**, 66, 411; **V**, 96, 160, 897; **VI**, 78, 161, 334, 392, 803, 936; **VII**, 56. Also see, OS **V**, 258. For oxidation of primary amines, see OS **V**, 341.

[284] Dimroth, K.; Tüncher, W. *Synthesis* ***1977***, 339.
[285] Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* ***1999****, 29*, 3435.
[286] Hyatt, J.A. *Tetrahedron Lett.* ***1977***, 141.
[287] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 543–557, 564–573.
[288] See Mannen, S.; Itano, H.A. *Tetrahedron* ***1973****, 29*, 3497.
[289] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004****, 45*, 1371.
[290] For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 233–256.
[291] Mobbs, D.B.; Suschitzky, H. *Tetrahedron Lett.* ***1971***, 361.
[292] Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* ***1993****, 34*, 141.
[293] Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* ***1998****, 39*, 2009.
[294] Ramalingam, T.; Reddy, B.V.S.; Srinivas, R.; Yadav, J.S. *Synth. Commun.* ***2000****, 30*, 4507.
[295] Barman, D.C.; Thakur, A.J.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 1196.
[296] Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* ***1983****, 56,* 914.
[297] Kosswig, K. *Liebigs Ann. Chem.* ***1971****, 749,* 206.
[298] Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* ***1999****, 64*, 7243.
[299] Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* ***2003****, 44*, 49.

B. Oxidations Involving Cleavage of Carbon–Carbon Bonds[300]

19-7 Oxidative Cleavage of Glycols and Related Compounds

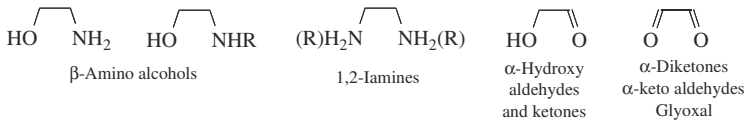
2/*O*-De-hydrogen-uncoupling



1,2-Diols (glycols) are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[301] The reaction generates 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the two carbons. The yields are so good that alkenes are often converted to diols (Reaction **15-48**), and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (Reaction **19-9**) or dichromate or permanganate (Reaction **19-10**). The diol can be generated and cleaved *in situ* from an alkene to give the carbonyl compounds.[302] A number of other oxidizing agents also give the same products, among them[303] aq sodium hypochlorite (NaOCl),[304] activated MnO_2,[305] O_2 and a Ru catalyst,[306] or PCC.[307] Permanganate, dichromate, and several other oxidizing agents[308] also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically.

The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. Chiral lead carboxylates have been prepared for the oxidative cleavage of 1,2-diols.[309] When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

Other compounds that contain oxygen atoms or nitrogen atoms on adjacent carbons undergo similar cleavage:



[300] See Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 137–254.

[301] See Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 2, Academic Press, NY, ***1988***, pp. 277–301, 432–437; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 3353–363; Perlin, A.S. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 189–212; Bunton, C.A. in Wiberg, K.B. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 367–407. Also see Rubottom, G.M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D Academic Press, NY, ***1982***, p. 1; Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971,*** *25*, 407; Fatiadi, A.J. *Synthesis* ***1976***, 65,133.

[302] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* ***2004,*** *6*, 3217.

[303] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1250–1255.

[304] Khurana, J.M.; Sharma, P.; Gogia, A.; Kandpal, B.M. *Org. Prep. Proceed. Int.* ***2007****, 39,* 185.

[305] See Ohloff, G.; Giersch, W. *Angew. Chem. Int. Ed.* ***1973****, 12,* 401.

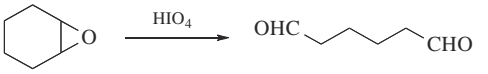
[306] Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***1999****, 1,* 713.

[307] Cisneros, A.; Fernández, S.; Hernández, J.E. *Synth. Commun.* ***1982****, 12,* 833.

[308] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1650–1652.

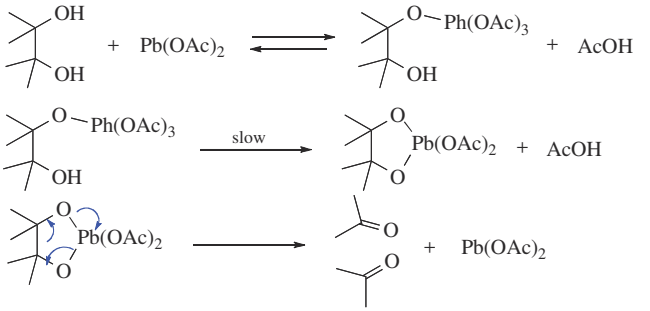
[309] Lena, J.I.C.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* ***2001****, 42*, 21.

Cyclic 1,2-diamines are cleaved to diketones with dimethyl dioxirane.[310] α-Diketones and α-hydroxy ketones are also cleaved by alkaline H_2O_2.[311] Periodic acid (HIO_4) has been used to cleave epoxides to aldehydes,[312] for example,

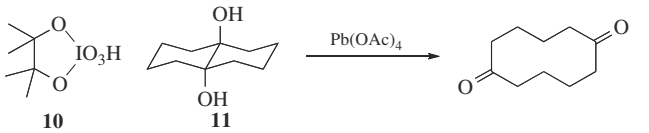


α-Hydroxy and α-keto acids are not cleaved by HIO_4 but are cleaved by $NaIO_4$ in methanol in the presence of a crown ether $Pb(OAc)_4$,[313] alkaline H_2O_2, and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give carboxylic acids. Also see, Reaction **19-12** and **19-13**.

The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee et al.:[314]



This mechanism is supported by (1) the kinetics are second order (first order in each reactant); (2) added acetic acid retards the reaction (drives the equilibrium to the left); and (3) *cis*-glycols react much more rapidly than *trans* glycols.[315] For periodic acid, the mechanism is similar, with the intermediate (**10**)[316]



10 **11**

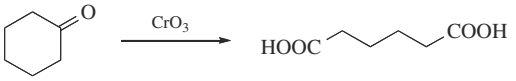
However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols that cannot form such an ester (e.g., **11**) are nevertheless cleaved by lead tetraacetate (although other glycols that cannot form cyclic esters are *not* cleaved, by either reagent[317]). To account for cases like **11**, a cyclic transition state has been proposed:[315]

OS **IV**, 124; **VII**, 185; **VIII**, 396.

[310] Gagnon, J.L.; Zajac Jr., W.W. *Tetrahedron Lett.* ***1995****, 36*, 1803.
[311] See Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* ***1977****, 42,* 4061.
[312] Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* ***1973***, 4599.
[313] Kore, A.R.; Sagar, A.D.; Salunkhe, M.M. *Org. Prep. Proceed. Int.* ***1995****, 27*, 373.
[314] Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* ***1933****, 507,* 159. For reviews, see Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 72–81; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 97–106.
[315] See Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* ***1956****, 599,* 81.
[316] Buist, G.J.; Bunton, C.A.; Hipperson, W.C.P. *J. Chem. Soc. B* ***1971***, 2128.
[317] Angyal, S.J.; Young, R.J. *J. Am. Chem. Soc.* ***1959****, 81,* 5251.

19-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols

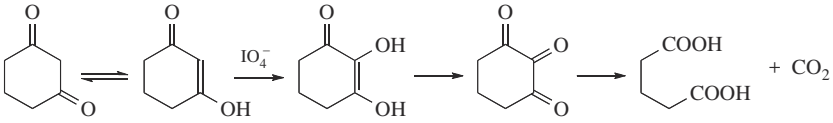
Cycloalkanone oxidative ring opening



Oxidative cleavage of open-chain ketones or alcohols[318] is a preparative procedure that is seldom useful, not because these compounds do not undergo oxidation (they do, except for diaryl ketones), but because the result is generally a hopeless mixture. Aryl methyl ketones (e.g., acetophenone), however, are readily oxidized to aryl carboxylic acids with Re_2O_7 and 70% aq *tert*-butyl hydroperoxide.[319] Oxygen with a mixture of Mn and Co catalysts give similar oxidative cleavage,[320] as do hypervalent iodine compounds.[321] Aldehydes, (e.g., $PhCH_2CHO$) are cleaved to benzaldehyde with phosphonium dichromate in refluxing acetonitrile.[322] 1,3-Diketones (e.g., 1,3-diphenyl-1,3-propanedione) are oxidatively cleaved with aq Oxone to give benzoic acid.[323] Cyclic α-chloro ketones are cleaved to give an α,ω-functionalized compound (acetal–ester) when treated with cerium (IV) sulfate tetrahydrate and O_2.[324]

Despite problems with acyclic ketones, the reaction is useful for the conversion of cyclic ketones and the corresponding secondary alcohols to the dicarboxylic acid in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Dichromate in acidic media and permanganate are the most common oxidizing agents, although autoxidation (oxidation with atmospheric oxygen) in alkaline solution[325] and potassium superoxide under phase-transfer conditions[326] have also been used. *O*-Silyl-ketones have been cleaved to esters using electrolysis in alcohol solvents.[327]

Cyclic 1,3-diketones, which exist mainly in the mono-enolic form, can be cleaved with sodium periodate with loss of one carbon, for example,[328]



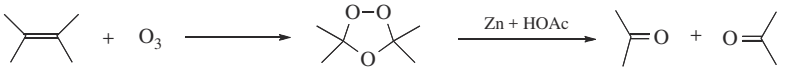
The species actually undergoing the cleavage is the triketone, so this is an example of Reaction **19-7**. Cyclic 1,3-diketones are converted to α,ω-diesters with an excess of $KHSO_5$ in methanol.[329]

OS **I**, 18; **IV**, 19; **VI**, 690. See also, OS **VI**, 1024.

[318] See Trahanovsky, W.S. *Methods Free-Radical Chem.* ***1973****, 4,* 133–169; Verter, H.S. in Zabicky, J. *The Chemistry of the Carbonyl Group*, pt. 2, Wiley, NY, ***1970***, pp. 71–156.
[319] Gurunath, S.; Sudalai, A. *Synlett* ***1999***, 559.
[320] Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* ***2002***, 610.
[321] Lee, J.C.; Choi, J.-H.; Lee, Y.C. *Synlett* ***2001***, 1563.
[322] Hajipour, A.R.; Mohammadpoor-Baltork, I.; Niknam, K. *Org. Prep. Proceed. Int.* ***1999****, 31*, 335.
[323] Ashford, S.W.; Grega, K.C. *J. Org. Chem.* ***2001****, 66*, 1523.
[324] He, L.; Horiuchi, C.A. *Bull. Chem. Soc. Jpn.* ***1999****, 72*, 2515.
[325] Bjørsvik, H.-R.; Liguori, L.; González, R.R.; Merinero, J.A.V. *Tetrahedron Lett.* ***2002****, 43*, 4985. See also, Osowska-Pacewicka, K.; Alper, H. *J. Org. Chem.* ***1988****, 53*, 808.
[326] Sotiriou, C.; Lee, W.; Giese, R.W. *J. Org. Chem.* ***1990****, 55,* 2159.
[327] Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* ***1992****, 57*, 4877.
[328] Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* ***1956****, 78*, 2489.
[329] Yan, J.; Travis, B.R.; Borhan, B. *J. Org. Chem.* ***2004****, 69*, 9299.

19-9 Ozonolysis

Oxo-uncoupling



12

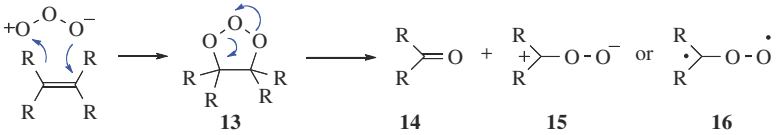
When compounds containing double bonds are treated with ozone, usually at low temperatures, initial formation of a 1,2,3-trioxolane is followed by formation of compounds called 1,2,4-trioxolanes (*ozonides*, **12**). These compounds can be isolated but, because some of them are explosive, they are decomposed with Zn and acetic acid or catalytic hydrogenation. More commonly they are decomposed with DMS[330] to give 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the alkene.[331] The decomposition of **12** has also been carried out with triethylamine[332] and with reducing agents (e.g., trimethyl phosphite[333] or thiourea).[334] However, ozonides can also be *oxidized* with oxygen, peroxyacids, or H_2O_2 to give ketones and/or carboxylic acids. Note that the presence of a hydrogen atom on the C=C unit (C=C—H) leads to differences in oxidation or reduction of **12**. In such a system, oxidation leads to the acid, whereas reduction leads to the aldehyde. Note that the presence of a hydrogen atom on the C=C unit (C=C—H) leads to differences in oxidation or reduction of **12**. In such a system, oxidation leads to the acid, whereas reduction leads to the aldehyde. It is also possible to reduce **12** with $LiAlH_4$, $NaBH_4$, BH_3, or catalytic hydrogenation with excess H_2 to give 2 molar equivalents of alcohol.[335] Ozonides can be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,[336] or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.[337] Ozonolysis is therefore an important synthetic reaction.[338]Ozonolysis can be done in solvent–water mixtures.[339]

Many alkenes undergo ozonolysis, including cyclic alkenes, where cleavage gives rise to one bifunctional product (an α,ω-difunctional molecule). Alkenes in which the double bond is connected to electron-donating groups react many times faster than those in which it is connected to electron-withdrawing groups.[340] Ozonolysis of compounds containing more than one double bond generally leads to cleavage of all the bonds. In some cases,

[330] Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* ***1966***, 4273.
[331] See Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*; Elsevier, NY, ***1984***; Bailey, P.S. *Ozonation in Organic Chemistry,* 2 Vols., Academic Press, NY, ***1978, 1982***. For reviews, see Odinokov, V.N.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1981****, 50*, 636; Belew, J.S. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 259–335; Menyailo, A.T.; Pospelov, M.V. *Russ. Chem. Rev.* ***1967****, 36*, 284.
[332] Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* ***1993****, 23*, 1543.
[333] Knowles, W.S.; Thompson, Q.E. *J. Org. Chem.* ***1960****, 25,* 1031.
[334] Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* ***1982****, 38,* 3013.
[335] See Flippin, L.A.; Gallagher, D.W.; Jalali-Araghi, K. *J. Org. Chem.* ***1989****, 54,* 1430.
[336] See White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3591.
[337] Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1978****, 17*, 939. See also, Cardinale, G.; Grimmelikhuysen, J.C.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* ***1984****, 40*, 1881.
[338] Drug synthesis: see Van Ornum, S.G.; Champeau, R.M.; Pariza, R. *Chem. Rev.* ***2006****, 106,* 2990.
[339] Schiaffo, C.E.; Dussault, P.H. *J. Org. Chem.* ***2008****, 73,* 4688.
[340] Pryor, W.A.; Giamalva, D.; Church, D.F. *J. Am. Chem. Soc.* ***1985****, 107,* 2793. See Kuczkowski, R.L. *Adv. Oxygenated Processes* ***1991****, 3,* 1; Gillies, C.W.; Kuczkowski, R.L. *Isr. J. Chem.* ***1983****, 23,* 446.

especially when bulky groups are present, conversion of the substrate to an epoxide (**15-50**) becomes an important side reaction and can be the main reaction.[341] Rearrangement is possible in some cases.[342] Ozonolysis of triple bonds[343] is less common and the reaction proceeds less easily, since ozone is an electrophilic agent[344] and prefers double to triple bonds (Sec. 15.B.i). Compounds that contain triple bonds generally give carboxylic acids, although sometimes ozone oxidizes them to α-diketones (Reaction **19-26**).

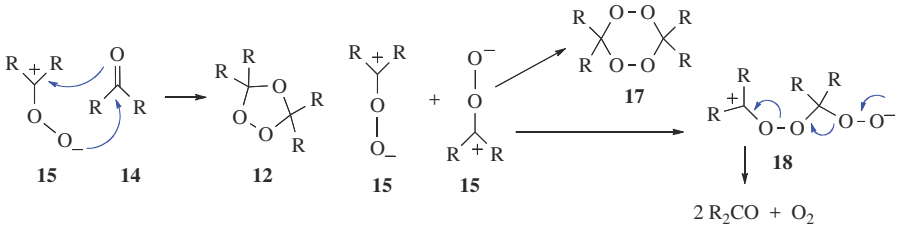
Aromatic compounds are attacked less readily than alkenes, but cleavage is known. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives 3 molar equivalents of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal/MeCOCHO/MeCOCOMe ratio of 3 : 2 : 1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[345]



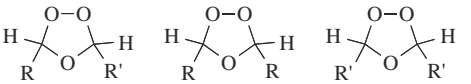
Although a large amount of work has been done on the mechanism of ozonization (formation of **12**), not all the details are known. Note that a primary ozonide has been trapped.[346] Criegee[347] formulated the basic mechanism. The first step of the *Criegee mechanism*[348] is a 1,3-dipolar addition (Reaction **15-58**) of ozone to the substrate to give the "initial" or "primary" ozonide, the structure of which has been shown to be the 1,2,3-trioxolane (**13**) by microwave and other spectral methods.[349] However, **13** is highly unstable and cleaves to an aldehyde or ketone (**14**) and an intermediate[350] that Criegee showed as a zwitterion (**15**), but which may be a diradical (**16**). This intermediate is usually referred to as a carbonyl oxide.[351] The carbonyl oxide, which will be represented as **15**, can then undergo various reactions, three of which lead to normal products. One is a recombination with **14**, which leads to ozonide **12**. The second is a dimerization to the bis(peroxide) **17**, and the third a kind of dimerization to **18**.[352] If the first path is taken (this

[341] See Bailey, P.S.; Hwang, H.H.; Chiang, C. *J. Org. Chem.* ***1985****, 50,* 231.
[342] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. *Synlett.* ***2000****, 1*269.
[343] See Pryor, W.A.; Govindan, C.K.; Church, D.F. *J. Am. Chem. Soc.* ***1982****, 104*, 7563.
[344] See Williamson, D.G.; Cvetanovic, R.J. *J. Am. Chem. Soc.* ***1968****, 90*, 4248; Razumovskii, S.D.; Zaikov, G.E. *J. Org. Chem. USSR* ***1972****, 8,* 468, 473; Klutsch, G.; Fliszár, S. *Can. J. Chem.* ***1972****, 50*, 2841.
[345] See O'Murchu, C. *Synthesis* ***1989***, 880.
[346] Jung, M.E.; Davidov, P. *Org. Lett.* ***2001****, 3*, 627.
[347] See Kuczkowski, R.L. *Acc. Chem. Res.* ***1983****, 16,* 42; Criegee, R. *Angew. Chem. Int. Ed.* ***1975****, 14,* 745; Murray, R.W. *Acc. Chem. Res.* ***1968****, 1*, 313.
[348] Also see Ponec, R.; Yuzhakov, G.; Haas, Y.; Samuni, U. *J. Org. Chem.* ***1997****, 62*, 2757.
[349] Gillies, J.Z.; Gillies, C.W.; Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1988****, 110,* 7991. See also, Kohlmiller, C.K.; Andrews, L. *J. Am. Chem. Soc.* ***1981****, 103,* 2578; McGarrity, J.F.; Prodolliet, J. *J. Org. Chem.* ***1984****, 49,* 4465.
[350] See Fajgar, R.; Vítek, J.; Haas, Y.; Pola, J. *Tetrahedron Lett.* ***1996****, 37*, 3391.
[351] See Sander, W. *Angew. Chem. Int. Ed.* ***1990****, 29,* 344; Brunelle, W.H. *Chem. Rev.* ***1991****, 91*, 335.
[352] Fliszár, S.; Chylinska, J.B. *Can. J. Chem.* ***1967****, 45*, 29; ***1968****, 46*, 783.

is normally possible only if **14** is an aldehyde; most ketones do not do this[353,354] the product is an ozonide (1,2,4-trioxolane, **12**),[355] and hydrolysis



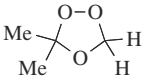
of the ozonide gives the normal products. If **17** is formed, hydrolysis of it gives one of the products, and, of course, **14**, which then does not undergo further reaction, is the other. If intermediate **18** is formed, direct decomposition is possible, as shown, to give the normal products and oxygen. In protic solvents, **15** is converted to a hydroperoxide, and these have been isolated [e.g., $Me_2C(OMe)OOH$ from $Me_2C{=}CMe_2$ in methanol]. Further evidence for the mechanism is that **17** can be isolated in some cases (e.g., from $Me_2C{=}CMe_2$). But perhaps the most impressive evidence comes from the detection of cross-products. In the Criegee mechanism, the two parts of the original alkene break apart and then recombine to form the ozonide. In the case of an unsymmetrical alkene ($RCH{=}CHR'$) there should be three ozonides:



since there are two different aldehydes (**14**) and two different species (**15**). These compounds can recombine in the three ways shown. Actually *six* ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.[356] Similar results have been reported for smaller alkenes (e.g., 2-pentene, 4-nonene, and even 2-methyl-2-pentene.[357] The last-mentioned case is especially interesting, since it is quite plausible that this compound would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. However, terminal alkenes give little or no cross-ozonide formation.[358] In general, the less alkylated end of the alkene tends to go to **14** and the other to **15**. Still other evidence[359] for the Criegee mechanism is (1) When $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO, the ozonide (**19**) could be isolated[354]; (2) **15** prepared in an entirely different manner

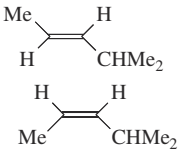
[353] See Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* ***1989****, 54,* 383.
[354] See Criegee, R.; Korber, H. *Chem. Ber.* ***1971****, 104*, 1812.
[355] Kamata, M.; Komatsu, K.i.; Akaba, R. *Tetrahedron Lett.* ***2001****, 42*, 9203. For a report of an isolable ozonide, see dos Santos, C.; de Rosso, C.R.S.; Imamura, P.M. *Synth. Commun.* ***1999****, 29,* 1903.
[356] Riezebos, G.; Grimmelikhuysen, J.C.; van Dorp, D.A. *Recl. Trav. Chim. Pays-Bas* ***1963****, 82,* 1234; Privett, O.S.; Nickell, E.C. *J. Am. Oil Chem. Soc.* ***1964****, 41,* 72.
[357] Loan, L.D.; Murray, R.W.; Story, P.R. *J. Am. Chem. Soc.* ***1965****, 87*, 737; Lorenz, O.; Parks, C.R. *J. Org. Chem.* ***1965****, 30,* 1976.
[358] Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969****, 34,* 1891.
[359] See Wojciechowski, B.J.; Chiang, C.; Kuczkowski, R.L. *J. Org. Chem.* ***1990****, 55,* 1120; Paryzek, Z.; Martynow, J.; Swoboda, W. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1220; Murray, R.W.; Morgan, M.M. *J. Org. Chem.* ***1991****, 56,* 684, 6123.

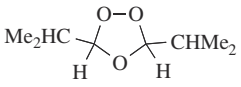
(photooxidation of diazo compounds), reacted with aldehydes to give ozonides[360]; and (3) *cis*-and *trans*-alkenes generally give the same ozonide, which would be expected if they cleave first.[361] However, this was not true for $Me_3CCH{=}CHCMe_3$, where the *cis*-alkene gave the *cis*-ozonide (chiefly), and the trans gave the trans.[362]



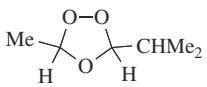
19

The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the cis/trans ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same.[363] If the Criegee mechanism operated as shown above, the cis/trans ratio for each of the two cross ozonides would have to be identical for the cis- and *trans*-alkenes, since in this mechanism they are completely cleaved.

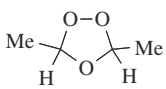




50–50
cis–trans



48–52
cis–trans



38–62
cis–trans

66–34
cis–trans

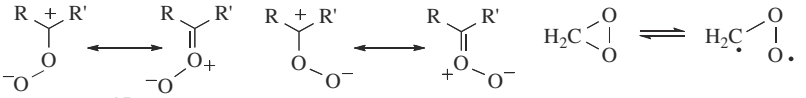
49–51
cis–trans

49–51
cis–trans

The above stereochemical results have been explained[364] on the basis of the Criegee mechanism with the following refinements: (1) The formation of **13** is stereospecific, as expected from a 1,3-dipolar cycloaddition. (2) Once formed, **15** and **14** remain attracted to each other, much like an ion pair. (3) Intermediate **15** exists in syn and anti forms, which are produced in different amounts and can hold their shapes, at least for a time. This is plausible if we remember that a C=O canonical form contributes to the structure of **19**. (4) The combination of **15** and **14** is also a 1,3-dipolar cycloaddition, so configuration is retained in this step too.[365]

Evidence that the basic Criegee mechanism operates even in these cases comes from ^{18}O labeling experiments, making use of the fact, mentioned above, that mixed ozonides (e.g., **15**) can be isolated when an external aldehyde is added. Both the normal and modified Criegee mechanisms predict that if ^{18}O-labeled aldehyde is added to the ozonolysis mixture, the label will appear in the ether oxygen (see the reaction between **15** and **14**), and this is what is found.[366] There is evidence that the *anti*-**15** couples much more readily than the *syn*-**15**.[367]

[360] Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1974****, 96,* 3330.
[361] See Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969****, 34,* 1896.
[362] See Kolsaker, P. *Acta Chem. Scand. Ser. B* ***1978***, *32*, 557.
[363] Murray, R.W.; Youssefyeh, R.D.; Story, P.R. *J. Am. Chem. Soc.* ***1966****, 88,* 3143, 3655; Story, P.R.; Murray, R. W.; Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1966****, 88,* 3144. Also see, Choe, J.; Srinivasan, M.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1983****, 105,* 4703.
[364] Keul, H.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1985****, 50,* 3371.
[365] See Choe, J.; Painter, M.K.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1984****, 106*, 2891.
[366] See Mazur, U.; Kuczkowski, R.L. *J. Org. Chem.* ***1979****, 44,* 3185.
[367] Mile, B.; Morris, G.M. *J. Chem. Soc. Chem. Commun.* ***1978***, 263.



syn-**15** *anti*-**15** **20** **16** (R=H)

The ozonolysis of ethylene[368] in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.[369] This reaction has been used to study the structure of the intermediate **15** or **16**. The compound dioxirane (**20**) was identified in the reaction mixture[370] at low temperatures and is probably in equilibrium with the biradical **16** (R = H). Dioxirane has been produced in solution, but it oxidatively cleaves dialkyl ethers (e.g., Et—O—Et) via a chain-radical process,[371] so the choice of solvent is important.

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the atmosphere and contributes to air pollution.[372] There is much evidence that the Criegee mechanism operates in the gas phase too, although the products are more complex because of other reactions that also take place.[373]

OS **V**, 489, 493; **VI**, 976; **VII**, 168; **IX**, 314. Also see, OS **IV**, 554. For the preparation of ozone, see OS **III**, 673.

19-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

Oxo-de-alkylidene-bisubstitution, and so on

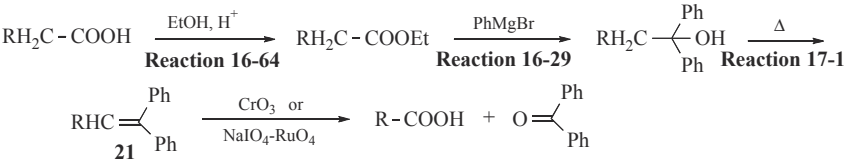
$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O + RCOOH$$

Carbon–carbon double bonds can be cleaved by many oxidizing agents,[374] the most common of which are permanganate in neutral or acid media and dichromate in acid media. The products are generally 2 molar equivalents of ketone, 2 molar equivalents of carboxylic acid, or 1 molar equivalent of each, depending on what groups are attached to the alkene. With ordinary solutions of permanganate or dichromate, yields are generally low and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (see Sec. 3.C.ii).[375] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux-von Rudloff reagent*: HIO_4 containing a trace of MnO_4^-.[376] The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage, and the

[368] See Samuni, U.; Fraenkel, R.; Haas, Y.; Fajgar, R.; Pola, J. *J. Am. Chem. Soc.* ***1996****, 118*, 3687.
[369] Fong, G.D.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1980****, 102*, 4763.
[370] Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1978****, 100,* 5117. See, however, Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* ***1988****, 53*, 5397.
[371] Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* ***1994****, 35,* 2981.
[372] See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984****, 84*, 437.
[373] See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984****, 84*, 437, pp. 452–454; Martinez, R.I.; Herron J.T. *J. Phys. Chem.* ***1988****, 92,* 4644.
[374] See Henry, P.M.; Lange, G.L. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 965–1098; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, D.C., ***1990***, pp. 77–84, 96–98; Badanyan, Sh.O.; Minasyan, T.T.; Vardapetyan, S.K. *Russ. Chem. Rev.* ***1987****, 56,* 740; Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 59–92. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 1634.
[375] Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972****, 94*, 4024. See also, Lee, D.G.; Chang, V.S. *J. Org. Chem.* ***1978****, 43,* 1532.
[376] von Rudloff, E. *Can. J. Chem.* ***1955****, 33*, 1714; ***1956****, 34*, 1413; ***1965****, 43,* 1784.

purpose of the HIO_4 is to reoxidize the manganate back to MnO_4^-. Another reagent that behaves similarly is $NaIO_4$–ruthenium tetroxide.[377] Oxidative cleavage of alkenes is catalyzed by Ru with $IO(OH)_5$.[378] Cyclic alkenes are cleaved to α,ω-diketones, keto-acids, or dicarboxylic acids. Cyclic alkenes are cleaved to dialdehydes with $KMnO_4{\cdot}CuSO_4$ in dichloromethane.[379] A combination of $RuCl_3/HIO_5$ oxidatively cleaves cyclic alkenes to dicarboxylic acids.[380]

The *Barbier–Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ($NaIO_4$—RuO_4 has also been used), but this is cleavage of a 1,1-diphenyl alkene (**21**), which generally gives good yields. Addition of a catalytic amount of OsO_4 to *Jones reagent* (Reaction **19-3**) leads to good yields of the carboxylic acid from simple alkenes.[381] A combination of Oxone and OsO_4 in DMF cleaves alkenes to carboxylic acids.[382] Cleavage of alkynes is generally rather difficult, but treatment of internal alkynes with an excess of Oxone with a Ru catalyst leads to aliphatic carboxylic acids.[383]



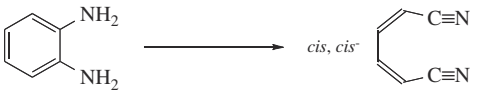
With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are *tert*-butyl iodoxybenzene,[384] $KMnO_4$ in THF—H_2O,[385] and $NaIO_4$—OsO_4.[386] Enol ethers, [$RC(OR')=CH_2$] have been cleaved to carboxylic esters [$RC(OR')=O$] by atmospheric oxygen.[387] Oxidative cleavage of alkenes is catalyzed by a Mn–porphyrin complex.[388]

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (Reaction **15-29**) or cyclic ester,[389] and then further oxidation as in Reaction **19-7**.[390] In line with the electrophilic attack on the alkene, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to

[377] Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, ***1973***, pp. 186–192. See Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 47.
[378] Shoair, A.G.F.; Mohamed, R.H. *Synth. Commun.* ***2006***, *36* , 59.
[379] Göksu, S.; Altundaş, R.; Sütbeyaz, Y. *Synth. Commun.* ***2000***, *30*, 1615.
[380] Griffith, W.P.; Shoair, A.G.; Suriaatmaja, M. *Synth. Commun.* ***2000***, *30*, 3091.
[381] Henry, J.R.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 4745.
[382] Travis, B.R.; Narayan, R.S.; Borhan, B. *J. Am. Chem. Soc.* ***2002***, *124*, 3824. See also, Whitehead, D.C.; Travis, B.R.; Borhan, B. *Tetrahedron Lett.* ***2006***, *47*, 3797.
[383] Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W. *J. Org. Chem.* ***2004***, *69*, 2221.
[384] Ranganathan, S.; Ranganathan, D.; Singh, S.K. *Tetrahedron Lett.* ***1985***, *26*, 4955.
[385] Viski, P.; Szeverényi, Z.; Simándi, L.I. *J. Org. Chem.* ***1986***, *51*, 3213.
[386] Pappo, R.; Allen, Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* ***1956***, *21*, 478.
[387] Taylor, R. *J. Chem. Res. (S)* ***1987***, 178. See Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* ***1985***, *50*, 4980.
[388] Liu, S.-T.; Reddy, K.V.; Lai, R.-Y. *Tetrahedron* ***2007***, *63*, 1821.
[389] See Lee, D.G.; Spitzer, U.A. *J. Org. Chem.* ***1976***, *41*, 3644; Lee, D.G.; Chang, V.S.; Helliwell, S. *J. Org. Chem.* ***1976***, *41*, 3644, 3646.
[390] There is evidence for an epoxide intermediate: Rocek, J.; Drozd, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 6668.

carboxylic acids with $Tl(III)NO_3$[391] or with [bis(trifluoroacetoxy)iodo]pentafluorobenzene [i.e., $C_6F_5I(OCOCF_3)_2$].[392]

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is RuO_4 along with a cooxidant (e.g., $NaIO_4$ or NaOCl and household bleach can be used). Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive cooxidant (e.g., NaOCl), the function of which is to oxidize RuO_2 back to ruthenium tetroxide. Examples[393] are the oxidation of naphthalene to phthalic acid[394] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid[395] (note the contrast with Reaction **19-11**). The latter conversion was also accomplished with ozone.[396] Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5. The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride by this reagent are important industrial procedures.[397] *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,[398] and with O_2 catalyzed by CuCl:[399]



The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the monomethylated dicarboxylic acids ($HO_2C—C=C—C=C—CO_2Me$).[400]

OS **II**, 53, 523; **III**, 39, 234, 449; **IV**, 136, 484, 824; **V**, 393; **VI**, 662, 690; **VII**, 397; **VIII**, 377, 490; **IX**, 530. Also see, OS **II**, 551.

19-11 Oxidation of Aromatic Side Chains

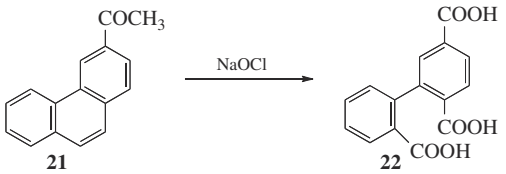
Oxo,hydroxy-de-dihydro,methyl-tersubstitution

$$ArR \xrightarrow{KMnO_4} ArCOOH$$

Alkyl chains on aromatic rings can be oxidized to CO_2H groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.[401] The method is most often applied to the methyl group ($CH_3 \rightarrow CO_2H$), although longer side chains can also be cleaved. Tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[402] It is usually difficult to oxidize an R group on a fused

[391] McKillop, A.; Oldenziel, O.H.; Swann, B.P.; Taylor, E.C.; Robey, R.L. *J. Am. Chem. Soc.* ***1973****, 95*, 1296.
[392] Moriarty, R.M.; Penmasta, R.; Awasthi, A.K.; Prakash, I. *J. Org. Chem.* ***1988****, 53,* 6124.
[393] See Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* ***1990****, 55*, 1928.
[394] Spitzer, U.A.; Lee, D.G. *J. Org. Chem.* ***1974****, 39,* 2468.
[395] Caputo, J.A.; Fuchs, R. *Tetrahedron Lett.* ***1967***, 4729.
[396] Klein, H.; Steinmetz, A. *Tetrahedron Lett.* ***1975***, 4249. See Liotta, R.; Hoff, W.S. *J. Org. Chem.* ***1980****, 45*, 2887; Chakraborti, A.K.; Ghatak, U.R. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 2605.
[397] See Pyatnitskii, Yu.I. *Russ. Chem. Rev.* ***1976****, 45,* 762.
[398] Nakagawa, K.; Onoue, H. *Tetrahedron Lett.* ***1965***, 1433; *Chem. Commun.* ***1966***, 396.
[399] Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* ***1976****, 41*, 1389.
[400] Tsuji, J.; Takayanag, H.i *Tetrahedron* ***1978****, 34,* 641; Bankston, D. *Org. Synth. 66,* 180.
[401] Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 105–109; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, OpenCourt Publishing Co., La Salle, IL, ***1980***, pp. 43–64. See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 23–33.
[402] Brandenberger, S.G.; Maas, L.W.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961****, 83*, 2146.

aromatic system without cleaving the ring or oxidizing it to a quinone (Reaction **19-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aq $Na_2Cr_2O_7$.[403] Aryl methyl groups are oxidized to aryl CO_2H with NaOCl in acetonitrile,[404] or with NBS in aqueous NaOH under photochemical conditions.[405] Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an α phenyl group. In such cases, the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, as in the cleavage of the 9,10-bond of dihydrophenanthrenes (**21** to **22**).



21 **22**

It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[406] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[407] Groups on the ring susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in Reaction **14-7**, with a hydroperoxide intermediate.[408]With this procedure it is possible to isolate ketones from $ArCH_2R$, and this is often done.[409]

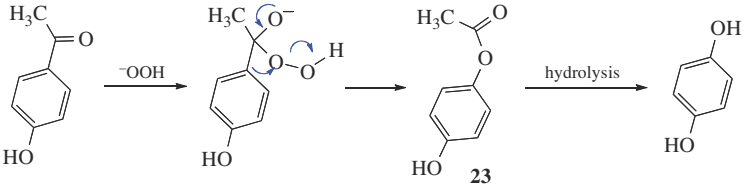
The mechanism has been studied for the following closely related reaction: $Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$.[410] A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \rightarrow Ar_2CH^{\bullet}$ or $Ar_2CH_2 \rightarrow Ar_2CH^{+}$. Either way this explains why tertiary groups are not converted to CO_2H and why the reactivity order is $CHR_2 > CH_2R > CH_3$, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 in Section 19.A. Just how the radical or the cation goes on to the product is not known.

When the alkyl group is one oxidizable to CO_2H (Reaction **19-11**), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[411] This reaction is used industrially to convert toluene to phenol.

In another kind of reaction, an aromatic aldehyde (ArCHO) or ketone (ArCOR′) is converted to a phenol (ArOH) on treatment with alkaline H_2O_2,[412] but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*.[413] The

[403] Friedman, L.; Fishel, D.L.; Shechter, H. *J. Org. Chem.* ***1965****, 30,* 1453.
[404] Yamazaki, S. *Synth. Commun.* ***1999****, 29*, 2211.
[405] Itoh, A.; Kodama, T.; Hashimoto, S.; Masaki, Y. *Synthesis* ***2003***, 2289.
[406] Onopchenko, A.; Schulz, J.G.D.; Seekircher, R. *J. Org. Chem.* ***1972****, 37,* 1414.
[407] See Foster, G.; Hickinbottom, W.J. *J. Chem. Soc.* ***1960***, 680; Ferguson, L.N.; Wims, A.I. *J. Org. Chem.* ***1960****, 25,* 668.
[408] Hermans, I.; Peeters, J.; Jacobs, P.A. *J. Org. Chem.* ***2007****, 72,* 3057.
[409] Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 508–543.
[410] Wiberg, K.B.; Evans, R.J. *Tetrahedron* ***1960****, 8*, 313.
[411] Kaeding, W.W. *J. Org. Chem.* ***1961****, 26*, 3144. See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry,* pt. B Academic Press, NY, ***1973***, pp. 91–94.
[412] For a convenient procedure, see Hocking, M.B. *Can. J. Chem.* ***1973****, 51*, 2384.
[413] See Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 749–752.

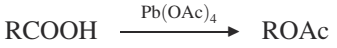
mechanism may be similar to that of the *Baeyer–Villiger Reaction* (**18-19**).[414] The intermediate **23** has been isolated.[415] The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH_2. In this case, acidic H_2O_2 was used.[416] The Dakin reaction has been done in ionic liquids.[417]



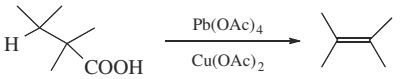
OS **I**, 159, 385, 392, 543; **II**, 135, 428; **III**, 334, 420, 740, 791, 820, 822; **V**, 617, 810. OS **I**, 149; **III**, 759.

19-12 Oxidative Decarboxylation

Acetoxy-de-carboxy-substitution



Hydro-carboxyl-elimination



Carboxylic acids can be decarboxylated[418] with lead tetraacetate to give a variety of products: an ester (ROAc), the alkane (RH) (see Reaction **12-40**), an alkene if α,β hydrogen is present, as well as numerous other products arising from rearrangements, internal cyclizations,[419] and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene. High yields of alkenes can also be obtained when R is primary or secondary using $Cu(OAc)_2$ along with the $Pb(OAc)_4$.[420] In the absence of Cu $(OAc)_2$, primary acids give mostly alkanes (though yields are generally low) and secondary acids may give carboxylic esters or alkenes. Other oxidizing agents,[421] including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.[422]

[414] See Hocking, M.B.; Bhandari, K.; Shell, B.; Smyth, T.A. *J. Org. Chem.* ***1982****, 47,* 4208.
[415] Hocking, M.B.; Ko, M.; Smyth, T.A. *Can. J. Chem.* ***1978****, 56*, 2646.
[416] Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* ***1984****, 49,* 4740.
[417] Zambrano, J.L.; Dorta, R. *Synlett* ***2003***, 1545.
[418] See Serguchev, Yu.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1980****, 49,* 1119; Sheldon, R.A.; Kochi, J.K. *Org. React*. ***1972****, 19*, 279.
[419] See Davies, D.I.; Waring, C. *J. Chem. Soc. C* ***1968***, 1865, 2337.
[420] Ogibin, Yu.N.; Katzin, M.I.; Nikishin, G.I. *Synthesis* ***1974***, 889.
[421] See Trahanovsky, W.S.; Cramer, J.; Brixius, D.W. *J. Am. Chem. Soc.* ***1974****, 96*, 1077; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 99–106. See also,; Fristad, W.E.; Fry, M.A.; Klang, J.A. *J. Org. Chem.* ***1983****, 48,* 3575; Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* ***1984***, 242.
[422] For another method, see Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron* ***1989****, 45,* 2615.

The mechanism with lead tetraacetate is generally accepted to be of the free radical type.[423] First, there is an interchange of ester groups:

$$Pb(OAc)_4 + RCOOH \longrightarrow \underset{\mathbf{24}}{Pb(OAc)_3OCOR} \quad \text{or} \quad \underset{\mathbf{25}}{Pb(OAc)_2(OCOR)_2}$$

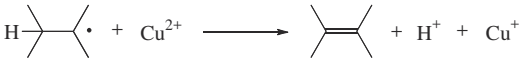
A free radical chain mechanism follows (shown for **24** although **25** and other lead esters can behave similarly)

$$\text{Initiation} \quad \underset{\mathbf{24}}{Pb(OAc)_3OCOR} \longrightarrow {\bullet}Pb(OAc)_3 + R{\bullet} + CO_2$$

$$R{\bullet} + Pb(OAc)_3OCOR \longrightarrow R^+ + {\bullet}Pb(OAc)_2OCOR + OAc^-$$

$$\text{Propagation} \quad {\bullet}Pb(OAc)_2OCOR \longrightarrow Pb(OAc)_2 + R{\bullet} + CO_2$$

Products can then be formed either from $R^{\bullet}$ or R^+. Primary $R^{\bullet}$ abstract H from solvent molecules to give RH. The R^+ ion can lose H^+ to give an alkene, react with HOAc to give the carboxylic ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. The radical $R^{\bullet}$ can also dimerize to give RR. The effect of Cu^{2+} ions[424] is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. The Cu^{2+} ion has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

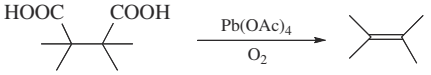


In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ($ArCH_2COOH \rightarrow ArCHO$) by tetrabutylammonium periodate.[425] Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($RCH_2COOH \rightarrow RC{\equiv}N$) by treatment with trifluoroacetic anhydride and $NaNO_2$ in F_3CCO_2H.[426]

See also, Reaction **14-37**.

19-13 Bis(decarboxylation)

Dicarboxy-elimination



Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bis(decarboxylated) with lead tetraacetate in the presence of O_2.[417] The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and

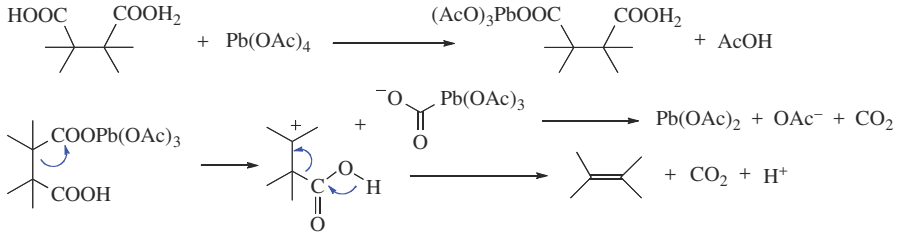
[423] See Cantello, B.C.C.; Mellor, J.M.; Scholes, G. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 348; Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. *Aust. J. Chem.* ***1974****, 27,* 1673, 1693.

[424] Kochi, J.K.; Bacha, J.D. *J. Org. Chem.* ***1968****, 33,* 2746; Torssell, K. *Ark. Kemi,* ***1970****, 31,* 401.

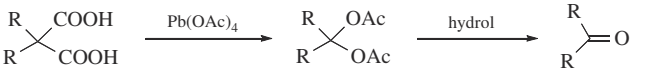
[425] Santaniello, E.; Ponti, F.; Manzocchi, A. *Tetrahedron Lett.* ***1980****, 21*, 2655. Also see Doleschall, G.; Tóth, G. *Tetrahedron* ***1980****, 36,* 1649.

[426] Smushkevich, Yu.I.; Usorov, M.I.; Suvorov, N.N. *J. Org. Chem. USSR* ***1975****, 11,* 653.

dl-2,3-diphenylsuccinic acid gave *trans*-stilbene)[427]; a concerted mechanism is thus unlikely. The following mechanism is compatible with the data:



though a free radical mechanism seems to hold in some cases. Bis(decarboxylation) of succinic acid derivatives to give alkenes[428] has also been carried out by other methods.[429] Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can be bis(decarboxylated) with lead tetraacetate,[430] *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[431]



A related reaction involves α-substituted aryl nitriles having a sufficiently acidic α hydrogen, which can be converted to ketones by oxidation with air under phase-transfer conditions.[432] The nitrile is added to NaOH in benzene or DMSO, containing a catalytic amount of triethylbenzylammonium chloride (TEBA).[433] This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in Reaction **19-60**.

C. Reactions Involving Replacement of Hydrogen by Heteroatoms

19-14 Hydroxylation at an Aliphatic Carbon

Hydroxylation or **Hydroxy-de-hydrogenation**

$$R_3CH \xrightarrow[\text{silica gel}]{O_3} R_3COH$$

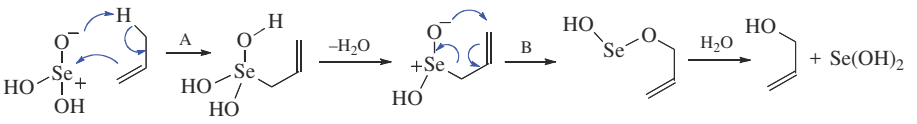
Compounds containing susceptible C—H bonds can be oxidized to alcohols.[434] Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and

[427] Corey, E.J.; Casanova, J. *J. Am. Chem. Soc.* ***1963****, 85,* 165.
[428] For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* ***1984****, 40,* 2585, pp. 2591–2608.
[429] Radlick, P.; Klem, R.; Spurlock, S.; Sims, J.J.; van Tamelen, E.E.; Whitesides, T. *Tetrahedron Lett.* ***1968***, 5117; Westberg, H.H.; Dauben Jr., H.J. *Tetrahedron Lett.* ***1968***, 5123. For additional references, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 253–254.
[430] See Salomon, R.G.; Roy, S.; Salomon, R.G. *Tetrahedron Lett.* ***1988****, 29,* 769.
[431] Tufariello, J.J.; Kissel, W.J. *Tetrahedron Lett.* ***1966***, 6145.
[432] For other methods of achieving this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 1260.
[433] See Kulp, S.S.; McGee, M.J. *J. Org. Chem.* ***1983****, 48,* 4097.
[434] Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 7–11; Lee, D.G. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 2–6; Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

secondary alcohols further. In the best method, the reagent is ozone and the substrate is absorbed on silica gel.[435] Yields as high as 99% have been obtained by this method. Other reagents are chromic acid,[436] ruthenium tetroxide (RuO_4),[437] thallium acetate,[438] sodium chlorite ($NaClO_2$) with a metalloporphyrin catalyst,[439] OsO_4,[440] and certain peroxybenzoic acids.[441] Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aq H_2O_2 in trifluoroacetic acid.[442] This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with *N*-haloamines and sulfuric acid (see Reaction **14-1**), the $\omega - 1$ position is the most favored. Another reagent[443] that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe(III)–porphyrin catalysts.[444] Use of an optically active Fe(III)–porphyrin gave modest enantioselective hydroxylation.[445]

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $R_3C^{\bullet}$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[446] The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.[447]

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also, Reaction **19-17**).[448] This reaction also produces conjugated aldehydes in some cases.[449] Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals, but includes two pericyclic steps (**A** and **B**):[450]



The step marked **A** is similar to the ene reaction (Reaction **15-23**). The step marked **B** is a [2,3]-sigmatropic rearrangement (see Reaction **18-35**). The reaction can also be

[435] Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T.H. *J. Org. Chem.* ***1975****, 40*, 2141; *Org. Synth.* ***VI***, 43; Keinan, E.; Mazur, Y. *Synthesis* ***1976***, 523; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, see pp. 418–419.
[436] Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 8–23.
[437] Bakke, J.M.; Braenden, J.E. *Acta Chem. Scand.* ***1991****, 45*, 418.
[438] Lee, J.C.; Park, C.; Choi, Y. *Synth. Commun.* ***1997****, 27*, 4079.
[439] Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Am. Chem. Soc.* ***1990****, 112*, 3689.
[440] Bales, B.C.; Brown, P.; Dehestani, A.; Mayer, J.M. *J. Am. Chem. Soc.* ***2005****, 127,* 2832.
[441] Schneider, H.; Müller, W. *J. Org. Chem.* ***1985****, 50,* 4609; Tori, M.; Sono, M.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* ***1985****, 58*, 2669. See also, Querci, C.; Ricci, M. *Tetrahedron Lett.* ***1990****, 31*, 1779.
[442] Deno, N.C.; Jedziniak, E.J.; Messer, L.A.; Meyer, M.D.; Stroud, S.G.; Tomezsko, E.S. *Tetrahedron* ***1977****, 33,* 2503.
[443] For other procedures, see Sharma, S.N.; Sonawane, H.R.; Dev, S. *Tetrahedron* ***1985****, 41,* 2483; Nam, W.; Valentine, J.S. *New J. Chem.* ***1989****, 13,* 677.
[444] See Groves, J.T.; Nemo, T.E. *J. Am. Chem. Soc.* ***1983****, 105,* 6243.
[445] Groves, J.T.; Viski, P. *J. Org. Chem.* ***1990****, 55*, 3628.
[446] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964****, 20*, 1151.
[447] Stewart, R.; Spitzer, U.A. *Can. J. Chem.* ***1978****, 56,* 1273.
[448] See Rabjohn, N. *Org. React.* ***1976****, 24,* 261; Jerussi, R.A. *Sel. Org. Transform.* ***1970****, 1*, 301; Trachtenberg, E. N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 123–153.
[449] Singh, J.; Sharma, M.; Kad, G.L.; Chhabra, B.R. *J. Chem. Res. (S)* ***1997***, 264.
[450] Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* ***1973****, 95,* 7917; Woggon, W.; Ruther, F.; Egli, H. *J. Chem. Soc. Chem. Commun.* ***1980***, 706. Also see Stephenson, L.M.; Speth, D.R. *J. Org. Chem.* ***1979****, 44,* 4683.

accomplished with *tert*-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).[451] The SeO_2 is the actual reagent; the peroxide reoxidizes the $Se(OH)_2$.[452] This method makes work up easier, but gives significant amounts of side products when the double bond is in a ring.[453] Alkynes generally give α,α′ dihydroxylation.[454] Allylic hydroxylation[455] with selenium dioxide often gives aldehydes, but in the presence of acetic anhydride and oxygen, SeO_2 converts alkenes to homoallylic acetates as the major product, C=C—C—C → C=C—C—C—OAc.[456]

Hydroxylation of unactivated sp^3 hybridized bonds is possible using an oxaziridine-mediated, organocatalyzed reaction.[457] Ruthenium tetroxide oxidizes alkanes.[458] Nanocrystalline cobalt oxide is another catalyst for alkane oxidation.[459] The H_2O_2—$NaVO_3$—H_2SO_4 system facilitates alkane oxidation in aqueous acetonitrile.[460]

Benzylic methylene groups are more readily oxidized to benzylic alcohols when compared to simple alkanes. Typical reagents include manganese salen and PhIO[461] or peroxides.[462] Oxidation to an acetoxy benzyl derivative was accomplished with $PhI(OAc)_2$ in acetic acid with a Pd catalyst,[463] and with PhI(OH)OTs in aq DMSO.[464] With minimal water, cerium (IV) triflate converts benzylic arenes to benzylic alcohols, although the major product is the ketone when >15% of water is present.[465]

Allylic benzyloxylation occurs when an alkene is treated with *t*-BuOOCOPh and a Cu—Na zeolite,[466] a Cu catalyst,[467] or with a chiral Cu catalyst to give modest enantioselectivity.[468] Allylic methylene groups can be converted to ester (—CH—OCOR) derivatives in a similar manner using copper triflate.[469] Cupric acetate has been used,[470] as well as Cu_2O.[471] A chiral Lewis acid has been used for an enantioselective allylic CH oxidation to an allylic acyl derivative.[472] α-Acetoxylation of allylic alkenes can proceed with allylic rearrangement.[473]

[451] Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977****, 99*, 5526. See also Singh, J.; Sabharwal, A.; Sayal, P.K.; Chhabra, B.R. *Chem. Ind. (London)* ***1989***, 533.
[452] See Sabol, M.R.; Wiglesworth, C.; Watt, D.S. *Synth. Commun.* ***1988****, 18*, 1.
[453] Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1982****, 47,* 2897.
[454] Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1979****, 44,* 4202.
[455] For a review, see Andrus, M.B.; Lashley, J.C. *Tetrahedron* ***2002****, 58,* 845.
[456] Koltun, E.S.; Kass, S.R. *Synthesis* ***2000***, 1366.
[457] Brodsky, B.H.; Du Bois, J. *J. Am. Chem. Soc.* ***2005****, 127,* 15391.
[458] Drees, M.; Strassner, T. *J. Org. Chem.* ***2006****, 71,* 1755.
[459] Davies, T.E.; García, T.; Solsona, B.; Taylor , S.H. *Chem. Commun.* ***2006***, 3417.
[460] Shul'pina, L.S.; Kirillova, M.V.; Pombeiro, A.J.L.; Shul'pin, G.B. *Tetrahedron* ***2009****, 65*, 2424.
[461] Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* ***1998****, 54*, 10017.
[462] Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* ***1995***, 1245.
[463] Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* ***2004****, 126*, 2300.
[464] Xie, Y.-Y.; Chen, Z.-C. *Synth. Commun.* ***2002****, 32,* 1875.
[465] Laali, K.K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 578.
[466] Carloni, S.; Frullanti, B.; Maggi, R.; Mazzacani, A.; Bigi, F.; Sartori, G. *Tetrahedron Lett.* ***2000****, 41*, 8947.
[467] LeBras, J.; Muzart, J. *Tetrahedron Asymmetry* ***2003***, *14,* 1911; Fache, F.; Piva, O. *Synlett* ***2002***, 2035.
[468] Lee, W.-S.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. *Tetrahedron Asymmetry* ***2001****, 12*, 1007.
[469] Sekar, G.; Datta Gupta, A.; Singh, V.K. *J. Org. Chem.* ***1998****, 63*, 2961; Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* ***2000****, 41*, 3941.
[470] Södergren, M.J.; Andersson, P.G. *Tetrahedron Lett.* ***1996****, 37*, 7577; Rispens, M.T.; Zondervan, C.; Feringa, B.L. *Tetrahedron Asymmetry,* ***1995****, 6*, 661.
[471] Levina, A.; Muzart, J. *Tetrahedron Asymmetry,* ***1995****, 6*, 147.
[472] Covell, D.J.; White, M.C. *Angew. Chem. Int. Ed.* ***2008****, 47,* 6448.
[473] Chen, M.S.; White, M.C. *J. Am. Chem. Soc.* ***2004****, 126*, 1346.

Hydroxylation can be accomplished using enzymatic systems. In the presence of *Bacillus megaterium* and oxygen, cyclohexane is converted to cyclohexanol.[474] Allylic oxidation to an allylic alcohol was accomplished with cultured cells of *Gossypium hirsutum*.[475] Benzylic arenes are converted to the corresponding α-hydroxy compound by treatment with the enzymes of *B. megaterium*, with modest enantioselectivity.[476] The reaction of tetradecanoic acid with the α-oxidase from *Pisum sativum*, in the presence of molecular oxygen, gives 2(*R*)-hydroxytetradecanoic acid with high asymmetric induction.[477]

Simple alkanes can be converted to esters with dialkyloxiranes. Cyclic alkanes are oxidized to alcohols with dimethyl dioxirane.[478] Cyclohexane was converted to cyclohexyl trifluoroacetate with di(trifluoromethyl) dioxirane and trifluoroacetic anhydride[479] and also with $RuCl_3/MeCO_3H/CF_3CO_2H$.[480] Dimethyl dioxirane converts alkanes to alcohols in some cases.[481] Adamantane is converted to adamantyl alcohol with DDQ (see Reaction **19-1**, category 3) and triflic acid.[482] The mechanism of oxygen insertion into alkanes has been examined.[483]

It is possible to perform the conversion $CH_2 \rightarrow C{=}O$ on an alkane, with no functional groups at all, although the most success has been achieved with substrates in which all CH_2 groups are equivalent (e.g., unsubstituted cycloalkanes). Hydrogen peroxide and trifluoroacetic acid has also been used for oxidation of alkanes.[484] With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.[485] The same type of conversion, with lower yields (20–30%), has been achieved with the *Gif system*.[486] There are several variations. One consists of pyridine–acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.[487] Other Gif systems use O_2 as oxidizing agent and Zn as a reductant.[488] The selectivity of the Gif systems toward alkyl carbons is $CH_2 > CH \geq CH_3$, which is unusual, and shows that a simple free radical mechanism (see Sec. 14.A.iv) is not involved.[489] Another reagent that can oxidize the CH_2 of an alkane is methyl(trifluoromethyl)dioxirane, but this produces CH—OH more often

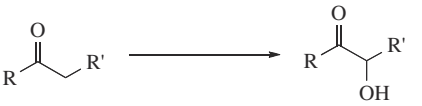
[474] Adam, W.; Lukacs, Z.; Saha-Möller, C.R.; Weckerle, B.; Schreier, P. *Eur. J. Org. Chem.* ***2000***, 2923.
[475] Hamada, H.; Tanaka, T.; Furuya, T.; Takahata, H.; Nemoto, H. *Tetrahedron Lett.* ***2001****, 42*, 909.
[476] Adam, W.; Lukacs, Z.; Harmsen, D.; Saha-Möller, C.R.; Schreier, P. *J. Org. Chem.* ***2000****, 65*, 878.
[477] Adam, W.; Boland, W.; Hartmann-Schreier, J.; Humpf, H.-U.; Lazarus, M.; Saffert, A.; Saha-Möller, C.R.; Schreier, P. *J. Am. Chem. Soc.* ***1998****, 120*, 11044.
[478] Curci, R.; D'Accolti, L.; Fusco, C. *Tetrahedron Lett.* ***2001****, 42*, 7087.
[479] Asensio, G.; Mello, R.; González-Nuñez, M.E.; Castellano, G.; Corral, J. *Angew. Chem. Int. Ed.* ***1996****, 35*, 217.
[480] Komiya, N.; Noji, S.; Murahashi, S.-I. *Chem. Commun.* ***2001***, 65.
[481] Murray, R.W.; Gu, D. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 451.
[482] Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3230.
[483] Freccero, M.; Gandolfi, R.; Sarzi-Amadé, M.; Rastelli, A. *Tetrahedron* ***2001****, 57*, 9843.
[484] Camaioni, D.M.; Bays, J.T.; Shaw, W.J.; Linehan, J.C.; Birnbaum, J.C. *J. Org. Chem.* ***2001****, 66*, 789.
[485] Sheu, C.; Richert, S.A.; Cofré, P.; Ross Jr., B.; Sobkowiak, A.; Sawyer, D.T.; Kanofsky, J.R. *J. Am. Chem. Soc.* ***1990****, 112*, 1936. See also, Sheu, C.; Sobkowiak, A.; Jeon, S.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990****, 112*, 879; Tung, H.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990****, 112,* 8214.
[486] Named for Gif-sur-Yvette, France, where it was discovered. See Schuchardt, U.; Jannini, M.J.D.M.; Richens, D.T.; Guerreiro, M.C.; Spinacé, E.V. *Tetrahedron* ***2001****, 57,* 2685.
[487] About-Jaudet, E.; Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* ***1990****, 31,* 1657. For a review of the mechanism, see Barton, D.H.R. *Chem. Soc. Rev.* ***1996****, 25*, 237.
[488] See Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron* ***1990****, 46*, 3743 and references cited therein.
[489] Barton, D.H.R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* ***1990****, 31,* 3097. For mechanistic studies, see Barton, D.H.R.; Doller, D.; Geletii, Y.V. *Tetrahedron Lett.* ***1991****, 32,* 3911 and references cited therein; Knight, C.; Perkins, M.J. *J. Chem. Soc. Chem. Commun.* ***1991***, 925. Also see, Minisci, F.; Fontana, F. *Tetrahedron Lett.* ***1994****, 35*, 1427; Barton, D.H.R.; Hill, D.R. *Tetrahedron Lett.* ***1994****, 35*, 1431.

than C=O (see Reactions **19-14** and **19-15**).[490] Cyclic alkanes are oxidized to a mixture of the alcohol and the ketone with $PhI(OAc)_2$ and a manganese complex in an ionic liquid.[491] Oxidation of cyclic alkanes to cyclic ketones was accomplished using a Ru catalyst.[492]

OS **IV**, 23; **VI**, 43, 946; **VII**, 263, 277, 282.

19-15 Oxidation of Methylene to OH, O_2CR, or OR

Hydroxy (or alkoxy) -de-dihydro-bisubstitution

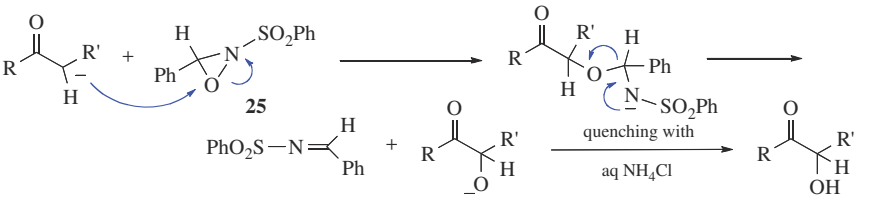


Methyl or methylene groups α to a carbonyl can be oxidized to give α-hydroxy ketones, aldehydes, or carboxylic acid derivatives. Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents[493] *o*-iodosobenzoic acid.[494] Dioxygen (O_2) and a chiral phase-transfer catalyst gave enantioselective α hydroxylation of ketones, if the α position was tertiary.[495] Dimethyl dioxirane is quite effective for hydroxylation of 1,3-dicarbonyl compounds,[496] and O_2 with a Mn catalyst also gives hydroxylation.[497] Oxygen with a Ce catalyst α-hydroxylates β-keto esters.[498] The Pd—C catalyzed α-oxygenation of 1,3-dicarbonyl compounds can be accomplished using O_2.[499] An engineered Cytochrome P450 BM-3 is effective for the enantioselective α-hydroxylation of esters of benzylic acids.[500] The reaction of ketones with $Ti(OiPr)_4$, diethyl tartrate and *tert*-butylhydroperoxide gave the α-hydroxy ketone with good enantioselectively, albeit in low yield.[501] α-Hydroxylation of ketones was reported using H_2O_2 and 12-tungstophosphoric acid–cetylpyridinium chloride as a catalyst.[502] Hypervalent iodine(III) sulfonate has been used for the α-hydroxylation of aryl ketones.[503]

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate anions (prepared by adding the ketone or ester to LDA) with a Mo peroxide reagent (MoO_5–pyridine–HMPA; called MoOPH) in THF–hexane at −70°C.[504] The enolate forms of amides and esters[505] and the enamine derivatives of ketones[506] can similarly be

[490] D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* ***2003****, 68*, 7806.
[491] Li, Z.; Xiu, C.-G.; Xu, C.-Z. *Tetrahedron Lett.* ***2003****, 44*, 9229.
[492] Che, C.-M.; Cheng, K.-W.; Chan, M.C.W.; Lau, T.-C.; Mak, C.-K. *J. Org. Chem.* ***2000****, 65*, 7996.
[493] See Moriarty, R.M.; Prakash, O. *Acc. Chem. Res.* ***1986****, 19*, 244. Also see, Reddy, D.R.; Thornton, E.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 172.
[494] Moriarty, R.M.; Hou, K.; Prakash, O.; Arora, S.K. *Org. Synth.* ***VII***, 263.
[495] Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* ***1988****, 29*, 2835.
[496] Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* ***2006****, 39,* 1.
[497] Christoffers, J. *J. Org. Chem.* ***1999****, 64*, 7668.
[498] Christoffers, J.; Werner, T. *Synlett* ***2002***, 119.
[499] Monguchi, Y.; Takahashi, T.; Iida, Y.; Fujiwara, Y.; Inagaki, Y.; Maegawa, T.; Sajiki, H. *Synlett* ***2008***, 2291.
[500] Landwehr, M.; Hochrein, L.; Otey, C.R.; Kasrayan, A.; Bäckvall, J.-E.; Arnold, F.H. *J. Am. Chem. Soc.* ***2006****, 128,* 6058.
[501] Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron* ***2002****, 58*, 7321.
[502] Zhang, Y.; Shen, Z.; Tang, J.; Zhang, Y.; Kong, L.; Zhang, Y. *Org. Biomol. Chem.* ***2006****, 4,* 1478.
[503] Huang, H.-Y.; Hou, R.-S.; Wang, H.-M.; Chen, L.-C. *Org. Prep. Proceed. Int.* ***2006****, 38,* 473.
[504] Vedejs, E.; Larsen, S. *Org. Synth.* ***VII***, 277; Gamboni, R.; Tamm, C. *Tetrahedron Lett.* ***1986****, 27,* 3999; *Helv. Chim. Acta* ***1986****, 69,* 615. See also, Hara, O.; Takizawa, J.-i.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* ***1999****, 40*, 7787.
[505] Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* ***1975***, 1731. For another method, see Pohmakotr, M.; Winotai, C. *Synth. Commun.* ***1988****, 18*, 2141.
[506] Cuvigny, T.; Valette, G.; Larcheveque, M.; Normant, H. *J. Organomet. Chem.* ***1978****, 155,* 147.

converted to their α-hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.[507]



Ketones are converted to α-hydroxy ketones by reaction of the enolate anion with a 2-sulfonyloxaziridine (e.g., **25**).[508] This is not a free radical process; the mechanism shown is likely. The method is also successful for carboxylic esters[509] and *N,N*-disubstituted amides,[510] and can be made enantioselective by the use of a chiral oxaziridine.[511] Dimethyldioxirane also oxidizes the enolate anions of ketones to α-hydroxy ketones.[512] Titanium enolates are oxidized with *tert*-butyl hydroperoxide[513] or with dimethyldioxirane[514] and hydrolyzed with aq ammonium fluoride to give the α-hydroxy ketone. Ketones are converted to the α-oxamino derivative (O=C—CH_2— → O=C—CHONHPh) with excellent enantioselectivity using PhN=O and L-proline[515] or (*S*)-proline.[516] Aldehydes undergo a similar oxidation.[517] α-Lithio sulfones have been hydroxylated with Me_3SiOOt-Bu.[518]



Dimethyldioxirane

Ketones have been α hydroxylated by conversion to the silyl enol ether, followed by treatment with *m*-chloroperoxybenzoic acid,[166] or with certain other oxidizing agents.[519] α-Hydroxyketones can be accomplished from silyl enol ethers with a catalytic amount of $MeReO_3$ and H_2O_2.[520] When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α-keto triflate.[521]

[507] Rubottom, G.M.; Gruber, J.M.; Juve, Jr., H.D.; Charleson, D.A. *Org. Synth.* ***VII***, 282. See also, Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989****, 30,* 3323.
[508] Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* ***1984****, 49,* 3241.
[509] For formation of α−benzyloxy lactones, see Brodsky, B.H.; DuBois, J. *Org. Lett.* ***2004****, 6*, 2619.
[510] Davis, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* ***1985****, 26*, 3539.
[511] Davis, F.A.; Sheppard, A.C.; Chen, B.; Haque, M.S. *J. Am. Chem. Soc.* ***1990****, 112*, 6679; Davis, F.A.; Weismiller, M.C. *J. Org. Chem.* ***1990****, 55*, 3715.
[512] Guertin, K.R.; Chan, T.H. *Tetrahedron Lett.* ***1991****, 32,* 715.
[513] Schulz, M.; Kluge, R.; Schüßler, M.; Hoffmann, F. *Tetrahedron* ***1995****, 51*, 3175.
[514] Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* ***1994****, 59*, 2358.
[515] Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* ***2004****, 69*, 5966; Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2004****, 43*, 1112.
[516] Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem. Int. Ed.* ***2004****, 43*, 1109.
[517] Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* ***2003****, 44*, 8293.
[518] Chemla, F.; Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* ***1993****, 130*, 547; ***1994****, 131*, 639.
[519] See Davis, F.A.; Sheppard, A.C. *J. Org. Chem.* ***1987****, 52*, 954; Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* ***1991***, 281.
[520] Stankovic, S.; Espenson, J.H. *J. Org. Chem.* ***1998****, 63*, 4129.
[521] Moriarty, R.M.; Epa, W.R.; Penmasta, R.; Awasthi, A.K. *Tetrahedron Lett.* ***1989****, 30,* 667.

Silyl ketene ethers are converted to α-hydroxy esters with H_2O_2 and methyl trioxorhenium.[522] The α′-position of α,β-unsaturated ketones can be selectively oxidized.[523] *N*-Acyl amines are converted to the α-hydroxy derivative with PhIO and a Mn salen catalyst.[524] Note that homoallylic-type oxidation occurs when an α,α-dimethyl oxime ether is treated with $PhI(OAc)_2$ and a Pd catalyst in acetic acid/acetic anhydride, converting one of the methyl groups to an acetoxymethyl.[525]

α-Acetoxylation of ketones with concurrent α-arylation occurs when ketones react with $Mn(OAc)_3$ in benzene.[526] α-Acetoxylation of ketones can occur under similar conditions without arylation.[527] α-Methyl ketones are converted to the α-acetoxy derivative under the same conditions.[528] Iodobenzene with 30% aq H_2O_2 and acetic anhydride generates α-acetoxy ketones.[529] Thallium(III) triflate converts acetophenone to α-formyloxy acetophenone.[530] Methanesulfonic acid and CuO converts ketones to α-mesyloxy (—OMs) ketones[531] and PhI(OH)OTs converts ketones to α-tosyloxy (—OTs) ketones.[532] *N*-Methyl-*O*-tosylhydroxylamine is another reagent that effects direct α-oxytosylation of ketones and aldehydes.[533] α-Acetoxylation of ketones results from *in situ* generation of hypervalent iodine species in the presence of acetic acid.[534]

OSCV 7, 277; OSCV 7, 263; OSCV 6, 43

19-16 Oxidation of Methylene to Heteroatom Functional Groups Other Than Oxygen or Carbonyl

Amino (or amido) -de-dihydro-bisubstitution



α-Amination or amidation of a CH unit is possible in some cases. Cyclic alkanes are converted to the *N*-alkyl *N*-tosylamine with PhI=NTs and a Cu complex.[535] Benzylic (CH) as in ethylbenzene, is oxidized with $PhI(OAc)_2$ in the presence of $TsNH_2$ and a fluorinated manganese porphyrin to give the corresponding *N*-tosylamine [PhCHMe(NHTs)].[536] Alkenes with an allylic CH react with PhI=NTs and a Ru catalysts to give an allylic

[522] Stankovic, S.; Espenson, J.H. *J. Org. Chem.* ***2000****, 65*, 5528.
[523] Demir, A.S.; Jeganathan, A. *Synthesis* ***1992***, 235.
[524] Punniyamurthy, T.; Katsuki, T. *Tetrahedron* ***1999****, 55*, 9439.
[525] Desai, L.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* ***2004****, 126*, 9542.
[526] Tanyeli, C.; Özdemïrhan, D.; Sezen, B. *Tetrahedron* ***2002****, 58*, 9983.
[527] Demir, A.S.; Reis, Ö.; Igdir, A.C. *Tetrahedron* ***2004****, 60*, 3427.
[528] Tanyeli, C.; Iyigün, C. *Tetrahedron* ***2003****, 59*, 7135.
[529] Sheng, J.; Li, X.; Tang, M.; Gao, B.; Huang, G. *Synthesis* ***2007***, 1165.
[530] Lee, J.C.; Jin, Y.S.; Choi, J.-H. *Chem. Commun.* ***2001***, 956.
[531] Lee, J.C.; Choi, Y. *Tetrahedron Lett.* ***1998****, 39*, 3171.
[532] Nabana, T.; Togo, H. *J. Org. Chem.* ***2002****, 67*, 4362. See Yamamoto, Y.; Togo, H. *Synlett* ***2006***, 708; Richardson, R.D.; Page, T.K.; Altermann, S.; Paradine, S.M.; French, A.N.; Wirth, T. *Synlett* ***2007***, 538; Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* ***2007***, 2168.
[533] John, O.R.S.; Killeen, N.M.; Knowles, D.A.; Yau, S.C.; Bagley, M.C.; Tomkinson, N.C.O. *Org. Lett.* ***2007****, 9,* 4009.
[534] Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K.*J. Am. Chem. Soc.* ***2005****, 127,* 12244.
[535] Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2003****, 125*, 12078.
[536] Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* ***2000****, 2*, 2233.

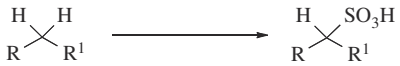
N-tosylamine.[537] When an α-keto ester reacts with DEAD and a chiral Cu complex, an α-carbamate is formed, $RCH(NHCO_2Et)C(=O)CO_2Et$, with modest enantioselectivity.[538]

Cyclic amines react with *Pseudomonas oleovorans* GPol to give hydroxy amines; *N*-benzylpyrrolidine is converted to 3-hydroxy *N*-benzylpyrrolidine.[539] *Sphingomonas* sp. HXN-200 gives similar results,[540] and lactams are converted to the corresponding 3-hydroxy lactam with *sphingomonas* sp. HXN-200.[541] *N*-Benzyl piperidine is converted to the 4-hydroxy derivative under the same conditions.[542] *N*-Benzyl phthalimide reacts with NBS, NaOAc, and acetic acid to give *N*-(α-acetoxybenzyl)phthalimide.[543]

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran, which was relatively stable under the conditions used, by electrolysis in water.[544] α-Hydroxy ethers are generated by reaction of SO_2/O_2 and a V catalyst with ethers.[545]

Similar reactions are possible, in some cases, to produce sulfur containing compounds.

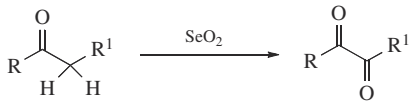
Sulfo-de-dihydro-bisubstitution



Cyclic alkanes are converted to the corresponding alkylsulfonic acid with SO_2/O_2 and a V catalyst.[546]

19-17 Oxidation of Methylene to Carbonyl

Oxo-de-dihydro-bisubstitution

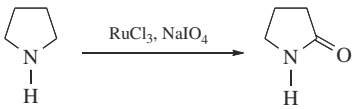


Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes (see Reaction **19-18**) and α-diketones.[547] The reaction can also be carried out α to an aromatic ring or to a double bond, although in the latter case, hydroxylation (see **19-14**) is the more common result. Selenium dioxide, (SeO_2) is often used, but the reaction has also been carried out with other oxidizing agents,[548] including hypervalent iodine compounds.[549] Sodium nitrite/HCl oxidizes cyclic ketones to the diketone.[550] Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see Reaction **19-11**). The benzylic

[537] Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* ***2000****, 65*, 7858.
[538] Juhl, K.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002****, 124*, 2420.
[539] Li, Z.; Feiten, H.-J.; van Beilen, J.B.; Duetz, W.; Witholt, B. *Tetrahedron Asymmetry* ***1999****, 10*, 1323.
[540] Li, Z.; Feiten, H.-J.; Chang, D.; Duetz, W.A.; Beilen, J.B.; Witholt, B. *J. Org. Chem.* ***2001****, 66*, 8424.
[541] Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* ***2000****, 2*, 3949.
[542] Chang, D.; Feiten, H.-J.; Engesser, K.-H.; van Beilen, J.; Witholt, B.; Li, Z. *Org. Lett.* ***2002****, 4*, 1859.
[543] Cho, S.-D.; Kim, H.-J.; Ahn, C.; Falck, J.R.; Shin, D.-S. *Tetrahedron Lett.* ***1999****, 40*, 8215.
[544] Wermeckes, B.; Beck, F.; Schulz, H. *Tetrahedron* ***1987****, 43,* 577.
[545] Miyafuji, A.; Katsuki, T. *Synlett* ***1997***, 836.
[546] Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* ***200****,122*, 7390.
[547] See Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***, pp. 115–180; Krongauz, E.S. *Russ. Chem. Rev.* ***1977****, 46*, 59; Rabjohn, N. *Org. React.* ***1976****, 24,* 261; Trachtenberg, E.N. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Marcel Dekker, NY, pp. 119–187.
[548] See Wasserman, H.H.; Ives, J.L. *J. Org. Chem.* ***1985****, 50*, 3573.
[549] Lee, J.C.; Park, H.-J.; Park, J.Y. *Tetrahedron Lett.* ***2002****, 43*, 5661.
[550] Rüedi, G.; Oberli, M.A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* ***2004***, 2315.

position of arenes have been oxidized to alkyl aryl ketones with several oxidizing agents, including the Jones reagent,[551] CrO_3 on silica,[552] PCC,[553] DDQ,[554] $KMnO_4$ supported on MnO_2,[555] $KMnO_4/CuSO_4$ neat[556] or with ultrasound,[557] manganese salen/PhIO,[558] *tert*-butylhydroperoxide and a Ru catalyst,[559] or H_2O_2 with a Cu catalyst.[560] The combination of O_2 and mcpba oxidizes benzylic arenes to aryl ketones.[561] The combination of HBr and H_2O_2 gives a similar oxidation.[562] Methyl ketones are oxidized to the α-keto ester in a two-step procedure using a fluorous selenic acid with an iodoxy benzene, followed by treatment with sodium metabisulfite ($Na_2S_2O_5$).[563]

Alkenes of the form C=C—CH_2 (an allylic position) have been oxidized to α,β-unsaturated ketones[564] by sodium dichromate in HOAc-Ac_2O, by *t*-BuOOH and Cr compounds,[565] *t*-BuOOH and a Pd[566] or Rh[567] catalyst. Thallium(III) nitrate in aq acetic acid converts allylic alkenes to the corresponding saturated ketone, even in the presence of a primary alcohol elsewhere in the molecule.[568] The propargylic position of internal alkynes are oxidized to give propargylic ketones with an iron catalyst,[569] with a dirhodium catalyst in water,[570] or with O_2/*t*-BuOOH in the presence of a Cu catalyst.[571] Chloramine-T (see Reaction **15-54**), O_2, and an Fe catalyst give selective oxidation of hydrocarbons to ketones.[572]



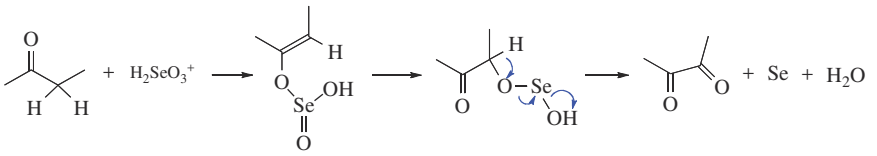
Cyclic amines are oxidized to lactams using a mixture of $RuCl_3$ and $NaIO_4$.[573] Lactams are also formed using $KMnO_4$ with benzyltriethylammonium chloride.[574] Tertiary amines are converted to amides[575] and cyclic tertiary amines can be converted to lactams by oxidation with

[551] Rangarajan, R.; Eisenbraun, E.J. *J. Org. Chem.* ***1985****, 50,* 2435.
[552] Borkar, S.D.; Khadilkar, B.M. *Synth. Commun.* ***1999****, 29*, 4295.
[553] Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* ***1986****, 16,* 1493.
[554] Lee, H.; Harvey, R.G. *J. Org. Chem.* ***1988****, 53,* 4587.
[555] Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004****, 60,* 11829.
[556] Shaabani, A.; Lee, D.G. *Tetrahedron Lett.* ***2001****, 42,* 5833.
[557] Meciarova, M.; Toma, S.; Heribanová, A. *Tetrahedron* ***2000****, 56,* 8561.
[558] Komiya, N.; Noji, S.; Murahashi, S.-I. *Tetrahedron Lett.* ***1998****, 39*, 7921; Lee, N.H.; Lee, C.-S.; Jung, D.-S. *Tetrahedron Lett.* ***1998****, 39*, 1385.
[559] Murahashi, S.-I.; Komiya, N.; Oda, Y.; Kuwabara, T.; Naota, T. *J. Org. Chem.* ***2000****, 65*, 9186.
[560] Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003****, 44*, 8955.
[561] Ma, D.; Xia, C.; Tian, H. *Tetrahedron Lett.* ***1999****, 40*, 8915.
[562] Khan, A.T.; Parvin, T.; Choudhury, L.H.; Ghosh, S. *Tetrahedron Lett.* ***2007****, 48*, 2271.
[563] Crich, D.; Zou, Y. *J. Org. Chem.* ***2005****, 70,* 3309.
[564] See Muzart, J. *Bull. Soc. Chim. Fr.* ***1986***, 65. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 1207–1210.
[565] Muzart, J. *Tetrahedron Lett.* ***1987****, 28*, 2131; Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* ***1987****, 52*, 5048.
[566] Yu, J.-Q.; Corey, E.J. *J. Am. Chem. Soc.* ***2003****, 125*, 3232.
[567] Catino, A.J.; Forslund, R.E.; Doyle, M.P. *J. Am. Chem. Soc.* ***2004****, 126*, 13622.
[568] Ferraz, H.M.C.; Longo, Jr., L.S.; Zukerman-Schpector, J. *J. Org. Chem.* ***2002****, 67*, 3518.
[569] Pérollier, C.; Sorokin, A.B. *Chem. Commun.* ***2002***, 1548.
[570] McLaughlin, E.C.; Doyle, M.P. *J. Org. Chem.* ***2008****, 73,* 4317.
[571] Ajjou, A.N.; Ferguson, G. *Tetrahedron Lett.* ***2006****, 47,* 3719.
[572] Li, S.-J.; Wan, Y.-G. *Tetrahedron Lett.* ***2005****, 46*, 8013.
[573] Sharma, N.K.; Ganesh, K.N. *Tetrahedron Lett.* ***2004****, 45*, 1403.
[574] Markgraf, J.H.; Stickney, C.A. *J. Heterocyclic Chem.* ***2000****, 37*, 109.
[575] Markgraf, J.H.; Sangani, P.K.; Finkelstein, M. *Synth. Commun.* ***1995****, 27*, 1285.

a Hg(II)—EDTA (EDTA = ethylenediaminetetraacetic acid) complex in basic solution.[576] Lactams, which need not be *N*-substituted, can be converted to cyclic imides by oxidation with a hydroperoxide or peroxyacid and an Mn(II) or Mn(III) salt.[577] Lactams are oxidized to cyclic imides with oxygen and $Co(OAc)_2$ in the presence *N*-hydroxysuccinimide.[578]

Ethers in which at least one group is a primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.[579] Molecular oxygen with a binuclear Cu(II) complex[580] or $PdCl_2/CuCl_2/CO$[581] also converts ethers to esters. Cyclic ethers are oxidized to lactones.[582] Cyclic ethers are oxidized to lactones with CrO_3/Me_3SiONO_2.[583] Lactones are also formed from cyclic ethers with $NaBrO_3—KHSO_4$ in water.[584] The reaction has also been accomplished with CrO_3 in H_2SO_4,[585] and with benzyltriethylammonium permanganate.[586]

Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol:[587]



In the other proposed mechanism,[588] the principal intermediate is α,β-ketoseleninic acid (O=C—CH—SeO_2H) and a selenate ester is not involved.

Oxidation of CH_2 to C=O groups is possible even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow[57] (see Reaction **19-2**). One of the CH_2 groups of *n*-hexadecanol monosuccinate [$CH_3(CH_2)_{14}CH_2OCOCH_2CH_2CO_2H$] was oxidized to a C=O group to give a mixture of it and benzophenone-4-carboxylic acid [*p*-$PhCOC_6H_4CO_2H$] in CCl_4.[589] Other remote oxidations[590] also have been reported. Among these are conversion of aryl ketones [$ArCO(CH_2)_3R$] to 1,4-diketones [$ArCO(CH_2)_4COR$] by photoirradiation in the presence of such oxidizing agents as $K_2Cr_2O_7$ or $KMnO_4$,[591] and conversion of alkyl ketones [$RCO(CH_2)_3R'$] to 1,3- and 1,4-diketones with

[576] Wenkert, E.; Angell, E.C. *Synth. Commun.* ***1988****, 18,* 1331.
[577] Doumaux Jr., A.R.; Trecker, D.J. *J. Org. Chem.* ***1970****, 35,* 2121.
[578] Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G.F. *J. Org. Chem.* ***2002****, 67*, 2671.
[579] Bakke, J.M.; Frøhaug, Az. *Acta Chem. Scand. B* ***1995****, 49*, 615; Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 222–225; Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* ***1981****, 46,* 3936.
[580] Minakata, S.; Imai, E.; Ohshima, Y.; Inaki, K.; Ryu, I.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* ***1996***, 19.
[581] Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* ***1994***, 1149.
[582] See Ferraz, H.M.C.; Longo, Jr., L.S. *Org. Lett.* ***2003****, 5*, 1337.
[583] Shahi, S.P.; Gupta, A.; Pitre, S.V.; Reddy, M.V.R.; Kumareswaran, R.; Vankar, Y.D. *J. Org. Chem.* ***1999****, 64*, 4509.
[584] Metsger, L.; Bittner, S. *Tetrahedron* ***2000****, 56*, 1905.
[585] Harrison, I.T.; Harrison, S. *Chem. Commun.* ***1966***, 752.
[586] Schmidt, H.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1979****, 18*, 69.
[587] Corey, E.J.; Schaefer, J.P. *J. Am. Chem. Soc.* ***1960****, 82*, 918.
[588] Sharpless, K.B.; Gordon, K.M. *J. Am. Chem. Soc.* ***1976****, 98,* 300.
[589] Breslow, R.; Scholl, P.C. *J. Am. Chem. Soc.* ***1971****, 93*, 2331. See also, Breslow, R.; Heyer, D. *Tetrahedron Lett.* ***1983****, 24*, 5039.
[590] See also, Beckwith, A.L.J.; Duong, T. *J. Chem. Soc. Chem. Commun.* ***1978***, 413.
[591] Mitani, M.; Tamada, M.; Uehara, S.; Koyama, K. *Tetrahedron Lett.* ***1984****, 25*, 2805. For an alternative photochemical procedure, see Negele, S.; Wieser, K.; Severin, T. *J. Org. Chem.* ***1998****, 63*, 1138.

$Na_2S_2O_8$ and $FeSO_4$.[592] 2-Octanol was oxidized to give 2-propyl-5-methyl γ-butyrolactone with lead tetraacetate in a CO atmosphere.[593]

OS **I**, 266; **II**, 509; **III**, 1, 420, 438; **IV**, 189, 229, 579; **VI**, 48; **IX**, 396. Also see, OS **IV**, 23.

19-18 Oxidation of Arylmethanes to Aldehydes

Oxo-de-dihydro-bisubstitution

$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO$$

Methyl groups on an aromatic ring can be oxidized to an aldehyde by several oxidizing agents. The reaction is a special case of **19-17**. When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*[594] and the yields are high.[595] Another oxidizing agent is a mixture of CrO_3 and Ac_2O, where the reaction stops at the aldehyde stage because the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde.

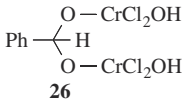
Among other oxidizing agents[596] that have been used to accomplish the conversion of $ArCH_3$ to ArCHO are ceric ammonium nitrate,[597] PCC,[598] hypervalent iodoso compounds (see Reaction **19-3**),[599] Bi-*t*-BuOOH,[600] and urea–H_2O_2 with microwave irradiation.[601] Oxidative of benzylic positions to the corresponding carbonyl has been reported using two heterogeneous catalysts.[602] Oxidation of $ArCH_3$ to carboxylic acids is considered at Reaction **19-11**.

Conversion of $ArCH_3$ to ArCHO can also be achieved indirectly by bromination to give $ArCHBr_2$ (**14-1**), followed by hydrolysis (Reaction **10-2**).

The mechanism of the *Étard reaction* is not completely known.[603] An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but the identity of the structure is not fully settled, although many proposals have been made as to its structure and as to how it is hydrolyzed. It is known that $ArCH_2Cl$ is not an intermediate (see Reaction **19-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[604] indicate that the complex from toluene is **26**, a structure first proposed by Étard. According to this proposal, the reaction

[592] Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* ***1984****, 25*, 4987.
[593] Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* ***1998****, 120*, 8692. Also see, Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* ***1994****, 116*, 5473.
[594] The name *Étard reaction* is often applied to any oxidation with chromyl chloride, for example, oxidation of glycols (**19-7**), alkenes (**19-10**), and so on.
[595] See Hartford, W.H.; Darrin, M. *Chem. Rev.* ***1958****, 58*, 1, see pp. 25–53.
[596] See Steckhan, E. *Top. Curr. Chem.* ***1987****, 142*, 1; pp. 12–17.
[597] Trahanovsky, W.S.; Young, L.B. *J. Org. Chem.* ***1966****, 31,* 2033; Syper, L. *Tetrahedron Lett.* ***1967***, 4193. See Ganin, E.; Amer, I. *Synth. Commun.* ***1995****, 25*, 3149.
[598] Hosseinzadeh, R.; Tajbakhsh, M.; Vahedi, H. *Synlett* ***2005***, 2769.
[599] Nicolaou, K.C.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* ***2001****, 123*, 3183.
[600] Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D.A.; Oldham, J.; Burton, A.J.; Barrett, A.G.M. *Org. Lett.* ***2005****, 7,* 4549.
[601] Paul, S.; Nanda, P.; Gupta, R. *Synlett* ***2004***, 531.
[602] Rajabi, F.; Clark, J.H.; Karimi, B.; Macquarrie, D.J. *Org. Biomol. Chem.* ***2005****, 3,* 725.
[603] For a review, see Nenitzescu, C.D. *Bull. Soc. Chim. Fr.* ***1968***, 1349.
[604] Wheeler, O.H. *Can. J. Chem.* ***1960****, 38*, 2137. See also, Makhija, R.C.; Stairs, R.A. *Can. J. Chem.* ***1968****, 46,* 1255.

stops after only two hydrogen atoms have been replaced because of the insolubility of **26**. There is a disagreement on how **26** is formed, assuming that the complex has this structure. Both an ionic[605] and a free radical[606] process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu et al.[607] On the basis of ESR studies, they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **26**. However, this view has been challenged by Wiberg and Eisenthal,[606] who interpret the ESR result as being in accord with **26**. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[608]

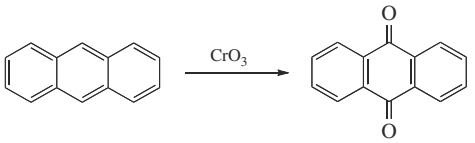


26

OS **II**, 441; **III**, 641; **IV**, 31, 713.

19-19 Oxidation of Aromatic Hydrocarbons to Quinones

Arene-quinone transformation



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[609] Yields are generally not high, although good yields have been reported with ceric ammonium sulfate.[610] Benzene cannot be so oxidized by strong oxidizing agents, but can be electrolytically oxidized to benzoquinone.[611] Naphthalene derivatives, however, are oxidized to naphthoquinones with H_5IO_6 and CrO_3.[612] 1,4-Dimethoxy aromatic compounds are oxidized to *p*-quinones with an excess of CoF_3 in water–dioxane.[613]

OS **IV**, 698, 757. Also see, OS **II**, 554.

[605] Stairs, R.A. *Can. J. Chem.* ***1964****, 42,* 550.

[606] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964****, 20,* 1151. See also, Gragerov, I.P.; Ponomarchuk, M.P. *J. Org. Chem. USSR* ***1969****, 6,* 1125.

[607] Necsoiu, I.; Przemetchi, V.; Ghenciulescu, A.; Rentea, C.N.; Nenitzescu, C.D. *Tetrahedron* ***1966****, 22*, 3037.

[608] Duffin, H.C.; Tucker, R.B. *Chem. Ind. (London)* ***1966***, 1262; *Tetrahedron* ***1968****, 24,* 6999.

[609] Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 242–247; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 94–96; Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 1, Academic Press, NY, ***1985***, pp. 182–185, 358–360; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 132–134.

[610] Periasamy, M.; Bhatt, M.V. *Synthesis* ***1977***, 330; Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S.S. *J. Org. Chem.* ***1988****, 53,* 1007.

[611] See Ito, S.; Katayama, R.; Kunai, A.; Sasaki, K. *Tetrahedron Lett.* ***1989****, 30*, 205.

[612] Yamazaki, S. *Tetrahedron Lett.* ***2001****, 42*, 3355.

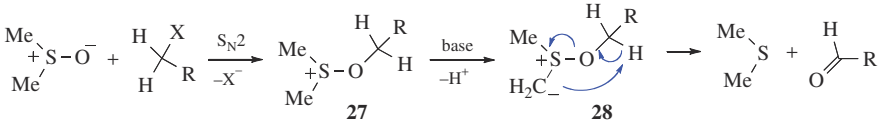
[613] Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* ***1999***, 1474.

19-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes[614]

Oxo-de-hydro,halo-bisubstitution

$$RCH_2Cl \xrightarrow{Me_2SO} RCHO$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with DMSO,[615] in what has been called the *Kornblum reaction*. In Kornblum's original work, the reaction of α-halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α-keto-aldehyde).[616] If the glyoxal could be removed from the reaction medium by distillation as it was formed, the reaction was very efficient. In many cases, it was difficult to isolate high-boiling glyoxals from DMSO. Primary and secondary[617] alkyl iodides or tosylates[618] can be converted to aldehydes or ketones, although they are much less reactive than α-halo ketones. Primary chlorides with DMSO, NaBr, and ZnO give the corresponding aldehyde when heated to 140 °C.[619] Benzylic halides are oxidized to aryl aldehydes with MnO_2[620] or with $NaIO_4$—LiBr.[621] Hydrogen peroxide in ethanol oxidizes organic halides to carbonyl compounds.[622] Pyridine *N*-oxide in the presence of silver oxide oxidizes benzylic and allylic halides.[623]



The mechanism of these DMSO oxidations is probably that shown with **27** and **28**,[624] although in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylid (**28**) is not an intermediate. Alkoxysulfonium salts (**27**) have been isolated.[625] This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the

[614] For reviews, see Tidwell, T.T. *Org. React.* ***1990****, 39,* 297; *Synthesis* ***1990***, 857; Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 2, Academic Press, NY, ***1988***, pp. 171–181, 402–406; Durst, T. *Adv. Org. Chem.* ***1969****, 6,* 285, pp. 343–356; Epstein, W.W.; Sweat, F.W. *Chem. Rev.* ***1967****, 67,* 247; Moffatt, J.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 1–64. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1222–1225.

[615] Nace, H.R.; Monagle, J.J. *J. Org. Chem.* ***1959****, 24,* 1792; Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959****, 81,* 4113. Also see Villemin, D.; Hammadi, M. *Synth. Commun.* ***1995****, 25*, 3141.

[616] Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. *J. Am. Chem. Soc.* ***1957****, 79,* 6562. Mg—Al hydrotalcites have been used as heterogeneous basic catalysts: see Kshirsagar, S.W.; Patil, N.R.; Samant, S.D. *Tetrahedron Lett.* ***2008****, 49*, 1160.

[617] Baizer, M.M. *J. Org. Chem.,* ***1960****, 25,* 670.

[618] Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959****, 81*, 4113.

[619] Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001****, 31,* 667; Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001****, 31,* 3395.

[620] Goswami, S.; Jana, S.; Dey, S.; Adak, A.K. *Chem. Lett.* ***2005****, 34,* 194.

[621] Ali Shaikh, T.M.; Emmanuvel, L.; Sudalai, A. *Synth. Commun.* ***2007****, 37*, 2641.

[622] Tang, J.; Zhu, J.; Shen, Z.; Zhang, Y. *Tetrahedron Lett.* ***2007****, 48,* 1919.

[623] Chen, D.X.; Ho, C.M.; Wu, Q.Y.R.; Wu, P.R.; Wong, F.M.; Wu, W. *Tetrahedron Lett.* ***2008****, 49,* 4147.

[624] See Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967****, 32,* 1926; Torssell, K. *Acta Chem. Scand.* ***1967****, 21,* 1.

[625] Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.* ***1973****, 95,* 8393.

intermediate **27**[626] is formed without the use of DMSO by treating the substrate with a complex generated from chlorine or NCS and DMS.[627] Also see the *Swern oxidation* in Reaction **19-3**.

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,[628] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl is alkyl. The first part of the reaction is conversion to the amine ($ArCH_2NH_2$), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual *Sommelet reaction*, although the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine. This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine.

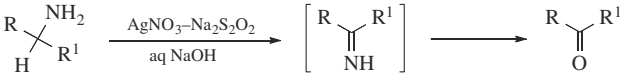
Pyridine followed by *p*-nitrosodimethylaniline and then water converts benzylic halides to aldehydes, and is called the *Kröhnke reaction*. Primary halides and tosylates have been oxidized to aldehydes by trimethylamine *N*-oxide,[629] and by pyridine *N*-oxide with microwave irradiation.[630]

Epoxides[631] have been used to give α-hydroxy ketones or aldehydes.[632]

OS **II**, 336: **III**, 811; **IV**, 690, 918, 932; **V**, 242, 668, 825, 852, 872. Also see, OS **V**, 689; **VI**, 218.

19-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides

Oxo-de-hydro,amino-bisubstitution (overall transformation)



Primary aliphatic amines can be oxidized to aldehydes or ketones. using silver compounds as shown.[633] Other reagents have been used,[634] including *N*-bromoacetamide[635] (for benzylic amines), or aq NaOCl with phase-transfer catalysts.[636] Several indirect methods for achieving the conversion $RR'CHNH_2 \rightarrow RR'C{=}O$ (R′ = alkyl, aryl, or H) have been reported.[637]

[626] For an alternateive, see Moffatt, J.G. *J. Org. Chem.* ***1971****, 36*, 1909 and references cited therein.
[627] See Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* ***1988***, 178.
[628] See Angyal, S.J. *Org. React.* ***1954****, 8,* 197.
[629] Franzen, V.; Otto, S. *Chem. Ber.* ***1961****, 94*, 1360. For the use of other amine oxides, see Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* ***1986****, 59,* 3287.
[630] Barbry, D.; Champagne, P. *Tetrahedron Lett.* ***1996****, 37*, 7725.
[631] See Olah, G.A.; Vankar, Y.D.; Arvanaghi, M. *Tetrahedron Lett.* ***1979***, 3653.
[632] Santosusso, T.M.; Swern, D. *J. Org. Chem.* ***1975****, 40,* 2764.
[633] See Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 2, Academic Press, NY, ***1988***, pp. 200–220, 411–415.
[634] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1225–1227; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 240.
[635] Banerji, K.K. *Bull. Chem. Soc. Jpn.* ***1988****, 61,* 3717.
[636] Lee, G.A.; Freedman, H.H. *Tetrahedron Lett.* ***1976***, 1641.
[637] See Babler, J.H.; Invergo, B.J. *J. Org. Chem.* ***1981****, 46*, 1937.

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aq bromine[638] and with neutral permanganate.[639] The other product of this reaction is the amine with one less alkyl group. Reaction of a primary amine with benzoyl peroxide/$CsCO_3$ and subsequent heating of the hydroxylamine product gives the ketone.[640] In a different type of procedure, primary alkyl primary amines can be converted to *gem*-dihalides [$RCH_2NH_2 \rightarrow RCHX_2$ (X = Br or Cl)] by treatment with an alkyl nitrite and the anhydrous copper(I) halide.[641]

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively ($RR'CHNO_2 \rightarrow RR'C{=}O$), with sodium chlorite under phase-transfer conditions,[642] tetrapropylammonium perruthenate (TPAP),[643] as well as with other reagents.[644]

19-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Esters

Oxo-de-dihydro-bisubstitution

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate,[645] nitric acid,[646] or H_5IO_6/CrO_3.[647] The reaction can be looked on as a combination of **19-3** and **19-23**. Aliphatic primary alcohols are converted to the carboxylic acid with 30% aq H_2O_2, tetrabutylammonium hydrogen sulfate and a W catalyst with microwave irradiation.[648] Benzylic alcohols are oxidized to benzoic acid derivatives by treatment first with TEMPO[649] (Sec. 5.C.i), and then $NaClO_2$.[650] Oxidation with 5% aq NaOCl and a Ni catalyst oxidizes primary alcohols to the corresponding acid.[651] Similar oxidation to the acid occurred with $NaIO_4/RuCl_3$ in aq acetonitrile,[652] or 30% aq H_2O_2 and a Co salen catalyst.[653] Oxammonium salts and $NaClO_2$ oxidize alcohols to carboxylic acids.[654]

[638] Deno, N.C.; Fruit Jr., R.E. *J. Am. Chem. Soc.* ***1968****, 90,* 3502.
[639] Rawalay, S.S.; Shechter, H. *J. Org. Chem.* ***1967****, 32*, 3129. For another procedure, see Monkovic, I.; Wong, H.; Bachand, C. *Synthesis* ***1985***, 770.
[640] Knowles, D.A.; Mathews, C.J.; Tomkinson, N.C.O. *Synlett* ***2008***, 2769.
[641] Doyle, M.P.; Siegfried, B. *J. Chem. Soc. Chem. Commun.* ***1976***, 433.
[642] Ballini, R.; Petrini, M. *Tetrahedron Lett.* ***1989****, 30*, 5329.
[643] Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 207.
[644] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1227–1228.
[645] See Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1998****, 39*, 1095.
[646] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 127–132; Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 2, Academic Press, NY, ***1988***, 148–165, 391–401. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1646–1650.
[647] Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* ***1998****, 39*, 5323
[648] Bogdal, D.; Lukasiewicz, M. *Synlett* ***2000***, 143.
[649] See DeLuca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* ***2003****, 68,* 4999.
[650] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *J. Org. Chem.* ***1999****, 64,* 2564.
[651] Grill, J.M.; Ogle, J.W.; Miller, S.A. *J. Org. Chem.* ***2006****, 71*, 9291.
[652] Prashad, M.; Lu, Y.; Kim, H.-Y.; Hu, B.; Repic, O.; Blacklock, T.J. *Synth. Commun.* ***1999****, 29,* 2937.
[653] Das, S.; Punniyamurthy, T. *Tetahedron Lett.* ***2003****, 44*, 6033.
[654] Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. *Chem. Commun.* ***2009***, 1739.

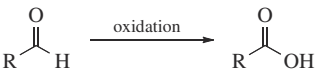
When acidic conditions are used, a considerable amount of carboxylic ester ($RCOOCH_2R$) is often isolated, although this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.[655] A mixture of Oxone and NaCl converts alcohols to symmetrical esters.[656] Aliphatic alcohols are converted to a symmetrical ester ($RCH_2OH \rightarrow RCOOCH_2R$) by oxidation with PCC on aluminum without solvent.[657] Hydrogen with a Ru—CO complex converts primary alcohols (ROH) to an ester (RCO_2R).[658] Iodine has been used to convert alcohols to esters.[659] Hydrogen transfer with a Ru catalyst has been used to convert primary alcohols to methyl esters.[660] Oxone in aq methanol also converts aryl aldehydes to the corresponding ester.[661] Allylic alcohols are converted to conjugated esters with MnO_2 and NaCN in methanol–acetic acid.[662] Primary alcohols are oxidized to the methyl ester with trichloroisocyanuric acid in methanol.[663] This reagent also converts diols to lactones. Lactones can be prepared by oxidizing diols in which at least one OH is primary,[664] and addition of a chiral additive (e.g., sparteine) leads to lactones with high asymmetric induction.[665]

Primary alcohols (RCH_2OH) can be directly oxidized to acyl fluorides (RCOF) with cesium fluoroxysulfate.[666] 2-(3-Hydroxypropyl)aniline was oxidized to an acyl derivative that cyclized to give a lactam when heated with a Rh catalyst.[667]

OS **I**, 138, 168; **IV**, 499, 677; **V**, 580; **VII**, 406; **IX**, 462; **81**, 195. Also see, OS **III**, 745.

19-23 Oxidation of Aldehydes to Carboxylic Acids, Carboxylic Esters, and Related Compounds

Hydroxylation or Hydroxy-de-hydrogenation



Oxidation of aldehydes to carboxylic acids is quite common[668] and has been carried out with many oxidizing agents, including permanganate in acid, basic, or neutral solution,[669]

[655] Craig, J.C.; Horning, E.C. *J. Org. Chem.* ***1960****, 25,* 2098. See also, Nwaukwa, S.O.; Keehn, P.M. *Tetrahedron Lett.* ***1982****, 23,* 35.
[656] Schulze, A.; Pagona, G.; Giannis, A. *Synth. Commun.* ***2006****, 36*, 1147.
[657] Bhar, S.; Chaudjuri, S.K. *Tetrahedron* ***2003****, 59,* 3493.
[658] Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* ***2005****, 127*, 10840.
[659] Mori, N.; Togo, H. *Tetrahedron* ***2005****, 61,* 5915.
[660] Owston, N.A.; Parker, A.J.; Williams, J.M.J. *Chem. Commun.* ***2008***, 624.
[661] Koo, B.-S.; Kim, E.-H.; Lee, K.-J. *Synth. Commun.* ***2002****, 32*, 2275.
[662] Foot, J.S.; Kanno, H.; Giblin, G.M.P.; Taylor, R.J.K. *Synlett* ***2002***, 1293.
[663] Hiegel, G.A.; Gilley, C.B. *Synth. Commun.* ***2003****, 33*, 2003.
[664] See Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* ***2007****, 9,* 1821. For a list of reagents used to effect this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1650–1652.
[665] Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J.M. *Chem. Lett.* ***1996***, 1043.
[666] Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* ***1989****, 30*, 6095.
[667] Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* ***2004****, 6*, 2785.
[668] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 241–263, 423–428; Chinn, L.J. *Selection of Oxidants in Synthesis,* Marcel Dekker, NY, ***1971***, pp. 63–70; Lee, D.G. in Augustine, R.L. *Oxidation,* Vol. 1, Marcel Dekker, NY, ***1969***, pp. 81–86.
[669] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 174–180; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1653–1661; Srivastava, R.G.; Venkataramani, P.S. *Synth. Commun.* ***1988****, 18*, 2193. See also, Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***.

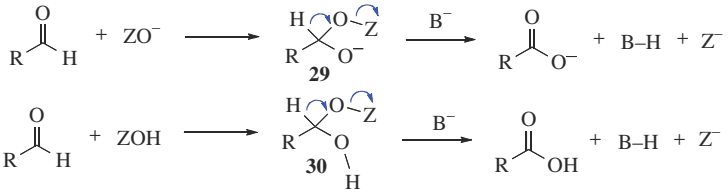
chromic acid,[670] bromine, and Oxone.[671] Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. *Benedict's* and *Fehling's solutions* oxidize aldehydes,[672] and there is a test for aldehydes that depends on this reaction, but the method is seldom used for preparative purposes and gives very poor results with aromatic aldehydes. α,β-Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.[673] Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid (RCO_3H),[674] which with another molecule of aldehyde disproportionates to give two molecules of acid (see Reaction **14-7**).[675] The air oxidation of aldehydes to carboxylic acids is mediated by a mixture of Pd/C—$NaBH_4$ and KOH.[676] An aldehyde can be converted to the carboxylic acid by treatment with 30% H_2O_2 and methyl(trioctyl) ammonium hydrogen sulfate at 90 °C.[677] Aryl aldehydes are similarly oxidized by a mixture of H_2O_2 and selenium dioxide (SeO_2).[678] Polymer-bound hypervalent iodine + TEMPO oxidizes aldehydes to acids.[679] Hydrogen peroxide oxidizes aldehydes to carboxylic acids in the presence of a $AgNO_3$ catalyst[680] or a Pd catalyst.[681]

Aryl aldehydes are converted to the corresponding aryl carboxylic ester with H_2O_2 and a V_2O_5 catalyst[682] or a titanosilicate[683] in an alcohol solvent. Esterification of aldehydes with alcohols uses an Ir catalyst.[684] The reaction of aldehydes with aq alcohols, in the presence of iodine and $NaNO_2$, gives an ester.[685] Organoboronic acids and molecular oxygen convert aldehydes to an ester using a Pd catalyst.[686] *N*-heterocyclic carbenes catalyze oxidation of aldehydes to the corresponding ester.[687] Aldehydes (RCHO) can be directly converted to carboxylic esters ($RCOOR'$) by treatment with Br_2 in the presence of an alcohol.[688]

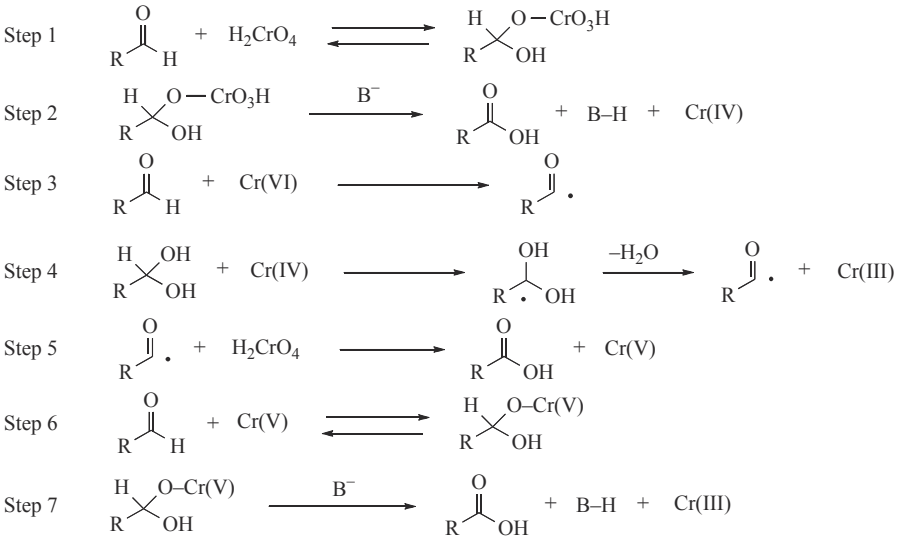
[670] See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 217–225.
[671] See Travis, B.R.; Sivakumar, M.; Hollist, G.O.; Borhan, B. *Org. Lett.* ***2003****, 5,* 1031.
[672] See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 31–34.
[673] Dalcanale, E.; Montanari, F. *J. Org. Chem.* ***1986****, 51*, 567. See also, Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* ***1990***, 565.
[674] See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.
[675] For reviews of the autoxidation of aldehydes, see Vardanyan, I.A.; Nalbandyan, A.B. *Russ. Chem. Rev.* ***1985****, 54,* 532 (gas phase); Sajus, L.; Sérée de Roch, I. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***, pp. 89–124 (liquid phase); Maslov, S.A.; Blyumberg, E.A. *Russ. Chem. Rev.* ***1976****, 45*, 155 (liquid phase). See Niclause, M.; Lemaire, J.; Letort, M. *Adv. Photochem.* ***1966****, 4*, 25. See Larkin, D.R. *J. Org. Chem.* ***1990****, 55*, 1563.
[676] Lim, M.; Yoon, C.M.; An, G.; Rhee, H. *Tetrahedron Lett.* ***2007****, 48*, 3835.
[677] Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* ***2000****, 41*, 1439.
[678] Wójtowicz, H.; Brzaszcz, M.; Kloc, K.; Mlochowski, J. *Tetrahedron* ***2001****, 57*, 9743.
[679] Tashino, Y.; Togo, H. *Synlett* ***2004***, 2010.
[680] Chakraborty, D.; Gowda, R.R.; Malik, P. *Tetrahedron Lett.* ***2009****, 50*, 6553.
[681] Kon, Y.; Imao, D.; Nakashima, T.; Sato, K. *Chem . Lett.* ***2009****, 38*, 430.
[682] Gopinath, R.; Patel, B.K. *Org. Lett.* ***2000****, 2*, 577.
[683] Chavan, S.P.; Dantale, S.W.; Govande, C.A.; Venkatraman, M.S.; Praveen, C. *Synlett* ***2002***, 267.
[684] Kiyooka, S.-i.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. *Tetrahedron* ***2007****, 63,* 12695.
[685] Kiran, Y.B.; Ikeda, R.; Sakai, N.; Konakahara, T. *Synthesis* ***2010***, 276.
[686] Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* ***2008****, 10,* 1537.
[687] Maki, B.E.; Scheidt, K.A. *Org. Lett.* ***2008****, 10,* 4331. Using boronic acdis: see Rosa, J.N.; Reddy, R.S.; Candeias, N.R.; Cal, P.M.S.D.; Gois, P.M.P. *Org. Lett.* ***2010****, 12*, 2686.
[688] Al Neirabeyeh, M.; Pujol, M.D. *Tetrahedron Lett.* ***1990****, 31*, 2273; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* ***1989****, 54,* 1212. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1661–1669.

Aldehydes react with amines, mediated by La catalysts, to give amides.[689]

Mechanisms of aldehyde oxidation[690] are not firmly established, but there are at least two main types: a free radical mechanism and an ionic one. In the free radical process, the aldehyde hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species ^{-}OZ to the carbonyl bond to give **29** in alkaline solution and **30** in acid or neutral solution. The aldehyde hydrogen of **29** or **30** is then lost as a proton to a base, while Z leaves with its electron pair.

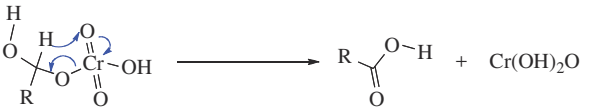


For oxidation with acid dichromate the picture seems to be quite complex, with several processes of both types going on:[691]

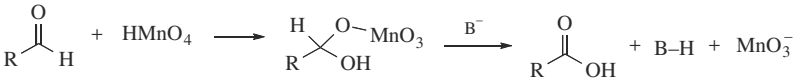


Steps 1 and 2 constitute an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced by an electron-transfer process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, Cr in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the chromic acid ester decomposes as follows:[692]

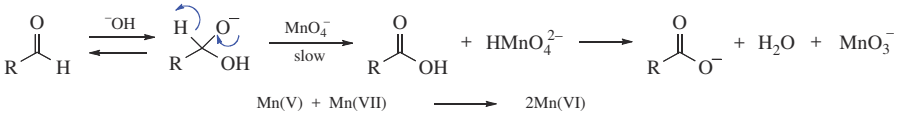
[689] Seo, S.Y.; Marks, T.J. *Org. Lett.* ***2008****, 10*, 317.
[690] See Rocek, J., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 461–505.
[691] Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1974****, 96*, 1889. See also, Sen Gupta, S.; Dey, S.; Sen Gupta, K.K. *Tetrahedron* ***1990****, 46*, 2431.
[692] See Rocek, J.; Ng, C. *J. Org. Chem.* ***1973****, 38*, 3348.



The mechanism with permanganate is less well known, but an ionic mechanism has been proposed[693] for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



For alkaline permanganate, the following mechanism has been proposed:[694]

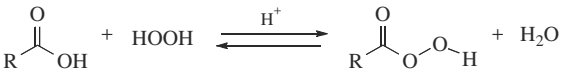


OS **I**, 166; **II**, 302, 315, 538; **III**, 745; **IV**, 302, 493, 499, 919, 972, 974.

The conversion of thioketones to sulfines ($R_2C{=}S{=}O$) is difficult to categorize into the sections available, and it placed after oxidation of ketones and aldehydes. The reaction of a thioketone with H_2O_2 and a catalytic amount of MTO (methyl trioxorhenium) gives the sulfine.[695]

19-24 Oxidation of Carboxylic Acids to Peroxy Acids

Peroxy-de-hydroxy-substitution

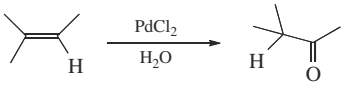


The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.[696] A mixture of $Me_2C(OMe)OOH$ and DCC has also been used.[697] Concentrated H_2SO_4 is a common catalyst for aliphatic R. The reaction is in equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R, the best catalyst is methanesulfonic acid, which is also used as the solvent.

D. Reactions in which Oxygen Is Added to the Substrate

19-25 Oxidation of Alkenes to Aldehydes and Ketones

1/Oxo-(1/→2/hydro)-*migro*-attachment



[693] See Freeman, F.; Lin, D.K.; Moore, G.R. *J. Org. Chem.* ***1982****, 47*, 56; Jain, A.L.; Banerji, K.K. *J. Chem. Res. (S)* ***1983***, 60.

[694] Freeman, F.; Brant, J.B.; Hester, N.B.; Kamego, A.A.; Kasner, M.L.; McLaughlin, T.G.; Paul, E.W. *J. Org. Chem.* ***1970****, 35,* 982.

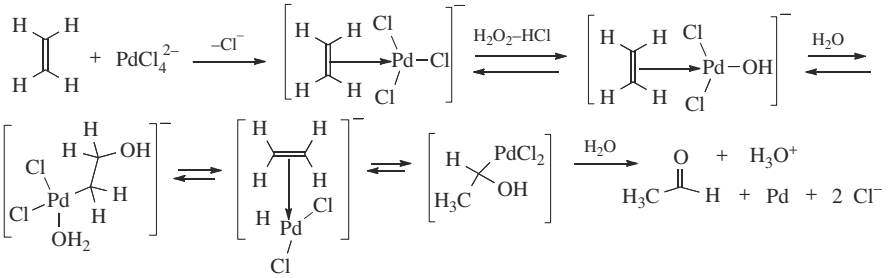
[695] Huang, R.; Espenson, J.H. *J. Org. Chem.* ***1999****, 64*, 6935.

[696] See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[697] Dussault, P.; Sahli, A. *J. Org. Chem.* ***1992****, 57*, 1009.

Monosubstituted and 1,2-disubstituted alkenes can be oxidized to aldehydes and ketones by $PdCl_2$, where the $PdCl_2$ is reduced to Pd.[698] Similar salts of noble metals also work, but 1,1-disubstituted alkenes generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene (the *Wacker process*),[699] but it is also suitable for laboratory preparations. The reagent is expensive, so the reaction is usually carried out with a cooxidant, often $CuCl_2$, whose function is to reoxidize the Pd to Pd(II). The $CuCl_2$ is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other cooxidants have been tried, among them O_3, Fe^{3+}, and PbO_2. Terminal alkenes are oxidized to methyl ketones with O_2 and a Pd catalyst.[700] The principal product is an aldehyde only from ethylene: With other alkenes *Markovnikov's rule* is followed, and ketones are formed predominantly.

The generally accepted mechanism shown below involves π complexes of Pd.[701] This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogen atoms of the acetaldehyde all come from the original ethylene and none from the solvent.



Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $Me_2C{=}CMe_2$ with peroxytrifluoroacetic acid–boron trifluoride to give Me_3COMe (pinacolone).[702] This reaction consists of epoxidation (**15-50**) followed by pinacol rearrangement of the epoxide (**18-2**). A migration is also involved in the conversion of $ArCH{=}CHCH_3$ to $ArCH(CH_3)CHO$ by treatment with $I_2{-}Ag_2O$ in aq dioxane.[703]

[698] See Henry, P.M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, ***1980***; Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer, NY, ***1980***, pp. 6–12; *Synthesis* ***1990***, 739; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 59–80; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, **1981**, pp. 189–193, 299–303; Jira, R.; Freiesleben, W. *Organomet. React*. ***1972***, *3*, 1, pp. 1–44; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 77–91; Hüttel, R. *Synthesis* ***1970***, 225, see pp. 225–236; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 88–111.

[699] Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed.* ***1962***, *1,* 80; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1; *The Merck Index, 14th ed.*, Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p ONR-98; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.,* Wiley–Interscience, New Jersey, ***2005***, pp. 676–677. See Muzart, J. *Tetrahedron* ***2007***, *63,* 7505.

[700] See Cornell, C.N.; Sigman, M.S. *Org. Lett.* ***2006***, *8,* 4117.

[701] See Cornell, C.N.; Sigman, M.S. *J. Am. Chem. Soc.* ***2005***, *127*, 2796; Keith, J.A.; Nielsen, R.J.; Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* ***2007***, *129,* 12342.

[702] Hart, H.; Lerner, L.R. *J. Org. Chem.* ***1967***, *32*, 2669.

[703] Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* ***1984***, 341.

Other reagents used have been $Pb(OAc)_4$—F_3CCO_2H[704] (e.g., $PhCH{=}CH_2 \rightarrow PhCH_2CHO$), H_2O_2 and a Pd catalyst,[705] H_2O—$PdCl_2$–polyethylene glycol.[706] Terminal alkenes react with ceric ammonium nitrate in methanol to give α-methoxy ketones.[707]

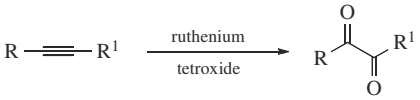
Alkenes have also been converted to more highly oxidized products. Examples are (1) Treatment with $KMnO_4$ in aq acetone containing acetic acid gives α-hydroxy ketones.[708] (2) 1,2-Disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone: $RCH{=}CR^1R^2 \rightarrow RCOCClR^1R^2$.[709] (3) α-Iodo ketones can be prepared by treating alkenes with bis(*sym*-collidine)iodine(I) tetrafluoroborate.[710] (4) Potassium permanganate in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[711]

Enol ethers are oxidized to carboxylic esters ($RCH{=}CHOR' \rightarrow RCH_2COOR'$) with PCC[712] and enamines to α-amino ketones with *N*-sulfonyloxaziridines.[713] Enamines ($R^1R^4C{=}CR^2NR_2^3$, $R^4 \neq H$) do not give these products, but lose the amino group to give α-hydroxy ketones [$R^1R^4C(OH)COR^2$].[713] Carboxylic acids can be prepared from terminal alkynes by conversion of the alkyne to its phenylthio ether ($RC{\equiv}CSPh$) and treatment of this with $HgSO_4$ in HOAc—H_2SO_4.[714] *Aza-Wacker reactions* are known.[715]

OS **VI**, 1028; **VII**, 137; **VIII**, 208.

19-26 The Oxidation of Alkynes to α-Diketones

Dioxo-biaddition



Internal alkynes have been oxidized[716] to α-diketones by several oxidizing agents,[717] including neutral $KMnO_4$,[718] bis(trifluoroacetoxy)iodobenzene,[719] $NaIO_4$—RuO_2,[720]

[704] Lethbridge, A.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 35.
[705] Roussel, M.; Mimoun, H. *J. Org. Chem.* ***1980****, 45*, 5387.
[706] Alper, H.; Januszkiewicz, K.; Smith, D.J.H. *Tetrahedron Lett.* ***1985****, 26*, 2263.
[707] Nair, V.; Nair, L.G.; Panicker, S.B.; Sheeba, V.; Augustine, A. *Chem. Lett.* ***2000***, 584.
[708] Srinivasan, N.S.; Lee, D.G. *Synthesis* ***1979***, 520. See also, Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* ***1989****, 54,* 5182.
[709] Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* ***1973****, 38,* 185. See also, Kageyama, T.; Tobito, Y.; Katoh, A.; Ueno, Y.; Okawara, M. *Chem. Lett.* ***1983***, 1481; Lee, J.G.; Ha, D.S. *Tetrahedron Lett.* ***1989****, 30*, 193.
[710] Evans, R.D.; Schauble, J.H. *Synthesis* ***1986***, 727.
[711] Jensen, H.P.; Sharpless, K.B. *J. Org. Chem.* ***1974****, 39,* 2314.
[712] Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* ***1977***, 3483. See Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* ***1987***, 1175.
[713] Davis, F.A.; Sheppard, A.C. *Tetrahedron Lett.* ***1988****, 29,* 4365.
[714] Abrams. S. R. *Can. J. Chem.* ***1983****, 61,* 2423.
[715] Liu, G.; Stahl, S.S. *J. Am. Chem. Soc.* ***2007****, 129,* 6328; Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* ***2008****, 10,* 173.
[716] See Haines, A.H. *Methods for the Oxidation of Organic Compounds,* Vol. 1, Academic Press, NY, ***1985***, pp. 153–162, 332–338; Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 513–570.
[717] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 92.
[718] See Tatlock, J.H. *J. Org. Chem.* ***1995****, 60*, 6221.
[719] Vasil'eva, V.P.; Khalfina, I.L.; Karpitskaya, L.G.; Merkushev, E.B. *J. Org. Chem. USSR* ***1987****, 23,* 1967.
[720] See Al-Rashid, Z.F.; Johnson, W.L.; Hsung, R.P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* ***2008****, 73*, 8780.

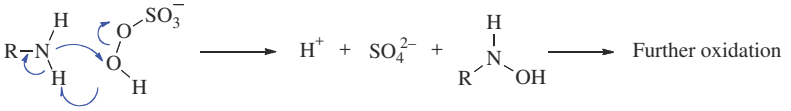
$MeReO_3/H_2O_2$,[721] or oxygen and a mixture of Pd and Cu catalysts.[722] A Ru complex with a small amount of trifluoroacetic acid converts internal alkynes to the α-diketone.[723] Ozone generally oxidizes triple-bond compounds to carboxylic acids (Reaction **19-9**), but α-diketones are sometimes obtained.[724] Selenium dioxide (SeO_2) with a small amount of H_2SO_4 oxidizes alkynes to α-diketones, as well as arylacetylenes to α-keto acids ($ArC{\equiv}CH \rightarrow ArCOCO_2H$).[725] A mixture of formic acid, methanesulfonic acid and DMSO with an HBr catalyst converts alkynes to α-diketones.[726]

19-27 Oxidation of Amines to Nitroso Compounds and Hydroxylamines and Related *N*-Oxo-de-dihydro-bisubstitution

$$ArNH_2 \xrightarrow{H_2SO_5} Ar{-}N{=}O$$

Primary aromatic amines can be oxidized[727] to nitroso compounds. Most often the conversion is accomplished by *Caro's acid* (H_2SO_5) or with H_2O_2 in HOAc.[728] Other reagents used for this oxidation are sodium perborate[729] H_2O_2 with a Ti complex,[730] HOF generated *in situ*,[731] and Na_2WO_4/H_2O_2.[732] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions they are generally oxidized to the nitroso compounds. Primary aliphatic amines can be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.[733]

The mechanism with H_2SO_5 has been postulated to be an example of category 5 (Sec. 19.A).[734]



Secondary amines (R_2NH) are oxidized to hydroxylamines (R_2NHOH), which are resistant to further oxidation, by dimethyldioxirane[735] and by benzoyl peroxide and

[721] Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1995****, 60*, 7728.
[722] Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* ***2009****, 11*, 1841.
[723] Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* ***2000****, 122*, 11380.
[724] Chu, J.H.; Chen, Y.-J.; Wu, M.-J. *Synthesis* ***2009***, 2115.
[725] Sonoda, N.; Yamamoto, Y.; Murai, S.; Tsutsumi, S. *Chem. Lett.* ***1972***, 229.
[726] Wan, Z.; Jones, C.D.; Mitchell, D.; Pu, J.Y.; Zhang, T.Y. *J. Org. Chem.* ***2006****, 71*, 826.
[727] Rosenblatt, D.H.; Burrows, E.P. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1085–1149; Challis, B.C.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 320–338; Hedayatullah, M. *Bull. Soc. Chim. Fr.* ***1972***, 2957.
[728] Holmes, R.R.; Bayer, R.P. *J. Am. Chem. Soc.* ***1960****, 82*, 3454.
[729] Zajac, Jr., W.W.; Darcy, M.G.; Subong, A.P.; Buzby, J.H. *Tetrahedron Lett.* ***1989****, 30,* 6495.
[730] Dewkar, G.K.; Nikalje, M.D.; Ali, I.S.; Paraskar, A.S.; Jagtap, H.S.; Sadalai, A. *Angew. Chem. Int. Ed.* ***2001****, 40*, 405.
[731] Dirk, S.M.; Mickelson, E.T.; Henderson, J.C.; Tour, J.M. *Org. Lett.* ***2002****, 2*, 3405.
[732] Corey, E.J.; Gross, A.W. *Org. Synth. 65*, 166.
[733] See Kahr, K.; Berther, C. *Chem. Ber.* ***1960****, 93,* 132.
[734] Gragerov, I.P.; Levit, A.F. *J. Gen Chem. USSR* ***1960****, 30,* 3690.
[735] Murray, R.W.; Singh, M. *Synth. Commun.* ***1989****, 19,* 3509. This reagent also oxidizes primary amines to hydroxylamines: Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* ***1990****, 55,* 1981.

Na_2HPO_4.[736] Oxone on silica also oxidizes secondary alcohols to the hydroxylamine.[737] Hydroxylamines are formed when secondary amines react with the enzyme cyclohexanone monooxygenase.[738] Carbamates (e.g., *N*-Boc amines) are converted to the *N*-hydroxy compound with bis(trifluoromethyl)dioxirane.[739] Dialkylamines are oxidized to the *N*-nitroso compound with N_2O_2 on poly(vinylpyrrolidinone).[740]

OS **III**, 334; **VIII**, 93; **80**, 207.

19-28 Oxidation of Primary Amines, Oximes, Azides, Isocyanates, or Nitroso Compounds to Nitro Compounds

$$R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2 \qquad R_2{=}NOH \xrightarrow{F_3CCOOOH} R_2CHNO_2$$

Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[741] This type of nitro compound is not easily prepared in other ways. All classes of primary amine (including primary, secondary, and tertiary alkyl, as well as aryl) are oxidized to nitro compounds in high yields with dimethyldioxirane.[742] Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,[743] various peroxyacids,[744] $MeReO_3/H_2O_2$,[745] Oxone,[746] *tert*-butyl hydroperoxide in the presence of certain Mo and V compounds,[747] and sodium perborate.[748] An aqueous solution of fluorine oxidizes amino esters to α-nitro esters.[749]

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds (RNCO $\rightarrow RNO_2$).[750] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, or sodium perborate,[751] among other ways.[741] Secondary hydroxylamines are also oxidized to nitrones with MnO_2 in dichloromethane.[752] Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.[753] An aqueous solution of fluorine also oxidizes azides to the corresponding nitro

[736] Biloski, A.J.; Ganem, B. *Synthesis* ***1983***, 537.
[737] Fields, J.D.; Kropp, P.J. *J. Org. Chem.* ***2000****, 65*, 5937.
[738] Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.; Zambianchi, F. *Tetahedron* ***2004****, 60*, 569.
[739] Detomaso, A.; Curci, R. *Tetrahedron Lett.* ***2001****, 42*, 755.
[740] Iranpoor, N.; Firouzabadi, H.; Pourali, A.R. *Synthesis* ***2003***, 1591.
[741] Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups,* Vol. 1, Wiley, NY, ***1969***, pp. 306–310. See also, Barnes, M.W.; Patterson, J.M. *J. Org. Chem.* ***1976****, 41,* 733. For reviews of oxidations of nitrogen compounds, see Butler, R.N. *Chem. Rev.* ***1984****, 84,* 249; Boyer, J.H. *Chem. Rev.* ***1980****, 80*, 495.
[742] Murray, R.W.; Rajadhyaksha, S.N.; Mohan, L. *J. Org. Chem.* ***1989****, 54,* 5783. See also, Zabrowski, D.L.; Moorman, A.E.; Beck, Jr., K.R. *Tetrahedron Lett.* ***1988****, 29,* 4501.
[743] See Keinan, E.; Mazur, Y. *J. Org. Chem.* ***1977****, 42* 844
[744] See Gilbert, K.E.; Borden, W.T. *J. Org. Chem.* ***1979****, 44,* 659.
[745] See Cardona, F.; Soldaini, G.; Goti, A. *Synlett* ***2004***, 1553.
[746] Webb, K.S.; Seneviratne, V. *Tetrahedron Lett.* ***1995****, 36*, 2377.
[747] Howe, G.R.; Hiatt, R.R. *J. Org. Chem.* ***1970****, 35*, 4007. See also, Nielsen, A.T.; Atkins, R.L.; Norris, W.P.; Coon, C.L.; Sitzmann, M.E. *J. Org. Chem.* ***1980****, 45,* 2341.
[748] McKillop, A.; Tarbin, J.A. *Tetrahedron* ***1987****, 43,* 1753.
[749] Harel, T.; Rozen, S. *J. Org. Chem.* ***2007****, 72,* 6500.
[750] Eaton, P.E.; Wicks, G.E. *J. Org. Chem.* ***1988****, 53*, 5353.
[751] Olah, G.A.; Ramaiah, P.; Lee, G.K.; Prakash, G.K.S. *Synlett* ***1992***, 337.
[752] Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* ***2001****, 42*, 6503.
[753] Corey, E.J.; Samuelsson, B.; Luzzio, F.A. *J. Am. Chem. Soc.* ***1984****, 106*, 3682.

compound.[754] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[755]

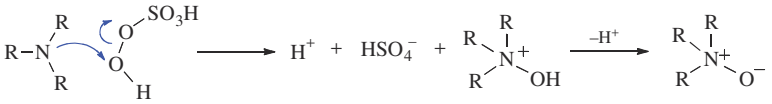
OS **III**, 334; **V**, 367, 845; **VI**, 803; **81**, 204.

19-29 Oxidation of Tertiary Amines to Amine Oxides

N-Oxygen-attachment

$$R_3N \xrightarrow{H_2O_2} R_3N^+—O^-$$

Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peroxyacids are also important reagents for this purpose. Pyridine and its derivatives are oxidized by peroxyacids[756] rather than hydrogen peroxide. Note, however, that urea–H_2O_2 in formic acid does indeed oxidize pyridine.[757] Oxidation with *Caro's acid* has been shown to proceed in this manner:[758]



This mechanism is the same as that of Reaction **19-27**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peroxyacids is probably the same. A green procedure for oxidation of tertiary amines has been developed, using a Mg—Al complex with aq H_2O_2.[759] Nitrones can be prepared using a ball-mill.[760]

An alternative oxidation using O_2 and a $RuCl_3$ catalyst converted pyridine to pyridine *N*-oxide.[761] Bromamine-T and $RuCl_3$ in aq acetonitrile also oxidizes pyridine to the *N*-oxide.[762] Tertiary amines are oxidized to the *N*-oxide with O_2 and Fe_2O_3 in the presence of an aliphatic aldehyde.[763] Oxygen and a Co–Schiff base complex also oxidizes tertiary amines, including pyridine.[764]

Analogous to the oxidation of tertiary amines, tertiary phosphines are oxidized to phosphine oxides ($R_3P=O$). Triphenylphosphine is converted to triphenylphosphine oxide with N_2O at 100 °C, for example. Triphenylphosphine is also oxidized with PhIO on Montmorillonite K-10.[765] *tert*-Butylhydroperoxide oxides $Ph_3P \rightarrow BH_3$ to $Ph_3P=O$.[766] *P*-Stereogenic phosphine oxides have been prepared.[767]

OS **IV**, 612, 704, 828; **VI**, 342, 501; **VIII**, 87.

[754] Carmeli, M.; Rozen, S. *J. Org. Chem.* ***2006****, 71,* 4585.
[755] See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 264–265.
[756] Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 31–41; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 21–72, 539–542.
[757] Balicki, R.; Golinski, J. *Synth. Commun.* ***2000****, 30*, 1529.
[758] Ogata, Y.; Tabushi, I. *Bull. Chem. Soc. Jpn.* ***1958****, 31,* 969.
[759] Choudary, B.M.; Bharathi, B.; Reddy, Ch.V.; Kantam, M.L.; Raghavan, K.V. *Chem. Commun.* ***2001***, 1736.
[760] Colacino, E.; Nun, P.; Maria Colacino, F.; Martinez, J.; Lamaty, F. *Tetrahedron* ***2008****, 64*, 5569.
[761] Jain, S.L.; Sain, B. *Chem. Commun.* ***2002***, 1040.
[762] Sharma, V.B.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2004****, 45*, 4281.
[763] Wang, F.; Zhang, H.; Song, G.; Lu, X. *Synth. Commun.* ***1999****, 29*, 11.
[764] Jain, S.L.; Sain, B. *Angew. Chem. Int. Ed.* ***2003****, 42*, 1265.
[765] Mielniczak, G.; Lopusinski, A. *Synlett* ***2001***, 505.
[766] Uziel, J.; Darcel, C.; Moulin, D.; Bauduin, C.; Juge, S. *Tetrahedron Asymmetry* ***2001****, 12*, 1441.
[767] Bergin, E.; O'Connor, C.T.; Robinson, S.B.; McGarrigle, E.M.; O'Mahony, C.P.; Gilheany, D.G. *J. Am. Chem. Soc.* ***2007****, 129*, 9566.

19-30 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids

Thiol-sulfonic acid oxidation

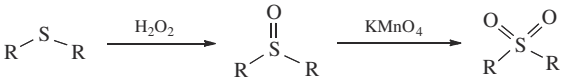
$$RSH \xrightarrow{HNO_3} RSO_3H$$

Thiols, sulfoxides, sulfones, disulfides,[768] and other sulfur compounds can be oxidized to sulfonic acids with various oxidizing agents, but for synthetic purposes the reaction is most important for thiols.[769] Among oxidizing agents used are boiling nitric acid, barium permanganate, and dimethyl dioxirane.[770] Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[771] Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.[772] Thiols can also be oxidized to disulfides (Reaction **19-34**).

OS **II**, 471; **III**, 226. Also see, OS **V**, 1070.

19-31 Oxidation of Thioethers to Sulfoxides and Sulfones

S-Oxygen-attachment



Thioethers can be oxidized to sulfoxides by 1 equiv of 30% H_2O_2 or by many other oxidizing agents,[773] including $NaIO_4$,[774] H_2O_2, and a $Sc(OTf)_3$ catalyst,[775] HIO_3/wet SiO_2,[776] dioxiranes,[777] $MeReO_3/H_2O_2$,[778] O_2 and a ceric ammonium nitrate catalyst,[779] KO_2/Me_3SiCl,[780] hexamethylene triamine–Br_2 with $CHCl_3$—H_2O,[781] $H_5IO_6/FeCl_3$,[782]

[768] See Savige, W.E.; Maclaren, J.A. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2; pp. 367–402, Pergamon, NY, ***1966***.

[769] See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group,* pt. 2, Wiley, NY, ***1974***, pp. 785–839; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 217–239.

[770] Gu, D.; Harpp, D.N. *Tetrahedron Lett.* ***1993****, 34*, 67. See Ballistreri, F.P.; Tomaselli, G.A.; Toscano, R.M. *Tetrahedron Lett.* ***2008****, 49*, 3291.

[771] Wallace, T.J.; Schriesheim, A. *Tetrahedron* ***1965****, 21*, 2271.

[772] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 202–214.

[773] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 252–263; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 233–378, pp. 235–255; Madesclaire, M. *Tetrahedron* ***1986****, 42,* 5459; Drabowicz, J.; Mikolajczyk, M. *Org. Prep. Proced. Int.* ***1982****, 14,* 45; Oae, S. in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 385–390; Holland, H.L. *Chem. Rev.* ***1988****, 88,* 473.

[774] Hiskey, R.G.; Harpold, M.A. *J. Org. Chem.* ***1967****, 32*, 3191; Varma, R.S.; Saini, R.K.; Meshram, H.M. *Tetrahedron Lett.* ***1997****, 38*, 6525.

[775] Matteucci, M.; Bhalay, G.; Bradley, M. *Org. Lett.* ***2003****, 5*, 235.

[776] Lakouraj, M.M.; Tajbakhsh, M.; Shirini, F.; Asady Tamami, M.V. *Synth. Commun.* ***2005****, 35,* 775.

[777] Colonna, S.; Gaggero, N. *Tetrahedron Lett.* ***1989****, 30,* 6233. For a discussion of the mechanism, see González-Núñez, M.E.; Mello, R.; Royo, J.; Ríos, J.V.; Asensio, G. *J. Am. Chem. Soc.* ***2002****, 124*, 9154.

[778] See Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* ***2001****, 66*, 8192.

[779] See Ali, M.H.; Kriedelbaugh, D.; Wencewicz, T. *Synthesis* ***2007***, 3507.

[780] Chen, Y.-J.; Huang, Y.-P. *Tetrahedron Lett.* ***2000****, 41,* 5233.

[781] Shaabani, A.; Teimouri, M.B.; Safaei, H.R. *Synth. Commun.* ***2000****, 30*, 265. See Kowalski, P.; Mitka, K.; Ossowska, K.; Kolarska, Z. *Tetrahedron* ***2005****, 61,* 1933.

[782] Kim, S.S.; Nehru, K.; Kim, S.S.; Kim, D.W.; Jung, H.C. *Synthesis* ***2002***, 2484.

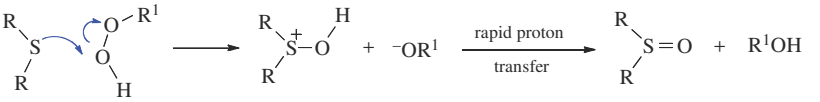
hypervalent iodine compounds,[783] and peroxyacids.[784] Sulfoxides can be further oxidized to sulfones by another equivalent of H_2O_2, $KMnO_4$, sodium perborate, or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.[785] Thioethers can be oxidized directly to the sulfone by treatment with TPAP,[786] H_2O_2[787] and an Fe catalyst,[788] a Zr catalyst,[789] a Ta catalyst,[790] a V catalyst,[791] an Au catalyst,[792] a Mo catalyst,[793] a flavin-ionic liquid catalyst,[794] urea–H_2O_2,[795] peroxy monosulfate and a Mn catalyst,[796] or nitric acid with P_2O_5 on silica gel.[797] These reactions give high yields, and many functional groups do not interfere.[798]

As with tertiary amines (Reaction **19-29**), racemic thioethers can be kinetically resolved by oxidation to sulfoxides with an optically active reagent, and this has often been done.[799] In addition, the use of chiral additives in conjunction with various oxidizing agents leads to chiral nonracemic sulfoxide with good-to-excellent enantioselectivity.[800] Asymmetric oxidation using bacterial monooxygenases is known,[801] and horseradish peroxidase gives modest enantioselectivity.[802] Chiral sulfur reagents are also known.[803] It is possible to oxidize a thioether to a sulfoxide in the presence of an alcohol moiety using MnO_2/HCl.[804] *N*-Sulfonyloxaziridines can be used to oxidize sulfides to sulfoxides.[805] Selenides (R_2Se) can be oxidized to selenoxides and selenones.[806] Alkyl disulfides give oxidation of one

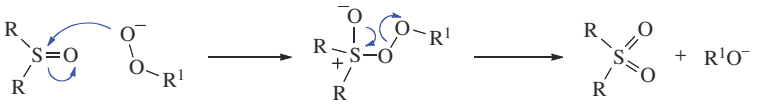
[783] See Koposov, A.Y.; Zhdankin, V.V. *Synthesis* ***2005***, 22.
[784] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, p. 16.
[785] See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, pp. 205–213.
[786] Guertin, K.R.; Kende, A.S. *Tetrahedron Lett.* ***1993***, *34*, 5369.
[787] Kaczorowska, K.; Kolarska, Z.; Mitka, K.; Kowalski, P. *Tetrahedron* ***2005***, *61,* 8315. See Velusamy, S.; Kumar, A.V.; Saini, R.; Punniyamurthy, T. *Tetrahedron Lett.* ***2005***, *46*, 3819.
[788] Margues, A.; Marin, M.; Ruasse, M.-F. *J. Org. Chem.* ***2001***, *66,* 7588.
[789] Bahrami, K. *Tetrahedron Lett.* ***2006***, *47,* 2009.
[790] Kirihara, M.; Yamamoto, J.; Noguchi, T.; Hirai, Y. *Tetrahedron Lett.* ***2009***, *50*, 1180.
[791] Trivedi, R.; Lalitha, P. *Synth. Commun.* ***2006***, *36,* 3777.
[792] Yuan, Y.; Bian, Y. *Tetrahedron Lett.* ***2007***, *48,* 8518.
[793] Jeyakumar, K.; Chand, D.K. *Tetrahedron Lett.* ***2006***, *47,* 4573; Gamelas, C.A; Lourenço, T.; da Costa, A.P.; Simplício, A.L.; Royo, B.; Romão, C.C. *Tetrahedron Lett.* ***2008***, *49,* 4708.
[794] Lindén, A.A.; Johansson, M.; Hermanns, N.; Bäckvall, J-E. *J. Org. Chem.* ***2006***, *71,* 3849.
[795] Balicki, R. *Synth. Commun.* ***1999***, *29*, 2235.
[796] Iranpoor, N.; Mohajer, D.; Rezaeifard, A.-R. *Tetrahedron Lett.* ***2004***, *45,* 3811.
[797] Hajipour, A.R.; Kooshki, B.; Ruoho, A.E. *Tetrahedron Lett.* ***2005***, *46,* 2643.
[798] SeeVenier, C.G.; Barager, III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77, pp. 85–86.
[799] For reviews, see Kagan, H.B.; Rebiere, F. *Synlett* ***1990***, 643; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Org. Prep. Proceed. Int.* ***1982***, *14*, 45, see p. 288.
[800] See Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* ***2005***, *127,* 1374; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* ***2007***, *129,* 8940; del Río, R.E.; Wang, B.; Achab, S.; Bohé, L. *Org. Lett.* ***2007***, *9,* 2265; Gao, J.; Guo, H.; Liu, S.; Wang, M. *Tetrahedron Lett.* ***2007***, *48,* 8453; Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2007***, *46,* 4729; Matsumoto, K.; Yamaguchi, T.; Katsuki, T. *Chem. Commun.* ***2008***, 1704; Kelly, P.; Lawrence, S.E.; Maguire, A.R. *Synlett* ***2007***, 1501; Jurok, R.; Cibulka, R.; Dvořáková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* ***2010***, 5217; Dieva, S.A.; Eliseenkova, R.M.; Efremov, Yu.Ya.; Sharafutdinova, D.R.; Bredikhin, A.A. *Russ. J. Org. Chem.* ***2006***, *42*, 12.
[801] Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* ***1996***, 2303; Pasta, P.; Carrea, G.; Holland, H.L.; Dallavalle, S. *Tetrahedron Asymmetry,* ***1995***, *6*, 933.
[802] Ozaki, S.-i.; Watanabe, S.; Hayasaka, S.; Konuma, M. *Chem. Commun.* ***2001***, 1654.
[803] Mikolajczyk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*, CRC Press, Boca Raton, FL, ***1997***.
[804] Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* ***1997***, *27*, 2857.
[805] See Jennings, W.B.; O'Shea, J.H.; Schweppe, A. *Tetrahedron Lett.* ***2001***, *42*, 101.
[806] See Reich, H.J. in Trahanovsky, W.S. *Oxidations in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 7–13; Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* ***1986***, *59,* 503.

sulfur to give a RS—S(=O)R compound with good enantioselectivity when using aq H_2O_2, a catalytic amount of a V catalyst, and a chiral Schiff base ligand.[807]

When the oxidizing agent is a peroxide, the mechanism[808] of oxidation to the sulfoxide is similar to that of Reaction **19-29**.[809]



The second oxidation, which is normally slower than the first, which is why sulfoxides are so easily isolable, has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile:[810]



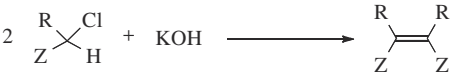
There are some reagents that oxidize sulfoxides in preference to sulfides (e.g., $NaMnO_4$).[811]

OS **V**, 791; **VI**, 403, 404, 482; **VII**, 453, 491; **VIII**, 464, 543; **IX**, 63; **80**, 190. Also see, OS **V**, 723; **VI**, 23.

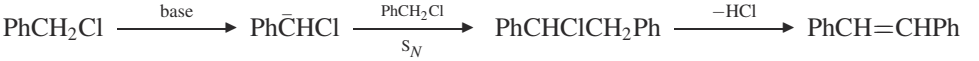
E. Oxidative Coupling

19-32 Coupling Involving Carbanions

De-hydro,chloro-coupling



Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to alkenes by treatment with bases. The Z group may be nitro, aryl, and so on. It is likely that in most cases the mechanism[812] involves nucleophilic substitution followed by elimination[813] (illustrated for benzyl chloride):



α,α-Dibromotoluenes ($ArCHBr_2$) give tolanes ($ArC{\equiv}CAr$) by debromination of the intermediates ArCBr=CBrAr.[814] In a related reaction, diarylmethane dihalides

[807] Blum, S.A.; Bergman, R.G.; Ellman, J.A. *J. Org. Chem.* ***2003****, 68*, 150.
[808] See Agarwal, A.; Bhatt, P.; Banerji, K.K. *J. Phys. Org. Chem.* ***1990****, 3,* 174; Lee, D.G.; Chen, T. *J. Org. Chem.* ***1991****, 56,* 5346.
[809] Modena, G.; Todesco, P.E. *J. Chem. Soc.* ***1962***, 4920, and references cited therein.
[810] Curci, R.; Di Furia, F.; Modena, G. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 603 and references cited therein. See also, Akasaka, T.; Ando, W. *J. Chem. Soc. Chem. Commun.* ***1983***, 1203.
[811] See Henbest, H.B.; Khan, S.A. *Chem. Commun.* ***1968***, 1036.
[812] See Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 548–554.
[813] See Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* ***1972****, 1,* 375; Hanna, S.B.; Wideman, L.G. *Chem. Ind. (London)* ***1968***, 486. Also see Bethell, D.; Bird, R. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1856.
[814] Vernigor, E.M.; Shalaev, V.K.; Luk'yanets, E.A. *J. Org. Chem. USSR* ***1981****, 17,* 317.

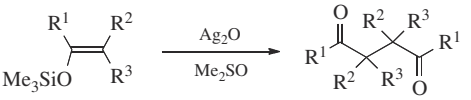
(Ar_2CX_2) have been dimerized to tetraaryl alkenes ($Ar_2C{=}CAr_2$) with Cu,[815] and with iron(II) oxalate dihydrate.[816]

A somewhat different type of coupling is observed when salts of β-keto esters, arylacetonitriles ($ArCH_2CN$), and other compounds of the form ZCH_2Z' are treated with an oxidizing agent (e.g., iodine,[817] or Cu(II) salts.][818] Arylmethanesulfonyl chlorides ($ArCH_2SO_2Cl$) couple to give ArCH=CHAr when treated with Et_3N.[819]

OS **II**, 273; **IV**, 372, 869, 914; **VIII**, 298. Also see, OS **I**, 46; **IV**, 877.

19-33 Dimerization of Silyl Enol Ethers or of Lithium Enolates

3/*O*-De-trimethylsilyl-1/*C*-coupling



31

Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in DMSO or certain other polar aprotic solvents.[820] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, although best yields are obtained when $R^2 = R^3 = H$. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers. Other reagents that have been used to achieve either symmetrical or cross-coupled products are iodosobenzene–BF_3–OEt_2,[821] ceric ammonium nitrate,[822] and lead tetraacetate.[823] If R^1 = OR (in which case the substrate is a ketene silyl acetal), dimerization with $TiCl_4$ leads to a dialkyl succinate (**31**, R^1 = OR).[824]

In a similar reaction, lithium enolates [$RC(OLi){=}CH_2$] were dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) with $CuCl_2$, $FeCl_3$, or copper(II) triflate, in a nonprotic solvent.[825]

OS **VIII**, 467.

19-34 Oxidation of Thiols to Disulfides

S-De-hydrogen-coupling

$$2\,RSH \xrightarrow{H_2O_2} RSSR$$

Thiols are easily oxidized to disulfides.[826] Hydrogen peroxide is the most common reagent,[827] but many oxidizing agents give the reaction, among them Br_2 on hydrated

[815] Buckles, R.E.; Matlack, G.M. *Org. Synth.* ***IV***, 914.
[816] Khurana, J.M.; Maikap, G.C.; Mehta, S. *Synthesis* ***1990***, 731.
[817] See Aurell, M.J.; Gil, S.; Tortajada, A.; Mestres, R. *Synthesis* ***1990***, 317.
[818] Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971****, 93,* 4605; Baudin, J.; Julia, M.; Rolando, C.; Verpeaux, J. *Bull. Soc. Chim. Fr.* ***1987***, 493.
[819] Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. *Tetrahedron Lett.* ***1984****, 25,* 4553.
[820] Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* ***1975****, 97,* 649.
[821] Moriarty, R.; Prakash, O.; Duncan, M.P. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 559.
[822] Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* ***1989****, 30,* 3707.
[823] Moriarty, R.M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* ***1987****, 28,* 873.
[824] Inaba, S.; Ojima, I. *Tetrahedron Lett.* ***1977***, 2009. See also, Totten, G.E.; Wenke, G.; Rhodes, Y.E. *Synth. Commun.* ***1985****, 15,* 291, 301.
[825] Frazier, Jr., R.H.; Harlow, R.L. *J. Org. Chem.* ***1980****, 45,* 5408.
[826] See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.
[827] See, however, Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.* ***1990****, 55*, 2337.

silica,[828] sodium perborate,[829] SmI_2,[830] PPh_3 with a Rh catalyst,[831] cetyltrimethylammonium dichromate,[832] and NO. Hydrogen peroxide (30%) in hexafluoro-2-propanol converts thiols to disulfides,[833] and solventless reactions on MnO_2,[834] PCC (Reaction **19-3**, category 1)[835] or SO_2Cl_2[836] are also effective. A potassium phosphate catalyst has been used for the oxidative coupling of thiols to disulfides.[837] Strong oxidizing agents may give Reaction **19-26**. Even oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see Reaction **19-75**), and the interconversion between cysteine and cystine is an important one in biochemistry.

The mechanism has been studied for several oxidizing agents and varies with the agent.[838] For oxygen it is[839]

$$RSH + B^- \rightleftharpoons RS^- + BH$$

$$RS^- + O_2 \longrightarrow RS\bullet + \bullet O_2^-$$

$$RS^- + \bullet O_2^- \longrightarrow RS\bullet + O_2^{2-}$$

$$2\,O_2^{2-} + 2\,BH \longrightarrow 2\,OH^- + 2\,B^- + O_2$$

With respect to the sulfur, this mechanism is similar to that of Reaction **14-16**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared[840] by treatment of a thiol RSH with diethyl azodicarboxylate (EtOOCN=NCOOEt) to give an adduct, to which another thiol (R′SH) is then added, producing the disulfide (RSSR′).[841]

OS **III**, 86, 116.

19.B.ii. Reductions

For the most part, reductions have been grouped into this chapter, with a few notable exceptions. Catalytic hydrogenation of alkenes and alkynes in Reactions **15-11** and **15-12**, hydrogenation of aromatic rings in Reaction **15-13**, and reductive cleavage of cyclopropanes in Reaction **15-15** were placed in Chapter 15 to coincide with addition reactions, and protonolysis of alkyl boranes in Reaction **15-16** was placed there also for continuity. In general, reductions of functional groups encompass a variety of reaction types. The reactions in this section are classified into groups depending on the type of bond change

[828] Ali, M.H.; McDermott, M. *Tetrahedron Lett.* ***2002****, 43*, 6271.
[829] McKillop, A.; Koyunçu, D. *Tetrahedron Lett.* ***1990****, 31*, 5007.
[830] Zhan, Z.-P.; Lang, K.; Liu, F.; Hu, L.-m. *Synth. Commun.* ***2004****, 34,* 3203.
[831] Tanaka, K.; Ajiki, K. *Tetahedron Lett.* ***2004****, 45*, 25.
[832] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004****, 45*, 1371. See also, Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* ***2004****, 45*, 1889.
[833] Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* ***2000***, 223.
[834] Firouzabadi, H.; Abbassi, M.; Karimi, B. *Synth. Commun.* ***1999****, 129*, 2527.
[835] Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.* ***2001****, 31*, 2777.
[836] Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* ***2004****, 45*, 8489.
[837] Joshi, A.V.; Bhusare, S.; Baidossi, M.; Qafisheh, N.; Sasson, Y. *Tetrahedron Lett.* ***2005****, 46*, 3583.
[838] Tarbell, D.S. in Kharasch, N. *Organic Sulfur Compounds*, Pergamon, Elmsford, NY, ***1961***, pp. 97–102.
[839] Wallace, T.J.; Schriesheim, A.; Bartok, W. *J. Org. Chem.* ***1963****, 28*, 1311.
[840] Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* ***1968***, 5907.
[841] Also see Boustany, K.S.; Sullivan, A.B. *Tetrahedron Lett.* ***1970***, 3547; Oae, S.; Fukushima, D.; Kim, Y.H. *J. Chem. Soc. Chem. Commun.* ***1977***, 407.

involved. These groups are (1) attack at carbon (C—O and C=O), (2) attack at non-carbonyl multiple bonds to heteroatoms, (3) reactions in which a heteroatom is removed from the substrate, (4) reduction with cleavage, (5) reductive coupling, and (6) reactions in which an organic substrate is both oxidized and reduced. Most of the reagents in this section are metal hydrides, metals with an acid or a protic solvent, hydrogen gas with a catalyst, and so on. Other reducing agents are available, and will be introduced in the appropriate section. Note that plants can be used as reducing agents.[842]

A. Selectivity[843]

It is often necessary to reduce one group in a molecule without affecting another reducible group (this is called chemoselectivity), and reducing agents are available that will do this. The most common broad-spectrum reducing agents are the metal hydrides[844] or hydrogen (with a catalyst).[845] Many different metal hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. The ease of reduction for various functional groups toward catalytic hydrogenation is acyl halides > alkyl nitro compounds > alkynes > aldehydes > alkenes > ketones > benzylic ethers > nitriles > esters > amides.[846] Futher, Table 19.2 and 19.4 list the reactivity of various functional groups with $LiAlH_4$, and BH_3, respectively.[846] Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[847] Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which groups.[848] Lithium aluminum hydride is very powerful and unselective reagent.[849] Other metal hydrides are generally used when chemoselectivity is required. As will be seen in Reaction **19-36**, less reactive (and more selective) reagents have been prepared by replacing some of the hydrogen atoms of $LiAlH_4$ with alkoxy groups.[850] Most of the metal hydrides are nucleophilic reagents and attack the

[842] Bruni, R.; Fantin, G.; Medici, A.; Pedrini, P.; Sacchetti, G. *Tetrahedron Lett.* ***2002****, 43*, 3377.

[843] See Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***; Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***; Candlin, J.P.; Rennie, R.A.C. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 77–135.

[844] See Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979****, 35,* 567; Walker, E.R.H. *Chem. Soc. Rev.* ***1976****, 5*, 23; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 209–251; Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***.

[845] See Rylander, P.N. *Aldrichimica Acta* ***1979****, 12,* 53. See also, Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***.

[846] Table 19.2 is from House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 9. Tables 19.3 and 19.4 are from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 213 and 232, respectively.

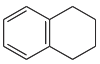
[847] The first 10 columns are from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979****, 35*, 567, p. 604. The column on $(i\text{-Bu})_2AlH$ is from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* ***1985****, 50*, 2443; the one on $NaAlEt_2H_2$ from Stinson, S.R. *Chem. Eng. News, Nov. 3,* ***1980****, 58,* No. 44, 19; and the one on $LiBEt_3H$ from Brown, H.C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* ***1980****, 45,* 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 129; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***, pp. 16–17; Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***, pp. 177–200.

[848] See also, the table in Hudlicky, M. *J. Chem. Educ.* ***1977****, 54*, 100.

[849] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–194.

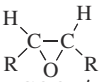
[850] See Málek, J. *J. Org. Chem.* ***1988****, 36*, 249; ***1985****, 34*, 1; Málek, J.; Cerny, M. *Synthesis* ***1972***, 217.

TABLE 19.2 The Ease of Reduction of Various Functional Groups Toward Catalytic Hydrogenation[846]

Reaction	Substrate[a]	Product	
19-39	RCOCl	RCHO	Easiest
19-45	RNO_2	RNH_2	
15-11	RC≡CR	RCH=CHR	
19-36	RCHO	RCH_2OH	
15-11	RCH=CHR	RCH_2CH_2R	
19-36	RCOR	RCHOHR	
19-56	$ArCH_2OR$	$ArCH_3 + ROH$	
19-43	RC≡N	RCH_2NH_2	
15-14			
19-38	RCOOR'	$RCH_2OH + R'OH$	
19-64	RCOHNR'	RCH_2NHR	
15-13			Most difficult
19-37	$RCOO^-$		Inert

[a] The groups are listed in approximate order of ease of reduction.

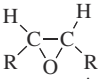
TABLE 19.3 The Ease of Reduction of Various Functional Groups with $LiAlH_4$ in Ether[a]

Reaction	Substrate[b]	Product	
19-36	RCHO	RCH_2OH	Easiest
19-36	RCOR	RCHOHR	
19-63	RCOCl	RCH_2OH	
19-38	Lactone	Diol	
19-35		RCH_2CHOHR	
19-38	RCOOR′	$RCH_2OH + R'OH$	
19-37	RCOOH	RCH_2OH	
19-37	$RCOO^-$	RCH_2OH	
19-64	$RCONR'_2$	$RCH_2NR'_2$	
19-43	RC≡N	RCH_2NH_2	
19-45	RNO_2	RNH_2	
19-80	$ArNO_2$	ArN=NAr	Most difficult
15-11	RCH=CHR′		Inert

[a] See Ref. 846.

[b] However, $LiAlH_4$ is a very powerful reagent, and less chemoselective than most of the other metal hydrides. Adapted material from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, *1972* p. 213, edited by Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.

TABLE 19.4 The Ease of Reduction of Various Functional Groups With Borane[a]

Reaction	Substrate[b]	Product	
19-37	RCOOH	RCH_2OH	Easiest
15-16	RCH=CHR	$(RCH_2CHR)_3B$	
19-36	RCOR	RCHOHR	
19-43	RCN	RCH_2NH_2	
19-35		RCH_2CHOHR	
19-38	RCOOR′	$RCH_2OH + R'OH$	Most difficult
19-39,**19-63**	RCOCl		Inert

[a]See ref 846.

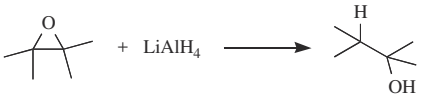
[b]It is evident that this reagent and $LiAlH_4$ (Table 19.2) complement each other.

Adapted material from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, p. 232, edited by Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.

TABLE 19.5 Reactivity of Various Functional Groups With Some Metal Hydrides and Toward Catalytic Hydrogenation[a]

Reaction[b]		A[c]	B[c]	C[c]	D[c,d]	E[c,e]	F[c,f]	G[c]	H[c]	I[c]	J[c,g]	K[c,h]	L[c]	M[c]	N[c]
19-36	RCHO → RCH_2OH	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-36	RCOR → RCHOHR	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-39′															
19-63	RCOCl → RCHO / RCH_2OH	+[i]	+	+	−	−	+	+	+	+	+	+	+	+	+
19-63	lactone → Diol	−	+	+	+	+	+	±	+	+	+	+	+	+	+
19-35	Epoxide → Alcohol	−	+	+	+	±	±	±	+	+	+	+	+	+	+
19-38	RCOOR' → RCH_2OH + R'OH	−	+	+	±	−	±	±	+	+	+	+	+	+	+
19-37	RCOOH → RCH_2OH	−	−	+	+	−	±	−	+	+	+	−	+	+	−
19-37	$RCOO^-$ → RCH_2OH	−	−	+	−	−	−	−	+	+	+	−	−		−
19-64															
19-41	$RCONR_2'$ → RCH_2NR_2' / RCHO	−	−	−	+	+	+	−	+	+	+	+	+	+	+
19-43	RC≡N → RCH_2NH_2	−	−	−	+	−	±	−	+	+	+	±	+[j]	+	+
19-45															
19-80	$RCONR_2'$ → RCH_2NR_2' / RCHO	−	−	−	−	−	−	−	+	+	−	−	+[j]	+	+
15-11	RCH=CHR → RCH_2CH_2R	−	−	−	+	+	+	−	−	−	−	+	−	−	+

TABLE 19.5 (*Continued*)

Reaction[b]	A[c]	B[c]	C[c]	D[c,d]	E[c,e]	F[c,f]	G[c]	H[c]	I[c]	J[c,g]	K[c,h]	L[c]	M[c]	N[c]
19-53 $RX + LiAlH_4 \longrightarrow RH$														
19-57 $R{-}OSO_2R' + LiAlH_4 \longrightarrow RH$														
19-35 														

[a]see Ref. 847.

[b]A ± ndicates a borderline case.

[c]**A** = $NaBH_4$ in EtOH, **B** = $NaBH_4$ + LiCl in diglyme, **C** = $NaBH_4 + AlCl_3$ in diglyme, **D** = BH_3–THF, **E** = bis [3-methyl-2-butylborane (disiamylborane)] in THF, **F** = 9-BBN, **G** = $LiAlH(Ot\text{-}Bu)_3$ in THF, **H** = $LiAlH(OMe)_3$ in THF, **I** = $LiAlH_4$ in ether, **J** = AlH_3 in THF, **K** = $LiBEt_3H$ **L** = $(i\text{Bu})_2AlH$ [DIBALH), **M** = $NaAl(OCH_2CH_2OMe)_2H_2$ **N** = catalytic hydrogenation.

[d]see Ref. 844.

[e]see Ref. 851

[f]see Ref. 852

[g]see Ref. 853

[h]see Ref. 854

[i]see Ref. 855

[j]see Ref. 856

[Reprinted with permission from Brown, H.C.; Krusgbanyrtgt, S. *Tetrahedron 1979*, *35*, 567, p. 604, Copyright 1979, with permission form Elsevier Science.] Reprinted with permission from Yoon, N.M.; Gyoung, Y.S. *J*. Org. *Chem.* ***1985***, 50, 2443. Copyright © 1985 American Chemical Society. Reprinted with perission from Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. Copyright © 1980 American Chemical Society.

carbon atom of a carbon-hetero single or multiple bond. However, BH_3[857,858] and AlH_3[859] are electrophiles (Lewis acids) and attack the heteroatom. This accounts for the different patterns of selectivity in the tables.

[851] Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970*** *, 92,* 7161. For reductions with thexylborane, see Brown, H.C.; Heim, P.; Yoon, N.M. *J. Org. Chem.* ***1972*** *, 37*, 2942.

[852] Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* ***1976*** *, 41*, 1778.

[853] See Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* 1968, *90*, 2927.

[854] Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980*** *, 45*, 1. See Brown, H.C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* ***1982*** *, 239,* 43.

[855] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970*** *, 92,* 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. Also see Wade, R.C. *J. Mol. Catal.,* ***1983*** *, 18,* 273; Lane, C.F. *Chem. Rev.* ***1976*** *, 76*, 773; *Aldrichimica Acta* ***1977*** *, 10,* 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979*** *, 12,* 3; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

[856] Reduced to a hydroxylamine (Reaction **19-46**).

[857] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970****, 92,* 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH_3, see Wade, R.C. *J. Mol. Catal.* ***1983****, 18,* 273 (BH_3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976****, 76*, 773; *Aldrichimica Acta* ***1977****, 10,* 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979****, 12,* 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

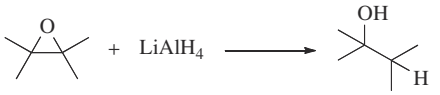
[858] Reacts with solvent, reduced in aprotic solvents.

[859] Reduced to an aldehyde (Reaction **19–44**).

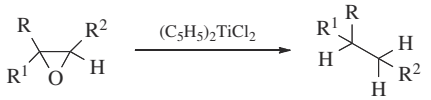
B. Attack at Carbon (C—O And C=O)

19-35 Reduction of Epoxides

(3) *OC-seco*-Hydro-de-alkoxylation



Reduction of epoxides is a special case of Reaction **19-56** and is easily carried out.[860] A common reagent is $LiAlH_4$,[861] which reacts by the S_N2-type mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, the hydrogen atom is usually delivered to the less substituted carbon. The reaction has also been carried out with other reagents (e.g., sodium amalgam in EtOH, Li in ethylenediamine,[862] and by catalytic hydrogenolysis).[863] Chemoselective and regioselective ring opening of allylic epoxides and of epoxy ketones and esters has been achieved with SmI_2,[864] HCOOH—NEt_3 and a Pd catalyst,[865] and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al; also known as Vitride).[866] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride (called Super Hydride).[867] For certain substrates, the epoxide ring can be opened the other way by reduction with $NaBH_4$—$ZrCl_4$,[868] Pd/C and $HCOONH_4$,[869] or with BH_3 in THF.[870]



Epoxy ketones are selectively reduced with lithium naphthalenide[871] or Cp_2TiCl in THF/MeOH[872] to the β-hydroxyketone. Other reduction methods can lead to the epoxy alcohol. Reduction of epoxy amides with SmI_2 in methanol gave the α-hydroxyamide.[873]

Epi-sulfides can be reduced to give the alkene using Bu_3SnH in the presence of BEt_3.[874]

[860] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1019–1027.
[861] See Healy, E.F.; Lewis, J.D.; Minniear, A.B. *Tetrahedron Lett.* ***1994***, *35*, 6647.
[862] Brown, H.C.; Ikegami, S.; Kawakami, J.H. *J. Org. Chem.* ***1970***, *35*, 3243.
[863] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 478–485; Oshima, M.; Yamazaki, H.; Shimizu, I.; Nizar, M.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 6280.
[864] Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 5259; Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1987***, *28*, 4437. See also, Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* ***1988***, 507.
[865] Noguchi, Y.; Yamada, T.; Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***2000****, 41*, 7493, 7499.
[866] Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4081.
[867] Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 8486.
[868] Laxmi, Y.R.S.; Iyengar, D.S. *Synth. Commun.* ***1997***, *27*, 1731.
[869] Ley, S.V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.Q.; Zhou, W. *Org. Lett.* ***2003****, 5*, 4665.
[870] See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 345–348. See also, Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Chem. Soc. Chem. Commun.* ***1976***, 672.
[871] Jankowska, R.; Liu, H.-J. ; Mhehe, G.L *Chem. Commun.* ***1999***, 1581.
[872] Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* ***2001****, 66*, 1046.
[873] Concellón, J.M.; Bardales, E. *Org. Lett.* ***2003****, 5*, 4783.
[874] Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* ***1994***, *35*, 6697.

The usual product of epoxide reductions is the alcohol, but epoxides are reduced all the way to the alkane by titanocene dichloride[875] and by $Et_3SiH—BH_3$.[876]

19-36 Reduction of Aldehydes and Ketones to Alcohols[877]

C,*O*-Dihydro-addition



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents.[878] Among the most common are the metal hydrides (e.g., $LiAlH_4$, $NaBH_4$, and related compounds).[879] These reagents have two main advantages over many other reducing agents: They do not reduce carbon–carbon double or triple bonds (with the exception of propargylic alcohols),[880] and with $LiAlH_4$ all four hydrogen atoms are theoretically usable for reduction. Methods are available for titering hydride reagents.[881] The scope of these reagents with ketones is similar to that with aldehydes. Lithium aluminum hydride reduces even sterically hindered ketones.

The reaction is broad and general. Lithium aluminum hydride easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes or ketones, containing double or triple bonds and/or nonreducible groups (e.g., NR_3, OH, OR, and F). If the molecule contains a group reducible by $LiAlH_4$ (e.g., NO_2, CN, COOR), then that group is usually reduced. Since $LiAlH_4$ reacts readily with water and alcohols, protic solvents must be excluded. Despite limited solubility, common solvents are ether and THF.

The compound $NaBH_4$ (sodium borohydride) has a similar scope, but is less reactive, so it is more selective and so may be used with NO_2, Cl, COOR, CN, and so on in the molecule. Another advantage of $NaBH_4$ is that it can be used in water or alcoholic solvents, and so reduces compounds, (e.g., sugars) that are not soluble in ethers.[882] Other solvents can be used with some modification of the borohydride. For example, butyltriphenylphosphonium borohydride reduces aldehydes to alcohols in dichloromethane.[883] Reduction with solid acid activated $NaBH_4$ has been reported.[884] A polymer-bound phase-transfer material with $NaBH_4$ in wet THF has also been used.[885] Sodium borohydride on

[875] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974****, 96*, 5290.
[876] Fry, J.L.; Mraz, T.J. *Tetrahedron Lett.* ***1979***, 849.
[877] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 347–422.
[878] See Hudlicky, M. *Reductions in Organic Chemistry,* Ellis Horwood, Chichester, ***1984***, pp. 96–129. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1075–1113.
[879] See Abdel-Magid, A.F. (Ed.) *Reductions in Organic Synthesis* American Chemical Society Washington, ***1996***; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajos, A. *Complex Hydrides*, Elsevier, NY, ***1979***; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 49–71; Wheeler, O.H. in Patai, S. *The Chemistry of the Carbonyl Group,* pt. 1, Wiley, NY, **1966**, pp. 507–566.
[880] See Meta, C.T.; Koide, K. *Org. Lett.* ***2004****, 6*, 1785.
[881] Hoye, T.R.; Aspaas, A.W.; Eklov, B.M.; Ryba, T.D. *Org. Lett.* ***2005****, 7,* 2205.
[882] See Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed.* ***1989****, 28*, 320.
[883] Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2001****, 31*, 1177.
[884] Cho, B.T.; Kang, S.K.; Kim, M.S.; Ryu, S.R.; An, D.K. *Tetrahedron* ***2006****, 62*, 8164.
[885] Tamami, B.; Mahdavi, H. *Tetrahedron* ***2003****, 59*, 821.

alumina, under microwave irradiation, is an effective reagent.[886] Sodium borohydride has been used on silica gel.[887]

Red-Al was prepared by Vit in 1967,[888] and its reducing power is close to that of $LiAlH_4$. In addition, it is stable to dry air (it does not ignite in even moist air or oxygen), and is thermally stable up to 200 °C. The greatest practical utility of Red-Al is its solubility in aromatic hydrocarbon and ether solvents, which allows it to be conveniently used for applications that require inverse addition of hydrides. Red-Al essentially reacts the same as $LiAlH_4$, reducing aldehydes, ketones[889] and acid derivatives to alcohols.[890] Reduction of conjugated carbonyls gives primarily 1,2-reduction to an allylic alcohol.[891] Other functional groups can be reduced.[892]

The C=C units in compounds that contain double bonds are generally not affected by metallic hydrides, and the C=C unit may be isolated or conjugated, but double bonds that are conjugated with the C=O group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.[893] Some reagents that reduce only the C=O bonds of α,β-unsaturated aldehydes and ketones are AlH_3,[894] $NaBH_4$, or $LiAlH_4$ in the presence of lanthanide salts,[895] Co complexes,[896] $NaBH_4$—$LiClO_4$,[897] Ni compounds,[898] $NaBH_3(OAc)$,[899] $Zn(BH_4)_2$[900] on Y-zeolite,[901] and Et_3SiH.[902] Also, both $LiAlH_4$[903] and $NaBH_4$[904] predominantly reduce only the C=O bonds of C=C—C=O systems in most cases, although substantial amounts of fully saturated alcohols have been found in some cases[903] (Reaction **15-14**). For some reagents that reduce only the C=C bonds of conjugated aldehydes and ketones, see Reaction **15-11**. A mixture of $InCl_3$ and $NaBH_4$ reduced both the C=C and C=O units of conjugated ketones.[905]

[886] Varma, R.S.; Saini, R.K. *Tetrahedron Lett.* ***1997****, 38*, 4337.
[887] Liu, W.-y.; Xu, Q.-h.; Ma, Y.-x. *Org. Prep. Proceed. Int.* ***2000****, 32*, 596.
[888] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis Vol. 2,* Wiley, New York, ***1969***, p. 382; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis Vol. 3,* Wiley, New York, ***1972***, p. 260; Vit, J.; Másensky, B.; Machácek, *J. Fr. Pa.*, 1,515,582 1968 [*Chem. Abstr. 70*: 115009x, ***1967***].
[889] Capka, M.; Chvalovsky, V.; Kochloefl, K.; Kraus, M. *Collect. Czech. Chem. Commun.* ***1969****, 34,* 118; Stotter, P.L.; Friedman, M.D.; Minter, D.E. *J. Org. Chem.* ***1985****, 50*, 29.
[890] Zurflüh, R.; Dunham. L.L.; Spain, V.L.; Siddall, J.B. *J. Am. Chem. Soc.* ***1970****, 92*, 425.
[891] Markezich, R.L.; Willy, W.E.; McCarry, B.E.; Johnson, W.S. *J. Am. Chem. Soc.* ***1973****, 95*, 4414; McCarry, B. E.; Markezich, R.L.; Johnson, W.S *J. Am. Chem. Soc.* ***1973****, 95,* 4416.
[892] See Kesenheimer, C.; Groth, U. *Org. Lett.* ***2006****, 8,* 2507; White, J.D.; Choi, Y. *Org. Lett.* ***2000****, 2,* 2373; Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988****, 53*, 4081. Maloney, D.J.; Hecht, S.M. *Org. Lett.* ***2005****, 7*, 4297
[893] See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones,* pt. 2, Wiley, NY, ***1989***, pp. 923–1022.
[894] Dilling, W.L.; Plepys, R.A. *J. Org. Chem.* ***1970****, 35,* 2971.
[895] See Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1929. See also, Chênevert, R.; Ampleman, G. *Chem. Lett.* ***1985***, 1489; Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985****, 15*, 985.
[896] Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001****, 3*, 2543.
[897] Halimjani, A.Z.; Saidi, M.R. *Synth. Commun.* ***2005****, 35,* 2271.
[898] Khurana, J.M.; Chauhan, S. *Synth. Commun.* ***2001****, 31*, 3485.
[899] Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* ***1989****, 54,* 5629.
[900] For a review of the reactivity of this reagent, see Ranu, B. *Synlett* ***1993***, 885.
[901] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Tetrahedron Lett.* ***1998****, 39*, 5151.
[902] Ojima, I.; Kogure, T. *Organometallics* ***1982****, 1*, 1390.
[903] Johnson, M.R.; Rickborn, B. *J. Org. Chem.* ***1970****, 35*, 1041.
[904] Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.* ***1949****, 71,* 122.
[905] Ranu, B.C.; Samanta, S. *Tetrahedron* ***2003****, 59*, 7901.

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*.[906] A number of reagents have been found to reduce aldehydes much faster than ketones. Among these[907] are sodium triacetoxyborohydride[908] ($NaBH_4$—HCO_2H),[909] zinc borohydride in THF,[910] a complex of $LiAlH_4$ and *N*-methyl-2-pyrrolidinone (of particular interest since it is stable in air and to heating),[911] and Raney nickel.[912]

Ketones can be chemoselectively reduced in the presence of aldehydes with $NaBH_4$ in aq EtOH at $-15\,^{\circ}C$ in the presence of cerium trichloride ($CeCl_3$).[913] The reagent lithium *n*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.[914] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β-unsaturated ketones with $NaBH_4$–50% MeOH—CH_2Cl_2 at $-78\,^{\circ}C$,[915] and with zinc borohydride.[916]

In general, $NaBH_4$ reduces carbonyl compounds in the order aldehydes > α,β-unsaturated aldehydes > ketones > α,β-unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.[917] A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of Dibal-H in the presence of the Lewis acid methylaluminum bis(2,16-di-*tert*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.[918] It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another.[919] For a discussion of selectivity in reduction reactions (see Sec. 19.B.ii-A). A syn-selective reduction of β-hydroxy ketones was achieved using $(i\text{PrO})_2TiBH_4$.[920] Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$—HCl, or sodium hydrosulfite ($Na_2S_2O_4$), as well as by other reducing agents.

The reagent lithium tri-*sec*-butylborohydride [LiBH(*sec*-Bu)$_3$, L-Selectride] reduces cyclic and bicyclic ketones in a highly stereoselective manner.[921] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity > 99%. Both L-Selectride and the potassium salt (K-Selectride) reduce carbonyls in cyclic and acyclic molecules with high diastereoselectivity.[922] The more usual reagents (e.g., $LiAlH_4$ and $NaBH_4$) reduce relatively

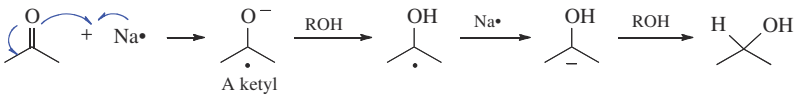
[906] See Luibrand, R.T.; Taigounov, I.R.; Taigounov, A.A. *J. Org. Chem.* ***2001****, 66*, 7254.
[907] See Borbaruah, M.; Barua, N.C.; Sharma, R.P. *Tetrahedron Lett.* ***1987****, 28,* 5741.
[908] Gribble, G.W.; Ferguson, D.C. *J. Chem. Soc. Chem. Commun.* ***1975***, 535. See also, Nutaitis, C.F.; Gribble, G. W. *Tetrahedron Lett.* ***1983****, 24,* 4287.
[909] Blanton, J.R. *Synth. Commun.* ***1997****, 27*, 2093.
[910] Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* ***1990***, *31*, 7663; See Ranu, B. *Synlett* ***1993***, 885.
[911] Fuller, J.C.; Stangeland, E.L.; Jackson, T.C.; Singaram, B. *Tetrahedron Lett.* ***1994****, 35*, 1515. See also, Mogali, S.; Darville, K.; Pratt, L.M. *J. Org. Chem.* ***2001****, 66*, 2368.
[912] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***2000***, 197.
[913] See Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* ***1992****, 33*, 6569.
[914] Lansbury, P.T.; Peterson, J.O. *J. Am. Chem. Soc.* ***1962****, 84,* 1756.
[915] Ward, D.E.; Rhee, C.K.; Zoghaib, W.M. *Tetrahedron Lett.* ***1988****, 29,* 517.
[916] Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* ***1990****, 55*, 5799.
[917] Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989****, 67*, 1206.
[918] Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***1988****, 110,* 2650.
[919] For lists, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1089–1092, and references given in Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989****, 67*, 1206.
[920] Ravikumar, K.S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* ***1999****, 64*, 5841.
[921] Krishnamurthy, S.; Brown, H.C. *J. Am. Chem. Soc.* ***1976****, 98,* 3383.
[922] K-Selectride: Lawson, E.C.; Zhang, H.-C.; Maryanoff, B.E. *Tetrahedron Lett.* ***1999****, 40,* 593.

unhindered cyclic ketones either with little or no stereoselectivity[923] or give predominant formation of the more stable isomer (axial attack).[924] Reduction of cyclohexanone derivatives with the very hindered $LiAlH(Cet_2CMe_3)_3$ gave primarily the cis-alcohol.[925] Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with $LiAlH_4$ and $NaBH_4$.

Other reagents reduce aldehydes and ketones to alcohols,[926] including the following:

1. *Hydrogen and a Catalyst.*[927] Common heterogeneous catalysts for carbonyls are Pt and Ru,[928] and homogeneous catalysts are commonly used,[929] especially for asymmetric hydrogenation (see **A** below). Before the discovery of the metal hydrides, this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N and C≡N bonds are often more susceptible to attack than C=O bonds.[930] For aromatic aldehydes and ketones, reduction to the hydrocarbon (Reaction **19-61**) is a side reaction via hydrogenolysis of the initially produced alcohol (Reaction **19-54**). The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **15–11**.[931]
2. *Sodium in Ethanol.*[932] This is called the *Bouveault–Blanc procedure* and was more popular for the reduction of carboxylic esters (Reaction **19-38**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

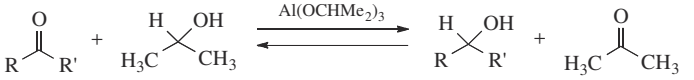
   For the reaction with sodium in ethanol the following mechanism[933] has been suggested:[934]



[923] Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979****, 11,* 53; Wigfield, D.C. *Tetrahedron* ***1979****, 35*, 449; Tramontini, M. *Synthesis* ***1982***, 605.
[924] See Mukherjee, D.; Wu, Y.; Fronczek, F.R.; Houk, K.N. *J. Am. Chem. Soc.* ***1988****, 110*, 3328.
[925] Boireau, G.; Deberly, A.; Toneva, R. *Synlett* ***1993***, 585
[926] See Feoktistov, L.G.; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electochemistry,* Marcel Dekker, NY, ***1983***, pp. 315–358, 315–326. See also, Coche, L.; Moutet, J. *J. Am. Chem. Soc.* ***1987****, 109*, 6887.
[927] Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis* American Chemical Society, Washington, DC, ***1996***, pp. 31–50; Parker, D. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Tanaka, K. in Cerveny, L. *Catalytic Hydrogenation*, Elsevier, NY, ***1986***, pp. 79–104; Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 66–77; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY., ***1967***, pp. 238–290.
[928] Hedberg, C.; Källström, K.; Arvidsson, P.I.; Brandt, P.; Andersson, P.G. *J. Am. Chem. Soc.* ***2005****, 127,* 15083.
[929] See Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 65–70; Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chemistry: Asian J.* ***2006****, 1,* 598.
[930] See Narasimhan, C.S.; Deshpande, V.M.; Ramnarayan, K. *J. Chem. Soc. Chem. Commun.* ***1988***, 99.
[931] See, however, Pavlenko, N.V. *Russ. Chem. Rev.* ***1989****, 58*, 453.
[932] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 152–160.
[933] Pradhan, S.K. *Tetrahedron* ***1986****, 42*, 6351; Huffman, J.W. *Acc. Chem. Res.* ***1983****, 16*, 399. See Rautenstrauch, V. *Tetrahedron* ***1988****, 44,* 1613; Song, W.M.; Dewald, R.R. *J. Chem. Soc. Perkin Trans. 2,* ***1989***, 269; Rassat, A. *Pure Appl. Chem.* ***1977****, 49,* 1049.
[934] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 151. See, however, Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed.* ***1985****, 24,* 499.

The ketyl intermediate can be isolated.[935] Lithium is often a superior metal for alkali metal reductions.[936]

3. *Other Metal Reductions*. A single carbonyl group of an α-diketone can be reduced to give an α-hydroxy ketone, by heating with Zn powder in aq DMF[937] or Zn in methanol in the presence of benzyltriethylammonium chloride.[938] Aluminum and NaOH in aq methanol reduces ketones.[939] β-Hydroxy ketones are reduced with good antiselectivity using an excess of SmI_2 in water,[940] and other ketones or aldehydes are reduced with SmI_2[941] in aq THF,[942] or in alcohols.[943] Other metals can be used, including $FeCl_3$/Zn in aq DMF[944] or Mg in alcohols.[945] 1,2-Diketones were reduced to the α-hydroxy ketone with TiI_4 in acetonitrile, followed by hydrolysis.[946] Ammonia and aq $TiCl_3$ in methanol reduces ketones.[947]
4. *Isopropyl Alcohol and Aluminum Isopropoxide*. This is called the *Meerwein–Ponndorf–Verley reduction*.[948] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **19-3**):

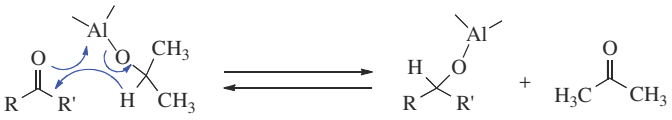


The equilibrium is shifted by removal of the acetone by distillation. There is a report of the reduction of benzaldehyde to benzyl alcohol by heating with 2-propanol at 225 °C for 1 day.[949] The reaction usually takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.[950] This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction. Zeolites have been used as a medium for this reduction.[951] This reduction can be done catalytically[952] and an

[935] See Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* ***1976****, 98,* 5035; ***1977****, 99,* 6280.
[936] Rees, N.V.; Baron, R.; Kershaw, N.M.; Donohoe, T.J.; Compton, R.G. *J. Am. Chem. Soc.* ***2008****, 130,* 12256.
[937] Kreiser, W. *Liebigs Ann. Chem.* ***1971****, 745*, 164.
[938] Kardile, G.B.; Desai, D.G.; Swami, S.S. *Synth. Commun.* ***1999****, 29*, 2129.
[939] Bhar, S.; Guha, S. *Tetrahedron Lett.* ***2004****, 45*, 3775.
[940] Keck, G.E.; Wager, C.A.; Sell, T.; Wager, T.T. *J. Org. Chem.* ***1999****, 64*, 2172.
[941] See Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2002****, 124*, 6895.
[942] Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2002****, 43*, 7197.
[943] Fukuzawa, S.-i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* ***2004***, 2863.
[944] Sadavarte, V.S.; Swami, S.S.; Desai, D.G. *Synth. Commun.* ***1998****, 28*, 1139.
[945] Kim, J.Y.; Kim, H.D.; Seo, M.J.; Kim, H.R.; No, Z.; Ha, D.-C.; Lee, G.H. *Tetrahedron Lett.* ***2006****, 47*, 9; Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers, II, R.A. *Org. Lett.* ***2004****, 6*, 2685.
[946] Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* ***2000****, 41*, 7939.
[947] Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* ***2001***, 2235.
[948] See Maruoka, K.; Saito, S.; Concepcion, A.B.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993****, 115*, 1183. For a microwave-induced version of this reaction, see Barbry, D.; Torchy, S. *Tetrahedron Lett.* ***1997****, 38*, 2959.
[949] Bagnell, L.; Strauss, C.R. *Chem. Commun.* ***1999***, 287.
[950] See Hutton, J. *Synth. Commun.* ***1979****, 9*, 483; Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* ***1984****, 49,* 2045; Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* ***1987***, 181.
[951] Corma, A.; Domine, M.E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* ***2002****, 124*, 3194.
[952] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Org. Lett.* ***2001****, 3,* 2391. See Albrecht, M.; Crabtree, R.H.; Mata, J.; Peris, E. *Chem. Commun.* ***2002***, 32.

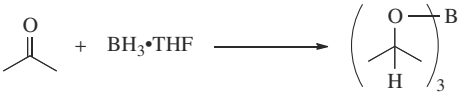
aluminum-free, Zr-zeolite catalyst has been developed.[953] Microwave irradiation of a ketone with 2-propanol, KOH, and activated alumina gives good yields of the alcohol.[954] When the carbonyl substrate has a stereogenic center, the reaction proceeds with good diastereoselectivity.[955] The use of chiral metal complexes leads to chiral hydrogen transfer.[956] A combination of 2-propanol with BINOL and $AlMe_3$ leads to reduction of α-chloroketones to the chlorohydrin with good enantioselectivity.[957]

The *Meerwein–Ponndorf–Verley reaction* usually[958] involves a cyclic transition state:[959]



but in some cases 2 molar equivalents of aluminum alkoxide are involved: one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[960] The alcohol solvent acts as a hydrogen donor in this reaction.[961] Although, for simplicity, the alkoxide is shown as a monomer, it actually exists as trimers and tetramers, which are the actual reactive species.[962] Note that supercritical 2-propanol has been used for reduction of ketones, without the need for a catalyst.[963]

5. *Boranes*. Borane (BH_3) and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (Reaction **15-16**).[964] That is, the boron adds to the oxygen and the hydrogen to the carbon:[965]



[953] Zhu, Y.; Chuah, G.; Jaenicke, S. *Chem. Commun.* ***2003***, 2734.
[954] Kazemi, F.; Kiasat, A.R. *Synth. Commun.* ***2002***, *32*, 2255.
[955] Yin, J.; Huffman, M.A.; Conrad, K.M.; Armstrong, III, J.D. *J. Org. Chem.* ***2006***, *71,* 840.
[956] Dong, Z.-R.; Li, Y.-Y.; Chen, J.-S.; Li, B.-Z.; Xing, Y.; Gao, J.-X. *Org. Lett.* ***2005***, *7*, 1043; Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem. Int. Ed.* ***2006***, *45,* 3819.
[957] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1020.
[958] See, however, Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 3593; Yamataka, H.; Hanafusa, T. *Chem. Lett.* ***1987***, 643.
[959] See Warnhoff, E.W.; Reynolds-Warnhoff, P.; Wong, M.Y.H. *J. Am. Chem. Soc.* ***1980***, *102*, 5956.
[960] Moulton, W.N.; Van Atta, R.E.; Ruch, R.R. *J. Org. Chem.* ***1961***, *26,* 290.
[961] Galian, R.E.; Litwinienko, G.; Pérez-Prieto, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***2007***, *129,* 9280.
[962] Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1969***, *91,* 394.
[963] Kamitanaka, T.; Matsuda, T.; Harada, T. *Tetrahedron* ***2007***, *63*, 1429.
[964] See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 324–335. See Cha, J. S.; Moon, S.J.; Park, J.H. *J. Org. Chem.* ***2001***, *66*, 7514.
[965] Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* ***1960***, *82,* 681; Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82,* 3866.

The resulting borate is then hydrolyzed to the alcohol. A variety of alkylboranes can be used for reduction.[966] Both 9-BBN[967] (Reaction **15-16**) and BH_3—Me_2S[968] reduce only the C=O group of conjugated aldehydes and ketones.[969] Tributylborane in ionic solvents reduces aldehydes to alcohols.[970] Enantioselective borane reductions lead to chiral alcohols.[971] Spiroborate esters have been used for enantioselective reduction,[972] and chiral boronic esters have also been used.[973]

Alane (AlH_3) derivatives can also be used, including diisobutylaluminum hydride.[974]

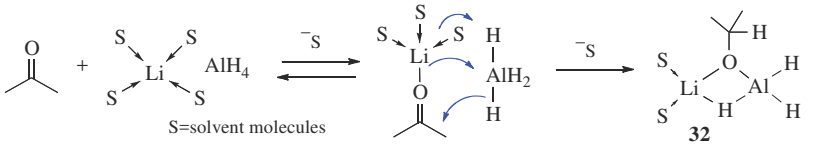
6. *Tin Hydrides*. Tributyltin hydride reduces aldehydes to primary alcohols by simply heating in methanol.[975] A mixture of Bu_3SnH and phenylboronic acid (Reaction **12-28**) reduces aldehydes in dichloromethane.[976] Reduction of ketones was achieved with Bu_2SnH_2 and a Pd catalyst.[977] Using triaryltin hydrides with $BF_3{\cdot}OEt_2$, where aryl is 2,6-diphenylbenzyl, selective reduction of aliphatic aldehydes in the presence of a conjugated aldehyde was achieved.[978] Tris(trimethylsilyl)methane has been used as a tin-free radical reducing agent.[979]
7. *Cannizzaro Reaction*. In the Cannizzaro reaction (see **19-81**), aldehydes without an α hydrogen are reduced to alcohols.
8. *Silanes*. In the presence of bases, certain silanes can selectively reduce carbonyls.[980] Transition metal complexes also catalyze hydrosilylation of ketones.[981] Controlling temperature and solvent leads to different ratios of *syn* and *anti* products.[982] Silanes reduce ketones in the presence of $BF_3{\cdot}OEt_2$.[983] Ketones are reduced with Cl_3SiH in the presence of pyrrolidine carbaldehyde[984] or under

[966] See Bae, J.W.; Lee, S.H.; Jung, Y.J.; Yoon, C.-O.M.; Yoon, C.M. *Tetrahedron Lett.* ***2001***, *42*, 2137.
[967] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1975***, *40,* 1864; Lane, C.F. *Aldrichimica Acta* ***1976***, *9*, 31.
[968] Mincione, E. *J. Org. Chem.* ***1978***, *43*, 1829.
[969] Bartoli, G.; Bosco, M.; Bellucci, M.C.; Daplozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* ***2000***, *2*, 45.
[970] Kabalka, G.W.; Malladi, R.R. *Chem. Commun.* ***2000***, 2191.
[971] Du, D.-M.; Fang, T.; Xu, J.; Zhang, S.-W. *Org. Lett.* ***2006***, *8*, 1327; Krzemiński, M.P.; Wojtczak, A. *Tetrahedron Lett.* ***2005***, *46,* 8299.
[972] Stepanenko, V.; De Jesús, M.; Correa, W.; Guzmán, I.; Vázquez, C.; de la Cruz, W.; Ortiz-Marciales, M.; Barnes, C.L. *Tetrahedron Lett.* ***2007***, *48,* 5799.
[973] Eagon, S.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* ***2007***, *48*, 9025.
[974] Nakamura, S.; Kuroyanagi, M.; Watanabe, Y.; Toru, T. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3143.
[975] Kamiura, K.; Wada, M. *Tetrahedron Lett.* ***1999***, *40*, 9059; Adams, C.M.; Schemenaur, J.E. *Synth. Commun.* ***1990***, *20*, 2359. For a review, see Kuivila, H.G. *Synthesis* ***1970***, 499.
[976] Yu, H.; Wang, B. *Synth. Commun.* ***2001***, *31*, 2719.
[977] Kamiya, I.; Ogawa, A. *Tetrahedron Lett.* ***2002***, *43*, 1701.
[978] Sasaki, K.; Komatsu, N.; Shivakawa, S.; Maruoka, K. *Synlett* ***2002***, 575.
[979] Perchyonok, V.T. *Tetrahedron Lett.* ***2006***, *47*, 5163.
[980] Ison, E.A.; Trivedi, E.R.; Corbin, R.A.; Abu-Omar, M.M. *J. Am. Chem. Soc.* ***2005***, *127*, 15374.
[981] For a review, see Díez-González, S.; Nolan, S.P. *Org. Prep. Proceed. Int.* ***2007***, *39*, 523. See Chen, T.; Liu, X.-G.; Shi, M. *Tetrahedron* ***2007***, *63,* 4874; Fernandes, A.C.; Fernandes, R.; Romão, C.R.; Royo, B. *Chem. Commun.* ***2005***, 213; Comte, V.; Balan, C.; Le Gendre, P.; Moïse, C. *Chem. Commun.* ***2007***, 713; Nishiyama, H.; Furuta, A. *Chem. Commun.* ***2007***, 760.
[982] See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.
[983] Smonou, I. *Tetrahedron Lett.* ***1994***, *35*, 2071.
[984] Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* ***1999***, *40*, 7507.

photochemical conditions.[985] Polymethylhydrosiloxane with tetrabutylammonium fluoride reduces α-amino ketones to give the syn amino alcohol.[986]

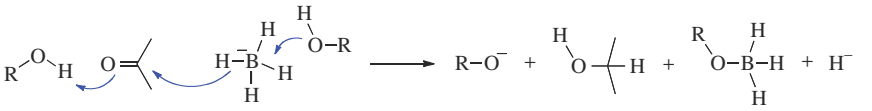
9. *Ammonium Formates*. Sodium formate and trialkylammonium formates can be used to reduce aldehydes and ketones to the corresponding alcohol. Decanal was reduced to decanol, for example, using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.[987] A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.[988] Transfer hydrogenation also occurs with formic acid–triethylamine and a Ru catalyst[989] in water.[990]
10. *Enzymatic Reductions*. Successful asymmetric reductions (see Section A) have been achieved with biologically derived reducing agents[991] (e.g., baker's yeast),[992] enzymes from other organisms,[993] or with other biocatalysts.[994] Ionic liquids have been used in conjugation with enzymatic reduction,[995] and enzymatic reduction has been done in supercritical CO_2.[996]

With most reagents there is an initial attack on the carbon of the carbonyl group by a hydride equivalent (H^-) although with BH_3[997] the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.[998] With $LiAlH_4$ or $NaBH_4$, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon. The following mechanism has been proposed for $LiAlH_4$:[999]



[985] Enholm, E.J.; Schulte II, J.P. *J. Org. Chem.* ***1999****, 64*, 2610.
[986] Nadkarni, D.; Hallissey, J.; Mojica, C. *J. Org. Chem.* ***2003****, 68,* 594.
[987] Babler, J.H.; Sarussi, S.J. *J. Org. Chem.* ***1981****, 46*, 3367.
[988] Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981****, 22*, 621.
[989] Morris, D.J.; Hayes, A.M.; Wills, M. *J. Org. Chem.* ***2006****, 71,* 7035.
[990] Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem. Int. Ed.* ***2005****, 44*, 3407.
[991] For a review, see Sih, C.J.; Chen, C. *Angew. Chem. Int. Ed.* ***1984****, 23,* 570.
[992] See Wolfson, A.; Dlugy, C.; Tavor, D.; Blumenfeld, J.; Shotland, Y. *Tetrahedron Asymmetry* ***2006****, 17,* 2043; Yadav, J.S.; Reddy, G.S.K.K.; Sabitha, G.; Krishna, A.D.; Prasad, A.R.; Rahaman, H.U.R.; Rao, K.V.; Rao, A.B. *Tetrahedron Asymmetry* ***2007****, 18,* 717.
[993] See Moore, J.C.; Pollard, D.J.; Kosjek, B.; Devine, P.N. *Acc. Chem. Res.* ***2007****, 40*, 1412; Ema, T.; Yagasaki, H.; Okita, N.; Takeda, M.; Sakai, T. *Tetrahedron* ***2006****, 62,* 6143; Hoyos, P.; Sansottera, G.; Fernández, M.; Molinari, F.; Sinisterra, J.V.; Alcántara, A.R. *Tetrahedron* ***2008****, 64,* 7929; Utsukihara, T.; Misumi, O.; Kato, N.; Kuroiwa, T.; Horiuchi, C.A. *Tetrahedron Asymmetry* ***2006****, 17,* 1179; Zhu, D.; Malik, H.T.; Hua, L. *Tetrahedron Asymmetry* ***2006****, 17,* 3010; Lavandera, I.; Höller, B.; Kern, A.; Ellmer, U.; Glieder, A.; de Wildeman, S.; Kroutil, W. *Tetrahedron Asymmetry* ***2008****, 19,* 1954. For enzymatic reduction of thio ketones, see Nielsen, J.K.; Madsen, J.Ø. *Tetrahedron Asymmetry,* ***1994****, 5*, 403.
[994] See Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron Asymmetry* ***2003****, 14*, 2659.
[995] Matsuda, T.; Yamagishi, Y.; Koguchi, S.; Iwai, N.; Kitazume, T. *Tetrahedron Lett.* ***2006****, 47,* 4619; Bräutigam, S.; Bringer-Meyer, S.; Weuster-Botz, D. *Tetrahedron Asymmetry* ***2007****, 18,* 1883.
[996] Matsuda, T.; Marukado, R.; Mukouyama, M.; Harada, T.; Nakamura, K. *Tetrahedron Asymmetry* ***2008****, 19,* 2272.
[997] See Brown, H.C.; Wang, K.K.; Chandrasekharan, J. *J. Am. Chem. Soc.* ***1983****, 105*, 2340.
[998] See Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979****, 11,* 53; Wigfield, D.C. *Tetrahedron* ***1979****, 35*, 449.
[999] Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976****, 98,* 5524.

Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether), the reaction did not take place.[1000] Complex **32** must be hydrolyzed to the alcohol. For $NaBH_4$, the Na^+ does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to B:[1001]



Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or $MR_mH_n^-$ or $M(OR)_mH_n^-$ etc.].

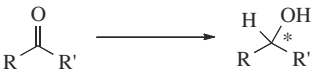
The question of whether the initial complex in the $LiAlH_4$ reduction (**32**, or H—C—OAl^-H_3 = **33**) can reduce another carbonyl to give $(H—C—O)_2Al^-H_2$, and so on has been controversial. It has been shown[1002] that this is probably not the case but that, more likely, **33** disproportionates to $(H—C—O)_4Al^-$ and AlH_4^-, which is the only attacking species. Disproportionation has also been reported in the $NaBH_4$ reaction.[1003]

Aluminate (**33**) is essentially $LiAlH_4$ with one of the hydrogen atoms replaced by an alkoxy group (i.e., $LiAlH_3OR$). The fact that **33** and other alkoxy derivatives of $LiAlH_4$ are less reactive than $LiAlH_4$ itself has led to the use of such compounds as reducing agents that are less reactive and more selective than $LiAlH_4$.[1004] An example is $LiAlH(O\text{-}t\text{-}Bu)_3$ (Reactions **19-39**–**19-41**; see also, Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that $LiAlH(Ot\text{-}Bu)_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.[1005] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause $LiAlH_4$ to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[1006]

For other reduction reactions of aldehydes and ketones, see **19-61**, **19-76**, and **19-81**.

A. Asymmetric Reduction

Unsymmetrical ketones are prochiral (Sec. 4.M); that is, reduction creates a new stereogenic center:



[1000] Pierre, J.; Handel, H. *Tetrahedron Lett.* ***1974***, 2317. See also, Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* ***1976***, 1677; Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

[1001] Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* ***1977***, *42,* 1108. See, however, Adams, C.; Gold, V.; Reuben, D. M.E. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1466, 1472; Kayser, M.M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* ***1983***, *24,* 1015.

[1002] Haubenstock, H.; Eliel, E.L. *J. Am. Chem. Soc.* ***1962***, *84,* 2363; Malmvik, A.; Obenius, U.; Henriksson, U. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1899, 1905.

[1003] Malmvik, A.; Obenius, U.; Henriksson, U. *J. Org. Chem.* ***1988***, *53*, 221.

[1004] For reviews of reductions with alkoxyaluminum hydrides, see Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Cerny, M. *Synthesis* ***1972***, 217.

[1005] Levine, S.G.; Eudy, N.H. *J. Org. Chem.* ***1970***, *35*, 549; Heusler, K.; Wieland, P.; Meystre, C. *Org. Synth.* ***V***, 692.

[1006] Brown, C.A.; Krishnamurthy, S.; Kim, S.C. *J. Chem. Soc. Chem. Commun.* ***1973***, 391.

The relative effectiveness of various reagents for reduction of eight other types of ketone was determined, using several different reducing agents.[1007] The ketones examined included heterocyclic, aralkyl, β-keto esters, β-keto acids,[1008] and so on.[991] Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively.[1009] Each reagent tends to show a specificity for certain types of ketones.[1010] Good enantioselectivity is usually obtained with the proper reagent.[1011] Substituents that are remote to the carbonyl group can play a role in facial selectivity of the reduction.[1012] Asymmetric reduction has been accomplished using bioreagents (e.g., enzymes, see item 10 above).

Asymmetric reduction with very high enantioselectivity has also been achieved with achiral reducing agents and optically active catalysts.[1013] Homogeneous catalytic asymmetric hydrogenation leads to reduction of substrates with high enantioselectivity.[1014] A typical chiral ligand is 2,2′-bis(diphenylphosphino)-1,1′-binaphthylruthenium acetate (BINAP, **34**), used with a metal catalysts [e.g., $Ru(OAc)_2$],[1015] β-Keto esters are reduced enantioselectively, for example.[1016] A variety of chiral additives and/or ligands have been used with catalytic hydrogenation reactions. Many functional groups can be tolerated.[1017] Asymmetric catalytic hydrogenation has been done in ionic liquids.[1018]

[1007] Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. *J. Org. Chem.* ***1987,*** *52*, 5406.

[1008] Wang, Z.; La, B.; Fortunak, J.M.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* ***1998,*** *39,* 5501.

[1009] See Singh, V.K. *Synthesis* ***1992***, 605; Midland, M.M. *Chem. Rev.* ***1989,*** *89,* 1553; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 105–130; in Morrison, J.D. *Asymmetric Synthesis*, Academic Press, NY, ***1983***, the articles by Midland, M.M. Vol. 2, pp. 45–69, and Grandbois, E.R.; Howard, S.I.; Morrison, J.D. Vol. 2, pp. 71–90; Haubenstock, H. *Top. Stereochem.* ***1983,*** *14,* 231.

[1010] For a list of many of these reducing agents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 1097–1111.

[1011] See Midland, M.M.; Kazubski, A.; Woodling, R.E. *J. Org. Chem.* ***1991,*** *56*, 1068.

[1012] Kaselj, M.; Gonikberg, E.M.; le Noble, W.J. *J. Org. Chem.* ***1998,*** *63*, 3218.

[1013] See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, ***2010***, pp. 391–411.

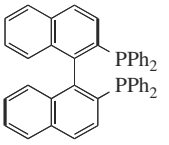
[1014] See Liang, Y.; Jing, Q.; Li, X.; Shi, L.; Ding, K. *J. Am. Chem. Soc.* ***2005,*** *127,* 7694; Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* ***2005,*** *127,* 8288; Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* ***2006,*** *128,* 8716; Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007,*** *129,* 1868; Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* ***2005,*** *70,* 2867; Truppo, M.D.; Pollard, D.; Devine, P. *Org. Lett.* ***2007,*** *9,* 335; Ngo, H.L.; Hu, A.; Lin, W. *Tetrahedron Lett.* ***2005,*** *46,* 595; Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* ***2008,*** *47,* 8920; Jiang, H.-y.; Yang, C.-f.; Li, C.; Fu, H.-y.; Chen, H.; Li, R.-x.; Li, X.-j. *Angew. Chem. Int. Ed.* ***2008,*** *47,* 9240; Burk, S.; Franciò, G.; Leitner, W. *Chem. Commun.* ***2005***, 3460; Li, W.; Sun, X.; Zhou, L.; Hou, G.; Shichao Yu, S.; Zhang, X. *J. Org. Chem.* ***2009,*** *74*, 1397; Martins, J.,E,D,; Wills, M. *Tetrahedron* ***2009,*** *65*, 5782; Li, W.; Hou, G.; Wang, C.; Jiang, Y.; Zhang, X. *Chem. Commun.* ***2010***, 3979.

[1015] See Noyori, R. *Science* ***1990,*** *248,* 1194; Noyori, R.; Takaya, H. *Acc. Chem. Res.* ***1990,*** *23,* 345; Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth. 67,* 20.

[1016] Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* ***1991,*** *32*, 4227. See also, Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* ***1988,*** *110,* 629.

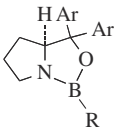
[1017] See Sun, L.; Tang, M.; Wang, H.; Wei, D.; Liu, L. *Tetrahedron Asymmetry* ***2008,*** *19,* 779; Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* ***2004,*** *6*, 2681; Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* ***2004,*** *126*, 1626; Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron Asymmetry* ***2004,*** *15*, 2185. Also see Sandoval, C.A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* ***2003,*** *125*, 13490.

[1018] Ngo, H.L.; Hu, A.; Lin, W. *Chem.. Commun.* ***2003***, 1912.



34

(*R*)-(+)-BINAP



35

A second approach is reduction with BH_3—THF or catecholborane,[1019] using an oxazaborolidine (**35**, R = H, Me, or *n*-Bu; Ar = Ph or β-naphthyl)[1020] or other chiral compounds[1021] as a catalyst. Both a polymer-bound oxazaborolidine[1022] and a dendritic chiral catalyst have been used in conjunction with borane,[1023] as well as other chiral additives can be used.[1024] Chiral sulfonamides have been used as additives.[1025]

Lithium aluminum hydride in combination with a chiral diol[1026] or other chiral ligands[1027] leads to enantioselective reduction, often in the presence of a transition metal complex.[1028] Chiral additives have also been used with $NaBH_4$.[1029] Examples include $LiBH_4/NiCl_2$ and a chiral amino alcohol,[1030] $NaBH_4$ with chiral Lewis acid complexes,[1031] or $NaBH_4/Me_3SiCl$ and a chiral ligand.[1032] A mixture of $NaBH_4$ and Me_3SiCl with a catalytic amount of a chiral, polymer-bound sulfonamide leads to asymmetric reduction.[1033]

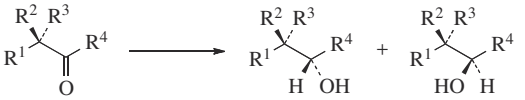
Enantioselective reduction is possible with the other methods mentioned above. Transition metal catalyzed asymmetric transfer hydrogenation is effective for the

[1019] See Ford, A.; Woodward, S. *Angew. Chem. Int. Ed.* ***1999****, 38*, 335.
[1020] See Santhi, V.; Rao, J.M. *Tetrahedron Asymmetry* ***2000****, 11*, 3553; Jones, S.; Atherton, J.C.C. *Tetrahedron Asymmetry* ***2000****, 11*, 4543; Cho, B.T.; Kim, D.J. *Tetrahedron Asymmetry* ***2001****, 12*, 2043; Jiang, B.; Feng, Y.; Hang, J.-F. *Tetrahedron Asymmetry* ***2001****, 12*, 2323; Gilmore, N.J.; Jones, S.; Muldowney, M.P. *Org. Lett.* ***2004****, 6*, 2805; Huertas, R.E.; Corella, J.A.; Soderquist, J.A. *Tetrahedron Lett.* ***2003****, 44*, 4435.
[1021] See Brunel, J.M.; Legrand, O.; Buono, G. *Eur. J. Org. Chem.* ***2000***, 3313; Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* ***2003****, 59*, 8411; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* ***2004****, 15*, 47; Zhang, Y.-X.; Du, D.-M.; Chen, X.; Lü, S.-F.; Hua, W.-T. *Tetrahedron Asymmetry* ***2004****, 15*, 177; Lindsay. D.M.; McArthur, D. *Chem. Commun.* ***2010***, 2474.
[1022] Price, M.D.; Sui, J.K.; Kurth, M.J.; Schore, N.E. *J. Org. Chem.* ***2002****, 67,* 8086.
[1023] Bolm, C.; Derrien, N.; Seger, A. *Chem. Commun.* ***1999***, 2087.
[1024] Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001****, 66,* 303; Zhou, H.; Lü, S.; Xie, R.; Chan, A.S. C.; Yang, T.-K. *Tetrahedron Lett.* ***2001****, 42*, 1107; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* ***2001****, 12*, 685.
[1025] Li, G.-Q.; Yan, Z.-Y.; Niu, Y.-N.; Wu, L.-Y.; Wei, H.-L.; Liang, Y.-M. *Tetrahedron Asymmetry* ***2008****, 19*, 816.
[1026] Ren, Y.; Tian, X.; Sun, K.; Xu, J.; Xu, X.; Lu, S. *Tetrahedron Lett.* ***2006****, 47*, 463.
[1027] Lange, D.A.; Neudörfl, J.-M.; Goldfuss, B. *Tetrahedron* ***2006****, 62,* 3704. In an ionic liquid: see Xiao, Y.; Malhotra, S.V. *Tetrahedron Asymmetry* ***2006****, 17,* 1062.
[1028] For a review, see Daverio, P.; Zanda, M. *Tetrahedron Asymmetry* ***2001****, 12*, 2225.
[1029] Kim, J.; Singaram, B. *Tetrahedron Lett.* ***2006****, 47,* 3901.
[1030] Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* ***1999****, 40*, 8375.
[1031] Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999****, 72*, 1109.
[1032] Jiang, B.; Feng, Y.; Zheng, J. *Tetrahedron Lett.* ***2000****, 41*, 10281.
[1033] Zhao, G.; Hu, J.-b.; Qian, Z.-s.; Yin, X.-x. *Tetrahedron Asymmetry* ***2002****, 13*, 2095.

preparation of chiral alcohols.[1034] Reduction with silanes and transition metal catalysts (e.g., Ru compounds) is also very effective.[1035] Chiral Ru catalysts have been used with triethylammonium formate for the enantioselective reduction.[1036] The transition metal catalyzed hydrosilylation of ketones gives chiral alcohols in the presence of suitable chiral ligands.[1037] Enantioselective reduction was observed with $PhSiH_3$ and Cu compounds with a chiral ligand,[1038] with a mixture of Ru and Ag catalysts,[1039] or with $Mn(dpm)_3$ and oxygen (dpm = diphenylmethylene).[1040] Enantioselective hydrosilylation is possible using chiral organocatalysts.[1041] A chiral Sm complex has been used in conjunction with 2-propanol.[1042] Chiral mercapto alcohols have also been used for asymmetric reduction.[1043]

Enantioselective reduction is usually not possible for aldehydes,[1044] since the products are primary alcohols in which the reduced carbon is not chiral. Instead deuterated aldehydes (RCDO) give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Alpine-Borane) with almost complete optical purity.[1045] Other chiral boranes can be used to reduce aldehydes or ketones.[1046]

In the above cases, an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition metal Lewis acid.[1047]



Diastereomers

[1034] Wu, X.; Li, X.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A.J.; Xiao, J. *Chemistry: European J.* ***2008****, 14,* 2209; Kawasaki, I.; Tsunoda, K.; Tsuji, T.; Yamaguchi, T.; Shibuta, H.; Uchida, N.; Yamashita, M.; Ohta, S. *Chem. Commun.* ***2005***, 2134; Li, X.; Blacker, J.; Houson, I.; Wu, X.; Xiao, J. *Synlett* ***2006***, 1155; Ito, M.; Shibata, Y.; Watanabe, A.; Ikariya, T. *Synlett* ***2009***, 1621; Zani, L.; Eriksson, L.; Adolfsson, H. *Eur. J. Org. Chem.* ***2008***, 4655.

[1035] Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron Asymmetry,* ***1995****, 6*, 2503.

[1036] Liu, P.N.; Gu, P.M.; Wang, F.; Tu, Y.Q. *Org. Lett.* ***2004****, 6*, 169; Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* ***2004****, 2*, 1818; Schlatter, A.; Kundu, M.K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* ***2004****, 43*, 6731.

[1037] Shaikh, N.S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2008****, 47*, 2497; Inagaki, T.; Yamada, Y.; Phong, L.T.; Furuta, A.; Ito, J.-i.; Nishiyama, H. *Synlett* ***2009***, 253; Ghoshal, A.; Sarkar, A.R.; Manickam, G.; Kumaran, R.S.; Jayashankaran, J. *Synlett* ***2010***, 1459.

[1038] Lipshutz, B.H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* ***2003****, 125*, 8779.

[1039] Gade, L.H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* ***2004****, 43*, 1014.

[1040] Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001****, 42*, 6651.

[1041] Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* ***2007***, 2977.

[1042] Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* ***2004****, 6*, 4695.

[1043] Yang, T.-K.; Lee, D.-S. *Tetrahedron Asymmetry* ***1999****, 10,* 405.

[1044] See, however, Li, X.; List, B. *Chem. Commun.* ***2007***, 1739. See also, Giacomini, D.; Galletti, P.; Quintavalla, A.; Gucciardo, G.; Paradisi, F. *Chem. Commun. 2007,* 4038.

[1045] Midland, M.M.; Greer, S.; Tramontano, A.; Zderic, S.A. *J. Am. Chem. Soc.* ***1979****, 101*, 2352. See also, Midland, M.M.; Zderic, S.A. *J. Am. Chem. Soc.* ***1982****, 104,* 525.

[1046] Ramachandran, P.V.; Pitre, S.; Brown, H.C. *J. Org. Chem.* ***2002****, 67*, 5315. For a discussion of the sources of stereoselectivity, see Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* ***2004****, 69*, 6860.

[1047] Dalton, D.M.; Gladysz, J.A. *J. Organomet. Chem.* ***1989****, 370,* C17.

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a stereogenic center α to the carbonyl group,[1048] even an achiral reducing agent can give more of one diastereomer than of the other (a diastereoselective reduction). Such reductions have been carried out with considerable success.[1049] In most such cases, *Cram's rule* (Sec. 4.H., category 1) is followed, but exceptions are known.[1050]

OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **VI**, 215, 769, 887; **VII**, 129, 215, 241, 402, 417; **VIII**, 302, 312, 326, 527; **IX**, 58, 362, 676.

19-37 Reduction of Carboxylic Acids to Alcohols

Dihydro-de-oxo-bisubstitution

$$RCOOH \xrightarrow{LiAlH_4} RCH_2OH$$

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[1051] The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,[1052] but not $NaBH_4$ (see Table 19.5).[1053] A combination of $NaBH_4$ and an arylboronic acid (Reaction **12-28**) is also effective.[1054] A mixture of $NaBH_4$, Me_2SO_4, and $B(OMe)_3$ is effective for the reduction of hydroxyl-substituted aromatic carboxylic acids.[1055] Benzyltriethylammonium borohydride is dichloromethane reduces carboxylic acids to the alcohol.[1056] Catalytic hydrogenation is generally ineffective.[1057]

Borane (BH_3) is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (although the reaction with double bonds takes place at about the same rate in ether solvents).[1058] For many years, borane was the reagent of choice for this reduction. Borane also reduces carboxylic acid salts.[1059] Aluminum hydride reduces COOH groups without affecting carbon–halogen bonds in the same molecule. The reduction has also been carried out with SmI_2 in basic media[1060] or aq H_3PO_4,[1061] or simply with SmI_2 in water.[1062] A mixture of $NaBH_4$ and I_2 has been used to reduced amino acids to amino alcohols.[1063]

OS **III**, 60; **VII**, 221; 530; **VIII**, 26, 434, 528.

[1048] See Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* ***1988****, 53,* 1021; Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* ***1988****, 110,* 3560.
[1049] See Nógrádi, M. *Stereoselective Synthesis* VCH, NY, ***1986***, pp. 131–148; Oishi, T.; Nakata, T. *Acc. Chem. Res.* ***1984****, 17,* 338.
[1050] See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988****, 110,* 4475.
[1051] See Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 322–373.
[1052] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1114–1116. Zinc borohydride has also been used; see Narashimhan, S.; Madhavan, S.; Prasad, K.G. *J. Org. Chem.* ***1995****, 60*, 5314.
[1053] See, however, Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* ***1983***, 835.
[1054] Tale, R.H.; Patil, K.M.; Dapurkar, S.E. *Tetrahedron Lett.* ***2003****, 44*, 3427.
[1055] Zhou, Y.; Gao, G.; Li, H.; Qu, J. *Tetrahedron Lett.* ***2008****, 49,* 3260.
[1056] Narashimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Synth. Commun.* ***2000****, 30*, 941.
[1057] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 78–79.
[1058] Brown, H.C.; Stocky, T.P. *J. Am. Chem. Soc.* ***1977****, 99,* 8218; Chen, M.H.; Kiesten, E.I.S.; Magano, J.; Rodriguez, D.; Sexton, K.E.; Zhang, J.; Lee, H.T. *Org. Prep. Proceed. Int.* ***2002****, 34*, 665.
[1059] Yoon, N.M.; Cho, B.T. *Tetrahedron Lett.* ***1982****, 23*, 2475.
[1060] Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* ***1992****, 65*, 3049.
[1061] Kamochi, Y.; Kudo, T. *Tetrahedron* ***1992****, 48*, 4301.
[1062] Kamochi, Y.; Kudo, T. *Chem. Lett.* ***1993***, 1495.
[1063] McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* ***1993****, 58*, 3568.

19-38 Reduction of Carboxylic Esters to Alcohols

Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution

$$RCOOR' \xrightarrow{LiAlH_4} RCH_2OH + R'OH$$

Lithium aluminum hydride reduces carboxylic esters to give two different alcohols, as shown.[1064] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R′OH, this is a method that is often a working equivalent of "hydrolyzing" esters. Reduction of lactones yields diols.[1065] Among the reagents used for this reduction[1066] are Dibal-H, lithium triethylborohydride, $LiAlH(O\textit{t}\text{-}Bu)_3$,[1067] and $BH_3—SMe_2$ in refluxing THF.[1068] Although $NaBH_4$ reduces phenolic esters, especially those containing electron-withdrawing groups,[1069] its reaction with other esters is usually so slow that it is not the reagent of choice, but there are many exceptions.[1070]) However, it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. Note that $NaBH_4$ reduces esters in the presence of certain compounds (see Table 19.5).[1071] Note that $NaBH_4$ in DMF—MeOH reduces aryl carboxylic esters to benzylic alcohols,[1072] and $NaBH_4$—LiCl with microwave irradiation also reduces esters to primary alcohols.[1073]

Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[1074] although high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations, but homogeneous catalytic hydrogenation procedures have been developed.[1075] Before the discovery of $LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault–Blanc procedure*.[1076] This procedure is still sometimes used where selectivity is necessary (see also, Reactions **19-62**, **19-65**, and **19-59**).

[1064] For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 391–531.
[1065] For a ring size-selective reduction using $SmI_2—H_2O$, see Duffy, L.A.; Matsubara, H.; Procter, D.J. *J. Am. Chem. Soc.* ***2008****, 130,* 1136.
[1066] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1116–1120.
[1067] Ayers, T.A. *Tetrahedron Lett.* ***1999****, 40,* 5467.
[1068] Brown, H.C.; Choi, Y.M. *Synthesis* ***1981***, 439; Brown, H.C.; Choi, Y.M.; Narasimhan, S. *J. Org. Chem.* ***1982****, 47,* 3153.
[1069] Takahashi, S.; Cohen, L.A. *J. Org. Chem.* ***1970****, 35*, 1505.
[1070] For example, see Brown, M.S.; Rapoport, H. *J. Org. Chem.* ***1963****, 28*, 3261; Boechat, N.; da Costa, J.C.S.; Mendonca, J.de S.; de Oliveira, P.S.M.; DeSouza, M.V.N. *Tetrahedron Lett.* ***2004****, 45*, 6021.
[1071] See also, Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* ***1984****, 57,* 1948; Guida, W.C.; Entreken, E.E.; Guida, W.C. *J. Org. Chem.* ***1984****, 49,* 3024.
[1072] Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* ***1999***, 1636.
[1073] Feng, J.-C.; Liu, B.; Dai, L.; Yang, X.-L.; Tu, S.-J. *Synth. Commun.* ***2001****, 31*, 1875.
[1074] For a review, see Adkins, H. *Org. React.* ***1954****, 8,* 1.
[1075] Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2006****, 45,* 1113.
[1076] Chablay, E. *Compt. Rend* ***1913****, 156,* 1020; Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* ***1904****, 31*, 666; Bouveault, L.; Blanc, G. *Compt. Rend.* ***1903****, 136,* 1676. See Bodnar, B.S.; Vogt, P.F. *J. Org. Chem.* ***2009****, 74*, 2598.

Silanes (e.g., Ph_2SiH_2), with a catalytic amount of triphenylphosphine and a Rh catalyst reduced esters to primary alcohols.[1077] Aliphatic silanes (e.g., $EtMe_2SiH$) also reduced esters with a Ru catalyst.[1078]

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834; **VI**, 781; **VII**, 356; **VIII**, 155; **IX**, 251.

19-39 Reduction of Acyl Halides

Hydro-de-halogenation or Dehalogenation

$$\text{RCOCl} \xrightarrow[-78^\circ\text{C}]{\text{LiAlH(O}t\text{-Bu)}_3} \text{RCHO}$$

Acyl halides can be reduced to aldehydes[1079] by treatment with lithium tri-*tert*-butoxyaluminum hydride in diglyme at −78 °C.[1080] The R group may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction with this reagent. Acyl halides can also be reduced to aldehydes by hydrogenolysis with Pd on barium sulfate as catalyst in what is called the *Rosenmund reduction*.[1081] A convenient hydrogenolysis procedure involves Pd on charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[1082] The reduction of acyl halides to aldehydes has also been carried out[1083] with Bu_3SnH,[1084] an $InCl_3$ catalyzed reaction using Bu_3SnH,[1085] $NaBH_4$ in a mixture of DMF and THF,[1086] with Sm—PBu_3,[1087] and with formic acid/NH_4OH.[1088] Polymethylhydrosiloxane (PMHS) reduces acid chlorides to aldehydes in the presence of a Pd catalyst.[1089] In some of these cases, the mechanisms are free radical.

There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see Reaction **19-41**). There is also a method in which the COOH group is replaced by a completely different CHO group (Reaction **16-87**).

OS **III**, 551, 627; **VI**, 529, 1007. Also see, OS **III**, 818; **VI**, 312.

[1077] Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* ***1999****, 40*, 6963.
[1078] Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* ***2002****, 67,* 4985.
[1079] See Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 211–232; Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251.
[1080] Cha, J.S.; Brown, H.C. *J. Org. Chem.* ***1993***, *58*, 4732 and references cited therein.
[1081] See Rylander, P.N. *Catalytic Hydrogenation Over Platinum Metals*, Academic Press, NY, ***1967***, pp. 398–404; Maier, W.F.; Chettle, S.J.; Rai, R.S.; Thomas, G. *J. Am. Chem. Soc.* ***1986***, *108*, 2608.
[1082] Peters, J.A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 21. See also, Burgstahler, A.W.; Weigel, L.O.; Shaefer, C.G. *Synthesis* ***1976***, 767.
[1083] See Leblanc, J.C.; Moise, C.; Tirouflet, J. *J. Organomet. Chem.* ***1985***, *292*, 225; Corriu, R.J.P.; Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1988***, *29*, 1271. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1265–1266.
[1084] See Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 2923.
[1085] Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2000****, 41*, 113.
[1086] Babler, J.H. *Synth. Commun.* ***1982***, *12*, 839. See Entwistle, I.D.; Boehm, P.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 27.
[1087] Jia, X.; Liu, X.; Li, J.; Zhao, P.; Zhang, Y. *Tetrahedron Lett.* ***2007****, 48*, 971.
[1088] Shamsuddin, K.M.; Zubairi, Md.O.; Musharraf, M.A. *Tetrahedron Lett.* ***1998***, *39*, 8153.
[1089] Lee, K.; Maleczka Jr., R.E. *Org. Lett.* ***2006****, 8,* 1887.

19-40 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes[1090]

Hydro-de-hydroxylation or Dehydroxylation (overall transformation)

$$\text{RCOOH} \longrightarrow \text{RCHO} \longleftarrow \text{RCOOR}'$$

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (Reaction **19-37**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes[1091] by treatment with Li in $MeNH_2$ or NH_3 followed by hydrolysis of the resulting imine,[1092] with

$$\text{RCOOH} \xrightarrow[\text{MeNH}_2]{\text{Li}} \text{RCH=N—Me} \xrightarrow{\text{H}_2\text{O}} \text{RCHO}$$

with thexylchloro(or bromo)borane–SMe_2[1093] (see Reaction **15-16** for the thexyl group), $Me_2N{=}CHCl^+\ Cl^-$ in pyridine,[1094] and with diaminoaluminum hydrides.[1095] Benzoic acid derivatives were reduced to benzaldehyde derivatives with NaH_2PO_2 and a diacylperoxide and Pd catalyst.[1096] Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with Dibal-H (*i*-Bu_2AlH) at -75 to $-70\,^\circ C$.[1097]

Carboxylic esters have been reduced to aldehydes with Dibal-H at $-70\,^\circ C$, with diaminoaluminum hydrides,[1098] and for phenolic esters with $LiAlH(O\textit{t}\text{-Bu})_3$ at $0\,^\circ C$.[1099] Pretreatment of the acid with Me_3SiCl followed by reduction with Dibal-H also gives the aldehyde.[1100] Aldehydes have also been prepared by reducing ethyl thiol esters (RCOSEt) with Et_3SiH and a Pd—C catalyst.[1101] Thioesters have been reduced to the aldehyde with Li metal in THF at $-78\,^\circ C$, followed by quenching with methanol.[1102]

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate [$Na_2Fe(CO)_4$].[1103] Heating a carboxylic acid, presumably to form the anhydride, and then reaction with Na/EtOH leads to the aldehyde.[1104]

Acid chlorides are reduced to aldehydes with Bu_3SnH and a Ni catalyst.[1105]

[1090] For a review, see Cha, J.S. *Org. Prep. Proced. Int.* ***1989***, *21*, 451.
[1091] See Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1987***, *28*, 3941; Cha, J.S.; Kim, J.E.; Yoon, M.S.; Kim, Y.S. *Tetrahedron Lett.* ***1987***, *28*, 6231. See also, the lists, in Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1265–1268.
[1092] Bedenbaugh, A.O.; Bedenbaugh, J.H.; Bergin, W.A.; Adkins, J.D. *J. Am. Chem. Soc.* ***1970***, *92*, 5774.
[1093] Chloro - see Brown, H.C.; Cha, J.S.; Yoon, N.M.; Nazer, B. *J. Org. Chem.* ***1987***, *52*, 5400; Bromo, see Cha, J. S.; Kim, J.E.; Lee, K.W. *J. Org. Chem.* ***1987***, *52*, 5030.
[1094] Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 1543.
[1095] Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.
[1096] Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2002***, 836.
[1097] Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525. See Song, J.I.; An, D.K. *Chem. Lett.* ***2007***, *36,* 886.
[1098] Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.
[1099] Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1964***, 867; Weissman, P.M.; Brown, H.C. *J. Org. Chem.* ***1966***, *31*, 283.
[1100] Chandrasekhar, S.; Kumar, M.S.; Muralidhar, B. *Tetrahedron Lett.* ***1998***, *39*, 909.
[1101] Fukuyama, T.; Lin, S.; Li, L. *J. Am. Chem. Soc.* ***1990***, *112*, 7050.
[1102] Penn, J.H.; Owens, W.H. *Tetrahedron Lett.* ***1992***, *33*, 3737.
[1103] Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2490; Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Tomi, K.; Takegami, Y. *Tetrahedron Lett.* ***1975***, 1063.
[1104] Shi, Z.; Gu, H. *Synth. Commun.* ***1997***, *27*, 2701.
[1105] Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron Lett.* ***1997***, *38*, 8093.

Also see, Reactions **19-62** and **19-38**.
OS **VI**, 312; **VIII**, 241, 498.

19-41 Reduction of Amides to Aldehydes

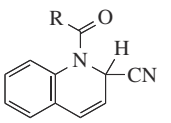
Hydro-de-dialkylamino-substitution

$$RCONR_2' + LiAlH_4 \longrightarrow RCHO + NHR_2'$$

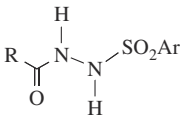
N,N-Disubstituted amides can be reduced to amines with $LiAlH_4$ (see Reaction **19-64**), but reduction to an aldehyde is possible.[1106] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents[1107] that give good yields of aldehydes are Dibal-H,[1108] $LiAlH(Ot\text{-}Bu)_3$, diaminoaluminum hydrides,[1109] disiamylborane (see Reaction **15-16** for the disiamyl group),[1110] and $Cp_2Zr(H)Cl$.[1111]

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. There are several examples:[1112]

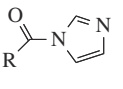
1. *Reissert Compounds.*[1113] Compounds, such as **36,** are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **36** with sulfuric acid gives the corresponding aldehyde.



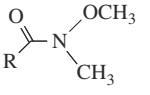
36



37



38



39

2. *Acyl Sulfonylhydrazides.* Compounds, such as **37**, are cleaved with base to give aldehydes. This reaction is known as the *McFadyen–Stevens reduction* and is applicable *only* to aromatic aldehydes or aliphatic aldehydes with no α hydrogen.[1114] Acyl imide (RCON=NH, see reaction **19-67**) has been proposed as an intermediate in this reaction.[1115]
3. *Acyl Imidazoles.* Compounds **38**[1116] can be reduced to aldehydes with $LiAlH_4$.

[1106] Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 220–225.
[1107] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp.1269–1271.
[1108] Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2046.
[1109] Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1975***, 875.
[1110] Godjoian, G.; Singaram, B. *Tetrahedron Lett.* ***1997***, *38*, 1717.
[1111] White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2000***, *122,* 11995.
[1112] See Craig, J.C.; Ekwurieb, N.N.; Fu, C.C.; Walker, K.A.M. *Synthesis* ***1981***, 303.
[1113] See Popp, F.D.; Uff, B.C. *Heterocycles* ***1985***, *23*, 731; Popp, F.D. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 609; *Adv. Heterocycl. Chem.* ***1979***, *24*, 187; ***1968***, *9*, 1. See Bridge, A.W.; Hursthouse, M.B.; Lehmann, C.W.; Lythgoe, D.J.; Newton, C.G. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1839 for isoquinoline Reissert salts.
[1114] Dudman, C.C.; Grice, P.; Reese, C.B. *Tetrahedron Lett.* ***1980***, *21*, 4645.
[1115] See Cacchi, S.; Paolucci, G. *Gazz. Chem. Ital.* ***1974***, *104*, 221; Matin, S.B.; Craig, J.C.; Chan, R.P.K. *J. Org. Chem.* ***1974***, *39*, 2285.
[1116] For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61.

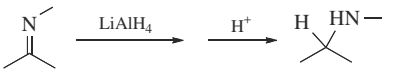
4. *Weinreb Amides*. A *N*-Methoxy-*N*-methyl amide (e.g., **39)** is referred to as a *Weinreb amide*.[1117] Reduction with and excess of $LiAlH_4$ or Dibal-H leads to the corresponding aldehyde, as does reaction with Cp_2ZrHCl.[1118]
5. See also, the *Sonn–Müller Method* (Reaction **19-44**).

OS **VIII**, 68. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

C. Attack at Non-Carbonyl Multiple Bonded Heteroatoms

19-42 Reduction of the Carbon–Nitrogen Double Bond (C=N)

C,*N*-Dihydro-addition



Imines and *Schiff bases*,[1119] hydrazones,[1120] and other C=N compounds can be reduced with $LiAlH_4$, $NaBH_4$,[1121] Na—EtOH, hydrogen and a catalyst, as well as with other reducing agents.[1122] Metal-free catalytic hydrogenation is known.[1123] Transfer hydrogenation of imines leads to amines.[1124] A mixture of Sm/I_2[1125] or In/NH_4Cl[1126] also reduces imines. Reduction with Bu_2SnClH in HMPA has been shown to be chemoselective for imines.[1127] Iminium salts are reduced by $LiAlH_4$ to the corresponding amine, although here there is no "addition" to the nitrogen:[1128] Silanes[1129] with a triarylborane catalyst reduces *N*-sulfonyl imines[1130] as does TiI_4.[1131] Imines are reduced with samarium bromide in HMPA,[1132] 2-propanol with a Ru catalyst,[1133] and with triethylammonium formate with microwave irradiation.[1134] Oximes are reduced with hydrogen gas and a catalytic amount of 48% HBr.[1135]

[1117] Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981****, 22,* 3815; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley–Interscience, New Jersey, **2005**, p. 866. See Sibi, M. P. *Org. Prep. Proceed. Int.* ***1993****, 25*, 15; Mentzel, M.; Hoffmann, H.M.R. *J. Prakt. Chem.* ***1997****, 339,* 517.
[1118] Spletstoser, J.T.; White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2007****, 129,* 3408; White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2000****, 122*, 11995; Wang, J.; Xu, H.; Gao, H.; Su, C.-Y.; Phillips, D.L. *Organometallics* ***2010****, 29*, 42; Gondi, V.B.; Hagihara, K.; Rawal, V.H. *Chem. Commun.* ***2010****, 46,* 904.
[1119] See Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1998****, 37*, 1103.
[1120] See Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* ***1992****, 114*, 6266.
[1121] Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.S. *Synlett* ***1999***, 1781.
[1122] See Harada, K. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 276–293; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 123–138.
[1123] Chase, P.A.; Welch, G.C.; Jurca, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* ***2007****, 46,* 8050.
[1124] Zhang, Z.; Schreiner, P.R. *Synlett* ***2007***, 1455.
[1125] Banik, B.K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F.F. *Tetrahedron Lett.* ***1999****, 40*, 6731.
[1126] Banik, B.K.; Hackfeld, L.; Becker, F.F. *Synth. Commun.* ***22001****, 31*, 1581.
[1127] Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* ***1998****, 63*, 383.
[1128] Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988,*** pp. 275–356.
[1129] See Malkov, A.V.; Mariani, A.; MacDougall, K.N.; Kocovsky, P. *Org. Lett.* ***2004****, 6*, 2253.
[1130] Blackwell, J.M.; Sonmor, E.R.; Scoccitti, T.; Piers, W.E. *Org. Lett.* ***2000****, 2*, 3921.
[1131] Shimizu, M.; Sahara, T.; Hayakawa, R. *Chem. Lett.* ***2001***, 792.
[1132] Knettle, B.W.; Flowers II, R.A. *Org. Lett.* ***2001****, 3*, 2321.
[1133] Samec, J.S.M.; Bäckvall, J.-E. *Chem. Eur. J.* ***2002****, 8*, 2955.
[1134] Moghaddam, F.M.; Khakshoor, O.; Ghaffarzadeh, M. *J. Chem. Res. (S)* ***2001***, 525.
[1135] Davies, I.W.; Taylor, M.; Marcoux, J.-F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P.J. *Tetrahedron Lett.* ***2000****, 41*, 8021.

Oximes are generally reduced to amines (Reaction **19-48**),[1136] but simple reduction to give hydroxylamines can be accomplished with borane[1137] or sodium cyanoborohydride.[1138] Oxime *O*-ethers are reduced with Bu_3SnH and $BF_3{\cdot}OEt_2$.[1139] Diazo compounds (ArN=NAr) are reductively cleaved to aniline derivatives with Zn and ammonium formate in methanol.[1140]

Reduction of imines has been carried out enantioselectively.[1141] Catalytic hydrogenation[1142] with a chiral Ir[1143] Re,[1144] Rh,[1145] or Pd[1146] catalyst is effective. Catalytic hydrogenation of iminium salts with a chiral Ru catalyst gives the amine.[1147] Enantioselective reduction of imines is possible using a mixture of *Escherichia coli* whole cells and $H_3N{\cdot}BH_3$.[1148] *Hantzsch ester* (see Reactions **15-14** and **16-17**) reduction of imine-esters, in the presence of a chiral phosphoric acid derivative, leads to chiral amino esters.[1149] In a related reaction, enamines were reduced by hydrogenation over a chiral Rh catalyst.[1150]

Hydrogenation of oximes with Pd/C and a Ni complex gives the imine, and in the presence of a lipase and ethyl acetate the final product was an acetamide, formed with high enantioselectivity.[1151] Catalytic-transfer hydrogenation of imines leads with a chiral catalyst to chiral amines.[1152] Conjugated *N*-sulfonyl imines are reduced to the conjugated sulfonamide with good enantioselectivity using a chiral rhodium catalyst in the presence of LiF and $PhSnMe_3$.[1153] Phosphinyl imines, $R_2C{=}N{-}P(=O)Ar_2$, are reduced with high enantioselectivity using a chiral Cu catalyst.[1154] Silanes (e.g., $PhSiH_3$) can be used for the reduction of imines, and in the presence of a chiral Ti catalyst the resulting amine was formed with excellent enantioselectivity.[1155] The enantioselective reduction of aromatic imines is possible using trichlorosilane.[1156] Enzymatic reduction of imines leads to chiral amines.[1157]

[1136] See Bolm, C.; Felder, M. *Synlett* ***1994***, 655; Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* ***1993****, 34*, 3271.
[1137] Kawase, M.; Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 643.
[1138] See Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979****, 11,* 201; Lane, C.F. *Synthesis* ***1975***, 135.
[1139] Ueda, M.; Miyabe, H.; Namba, M.; Nakabayashi, T.; Naito, T. *Tetrahedron Lett.* ***2002****, 43*, 4369.
[1140] Gowda, S.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2002****, 43*, 1329.
[1141] See Denmark, S.E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* ***1994****, 116*, 8797; Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994****, 35*, 5389. For a review of asymmetric reductions involving the C=N unit, see Zhu, Q.-C.; Hutchins, R.O. *Org. Prep. Proceed. Int.* ***1994****, 26*, 193.
[1142] Hou, G.; Gosselin, F.; Li, W.; McWilliams, J.C.; Sun, Y.; Weisel, M.; O'Shea, P.D.; Chen, C.-y.; Davies, I.W.; Zhang, X. *J. Am. Chem. Soc.* ***2009****, 131*, 9882.
[1143] See Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* ***2008****, 130*, 14450; Vargas, S.; Rubio, M.; Suárez, A.; Pizzano, A. *Tetrahedron Lett.* ***2005****, 46,* 2049.
[1144] Nolin, K.A.; Ahn, R.W.; Toste, F.D. *J. Am. Chem. Soc.* ***2005****, 127,* 12462.
[1145] Li, C.; Xiao, J. *J. Am. Chem. Soc.* ***2008****, 130,* 13208.
[1146] Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* ***2001****, 3*, 313.
[1147] Magee, M.P.; Norton, J.R. *J. Am. Chem. Soc.* ***2001****, 123*, 1778.
[1148] Dunsmore, C.J.; Carr, R.; Fleming, T.; Turner, N.J. *J. Am. Chem. Soc.* ***2006****, 128*, 2224.
[1149] Li, G.; Liang, Y.; Antilla, J.C. *J. Am. Chem. Soc.* ***2007****, 129,* 5830.
[1150] Tararov, V.I.; Kadyrov, R.; Riermeier, T.H.; Holz, J.; Börner, A. *Tetrahedron Lett.* ***2000****, 41*, 2351.
[1151] Choi, Y.K.; Kim, M.J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* ***2001****, 3*, 4099.
[1152] Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* ***2005****, 7*, 3781.
[1153] Hayashi, T.; Ishigedani, M. *Tetrahedron* ***2001****, 57*, 2589.
[1154] Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* ***2004****, 43*, 2228.
[1155] Hansen, M.C.; Buchwald, S.L. *Org. Lett.* ***2000****, 2*, 713.
[1156] For a review, see Guizzetti, S.; Benaglia, M. *Eur. J. Org. Chem.* ***2010***, 5529. See Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* ***2006****, 47*, 3751; Malkov, A.V.; Stončius, S.; MacDougall, K.N.; Mariani, A.; McGeoch, G.D.; Kočovský, P. *Tetrahedron* ***2006****, 62,* 264; Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chemistry: European J.* ***2008****, 14,* 8789; Malkov, A.V.; Figlus, M.; Cooke, G.; Caldwell, S.T.; Rabani, G.; Prestly, M.R.; Kočovský, P. *Org. Biomol. Chem.* ***2009****, 7*, 1878; Malkov, A.V.; Vranková, K.; Sigerson, R.C.; Stončius, S.; Kočovský, P. *Tetrahedron* ***2009****, 65*, 9481.
[1157] Vaijayanthi, T.; Chadha, A. *Tetrahedron Asymmetry* ***2008****, 19*, 93.

Oxime ethers are reduced with borane and a chiral spiroborate ester catalyst.[1158]

Isocyanates have been catalytically hydrogenated to *N*-substituted formamides: RNCO → R–NH–CHO.[1159] Isothiocyanates were reduced to thioformamides with SmI_2 in HMPA/*t*-BuOH.[1160]

OS **III**, 328, 827; **VI**, 905; **VIII**, 110, 568. Also see, OS **IV**, 283.

19-43 The Reduction of Nitriles to Amines

***CC*,*NN*-Tetrahydro-biaddition**

$$R{-}C{\equiv}N + LiAlH_4 \longrightarrow R{-}CH_2{-}NH_2$$

Nitriles can be reduced to primary amines with many reducing agents,[1161] including $LiAlH_4$, and $BH_3{\cdot}SMe_2$.[1162] The reagent $NaBH_4$ does not generally reduce nitriles except in alcoholic solvents with a catalyst (e.g., $CoCl_2$,[1163] $NiCl_2$,[1164] or Raney nickel).[1165] Lithium dimethylaminoborohydride ($LiBH_3NMe_2$) reduces aryl nitriles to the corresponding benzylamines.[1166]

The reduction of nitriles is of wide scope and has been applied to many nitriles. Catalytic hydrogenation converts nitriles to primary amines,[1167] but secondary amines [$(RCH_2)_2NH$] are often side products.[1168] These can be avoided by adding a compound (e.g., acetic anhydride), which removes the primary amine as soon as it is formed,[1169] or by the use of excess ammonia to drive the equilibria backward.[1170] Sponge nickel[1171] or nickel on silica gel[1172] have been used for the catalytic hydrogenation of aryl nitriles to amines.

Attempts to stop with the addition with only 1 equiv of hydrogen, have failed; that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (Reaction **19-44**).

[1158] Chu, Y.; Shan, Z.; Liu, D.; Sun, N. *J. Org. Chem.* ***2006****, 71,* 3998; Huang, K.; Merced, F.G.; Ortiz-Marciales, M.; Meléndez, H.J.; Correa, W.; De Jesús, M. *J. Org. Chem.* ***2008****, 73,* 4017.

[1159] Howell, H.G. *Synth. Commun.* ***1983****, 13*, 635.

[1160] Park, H.S.; Lee, I.S.; Kim, Y.H. *Chem. Commun.* ***1996***, 1805.

[1161] See Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 307–340; Enthaler, S.; Addis, D.; Junge, K.; Erre, G.; Beller, M. *Chemistry: European J.* ***2008****, 14,* 9491. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 875–878.

[1162] See Brown, H.C.; Choi, Y.M.; Narasimhan, S. *Synthesis* ***1981***, 605.

[1163] Satoh, T.; Suzuki, S. *Tetrahedron Lett.* ***1969***, 4555. For a discussion of the mechanism, see Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1982****, 104,* 6801.

[1164] Khurana, J.M.; Kukreja, G. *Synth. Commun.* ***2002****, 32*, 1265.

[1165] Egli, R.A. *Helv. Chim. Acta* ***1970****, 53*, 47.

[1166] Thomas, S.; Collins, C.J.; Cuzens, J.R.; Spieciarich, D.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* ***2001****, 66*, 1999.

[1167] See Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. *J. Am. Chem. Soc.* ***2010****, 132,* 7854.

[1168] See Galán, A.; de Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A.M. *J. Org. Chem.* ***1991****, 56,* 452.

[1169] See Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* ***1960****, 25,* 1658.

[1170] For example, see Freifelder, M. *J. Am. Chem. Soc.* ***1960****, 82*, 2386.

[1171] Tanaka, K.; Nagasawa, M.; Kasuga, Y.; Sakamura, H.; Takuma, Y.; Iwatani, K. *Tetrahedron Lett.* ***1999****, 40*, 5885.

[1172] Takamizawa, S.; Wakasa, N.; Fuchikami, T. *Synlett* ***2001***, 1623.

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$.[1173]

$$RCN \xrightarrow{R'_3O^+BF_4^-} R{-}C{\equiv}\overset{+}{N}{-}R' \xrightarrow[\text{diglyme}]{NaBH_4} RCH_2{-}NH{-}R'$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see Reaction **16-8**), this is a method for the conversion of nitriles to secondary amines.

Note that the related compounds, the isonitriles ($R{-}N^+{\equiv}CO^-$, also called isocyanides) have been reduced to *N*-methylamines with $LiAlH_4$, as well as with other reducing agents.

OS **III**, 229, 358, 720; **VI**, 223.

19-44 The Reduction of Nitriles to Aldehydes

Hydro,oxy-de-nitrilo-tersubstitution

$$R{-}C{\equiv}N \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, } SnSl_2} RCH{=}O \qquad \underset{\mathbf{40}}{RCCl{=}\overset{+}{N}H_2Cl^-}$$

There are two principal methods for the reduction of nitriles to aldehydes.[1174] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt (**40**). Subsequent reduction of (**40**) with anhydrous $SnCl_2$ gives RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (Reaction **16-2**) to the aldehyde. The *Stephen reduction* is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[1175] It is also possible to prepare **40** in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the *Sonn–Müller method*. Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid converts aryl nitriles to aryl aldehydes.[1176]

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 molar equivalent of hydrogen and subsequent hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This reaction has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[1177] $LiAlH(NR_2)_3$,[1178] and Dibal-H.[1179] The metal hydride method is useful for aliphatic and aromatic nitriles.

OS **III**, 626, 818; **VI**, 631.

[1173] Borch, R.F. *Chem. Commun.* ***1968***, 442.

[1174] Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1271–1272.

[1175] Zil'berman, E.N.; Pyryalova, P.S. *J. Gen. Chem. USSR* ***1963****, 33,* 3348.

[1176] Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* ***2002****, 43*, 1395.

[1177] Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* ***1964****, 86,* 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* ***1988****, 36,* 249, see pp. 287–289, 438–448.

[1178] Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* ***1992****, 24*, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* ***1994****, 26*, 583.

[1179] Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* ***1970****, 35,* 858.

19-45 Reduction of Nitro Compounds to Amines

$$RNO_2 \xrightarrow[HCl]{Zn} RNH_2$$

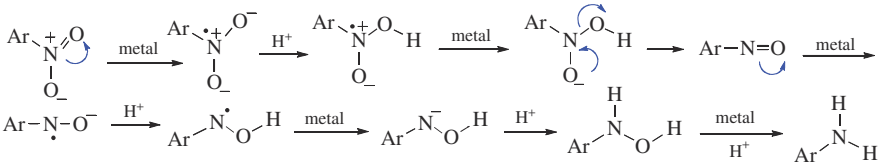
Both aliphatic[1180] and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.[1181] Chemoselective catalytic hydrogenation of nitro compounds is possible.[1182] Transfer hydrogenation is used to reduce nitro compounds.[1183] Indium metal in aq ethanol with ammonium chloride[1184] or with water in aq THF[1185] also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.[1186] Both samarium metal in methanol with ultrasound,[1187] and a mixture of SmI_2–water and an amine reduce nitro compounds.[1188] Alternative reduction methods use ultrasound with Al(Hg) in aq THF[1189] or with stannous chloride in an ionic liquid.[1190] Some other reagents used[1191] were $Et_3SiH/RhCl(PPh)_3$,[1192] $AlH_3—AlCl_3$, formic acid and Pd—C,[1193] or formic acid with Raney nickel in methanol.[1194] The reaction with sulfides or polysulfides is called the *Zinin reduction*.[1195] Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4$—Pd—C.[1196] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (although ketones are reduced, see Reaction **19-33**). With optically active alkyl substrates this method gives retention of configuration.[1197]

[1180] See Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1966****, 35,* 19.
[1181] For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* ***2004****, 69,* 4835.
[1182] Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *Org. Lett.* ***2008****, 10,* 1601. See also Gelder, E.A.; Jackson, S.D.; Lok, C.M. *Chem. Commun.* ***2005***, 522; Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. *Chem. Commun.* ***2005***, 5298.
[1183] Soltani, O.; Ariger, M.A.; Carreira, E.M. *Org. Lett.* ***2009****, 11,* 4196.
[1184] Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* ***2000****, 30,* 3745.
[1185] Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* ***2001***, 81.
[1186] Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* ***2003****, 44,* 77.
[1187] Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000****, 41,* 5603.
[1188] Ankner, T.; Hilmersson, G. *Tetrahedron Lett.* ***2007****, 48*, 5707.
[1189] Fitch, R.W.; Luzzio, F.A. *Tetrahedron Lett.* ***1994****, 35*, 6013.
[1190] Rai, G.; Jeong, J.M.; Lee, Y.-S.; Kim, H.W.; Lee, D.S.; Chung, J.-K.; Lee, M.C. *Tetrahedron Lett.* ***2005****, 46,* 3987.
[1191] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 821–828.
[1192] Brinkman, H.R. *Synth. Commun.* ***1996****, 26*, 973.
[1193] Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 443. See also, Terpko, M.O.; Heck, R.F. *J. Org. Chem.* ***1980****, 45*, 4992; Babler, J.H.; Sarussi, S.J. *Synth. Commun.* ***1981****, 11,* 925.
[1194] Gowda, D.C.; Gowda, A.S.P.; Baba, A.R.; Gowda, S. *Synth. Commun.* ***2000****, 30,* 2889.
[1195] For a review of the Zinin reduction, see Porter, H.K. *Org. React.* ***1973****, 20*, 455.
[1196] Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* ***1984****, 25*, 3415; Abiraj, K.; Srinivasa, G.R.; Gowda, D.C. *Synth. Commun.* ***2005****, 35,* 223.
[1197] Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* ***1988****, 29*, 5733.

Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (Reaction **19-80**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts (e.g., $NiCl_2$ or $CoCl_2$[1198] and $ZrCl_4$).[1199] Borohydride exchange resin (BER) in the presence of $Ni(OAc)_2$, however, gives the amine.[1200] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[1201] or in cleavage of the nitro group from the ring.[1202] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[1203] Bakers yeast reduces aromatic nitro compounds to aniline derivatives.[1204] A combination of $NaH_2PO_2/FeSO_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.[1205] Hydrazine on alumina, with $FeCl_3$ and microwave irradiation, accomplishes this reduction.[1206] Hydrazine–formic acid with Raney nickel in methanol reduces aromatic nitro compounds.[1207] Heating aromatic nitro compounds with 57% HI reduces the nitro group to the amino group.[1208]

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (Reaction **19-46**), hydrazobenzenes, azobenzenes (Reaction **19-80**), and azoxybenzenes (Reaction **19-79**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

The mechanisms of these reductions have not been much studied, although it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (Reaction **19-47**), and hydroxylamines can be isolated (Reaction **19-46**). With metals and acid the following path has been suggested[1209]:



[1198] See He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* ***1989****, 19,* 3047 and references cited therein.
[1199] Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* ***2000***, 683.
[1200] Yoon, N.M.; Choi, J. *Synlett* ***1993***, 135.
[1201] Severin, T.; Schmitz, R. *Chem. Ber.* ***1962****, 95*, 1417; Severin, T.; Adam, M. *Chem. Ber.* ***1963****, 96,* 448.
[1202] Kaplan, L.A. *J. Am. Chem. Soc.* ***1964****, 86,* 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* ***1970***, 63.
[1203] See Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London)* ***1983***, 477; Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* ***1983****, 56,* 3159.
[1204] Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* ***1994****, 35*, 3965.
[1205] Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* ***2000***, 993.
[1206] Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* ***2001****, 42*, 5347.
[1207] Gowda, S.; Gowda, D.C. *Tetrahedron* ***2002****, 58*, 2211.
[1208] Kumar, J.S.D.; Ho, M.M.; Toyokuni, T. *Tetrahedron Lett.* ***2001****, 42*, 5601.
[1209] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 M aq KCN with UV light.[1210] The reaction has also been performed electrochemically.[1211] When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

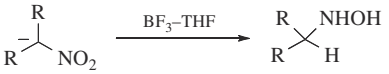
Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol, leads to the *N,N*-diallyl or dibenzyl aniline.[1212] A similar reaction occurs with nitrobenzene, allyl bromide, and In metal in aq acetonitrile.[1213]

OS **I**, 52, 240, 455, 485; **II**, 130, 160, 175, 254, 447, 471, 501, 617; **III**, 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV**, 31, 357; **V**, 30, 346, 552, 567, 829, 1067, 1130; **81**, 188.

19-46 Reduction of Nitro Compounds to Hydroxylamines

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,[1214] hydroxylamines are formed. Among other reagents used for this purpose have been SmI_2,[1215] N_2H_4—Rh—C,[1216] and $KBH_4/BiCl_3$.[1217] Borane in THF reduces aliphatic nitro enolate anions to hydroxylamines[1218]:



Nitro compounds have been reduced electrochemically, to hydroxylamines, as well as to other products.[1219]

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **VIII**, 16.

19-47 Reduction of Nitroso Compounds and Hydroxylamines to Amines

***N*-Dihydro-de-oxo-bisubstitution**

$$RNO \xrightarrow[HCl]{Zn} RNH_2$$

[1210] Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* ***1971***, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1971****, 90,* 1333.
[1211] Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1988***, 59.
[1212] Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetahedron Lett.* ***2000****, 41,* 4827.
[1213] Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* ***2001****, 31,* 2277.
[1214] See Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* ***1978****, 34*, 213.
[1215] Kende, A.S.; Mendoza, J.S. *Tetrahedron Lett.* ***1991****, 32,* 1699.
[1216] Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.* ***67***, 187.
[1217] Ren, P.D-D.; Pan, X.-W.; Jin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997****, 27*, 3497.
[1218] Feuer, H.; Bartlett, R.S.; Vincent, Jr., B.F.; Anderson, R.S. *J. Org. Chem.* ***1965****, 31,* 2880.
[1219] See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 188–198; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 285–313.

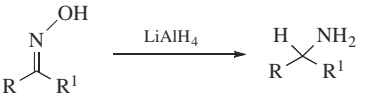
N-Hydro-de-hydroxylation or *N*-Dehydroxylation

$$RNHOH \xrightarrow[HCl]{Zn} RNH_2$$

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (Reaction **19-45**). Reaction with CuCl, and then phenylboronic acid (Reaction **12-28**), also reduces nitroso compounds to the amine.[1220] A hydroxylamine can be reduced to the amine with CS_2 in acetonitrile.[1221] Indium metal in EtOH/aq NH_4Cl reduces hydroxylamines to the amine.[1222] *N*-Nitroso compounds are similarly reduced to hydrazines ($R_2N—NO \rightarrow R_2N—NH_2$).[1223]

OS **I**, 511; **II**, 33, 202, 211, 418; **III**, 91; **IV**, 247. See also, OS **VIII**, 93.

19-48 Reduction of Oximes to Primary Amines or Aziridines

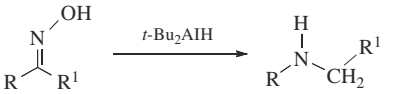


Both aldoximes and ketoximes can be reduced to primary amines with $LiAlH_4$. The reaction is slower than similar reduction of ketones, so that, for example, PhCOCH=NOH gave 34% PhCHOHCH=NOH.[1224] Among other reducing agents that give this reduction[1225] are zinc and acetic acid, BH_3,[1226] $NaBH_3CN—TiCl_3$,[1227] PMHS with Pd-C,[1228] and sodium and an alcohol.[1229] Catalytic hydrogenation is also effective.[1230] Reduction of oximes with In metal in acetic anhydride/acetic acid–THF leads to the acetamide.[1231]

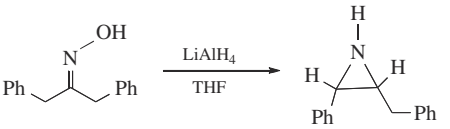
The reduction has been performed enantioselectively with Baker's yeast[1232] and with Ph_2SiH_2 and an optically active Rh complex catalyst.[1233] Oxime *O*-ethers are reduced to the amine with modest enantioselectivity using a chiral boron compound.[1234]

[1220] Yu, Y.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2004****, 6*, 2631.
[1221] Schwartz, M.A.; Gu, J.; Hu, X. *Tetrahedron Lett.* ***1992****, 33*, 1687.
[1222] Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* ***2003****, 5,* 1773.
[1223] See Lunn, G.; Sansone, E.B.; Keefer, L.K. *J. Org. Chem.* ***1984****, 49,* 3470.
[1224] Felkin, H. *C.R. Acad. Sci.* ***1950****, 230,* 304.
[1225] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 845–846.
[1226] Feuer, H.; Braunstein, D.M. *J. Org. Chem.* ***1969****, 34,* 1817.
[1227] Leeds, J.P.; Kirst, H.A. *Synth. Commun.* ***1988****, 18,* 777.
[1228] Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synlett* ***2000***, 1351.
[1229] See Sugden, J.K.; Patel, J.J.B. *Chem. Ind. (London)* ***1972***, 683.
[1230] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 139–159.
[1231] Harrison, J.R.; Moody, C.J.; Pitts, M.R. *Synlett* ***2000***, 1601.
[1232] Gibbs, D.E.; Barnes, D. *Tetrahedron Lett.* ***1990****, 31,* 5555.
[1233] Brunner, H.; Becker, R.; Gauder, S. *Organometallics* ***1986****, 5*, 739; Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* ***2001***, 2360.
[1234] Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Russey, E.; Tissandié, S.; Maftouh, M.; Roger, P. *Tetrahedron Asymmetry* ***2001****, 12,* 2185; Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F.G.; Ayala, A.M.; Correa, W.; De Jesús, M. *Org. Lett.* ***2007****, 9,* 1793.

When the reducing agent is Dibal-H, the product is a secondary amine, arising from a rearrangement[1235]:



With certain oximes (e.g., those of the type $ArCH_2CR{=}NOH$), treatment with $LiAlH_4$ gives aziridines,[1236] for example,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn—HCl and H_2 and Raney nickel.

Oximes have been reduced in a different way, to give imines ($RR'C{=}NOH \rightarrow RR'C{=}NH$), which are generally unstable, but which can be trapped to give useful products. Among reagents used for this purpose have been Bu_3P–SPh_2[1237] and $Ru_3(CO)_{12}$.[1238] Oximes can also be reduced to hydroxylamines (Reaction **19-42**). Nitrones have been reduced to imines using $AlCl_3{\cdot}6\ H_2O$/KI followed by $Na_2S_2O_3$—H_2O.[1239].

OS **II**, 318; **III**, 513; **V**, 32, 83, 373, 376.

19-49 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$RCH_2NO_2 \xrightarrow[HOAc]{Zn} RCH{=}NOH$$

Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in acetic acid[1240] or with other reagents, among them CS_2—NEt_3,[1241] $CrCl_2$,[1242] and (for α-nitro sulfones) $NaNO_2$.[1243] α-Nitro alkenes have been converted to oximes (—C=C—$NO_2 \rightarrow$ —CH—C=NOH) with sodium hypophosphite, In with aq. NH_4Cl/MeOH,[1244] and with Pb—HOAc—DMF, as well as with certain other reagents.[1245]

$$RCH_2NO_2 \xrightarrow{NaBH_2S_3} RC{\equiv}N$$

[1235] Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1983****, 24,* 4711.
[1236] For a review, see Kotera, K.; Kitahonoki, K. *Org. Prep. Proced.* ***1969****, 1,* 305. See Tatchell, A.R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1294; Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett.* ***1974***, 131; Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* ***1974***, 1605.
[1237] Barton, D.H.R.; Motherwell, W.B.; Simon, E.S.; Zard, S.Z. *J. Chem. Soc. Chem. Commun.* ***1984***, 337.
[1238] Akazome, M.; Tsuji, Y.; Watanabe, Y. *Chem. Lett.* ***1990***, 635.
[1239] Boruah, M.; Konwar, D. *Synlett* ***2001***, 795.
[1240] Johnson, K.; Degering, E.F. *J. Am. Chem. Soc.* ***1939****, 61*, 3194.
[1241] Albanese, D.; Landini, D.; Penso, M. *Synthesis* ***1990***, 333.
[1242] Hanson, J.R. *Synthesis* ***1974***, 1, pp. 7–8.
[1243] Zeilstra, J.J.; Engberts, J.B.F.N. *Synthesis* ***1974***, 49.
[1244] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 1447.
[1245] See Kabalka, G.W.; Pace, E.D.; Wadgaonkar, P.P. *Synth. Commun.* ***1990****, 20*, 2453; Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* ***1990***, 477.

Primary aliphatic nitro compounds can be reduced to aliphatic nitriles with *t*-BuN≡C/BuN=C=O.[1246] Secondary compounds give mostly ketones (e.g., nitrocyclohexane gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% *N*-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent (see also, Reaction **19-45**).

OS **IV**, 932.

19-50 Reduction of Azides to Primary Amines

N-Dihydro-de-diazo-bisubstitution

$$RN_3 \xrightarrow{LiAlH_4} RNH_2$$

Azides are easily reduced to primary amines by $LiAlH_4$, as well as by a number of other reducing agents,[1247] including $NaBH_4$, $NaBH_4/LiCl$,[1248] $NaBH_4/CoCl_2/H_2O$,[1249] $NaBH_4/ZrCl_4$,[1250] H_2 and a catalyst, Mg or Ca in MeOH,[1251] $Sm/NiCl_2$,[1252] Sm/I_2,[1253] $CeCl_3$,[1254] Zn/NH_4Cl/aq EtOH,[1255] baker's yeast,[1256] and In metal in EtOH.[1257] Triethylsilane has been used for the radical reduction of azides to amines.[1258]

Reaction with PPh_3 leads to a phosphazide ($Ph_3P{=}N{-}N{=}N{-}R$), which loses nitrogen in what is called the *Staudinger reaction*[1259]: a method to prepare phosphazo compounds, but in this case leads to reduction. Alkylation is possible, and the reaction of an alkyl azide with PMe_3, and then an excess of iodomethane, leads to the *N*-methylated amine.[1260] The reaction is diastereoselective.[1261] Chiral *N*-heterocyclic carbenes catalyze the *Staudinger reaction* of ketenes with imines to form β-lactam derivatives.[1262] This reaction, combined with RX → RN_3 (**10-43**), is an important way of converting alkyl halides (RX) to primary amines (RNH_2); in some cases the two procedures have been

[1246] El Kaim, L.; Gacon, A. *Tetrahedron Lett.* ***1997****, 38*, 3391.

[1247] For a review, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988****, 88,* 297, see pp. 321–327. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 815–820; Rolla, F. *J. Org. Chem.* ***1982****, 47,* 4327.

[1248] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000****, 30*, 4495.

[1249] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* ***2000***, 646.

[1250] Chary, K.P.; Ram, S.R.; Salahuddin, S.; Iyengar, D.S. *Synth. Commun.* ***2000****, 30*, 3559.

[1251] Maiti, S.N.; Spevak, P.; Narender Reddy, A.V. *Synth. Commun.* ***1988****, 18,* 1201.

[1252] Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* ***2002****, 32*, 189.

[1253] Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* ***1997****, 38*, 1065.

[1254] Bartoli, G.; Di Antonio, G.; Giovannini, R.; Giuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E. *J. Org. Chem.* ***2008****, 73*, 1919.

[1255] Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* ***2002****, 32*, 3279.

[1256] Kamal, A.; Damayanthi, Y.; Reddy, B.S.N.; Lakminarayana, B.; Reddy, B.S.P. *Chem. Commun.* ***1997***, 1015; Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synlett* ***1996***, 1193.

[1257] Reddy, G.V.; Rao, G.V.; Iyengar, D.S. *Tetrahedron Lett.* ***1999****, 40*, 3937.

[1258] Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* ***2006****, 71*, 5822.

[1259] Staudinger, H.; Meyer, J. *Helv. Chim. Acta* ***1919****, 2,* 635. See Golobov, Y.G.; Zhmurova, I.N.; Kasukhin, L.F. *Tetrahedron* ***1981****, 37*, 437; Tian, W.Q.; Wang, Y.A. *J. Org. Chem.* ***2004****, 69,* 4299; Lin, F.L.; Hoyt, H.M.; van Halbeek, H.; Bergman, R.G.; Bertozzi, C.R. *J. Am. Chem. Soc.* ***2005****, 127,* 2686. For a modification that leads to β-lactams, see Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* ***2006****, 128,* 6060.

[1260] Kato, H.; Ohmori, K.; Suzuki, K. *Synlett* ***2001***, 1003.

[1261] Hu, L.; Wang, Y.; Li, B.; Du, D.-M.; Xu, J. *Tetrahedron* ***2007****, 63*, 9387.

[1262] Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* ***2008****, 10,* 277.

combined into one laboratory step.[1263] Sulfonyl azides (RSO_2N_3) have been reduced to sulfonamides (RSO_2NH_2) by irradiation in isopropyl alcohol[1264] and with NaH.[1265]

OS **V**, 586; **VII**, 433.

19-51 Reduction of Miscellaneous Nitrogen Compounds

Isocyanate-methylamine transformation

$$R{-}N{=}C{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

Isothiocyanate-methylamine transformation

$$R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

***N,N*-Dihydro-addition**

$$Ar{-}N{=}N{-}Ar \xrightarrow[cat]{H_2} Ar{-}NH{-}NH{-}Ar$$

Diazonium-arylhydrazone reduction

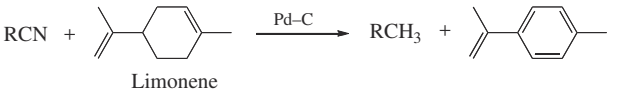
$$ArN_2^+Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$$

***N*-Hydro-de-nitroso-substitution**

$$R_2N{-}NO \xrightarrow[Ni]{H_2} R_2NH$$

Isocyanates and isothiocyanates are reduced to methylamines on treatment with $LiAlH_4$. Azo compounds are not usually reduced by $LiAlH_4$,[1266] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, Reaction **19-80**), but they can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[1267] (see Reaction **15-11**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.[1268] The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (Reaction **19-69**). *N*-Nitrosoamines can be denitrosated to secondary amines by a number of reducing agents, including H_2 and a catalyst,[1269] $BF_3{-}THF{-}NaHCO_3$,[1270] and $NaBH_4{-}TiCl_4$,[1271] as well as by hydrolysis.[1272]

[1263] See Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. ***1987***, 487. The Reactions **10-48**, **10-43**, and **19-50** have also been accomplished in one laboratory step: Koziara, A. *J. Chem. Res. (S)* ***1989***, 296.
[1264] Reagen, M.T.; Nickon, A. *J. Am. Chem. Soc.* ***1968***, *90*, 4096.
[1265] Lee, Y.; Closson, W.D. *Tetrahedron Lett.* ***1974***, 381.
[1266] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 601, 604–614.
[1267] See Ioffe, B.V.; Sergeeva, Z.I.; Dumpis,Yu.Ya. *J. Org. Chem. USSR* ***1969***, *5,* 1683.
[1268] Huisgen, R.; Lux, R. *Chem. Ber.* ***1960***, *93,* 540.
[1269] Enders, D.; Hassel, T.; Pieter, R.; Renger, B.; Seebach, D. *Synthesis* ***1976***, 548.
[1270] Jeyaraman, R.; Ravindran, T. *Tetrahedron Lett.* ***1990***, *31*, 2787.
[1271] Kano, S.; Tanaka, Y.; Sugino, E.; Shibuya, S.; Hibino, S. *Synthesis* ***1980***, 741.
[1272] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40,* 34, pp. 41–42.



Limonene

A cyano group can be reduced to a methyl group by treatment with a terpene (e.g., limonene), which acts as reducing agent in the presence of Pd–charcoal.[1273] Hydrogen gas (H_2) is also effective,[1274] although higher temperatures are required. The R group may be alkyl or aryl.

Aryl nitro compounds are reduced to diaryl hydrazines with Al−KOH in methanol.[1275]

OS **I**, 442; **III**, 475. Also see, OS **V**, 43.

D. Reactions in which a Heteroatom Is Removed from the Substrate

19-52 Reduction of Silanes to Methylene Compounds

_Si_-Hydrogen-uncoupling

$$R-SiR'_3 \longrightarrow R-H$$

In certain cases, the C−Si bond of silanes can be converted to C−H. α-Silyl esters are reduced to esters with mercuric acetate and tetrabutylammonium fluoride, for example.[1276]

19-53 Reduction of Alkyl Halides

Hydro-de-halogenation or Dehalogenation

$$RX \longrightarrow RH$$

This type of reduction can be accomplished with many reducing agents.[1277] A powerful but highly useful reagent ($LiAlH_4$)[1278] reduces almost all types of alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.[1279] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, lithium triethylborohydride ($LiEt_3BH$; Super hydride), rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.[1280] A complex formed from lithium trimethoxyaluminum hydride [$LiAlH(OMe)_3$] and CuI is another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides.[1281] Sodium borohydride ($NaBH_4$) is a milder reducing agent that reduces primary, secondary, and some tertiary[1282]

[1273] Kindler, K.; Lührs, K. *Chem. Ber.* ***1966****, 99,* 227; *Liebigs Ann. Chem.* ***1967****, 707,* 26.
[1274] See also, Brown, G.R.; Foubister, A.J. *Synthesis* ***1982***, 1036.
[1275] Khurana, J.M.; Singh, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 1893.
[1276] Poliskie, G.M.; Mader, M.M.; van Well, R. *Tetrahedron Lett.* ***1999****, 40,* 589.
[1277] See Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 29–39.
[1278] See Pizey, J.S. *Synthetic reagents,* Vol. 1, Wiley, NY, ***1974***, pp. 101–294; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajós, A. *Complex Hydrides,* Elsevier, NY, ***1979***.
[1279] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1982***, *47*, 276.
[1280] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 849; ***1983***, *48*, 3085.
[1281] Masamune, S.; Bates, G.S.; Georghiou, P.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3686.
[1282] Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.

halides in good yield, in a dipolar aprotic solvent (e.g., Me_2SO, DMF, or sulfolane)[1283] at room temperature or above without affecting other functional groups that would be reduced by $LiAlH_4$ (e.g., CO_2H, CO_2R, CN).[1284] A mixture of $NaBH_4$ and $InCl_3$ efficiently reduces secondary bromides.[1285] Borohydride exchange resin is also an effective reducing agent in the presence of metal catalysts [e.g., $Ni(OAc)_2$].[1286]

Other reducing agents[1287] include Zn (with acid or base), $SnCl_2$, and Et_3SiH in the presence of an $AlCl_3$,[1288] and also an Ir[1289] or In[1290] catalyst. Diethyl phosphonate–Et_3N,[1291] phosphorus tris(dimethylamide) $[(Me_2N)_3P]$,[1292] and organotin hydrides (R_nSnH_{4-n})[1293] (chiefly Bu_3SnH) usually used in conjunction with a radical-initiator (e.g., AIBN),[1294] or with transition metal salts (e.g., $InCl_3$).[1295] A water-soluble organotin hydride has been developed [$(MeOCH_2CH_2OCH_2CH_2CH_2)_3SnH$], which reduces alkyl halides.[1296] Raney nickel in 2-propanol reduces primary iodides in the presence of a lactone moiety.[1297] Aluminum amalgam efficiently reduced an iodohydrin to the alcohol.[1298]

Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation.[1299] Raney nickel by itself can reduce alkyl halides.[1300] Homogeneous, chiral transition metal complexes can be used for the asymmetric hydrogenation of halides.[1301]

Alkali metals (e.g., Li[1302] or Na[1303] in *t*-BuOH or THF) are good reducing agents for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens). Zinc and ammonium chloride in alcohol facilitates

[1283] Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* ***1978***, *43*, 2259.

[1284] See Bergbreiter, D.E.; Blanton, J.R. *J. Org. Chem.* ***1987***, *52*, 472.

[1285] Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* ***2002****, 124*, 906.

[1286] Yoon, N.M.; Lee, H.J.; Ahn, J.H.; Choi, J. *J. Org. Chem.* ***1994***, *59*, 4687.

[1287] See Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 103; Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 29–39.

[1288] Doyle, M.P.; McOsker, C.C.; West, C.T. *J. Org. Chem.* ***1976***, *41*, 1393; Parnes, Z.N.; Romanova, V.S.; Vol'pin, M.E. *J. Org. Chem. USSR* ***1988***, *24*, 254.

[1289] Yang, J.; Brookhart, M. *J. Am. Chem. Soc.* ***2007****, 129*, 12656.

[1290] Miura, K.; Tomita, M.; Yamada, Y.; Hosomi, A. *J. Org. Chem.* ***2007****, 72*, 787.

[1291] Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1881.

[1292] Downie, I.M.; Lee, J.B. *Tetrahedron Lett.* ***1968***, 4951.

[1293] Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* ***1963***, *28*, 703. For a novel trialkyltin hydride, see Gastaldi, S.; Stein, D. *Tetrahedron Lett.* ***2002****, 43*, 4309.

[1294] See Neumann, W.P. *Synthesis* ***1987***, 665; Kuivila, H.G. *Synthesis* ***1970***, 499, *Acc. Chem. Res.* ***1968***, *1*, 299; Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* ***1996***, *37*, 6759.

[1295] Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* ***2004****, 6*, 4981.

[1296] Light, J.; Breslow, R. *Tetrahedron Lett.* ***1990***, *31*, 2957.

[1297] Mebane, R.C.; Grimes, K.D.; Jenkins, S.R.; Deardorff, J.D.; Gross, B.H. *Synth. Commun.* ***2002****, 32*, 2049.

[1298] Wang, Y.-C.; Yan, T.-H. *Chem. Commun.* ***2000***, 545.

[1299] Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***; Kantam, M.L.; Rahman, A.; Bandyopadhyay, T.; Haritha, Y. *Synth. Commun.* ***1999****, 29* , 691. See Ye, P.; Gellman, A.J. *J. Am. Chem. Soc.* ***2008****, 130*, 8518.

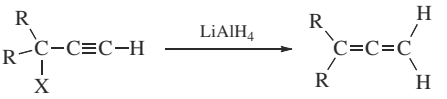
[1300] See Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

[1301] Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* ***2007****, 9,* 255.

[1302] See Fieser, L.F.; Sachs, D.H. *J. Org. Chem.* ***1964***, *29*, 1113; Berkowitz, D.B. *Synthesis* ***1990***, 649.

[1303] See Gassman, P.G.; Aue, D.H.; Patton, D.S. *J. Am. Chem. Soc.* ***1968***, *90*, 7271; Gassman, P.G.; Marshall, J.L. *Org. Synth.* ***V***, 424.

dehalogenation with microwave irradiation.[1304] Nickel boride facilitates debromination.[1305] Propargylic halides can often be reduced with allylic rearrangement to give allenes.[1306]



The choice of a reducing agent usually depends on what other functional groups are present since each reducing agent reduces certain groups and not others. This type of selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide), but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α-halo ketones, leaving the carbonyl group intact.[1307] Among them are decaborane with 10% Pd/C,[1308] Bi in aq THF[1309] or In metal in water,[1310] and *i*-$Bu_2AlH-SnCl_2$.[1311] Ionic liquids promote the selective debromination of α-bromo ketones.[1312] Debromination is also induced by indium metal in a carboxylic acid.[1313] In a similar chemoselective reaction, the halogen in α-haloimines has been reduced with $SnCl_2$/MeOH without reducing the C=N bond.[1314]

Tertiary alkyl, benzylic, and allylic halides are reduced by $NaBH_3CN-SnCl_2$[1315], but do not react with primary or secondary alkyl or aryl halides. Sodium cyanoborohydride ($NaBH_3CN$) in HMPA is another highly selective reagent, in this case for primary and secondary iodo and bromo groups.[1316] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.[1317] See Section 19.B.ii-A for a discussion of selectivity in reduction reactions.

Alkyl halides, including fluorides and polyhalides, can be reduced with Mg and a secondary or tertiary alcohol (most often 2-propanol).[1318] This is actually an example of the occurrence in one step of the sequence:

$$RX \longrightarrow RMgX \xrightarrow{H^+} RH$$

More often the process is carried out in two separate steps (Reactions **12-36** and **12-22**).

[1304] Li, J.; Ye, D.; Liu, H.; Luo, X.; Jiang, H. *Synth. Commun.* ***2008****, 38,* 567.
[1305] Khurana, J.M.; Kandpal, B.M.; Kukreja, G.; Sharma, P. *Can. J. Chem.* ***2006****, 84*, 1019.
[1306] See Claesson, A.; Olsson, L. *J. Am. Chem. Soc.* ***1979***, *101*, 7302.
[1307] See Noyori, R.; Hayakawa, Y. *Org. React.* ***1983***, *29*, 163.
[1308] Lee, S.H.; Jung, Y.J.; Cho, Y.J.; Yoon, C.-O.M.; Hwang, H.-J.; Yoon, C.M. *Synth. Commun.* ***2001****, 31*, 2251.
[1309] Ren, P.-D.; Hin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 2577.
[1310] Park, L.; Keum, G.; Kang, S.B.; Kim, K.S.; Kim, Y. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 4462.
[1311] Oriyama, T.; Mukaiyama, T. *Chem. Lett.* ***1984***, 2069.
[1312] Ranu, B.C.; Chattopadhyay, K.; Jana, R. *Tetrahedron* ***2007****, 63,* 155.
[1313] Lee, S.H.; Cho, M.Y.; Nam, M.H.; Park, Y.S.; Yoo, B.W.; Lee, C.-W.; Yoon, C.M. *Synth. Commun.* ***2005****, 35,* 1335.
[1314] Aelterman, W.; Eeckhaut, A.; De Kimpe, N. *Synlett* ***2000***, 1283.
[1315] Kim, S.; Ko, J.S. *Synth. Commun.* ***1985***, *15*, 603.
[1316] Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E. *J. Org. Chem.* ***1977***, *42*, 82.
[1317] See Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* ***1981***, *22*, 2583. See also, Brandänge, S.; Dahlman, O.; Ölund, J. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 141.
[1318] Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. *Proc. Chem. Soc.* ***1963***, 219.

Vinyl halides can be reduced to the corresponding alkene is some cases.[1319] When vinyl dibromides (e.g., $RCH{=}CBr_2$) are treated with $(MeO)_2P(=O)H$ and triethylamine, for example, the product is the vinyl bromide ($RCH{=}HBr$).[1320] Indium metal in ethanol accomplishes the same transformation.[1321] Similar reduction occurs when vinyl diiodides are treated with Zn−Cu in acetic acid.[1322]

With $LiAlH_4$ and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion equivalents. The mechanism is S_N2 rather than S_N1, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since *Walden inversion* has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with $LiAlH_4$ indicate that the S_N1 mechanism can take place.[1323] There is evidence that $LiAlH_4$ and other metal hydrides can also reduce halides by an SET mechanism,[1324] especially those (e.g., vinylic,[1325] cyclopropyl,[1326] or bridgehead halides) that are resistant to nucleophilic substitution. Reduction of halides by $NaBH_4$ in 80% aq diglyme[1327] and by BH_3 in nitromethane[1328] takes place by an S_N1 mechanism. It is known that $NaBH_4$ in sulfolane reduces tertiary halides possessing a β hydrogen by an elimination–addition mechanism.[1329]

The mechanism for reduction of alkyl halides is not always nucleophilic substitution. For example, reductions with organotin hydrides generally[1330] take place by free radical mechanisms,[1331] as do those with $Fe(CO)_5$.

OS **I**, 357, 358, 548; **II**, 320, 393; **V**, 424; **VI**, 142, 376, 731; **VIII**, 82. See also, OS **VIII**, 583.

19-54 Reduction of Alcohols[1332]

Hydro-de-hydroxylation or Dehydroxylation

$$ROH + H_2 \xrightarrow{\text{cat}} RH$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.[1333] Diaryl

[1319] See Curran, D.P. *Synthesis* ***1988***, 417, 489.
[1320] Abbas S.; Hayes, C.J.; Worden, S. *Tetrahedron Lett.* ***2000****, 41*, 3215.
[1321] Ranu, B.C.; Samanta, S.; Guchhait, S.K. *J. Org. Chem.* ***2001****, 66*, 4102.
[1322] Kdota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrhaedron Lett.* ***2003****, 44*, 8645.
[1323] See Kraus, W.; Chassin, C. *Tetrahedron Lett.* ***1970***, 1443. See Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* ***2001****, 42*, 939.
[1324] Ashby, E.C.; Deshpande, A.K. *J. Org. Chem.* ***1994***, *59*, 3798. See however Park, S.; Chung, S.; Newcomb, M. *J. Org. Chem.* ***1987***, *52*, 3275.
[1325] Chung, S. *J. Org. Chem.* ***1980***, *45*, 3513.
[1326] Hatem, J.; Waegell, B. *Tetrahedron* ***1990***, *46*, 2789.
[1327] Bell, H.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1966***, *88*, 1473.
[1328] Matsumura, S.; Tokura, N. *Tetrahedron Lett.* ***1969***, 363.
[1329] Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971****, 36*, 1568.
[1330] For an exception, see Carey, F.A.; Tramper, H.S. *Tetrahedron Lett.* ***1969***, 1645.
[1331] Tanner, D.D.; Singh, H.K. *J. Org. Chem.* ***1986***, *51*, 5182.
[1332] For a review, see Müller, P. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 515–522.
[1333] See Rylander, P.N. *Hydrogenation Methods,* Academic Prss, NY, ***1985***, pp. 157–163, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 449–468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, E.I. *Russ. Chem. Rev.* ***1966***, *35*, 546.

and triarylcarbinols are similarly easy to reduce with $LiAlH_4-AlCl_3$,[1334] with $NaBH_4$ in F_3CCOOH,[1335] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used,[1336] including $Me_3SiCl-NaI$,[1337] $Et_3SiH-BF_3$,[1338] $SmI_2-THF-HMPA$,[1339] and Sn/HCl. The reduction of secondary alcohols was accomplished using Ph_2SiClH and $InCl_3$.[1340] 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.[1341] Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.[1342] Reagents that reduce the OH group of α–hydroxy ketones without affecting the C=O group include red phosphorus–iodine,[1343] and Me_3SiI.[1344]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (Reaction **19-57**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine–SO_3 in THF, followed by $LiAlH_4$.[1345] Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl.[1346] In this case, the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see Reaction **19-59**.

The mechanisms of most alcohol reductions are obscure.[1347] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[1348] The mechanism of electroreduction of allylic alcohols in acidic aqueous media has been examined.[1349]

OS **I**, 224; **IV**, 25, 218, 482; **V**, 339; **VI**, 769.

19-55 Reduction of Phenolic and Other Hydroxyaryl Compounds

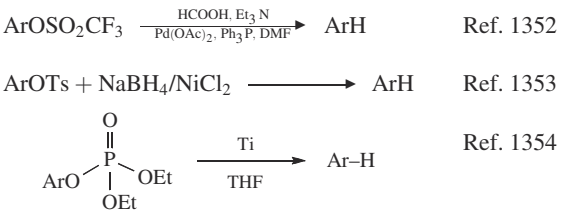
Hydro-de-hydroxylation or Dehydroxylation, and so on

$$\text{ArOH} \xrightarrow{\text{Zn}} \text{ArH}$$

[1334] Avendaño, C.; de Diego, C.; Elguero, J. *Monatsh. Chem.* ***1990***, *121*, 649.
[1335] See Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Also see, Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* ***1990***, *20*, 487.
[1336] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 44–46.
[1337] Cain, G.A.; Holler, E.R. *Chem. Commun.* ***2001***, 1168.
[1338] Orfanopoulos, M.; Smonou, I. *Synth. Commun.* ***1988***, *18*, 833; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* ***1988***, *29*, 5793; Wustrow, D.J.; Smith, III, W.J.; Wise, L.D. *Tetrahedron Lett.* ***1994***, *35*, 61.
[1339] Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.
[1340] Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* ***2001***, *66,* 7741.
[1341] Krafft, M.E.; Crooks, III, W.J. *J. Org. Chem.* ***1988***, *53*, 432. For another catalyst, see Parnes, Z.N.; Shaapuni, D.Kh.; Kalinkin, M.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1592.
[1342] See Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* ***VI***, 769; *Tetrahedron* ***1977***, *33*, 511. For another reagent, see Lee, J.; Alper, H. *Tetrahedron Lett.* ***1990***, *31*, 4101.
[1343] Ho, T.L.; Wong, C.M. *Synthesis* ***1975***, 161.
[1344] Ho, T.L. *Synth. Commun.* ***1979***, *9*, 665.
[1345] Corey, E.J.; Achiwa, K. *J. Org. Chem.* ***1969***, *34*, 3667.
[1346] Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* ***1981***, 32.
[1347] See Garbisch, Jr., E.W.; Schreader, L.; Frankel, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4233; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.
[1348] Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.
[1349] Shukun, H.; Yougun, S.; Jindong, Z.; Jian, S. *J. Org. Chem.* ***2001***, *66*, 4487.

Oxygenated compounds (e.g., phenols, phenolic esters, and ethers) can be reduced.[1350] Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see Reaction **15-13**) is a side product.[1351]

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:



With a Pd−C catalyst, phenol derivatives are deoxygenated using Mg and MeO in the presence of ammonium acetate.[1355] Palladium-on-carbon also mediated hydrodexoygenation of phenol derivatives in the presence of diethylamine.[1356]

OS **VI**, 150. See also, OS **VII**, 476.

19-56 Replacement of Alkoxyl by Hydrogen

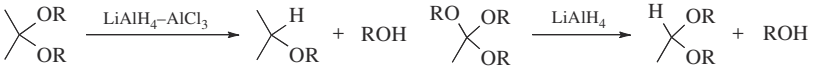
Hydro-de-alkoxylation or Dealkoxylation

$$R-O-R' \longrightarrow R-H + R'-H \qquad R, R' = \text{allyl, aryl, vinyl, benzylic}$$

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported[1357] [e.g., THF treated with $LiAlH_4-AlCl_3$[1358] or with a mixture of $LiAlH(O\textit{t}\text{-Bu})_3$ and Et_3B[1359] gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers].[1360] Certain types of ethers can be cleaved quite well by reducing agents.[1361]

[1350] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 44–52ff.
[1351] Shuikin, N.I.; Erivanskaya, L.A. *Russ. Chem. Rev.* ***1960****, 29,* 309, see pp. 313–315. See also, Bagnell, L.J.; Jeffery, E.A. *Aust. J. Chem.* ***1981****, 34,* 697.
[1352] Cacchi, S.; Ciattini. P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1986****, 27*, 5541. See also, Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* ***1990***, *55*, 350.
[1353] Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1897.
[1354] Welch, S.C.; Walters, M.E. *J. Org. Chem.* ***1978****, 43,* 4797. See also, Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1973****, 38,* 2314.
[1355] Sajiki, H.; Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Hirota, K. *Org. Lett.* ***2006****, 8,* 987.
[1356] Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* ***2007****, 63,* 1270.
[1357] Ranu, B.C.; Bhar, S. *Org. Prep. Proceed. Int.* ***1996***, *28*, 371.
[1358] Bailey, W.J.; Marktscheffel, F. *J. Org. Chem.* ***1960***, *25*, 1797.
[1359] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1979***, *44*, 3678.
[1360] For a review of ether reduction, see Müller, P. in Patai, S. *The Chemisry of Functional Groups, Supplement E,* pt. 1, Wiley, NY, ***1980***, pp. 522–528.
[1361] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 1013–1019.

Among these are allyl aryl,[1362] vinyl aryl,[1363] benzylic ethers,[1333,1364] and anisole[1365] (for epoxides, see Reaction **19-35**). 7-Oxobicyclo[2.2.1]heptanes can be reductively cleaved with Dibal-H and nickel catalysts.[1366] α-Methoxy ketones are demethoxylated (O=C−COMe → O=C−CH) with SmI_2.[1367]



Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection (Reaction **16-5**). However, a combination of $LiAlH_4$ and $AlCl_3$[1368] does reduce acetals and ketals, removing one group, as shown above.[1369] The actual reducing agents in this case are primarily chloroaluminum hydride (AlH_2Cl) and dichloroaluminum hydride ($AlHCl_2$), which are formed from the reagents.[1370] This conversion can also be accomplished with Dibal-H,[1371] as well as with other reagents.[1372] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (Reaction **10-6**). Mixed ketals [R(OMe)OR′] can be demethoxylated (to give RHOR′) with $Bn_3SnCl/NaCHBH_3$ in the presence of AIBN.[1373]

OS **III**, 693; **IV**, 798; **V**, 303. Also see, OS **III**, 742; **VII**, 386.

19-57 Reduction of Tosylates and Similar Compounds

Hydro-de-sulfonyloxy-substitution

$$RCH_2OTs + LiAlH_4 \longrightarrow RCH_3$$

Tosylates and other sulfonates can be reduced[1374] with $LiAlH_4$,[1375] with $NaBH_4$ in a dipolar aprotic solvent,[1376] with $LiEt_3BH$, with *i*-Bu_2AlH (Dibal-H),[1377] or with $Bu_3SnH-NaI$.[1378] The Ni catalyzed reduction of aryl tosylates proceeds in the presence

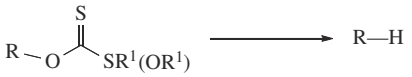
[1362] Rao, G.V.; Reddy, D.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000****, 30,* 3565.
[1363] Tweedie, V.L.; Barron B.G. *J. Org. Chem.* ***1960***, *25*, 2023. See also, Hutchins, R.O.; Learn, K. *J. Org. Chem.* ***1982***, *47*, 4380.
[1364] Shi, L.; Xia, W.J.; Zhang, F.M.; Tu, Y.Q. *Synlett* ***2002***, 1505. See also, Olivero, S.; Duñach, E. *Tetrahedron Lett.* ***1997***, *38*, 6193.
[1365] Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* ***1994***, *35*, 8727.
[1366] Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* ***1995***, *117*, 532.
[1367] Mikami, K.; Yamaoka, M.; Yoshida, A. *Synlett* ***1998***, 607.
[1368] See Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 1–94.
[1369] Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* ***1962***, *84*, 2371.
[1370] Ashby, E.C.; Prather, J. *J. Am. Chem. Soc.* ***1966***, *88*, 729; Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* ***1967***, *45*, 207.
[1371] See Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* ***1983***, 1593.
[1372] See Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* ***2004****, 45*, 4499; Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 931–942.
[1373] Srikrishna, A.; Viswajanani, R. *Synlett* ***1995***, 95.
[1374] For a list of substrate types and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations, 2nd* ed., Wiley–VCH, NY, ***1999***, pp. 46–52.
[1375] See Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. *J. Org. Chem.* ***2005****, 70,* 207.
[1376] Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495.
[1377] Janssen, C.G.M.; Hendriks, A.H.M.; Godefroi, E.F. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 220.
[1378] Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* ***1983***, 795.

of borane hydrides.[1379] The scope of the reaction seems to be similar to that of **19-53**. When the reagent is $LiAlH_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O, but the order is reversed in diglyme.[1380] The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa.

OS **VI**, 376, 762; **VIII**, 126. See also, OS **VII**, 66.

19-58 Hydrogenolysis of esters (Barton–McCombie Reaction)

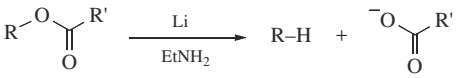
Hydro-de-thioacetoxylation



Alcohols can readily be converted to carbonate and thiocarbonate derivatives. Under radical conditions,[1381] using AIBN (Sec. 14.A.i) and Bu_3SnH, the carbonate or thiocarbonate unit is reduced and replaced with hydrogen. The overall process is reduction of the ROH unit to RH and is called the *Barton–McCombie reaction*.[1382] Both $PhSiH_3$/AIBN[1383] and $PhSiH_2-BEt_3{\cdot}O_2$ can be used.[1384] This reaction can be catalytic in Bu_3SnH.[1385] Variations include reduction of ROCSNHPh derivatives using Ph_3SiH/BEt_3.[1386] Another variation used water as the hydrogen atom source when BMe_3 was used.[1387] Tetrabutylammonium peroxydisulfate and formate ion has been used.[1388]

19-59 Reductive Cleavage of Carboxylic Esters

Hydro-de-acyloxylation or Deacyloxylation



The alkyl group (R) of certain carboxylic esters can be reduced to RH[1389] by treatment with lithium in ethylamine.[1390] The reaction is successful when R is a tertiary or a sterically

[1379] Kogan, V. *Tetrahedron Lett.* ***2006****, 47*, 7515.
[1380] Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 2550.
[1381] Barton, D.H.R.; Jaszberenyi, J.Cs.; Tang, D. *Tetrahedron Lett.* ***1993***, *34*, 3381.
[1382] See Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* ***1983***, *105*, 4059; Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997****, 119,* 6949; *The Merck Index, 14th Ed.* Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p ONR-6; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley-Interscience, New Jersey, ***2005***, pp. 68–69.
[1383] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 2793.
[1384] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 7193.
[1385] Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997***, *119*, 6949.
[1386] Oba, M.; Nishiyama, K. *Tetrahedron* ***1994***, *50*, 10193.
[1387] Spiegel, D.A.; Wiberg, K.B.; Schacherer, L.N.; Medeiros, M.R.; Wood, J.L. *J. Am. Chem. Soc.* ***2005****, 127,* 12513.
[1388] Park, H.S.; Lee, H.Y.; Kim, Y.H. *Org. Lett.* ***2005****, 7,* 3187.
[1389] See Hartwig, W. *Tetrahedron* ***1983***, *39*, 2609.
[1390] Barrett, A.G.M.; Godfrey, C.R.A.; Hollinshead, D.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; Joukhadar, L.; McGhie, J.F.; Misra, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 1501. See Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. *J. Org. Chem.* ***2000****, 65*, 7098.

hindered secondary alkyl group. A free radical mechanism is likely.[1391] Similar reduction, also by a free radical mechanism, has been reported with sodium in HMPA–*t*-BuOH.[1392] In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method of accomplishing Reaction **19-54** for tertiary R.[1393] The same thing can be done for primary and secondary R by treating alkyl chloroformates (ROCOCl) with tri-*n*-propylsilane in the presence of *tert*-butylperoxide[1394] and by treating thiono ethers [ROC(=S)W, where W can be OAr or other groups] with Ph_2SiH_2[1395] or Ph_3SiH[1396] and a free radical initiator. Allylic acetates can be reduced with $NaBH_4$ and a Pd complex,[1397] and with SmI_2–Pd(0).[1398] For other carboxylic ester reductions, see Reactions **19-62**, **19-38**, and **19-65**.

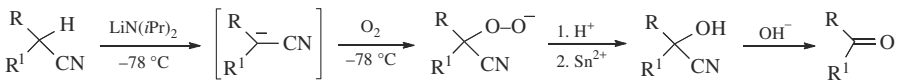
Note that acid chlorides can be reduced (R–COCl → R–H) using $(Me_3Si)_3SiH$/AIBN.[1399]

OS **VII**, 139.

19-60 Reduction of Hydroperoxides and Peroxides

$$R{-}O{-}O{-}H \xrightarrow{LiAlH_4} ROH$$

Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P[1400] or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[1401]



The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.[1402] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at −78 °C followed by O_2. The hydroperoxy nitrile is then reduced to the cyanohydrin, which is cleaved (the reverse of Reaction **16-52**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R′ = H).

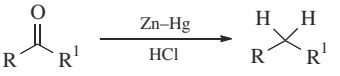
[1391] Barrett, A.G.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; McGhie, J.F. *J. Chem. Soc. Chem. Commun.* ***1979***, 1173.
[1392] Deshayes, H.; Pete, J. *Can. J. Chem.* ***1984***, *62*, 2063.
[1393] Also see, Barton, D.H.R.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1603.
[1394] Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1207.
[1395] See Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* ***1990***, *31*, 4681, and references cited therein. For similar methods, see Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2578; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *Tetrahedron Lett.* ***1990***, *31*, 5093.
[1396] Oba, M.; Nishiyama, K. *Synthesis* ***1994***, 624.
[1397] Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* ***1980***, *21*, 27. See also, Ipaktschi, J. *Chem. Ber.* ***1984***, *117*, 3320.
[1398] Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1986***, *27*, 601, 5237. See also, Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30,* 2945.
[1399] Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* ***1992***, *33*, 1787.
[1400] See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 318–320.
[1401] Rebeller, M.; Clément, G. *Bull. Soc. Chim. Fr.* ***1964***, 1302.
[1402] Freerksen, R.W.; Selikson, S.J.; Wroble, R.R.; Kyler, K.S.; Watt, D.S. *J. Org. Chem.* ***1983***, *48,* 4087.

Peroxides are cleaved to 2 molar equivalents of alcohols by $LiAlH_4$, Mg/MeOH,[1403] or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$.[1404] In a similar reaction, disulfides (RSSR′) can be converted to sulfides RSR′ by treatment with tris(diethylamino)phosphine $[(Et_2N)_3P]$.[1405]

OS **VI**, 130.

19-61 Reduction of Carbonyl to Methylene in Aldehydes and Ketones

Dihydro-de-oxo-bisubstitution



There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[1406] Two old but still popular methods are the *Clemmensen reduction*[1407] and the *Wolff–Kishner reduction*. The *Clemmensen reduction* consists of heating the aldehyde or ketone with zinc amalgam and aq HCl.[1408] Ketones are reduced more often than aldehydes. In the *Wolff–Kishner reduction*,[1409] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang–Minlon modification*[1410] of the *Wolff–Kishner reduction*, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. A microwave-assisted *Huang–Minlon* procedure has been reported.[1411] The reaction can be carried out under more moderate conditions (room temperature) in DMSO with potassium *tert*-butoxide as base.[1412] A new modification of the reduction treats a ketone with hydrazine in toluene with microwave irradiation, and subsequent reaction with KOH with microwave irradiation completes the *Wolff–Kishner reduction*.[1413] The *Wolff–Kishner reduction* can also be applied to the semicarbazones of aldehydes or ketones.

The *Clemmensen reduction* is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases, the *Wolff–Kishner reduction* is quite useful. For high-molecular-weight substrates, a modified *Clemmensen reduction*, using activated zinc and gaseous HCl in an organic solvent (e.g., as ether or acetic anhydride) has proved successful.[1414] The *Clemmensen* and *Wolff–Kishner reductions* are complementary, since the former uses acidic and the latter basic conditions.

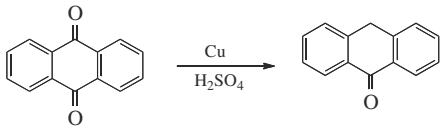
[1403] Dai, P.; Dussault, P.H.; Trullinger, T.K. *J. Org. Chem.* ***2004****, 69*, 2851.
[1404] Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* ***1955****, 591*, 138. See also, Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 320–322.
[1405] Harpp, D.N.; Gleason, J.G. *J. Am. Chem. Soc.* ***1971****, 93*, 2437. For another method, see Comasseto, J.V.; Lang, E.S.; Ferreira, J.T.B.; Simonelli, F.; Correi, V.R. *J. Organomet. Chem.* ***1987****, 334,* 329.
[1406] See Reusch, W. in Augustine, R.L. *Reduction* , Marcel Dekker, NY, ***1968***, pp. 171–211.
[1407] See, however, Bailey, K.E.; Davis, B.R. *Aust. J. Chem.* ***1995****, 48*, 1827. Also see, Rosnati, V. *Tetrahedron Lett*. ***1992****, 33*, 4791.
[1408] Seee Vedejs, E. *Org. React.* ***1975****, 22,* 401. For a discussion of experimental conditions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 1287–1289.
[1409] See Todd, D. *Org. React.* ***1948****, 4,* 378.
[1410] Huang-Minlon *J. Am. Chem. Soc.* ***1946****, 68,* 2487; ***1949****, 71,* 3301.
[1411] Jaisankar, P.; Pal, B.; Giri, V.S. *Synth. Commun.* ***2002****, 32*, 2569.
[1412] Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962****, 84,* 1734.
[1413] Gadhwal, S.; Baruah, M.; Sandhu, J.S. *Synlett* ***1999***, 1573.
[1414] Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* ***1972****, 45*, 264.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under *Clemmensen* conditions,[1415] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, Reaction **19-54**) or alkenes, and 1,3-diones usually undergo rearrangement (e.g., $MeCOCH_2COMe \rightarrow MeCOCHMe_2$).[1416] Neither method is suitable for α,β-unsaturated ketones, which give pyrazolines[1417] under *Wolff–Kishner* conditions. Under *Clemmensen* conditions, both groups of these molecules may be reduced or if only one group is reduced, it is the C=C bond.[1418] Sterically hindered ketones are resistant to both the *Clemmensen* and *Huang–Minlon* procedures, but can be reduced by vigorous treatment with anhydrous hydrazine.[1419] In the *Clemmensen reduction*, pinacols (Reaction **19-76**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2.[1420] Among these are Me_3SiCl followed by $Et_3SiH/TiCl_4$,[1421] $Ni(OAc)_2$ on borohydride exchange resin,[1422] Et_3SiH on pyridinium poly(hydrogen fluoride) (PPHF),[1423] and, for aryl ketones (ArCOR and ArCOAr), $NaBH_3CN$ in THF–aq HCl,[1424] Ni−Al in H_2O,[1425] $HCOONH_4$−Pd−C,[1426] or trialkylsilanes in F_3CCOOH.[1427] Hydrogenation with a heterogeneous Cu–silica catalyst has been used.[1428] Silanes (e.g., Et_3SiH) and a triarylborane catalyst reduce aliphatic aldehydes to methyl, $-CHO \rightarrow -CH_3$.[1429] Zinc oxide/triethylsilane has been used,[1430] and also titanocene dichloride $[(C_5H_5)_2TiCl_2]$.[1431] Most of these reagents also reduce aryl aldehydes (ArCHO) to methylbenzenes ($ArCH_3$).[1432] One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst[1433] or by HI in refluxing acetic acid.[1434] One carbonyl group of quinones (e.g., **41**), can be reduced with Cu and H_2SO_4 or with Sn and HCl.[1435] One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.[1436]

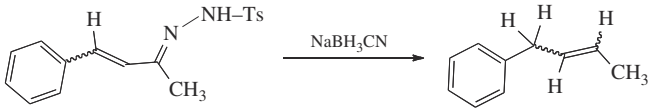
[1415] See Buchanan, J.G.S.; Woodgate, P.D. *Q. Rev. Chem. Soc.* ***1969****, 23,* 522.
[1416] Galton, S.A.; Kalafer, M.; Beringer, F.M. *J. Org. Chem.* ***1970****, 35,* 1.
[1417] Pyrazolines can be converted to cyclopropanes; see Reaction **17-34**.
[1418] See, however, Banerjee, A.K.; Alvárez, J.; Santana, M.; Carrasco, M.C. *Tetrahedron* ***1986****, 42*, 6615.
[1419] Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* ***1955***, 2056.
[1420] For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 61–66.
[1421] Yato, M.; Homma, K.; Ishida, A. *Heterocycles* ***1995****, 41*, 17.
[1422] Bandgar, B.P.; Nikat, S.M.; Wadgaonkar, P.P. *Synth. Commun.* ***1995****, 25*, 863.
[1423] Olah, G.A.; Wang, Q.; Prakash, G.K.S. *Synlett* ***1992***, 647.
[1424] Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Synlett* ***2001***, 1391.
[1425] Ishimoto, K.; Mitoma, Y.; Negashima, S.; Tashiro, H.; Prakash, G.K.S.; Olah, G.A.; Tahshiro, M. *Chem. Commun.* ***2003***, 514.
[1426] Ram, S.; Spicer, L.D. *Tetrahedron Lett.* ***1988****, 29*, 3741.
[1427] West, C.T.; Donnelly, S.J.; Kooistra, D.A.; Doyle, M.P. *J. Org. Chem.* ***1973****, 38,* 2675. See also, Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* ***1986***, 770.
[1428] Zaccheria, F.; Ravasio, N.; Ercoli, M.; Allegrini, P. *Tetrahedron Lett.* ***2005****, 46,* 7743.
[1429] Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* ***2001****, 66,* 1672.
[1430] Li, Z.; Deng, G.; Li, Y.-C. *Synlett* ***2008***, 3053.
[1431] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974****, 96,* 5290.
[1432] See Zahalka, H.A.; Alper, H. *Organometallics* ***1986****, 5*, 1909.
[1433] Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963****, 2,* 370.
[1434] Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* ***1964****, 86,* 3068.
[1435] Meyer, K.H. *Org. Synth.* ***I***, 60; Macleod, L.C.; Allen, C.F.H. *Org. Synth.* ***II***, 62.
[1436] Cormier, R.A.; McCauley, M.D. *Synth. Commun.* ***1988****, 18,* 675.

Simply heating a ketone in supercritical 2-propanol reduces the ketone to the methylene compound.[1437]

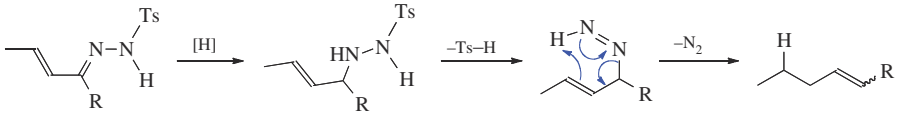


41

An indirect method of accomplishing the reaction is reduction of tosylhydrazones ($R_2C{=}N{-}NHTs$) to R_2CH_2 with $NaBH_4$, BH_3, catecholborane, bis(benzyloxy)borane, or $NaBH_3CN$. The reduction of α,β-unsaturated tosylhydrazones with $NaBH_3CN$, with $NaBH_4{-}HOAc$, or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring,[1438] for example,

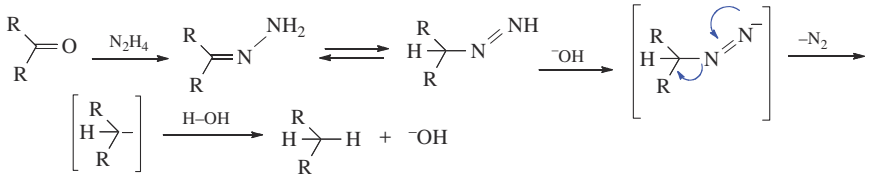


A cyclic mechanism is apparently involved:



Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization using Raney nickel or another reagent (Reaction **14-27**).

The first step in the mechanism[1439] of the *Wolff–Kishner reduction* consists of formation of the hydrazone (**16-14**). It is this species that undergoes reduction in the presence of base, most likely in the following manner:



[1437] Hatano, B.; Tagaya, H. *Tetraehedron Lett.* ***2003****, 44*, 6331.
[1438] Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* ***1978****, 43*, 2299; Greene, A.E. *Tetrahedron Lett.* ***1979***, 63.
[1439] Szmant, H.H. *Angew. Chem. Int. Ed.* ***1968****, 7,* 120. Also see Taber, D.F.; Stachel, S.J. *Tetrahedron Lett*. ***1992****, 33*, 903.

Not much is known about the mechanism of the *Clemmensen reduction*. Several mechanisms have been proposed,[1440] including one going through a zinc–carbene intermediate.[1441] One thing reasonably certain is that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the *Wolff–Kishner reduction* either.

It is interesting to see that amines can be deaminated to give the corresponding methylene compounds with low-valent titanium ($TiCl_3$/Li/THF).[1442]

OS **I**, 60; **II**, 62, 499; **III**, 410, 444, 513, 786; **IV**, 203, 510; **V**, 533, 747; **VI**, 62, 293, 919; **VII**, 393. Also see, OS **IV**, 218; **VII**, 18.

19-62 Reduction of Carboxylic Esters to Ethers

Dihydro-de-oxo-bisubstitution

$$RCOOR' \xrightarrow[LiAlH_4]{BF_3-\text{etherate}} RCH_2OR'$$

Carboxylic esters and lactones have been reduced to ethers, although 2 molar equivalents of alcohol are more commonly obtained (Reaction **19-38**). Reduction to ethers has been accomplished with a reagent prepared from BF_3–etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[1443] with trichlorosilane and UV light,[1444] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give **19-38**. Acyloxy groups are reduced by cleavage of the C−C=O bond, R(Ar)COO−C → C−H) with an excess of Ph_2SiH_2 and di-*tert*-butyl peroxide.[1445] Esters are reduced to ethers using Et_3SiH and $TiCl_4$,[1446] BF_3,[1447] In(III) compounds,[1448] or $FeCl_3$.[1449] Lactones are converted to cyclic ethers[1450] by treatment with Cp_2TiCl_2 followed by Et_3SiH on Amberlyst 15.[1451]

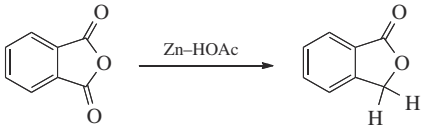
Thiono esters (RCSOR′) can be reduced to ethers (RCH_2OR') with Raney nickel (Reaction **14-27**).[1452] Reaction of thio esters (e.g., C−OC(=O)Ph) with Ph_2SiH_2 and Ph_3SnH with BEt_3, followed by AIBN (Sec. 14.A.i) leads to reduction of the C=S unit to give an ether.[1453] Since the thiono esters can be prepared from carboxylic esters (Reaction **16-11**), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters (RCOSR′) have been reduced to thioethers (RCH_2SR').[1454]

See also, Reactions **19-65** and **19-59**.

[1440] See Di Vona, M.L.; Rosnati, V. *J. Org. Chem.* ***1991****, 56,* 4269.
[1441] Burdon, J.; Price, R.C. *J. Chem. Soc. Chem. Commun.* ***1986***, 893.
[1442] Talukdar, S.; Banerji, A. *Synth. Commun,* ***1996****, 26*, 1051.
[1443] Ager, D.J.; Sutherland, I.O. *J. Chem. Soc. Chem. Commun.* ***1982***, 248. See also, Dias, J.R.; Pettit, G.R. *J. Org. Chem.* ***1971****, 36,* 3485.
[1444] Baldwin, S.W.; Haut, S.A. *J. Org. Chem.* ***1975****, 40*, 3885. See also, Kraus, G.A.; Frazier, K.A.; Roth, B.D.; Taschner, M.J.; Neuenschwander, K. *J. Org. Chem.* ***1981****, 46,* 2417.
[1445] Kim, J.-G.; Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004****, 45*, 3031.
[1446] Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* ***2001****, 57*, 5353.
[1447] Morra, N.A.; Pagenkopf, B.L. *Synthesis* ***2008***, 511.
[1448] Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T. *Synthesis* ***2008***, 3533.
[1449] Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* ***2005***, 183.
[1450] See Pettit, G.R.; Kasturi, T.R.; Green, B.; Knight, J.C. *J. Org. Chem.* ***1961****, 26,* 4773; Edward, J.T.; Ferland, J.M. *Chem. Ind. (London)* ***1964***, 975.
[1451] Hansen, M.C.; Verdaguer, X.; Buchwald, S.L. *J. Org. Chem.* ***1998****, 63*, 2360.
[1452] Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981****, 46,* 831.
[1453] Jang, D.O.; Song, S.H. *Synlett* ***2000***, 811; Jang, D.O.; Song, S.H.; Cho, D.H. *Tetrahedron* ***1999****, 55,* 3479.
[1454] Eliel, E.L.; Daignault, R.A. *J. Org. Chem.* ***1964****, 29,* 1630; Bublitz, D.E. *J. Org. Chem.* ***1967****, 32,* 1630.

19-63 Reduction of Cyclic Anhydrides to Lactones and Acid Derivatives to Alcohols

Dihydro-de-oxo-bisubstitution



Cyclic anhydrides are reduced with Zn−HOAc to give lactones, and also with hydrogen and Pt or $RuCl_2(Ph_3P)_3$,[1455] with $NaBH_4$.[1456] With cyclic anhydrides the reaction with $LiAlH_4$ can be controlled to give either diols or lactones,[1457] although diols are the more usual product. A BINOL–$LiAlH_4$–EtOH complex, however, gives smooth reduction to the lactone.[1458] With some reagents the reaction can be accomplished regioselectively; that is, only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.[1459] Open-chain anhydrides either are not reduced at all (e.g., with $LiAlH_4$ or $NaBH_4$) or give 2 molar equivalents of alcohol. The $NaBH_4$ in THF, with dropwise addition of methanol, reduces open-chain anhydrides to 1 equiv of primary alcohol and 1 equiv of carboxylic acid.[1460]

Acyl halides are reduced[1461] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 19.4), but not by borane.

In general, reduction of amides to alcohols is difficult. More commonly the amide is reduced to an amine. An exception uses LiH_2NBH_3 to give the alcohol.[1462] Reduction with sodium metal in propanol also gives the alcohol.[1463] Acyl imidazoles are also reduced to the corresponding alcohol with $NaBH_4$ in aq HCl.[1464]

There are no *Organic Syntheses* references, but see OS **II**, 526, for a related reaction. See OS **VI**, 482 for reduction to alcohols and OS **IV**, 271 for reduction of acyl halides.

19-64 Reduction of Amides to Amines

Dihydro-deoxo-bisubstitution

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

A useful reagent is $LiAlH_4$, although the reaction is more difficult than the reduction of most other functional groups. Other groups are often reduced without disturbing an amide function. Although $NaBH_4$ by itself does not reduce amides, it does so in the presence

[1455] Morand, P.; Kayser, M.M. *J. Chem. Soc. Chem. Commun.* ***1976***, 314. See also, Hara, Y.; Wada, K. *Chem. Lett.* ***1991***, 553.
[1456] Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* ***1970****, 35*, 3574.
[1457] Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* ***1967****, 32,* 3919.
[1458] Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* ***1993****, 34*, 1167.
[1459] See Soucy, C.; Favreau, D.; Kayser, M.M. *J. Org. Chem.* ***1987****, 52,* 129.
[1460] Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* ***1987***, 647.
[1461] See Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1263–1264.
[1462] Myers, A.G.; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* ***1996****, 37*, 3623.
[1463] Moody, H.M.; Kaptein, B.; Broxterman, Q.B.; Boesten, W.H.J.; Kamphuis, J. *Tetrahedron Lett.* ***1994****, 35*, 1777.
[1464] Sharma, R.; Voynov, G.H.; Ovaska, T.V.; Marquez, V.E. *Synlett* ***1995***, 839.

of certain other reagents[1465] including iodine.[1466] Lithium borohydride reduces acetamides.[1467] Substituted amides can be reduced with these powerful reagents, and secondary amides are reduced to secondary amine and tertiary amides to tertiary amines. Borane[1468] and sodium in 1-propanol[1469] are good reducing agents for all three types of amides. Lithium triethylborohydride produces the alcohol with most *N,N*-disubstituted amides, but not with unsubstituted or *N*-substituted amides.[1470] Sodium (dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.[1471]

Amides can be reduced[1472] to amines by catalytic hydrogenation,[1473] but high temperatures and pressures are usually required. Another reagent that reduces disubstituted amides to amines is trichlorosilane.[1474] Other silanes (e.g., Et_3SiH) in the presence of a Re[1475] Pt,[1476] In,[1477] Zn,[1478] or Ru,[1479] catalyst, reduce amides to amines. Electrolytic reduction of carbamates to give an amine are possible.[1480]

Hantzsch esters (see Reactions **15-14** and **16-17**) have been used for metal-free reduction of amides to amines.[1481]

With some $RCONR_2$, $LiAlH_4$ causes cleavage, and the aldehyde (Reaction **10-41**) or alcohol is obtained. Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, although cleavage sometimes occurs here too. A mixture of $LiBHEt_3/Et_3SiH$ is also effective.[1482] Lactams are also reduced to cyclic amines with 9-BBN[1483] (Reaction **15-16**) or $LiBH_3NMe_2$.[1484]

Imides are generally reduced on both sides,[1485] although it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, although with acyclic imides cleavage is often obtained.[1486]

[1465] See Wann, S.R.; Thorsen, P.T.; Kreevoy, M.M. *J. Org. Chem.* ***1981****, 46*, 2579; Mandal, S.B.; Giri, V.S.; Pakrashi, S.C. *Synthesis* ***1987***, 1128; Akabori, S.; Takanohashi, Y. *Chem. Lett.* ***1990***, 251.
[1466] Prasad, A.S.B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* ***1992****, 48*, 4623.
[1467] Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* ***2002****, 43*, 4417.
[1468] See Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* ***1991****, 21*, 1579.
[1469] Bhandari, K.; Sharma, V.L.; Chatterjee, S.K. *Chem. Ind. (London)* ***1990***, 547.
[1470] Brown, H.C.; Kim, S.C. *Synthesis* ***1977***, 635.
[1471] Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* ***1984****, 49,* 2438.
[1472] See Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 795–801; Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, p. 544. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 869–872.
[1473] Aoun, R.; Renaud, J.-L.; Dixneuf, P.H.; Bruneau, C. *Angew. Chem. Int. Ed.* ***2005****, 44*, 2021; Magro, A.A.N.; Eastham, G.R.; Cole-Hamilton, D.J. *Chem. Commun.* ***2007***, 3154.
[1474] Nagata, Y.; Dohmaru, T.; Tsurugi, J. *Chem. Lett.* ***1972***, 989. See also, Benkeser, R.A.; Li, G.S.; Mozdzen, E.C. *J. Organomet. Chem.* ***1979****, 178,* 21.
[1475] Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* ***2001****, 42*, 1945.
[1476] Hanada, S.; Motoyama, Y.; Nagashima, H. *Tetrahedron Lett.* ***2006****, 47*, 6173.
[1477] Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett.* ***2008****, 49*, 6873.
[1478] Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* ***2010****, 132,* 1770.
[1479] Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* ***2007****, 72,* 7551.
[1480] Franco, D.; Duñach, E. *Tetrahedron Lett.* ***2000****, 41*, 7333.
[1481] Barbe, G.; Charette, A.B. *J. Am. Chem. Soc.* ***2008****, 130*, 18.
[1482] Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M.C.; García Ruano, J.L.G. *Tetrahedron Lett.* ***1994****, 35*, 2053.
[1483] Colllins, C.J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* ***1999****, 40*, 3673.
[1484] Flaniken, J.M.; Collins, C.J.; Lanz, M.; Singaram, B. *Org. Lett.* ***1999****, 1,* 799.
[1485] See Akula, M.R.; Kabalka, G.W. *Org. Prep. Proceed. Int.* ***1999****, 31*, 214.
[1486] Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* ***1952****, 74,* 3861.

Note that imides can be reduced to hydroxy lactams using different reagents, including $NaBH_4$.[1487]

OS **IV**, 339, 354, 564; **VI**, 382; **VII**, 41.

19-65 Reduction of Carboxylic Acids and Esters to Alkanes

Trihydro-de-alkoxy,oxo-tersubstitution, and so on

$$RCOOR' \xrightarrow{(C_5H_5)_2TiCl_2} RCH_3 + R'OH$$

The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of Reactions **19-59**, **19-62**, or **19-38**. The products are the alkane RCH_3 and the alcohol $R'OH$. The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[1488] The following sequence has been suggested[1488]:

$$ArCOOH \xrightarrow{SiHCl_3} (ArCO)_2O \xrightarrow[R_3N]{SiHCl_3} ArCH_2SiCl_3 \xrightarrow[MeOH]{KOH} ArCH_3$$

Esters of aromatic acids are not reduced by this procedure, so an aromatic COOH group can be reduced in the presence of a $COOR'$ group.[1489] However, it is also possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.[1490] Both *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols ($HOC_6H_4CH_3$) with sodium bis(2-methoxyethoxy)aluminum hydride [$NaAlH_2(OC_2H_4OMe)_2$, Red-Al].[1491] Heating a 2-pyridylbenzyl ester with ammonium formate and a Ru catalyst leads to reduction of the CH_3COO unit to the alkane.[1492]

Carboxylic acids can also be converted to alkanes, indirectly,[1493] by reduction of the corresponding tosylhydrazides ($RCONHNH_2$) with $LiAlH_4$ or borane.[1494]

OS **VI**, 747.

19-66 Hydrogenolysis of Nitriles

Hydro-de-cyanation

$$R{-}CN \longrightarrow R{-}H$$

This transformation is not common, but given the proliferation of nitriles in organic chemistry, it is potentially quite useful. In the presence of mercuric compounds, tertiary nitriles can be reduced to the hydrocarbon with sodium cyanoborohydride.[1495]

[1487] See Issa, F.; Fischer, J.; Turner, P.; Coster, M.J. *J. Org. Chem.* ***2006****, 71,* 4703.
[1488] Benkeser, R.A.; Foley, K.M.; Gaul, J.M.; Li, G.S. *J. Am. Chem. Soc.* ***1970****, 92,* 3232.
[1489] Benkeser, R.A.; Ehler, D.F. *J. Org. Chem.* ***1973****, 38*, 3660.
[1490] Benkeser, R.A.; Mozdzen, E.C.; Muth, C.L. *J. Org. Chem.* ***1979****, 44,* 2185.
[1491] Cerny, M.; Málek, J. *Collect. Czech. Chem. Commun.* ***1970****, 35,* 2030.
[1492] Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* ***2001****, 123*, 4849.
[1493] See Le Deit, H.; Cron S.; Le Corre, M. *Tetrahedron Lett.* ***1991****, 32,* 2759.
[1494] Attanasi, O.; Caglioti, L.; Gasparrini, F.; Misiti, D. *Tetrahedron* ***1975****, 31*, 341, and references cited therein.
[1495] Sassaman, M.B. *Tetrahedron* ***1996***, *52*, 10835.

gem-Dinitriles can be reduced to the corresponding mono-nitrile with SmI_2.[1496] Hydrosilanes facilitate reductive cleavage of nitriles in the presence of a Rh catalyst.[1497]

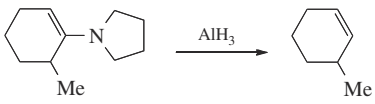
19-67 Reduction of the C−N Bond

Hydro-de-amination or Deamination

$$RNH_2 \longrightarrow RH$$

Benzylic amines are particularly susceptible to hydrogenolysis by catalytic hydrogenation[1498] or dissolving metal reduction.[1499] Note that the *Wolff–Kishner reduction* in Reaction **19-61** involved formation of a hydrazone and deprotonation by base that led to loss of nitrogen and reduction. Ceric ammonium nitrate in aq acetonitrile has also been shown to reductively cleave the *N*-benzyl group.[1500] Primary amines have been reduced to RH with hydroxylamine-*O*-sulfonic acid and aq NaOH to give the hydrocarbon, nitrogen gas, and the sulfate anion.[1501] It is postulated that R−N=N−H is an intermediate that decomposes to the carbocation. An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide ($RNHSO_2R'$) (Reaction **16-102**) and subsequent treatment with NH_2OSO_2OH[1502] or NaOH, and then NH_2Cl.[1503] Tosylaziridines derived from terminal alkenes are reduced to the corresponding primary tosylamine with polymethylhydrosiloxane/Pd-C.[1504] Aziridines can be reduced in the same way as epoxides (Reaction **19-35**).

Other indirect methods involve reduction of *N,N*-ditosylates (Sec. 10.G.iii) with $NaBH_4$ in HMPA[1505] and modifications of the *Katritzky pyrylium–pyridinium method*.[1506] Allylic and benzylic amines[1333] can be reduced by catalytic hydrogenolysis. Aziridines can be reductively opened with SmI_2[1507] or with Bu_3SnH and AIBN.[1508] The C−N bond of enamines is reductively cleaved to give an alkene with alane (AlH_3)[1509]:



and with 9-BBN (Reaction **15-16**) or borane methyl sulfide (BMS).[1510] Since enamines can be prepared from ketones (Reaction **16-13**), this is a way of converting ketones to alkenes.

[1496] Kang, H.-Y.; Hong, W.S.; Cho, Y.S.; Koh, H.Y. *Tetrahedron Lett.* ***1995***, *36*, 7661.
[1497] Tobisu, M.; Nakamura, R.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* ***2009****, 131,* 3174.
[1498] Hartung, W.H.; Simonoff, R. *Org. React.* ***1953****, 7,* 263.
[1499] du Vigneaud, V.; Behrens, O.K. *J. Biol. Chem.* ***1937****, 117,* 27.
[1500] Bull, S.D.; Davies, S.G.; Fenton, G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3765.
[1501] Doldouras, G.A.; Kollonitsch, J. *J. Am. Chem. Soc.* ***1978***, *100*, 341.
[1502] Nickon, A.; Hill, R.H. *J. Am. Chem. Soc.* ***1964***, *86*, 1152.
[1503] Guziec, Jr., F.S.; Wei, D. *J. Org. Chem.* ***1992***, *57*, 3772.
[1504] Chandrasekhar, S.; Ahmed, M. *Tetahedron Lett.* ***1999****, 40,* 9325.
[1505] Hutchins, R.O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* ***1975***, *40*, 2018.
[1506] See Katritzky, A.R.; Bravo-Borja, S.; El-Mowafy, A.M.; Lopez-Rodriguez, G. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1671.
[1507] Molander, G.A.; Stengel, P.J. *Tetrahedron* ***1997***, *53*, 8887.
[1508] Schwan, A.L.; Refvik, M.D. *Tetrahedron Lett.* ***1993***, *34*, 4901.
[1509] Coulter, J.M.; Lewis, J.W.; Lynch, P.P. *Tetrahedron* ***1968***, *24*, 4489.
[1510] Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* ***1989***, *111*, 384.

In the latter case, BMS gives retention of configuration [an (*E*)-isomer gives the (*E*)-product], while 9-BBN gives the other isomer.[1510] Diazo ketones are reduced to methyl ketones by HI: $RCOCHN_2 + HI \rightarrow RCOCH_3$.[1511]

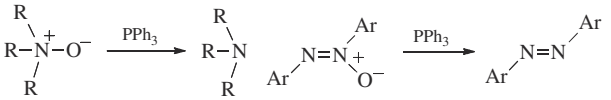
Quaternary ammonium salts can be cleaved with $LiAlH_4$, $R_4N^+ + LiAlH_4 \rightarrow R_3N + R^-$, as can quaternary phosphonium salts (R_4P^+). Other reducing agents have also been used (e.g., lithium triethylborohydride, which preferentially cleaves methyl groups,[1512] and Na in liquid ammonia). When quaternary salts are reduced with Na(Hg) in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups.

Nitro compounds (RNO_2) can be reduced to RH[1513] by sodium methylmercaptide (CH_3SNa) in an aprotic solvent[1514] or by Bu_3SnH.[1515] Both reactions have free radical mechanisms.[1516] Tertiary nitro compounds can be reduced to RH by NaHTe.[1517] The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[1518] Reduction of the C−N bond on aromatic amines with Li metal in THF generates the aryl compounds.[1519] Sodium nitrite, sodium bisulfite in EtOH/water/acetic acid does a similar reduction.[1520] Conversion of the aniline derivative to the methanesulfonamide and subsequent treatment with NaH and NH_2Cl gives the same result.[1521] The Bu_3SnH reagent also reduces isocyanides (RNC, prepared from RNH_2 by formylation followed by Reaction **17-31**) to RH,[1522] a reaction that can also be accomplished with Li or Na in liquid NH_3,[1523] or with K and a crown ether in toluene.[1524] α-Nitro ketones can be reduced to ketones with $Na_2S_2O_4$−Et_3SiH in HMPA−H_2O.[1525]

OS **III**, 148; **IV**, 508; **VIII**, 152.

19-68 Reduction of Amine Oxides and Azoxy Compounds

N-Oxygen-detachment



[1511] For example, see Pojer, P.M.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* ***1968***, *21*, 1375.
[1512] Cooke, Jr., M.P.; Parlman, R.M. *J. Org. Chem.* ***1975***, *40*, 531.
[1513] See Fessard, T.C.; Motoyoshi, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2007***, *46*, 2078.
[1514] Kornblum, N.; Carlson, S.C.; Smith, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 647; Kornblum, N.; Widmer, J.; Carlson, S.C. *J. Am. Chem. Soc.* ***1979***, *101*, 658.
[1515] See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, 1–45; Rosini, G.; Ballini, R. *Synthesis* ***1988***, 833, see pp. 835–837; Ono, N.; Kaji, A. *Synthesis* ***1986***, 693. See Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3629.
[1516] Tanner, D.D.; Harrison, D.J.; Chen, J.; Kharrat, A.; Wayner, D.D.M.; Griller, D.; McPhee, D.J. *J. Org. Chem.* ***1990***, *55*, 3321; Bowman, W.R.; Crosby, D.; Westlake, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 73.
[1517] Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 1067.
[1518] See Kniel, P. *Helv. Chim. Acta* ***1968***, *51*, 371. For another method, see Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* ***1983***, *105*, 4017.
[1519] Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* ***1999***, *40*, 8291.
[1520] Geoffroy, O.J.; Morinelli, T.A.; Meier, G.B. *Tetrahedron Lett.* ***2001***, *42*, 5367.
[1521] Wang, Y.; Guziec Jr., F.S. *J. Org. Chem.* ***2001***, *66*, 8293.
[1522] Barton, D.H.R.; Bringmann, G.; Motherwell, W.B. *Synthesis* ***1980***, 68.
[1523] See Yadav, J.S.; Reddy, P.S.; Joshi , B.V. *Tetrahedron Lett.* ***1988***, *44*, 7243.
[1524] Ohsawa, T.; Mitsuda, N.; Nezu, J.; Oishi, T. *Tetrahedron Lett.* ***1989***, *30*, 845.
[1525] Kamimura, A.; Kurata, K.; Ono, N. *Tetrahedron Lett.* ***1989***, *30*, 4819.

Amine oxides[1526] and azoxy compounds (both alkyl and aryl)[1527] can be reduced practically quantitatively with triphenylphosphine.[1528] Other reducing agents have also been used, including $LiAlH_4$, $NaBH_4/LiCl$,[1529] H_2-Ni, PCl_3, Ga/H_2O,[1530] or $In/TiCl_4$.[1531] Indium metal with aq ammonium chloride in methanol gives good yields of pyridine from pyridine *N*-oxide.[1532] Similar results are obtained using ammonium formate and Raney nickel[1533] or zinc.[1534] Sodium in ethanol, in a sealed tube, reduces pyridine *N*-oxide to pyridine.[1535] Similar reduction was accomplished with $Mo(CO)_6$ in ethanol.[1536] Indium (III) chloride has been used for the reduction of quinoline *N*-oxide to quinoline.[1537] Nitrile oxides[1538] ($R-C\equiv N^+-O^-$) can be reduced to nitriles with trialkylphosphines,[1539] and isocyanates (RNCO) to isocyanides (RNC) with $Cl_3SiH-Et_3N$.[1540]

Analogous to amino *N*-oxides, phosphine oxides ($R_3P=O$) are reduced to phosphines (R_3P). Treatment of a phosphine oxide with MeOTf followed by reduced with $LiAlH_4$[1541] or Dibal-H[1542] gives the phosphine. Chiral phosphine oxides are reduced to the phosphine with excellent enantioselectivity using PPh_3 and Cl_3SiH.[1543]

OS **IV**, 166. See also, OS **VIII**, 57.

19-69 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or **Hydro-de-diazoniation**

$$ArN_2^+ + H_3PO_2 \longrightarrow ArH$$

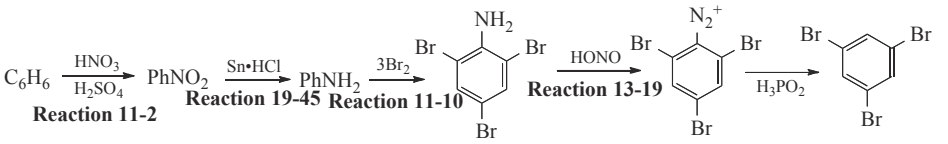
Reduction of a diazonium group (*dediazoniation*) provides an indirect method for the removal of an amino group from an aromatic ring.[1544] A common method uses hypophosphorous acid (H_3PO_2), although many other reducing agents[1545] have been used,

[1526] See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 120–134; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 166–231.
[1527] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 602–603, 614–624.
[1528] See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 295–350.
[1529] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3511.
[1530] Han, J.H.; Choi, K.I.; Kim, J.H.; Yoo, B.W. *Synth. Commun.* ***2004***, *34*, 3197.
[1531] Yoo, B.W.; Choi, K.H.; Choi, K.I.; Kim, J.H. *Synth. Commun.* ***2003***, *33*, 4185.
[1532] Yadav, J.S.; Reddy, B.V.S.; Reddy, M.M. *Tetrahedron Lett.* ***2000***, *41*, 2663.
[1533] Balicki, R.; Maciejewski, G. *Synth. Commun.* ***2002***, *32*, 1681.
[1534] Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* ***2003***, *33*, 4137.
[1535] Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V.R.; González, R.R. *J. Org. Chem.* ***2005***, *70*, 3218.
[1536] Yoo, B.W.; Choi, J.W.; Yoon, C.M. *Tetrahedron Lett.* ***2006***, *47*, 125.
[1537] Ilias, Md.; Barman, D.C.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 1877.
[1538] See Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 55–74; Grundmann, C. *Fortschr. Chem. Forsch.* ***1966***, *7*, 62.
[1539] Grundmann, C.; Frommeld, H.D. *J. Org. Chem.* ***1965***, *30*, 2077.
[1540] Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* ***1983***, *39*, 2989.
[1541] Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* ***2001***, *3*, 87.
[1542] Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C.H. *Org. Lett.* ***2005***, *7*, 4277.
[1543] Wu, H.-C.; Yu, J.-Q.; Spencer, J.B. *Org. Lett.* ***2004***, *6*, 4675.
[1544] See Zollinger, H. in Patai, S.; Rappoport, Z. *The Chemistry of Functinal Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 603–669.
[1545] For lists of some of these, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 39–41; Tröndlin, F.; Rüchardt, C. *Chem. Ber.* ***1977***, *110*, 2494.

including HMPA,[1546] thiophenol,[1547] and sodium stannite (Na_2SnO_2). Ethanol was the earliest reagent used, and it frequently gives good yields, but ethers (ArOEt) are often side products. When H_3PO_2 is used, 5–15 molar equivalents of this reagent are required per molar equivalent of substrate. Diazonium salts can be reduced in nonaqueous media by several methods, including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN[1548] and by isolation as the BF_4^- salt and reduction of this with $NaBH_4$ in DMF.[1549] Aromatic amines can be deaminated ($ArNH_2 \rightarrow ArH$) in one laboratory step by treatment with an alkyl nitrite in DMF[1550] or boiling THF.[1551] The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic (S_N1) mechanism while the reduction to ArH proceeds by a free radical process.[1552] The reduction with H_3PO_2 is also believed to have a free radical mechanism.[1553] In the reduction with $NaBH_4$, an aryldiazene intermediate (ArN=NH) has been demonstrated,[1554] arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.[1555] It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical (AR•) or the corresponding anion (Ar^-) may be involved.[1556]

The dediazoniation reaction is used for functionalization of aromatic rings, to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho–para directing; however, this compound is easily prepared by the following sequence:



Many other compounds that would otherwise be difficult to prepare are easily synthesized with the aid of the dediazoniation reaction.

Unwanted dediazoniation can be suppressed by using hexasulfonated calix[6]arenes (see Sec. 3.C.ii).[1557]

OS **I**, 133, 415; **II**, 353, 592; **III**, 295; **IV**, 947; **VI**, 334.

[1546] Shono, T.; Matsumura, Y.; Tsubata, K. *Chem. Lett.* ***1979***, 1051.
[1547] See Korzeniowski, S.H.; Blum, L.; Gokel, G.W. *J. Org. Chem.* ***1977****, 42,* 1469.
[1548] Nakayama, J.; Yoshida, M.; Simamura, O. *Tetrahedron* ***1970****, 26,* 4609.
[1549] Hendrickson, J.B. *J. Am. Chem. Soc.* ***1961****, 83*, 1251. See also, Threadgill, M.D.; Gledhill, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 873.
[1550] Doyle, M.P.; Dellaria, Jr., J.F.; Siegfried, B.; Bishop, S.W. *J. Org. Chem.* ***1977****, 42,* 3494.
[1551] Cadogan, J.I.G.; Molina, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 541.
[1552] See Broxton, T.J.; Bunnett, J.F.; Paik, C.H. *J. Org. Chem.* ***1977****, 42,* 643.
[1553] See Levit, A.F.; Kiprianova, L.A.; Gragerov, I.P. *J. Org. Chem. USSR* ***1975****, 11*, 2395.
[1554] König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972****, 11,* 45.
[1555] Smith III, M.R.; Hillhouse, G.L. *J. Am. Chem. Soc.* ***1988****, 110,* 4066.
[1556] See König, E.; Musso, H.; Záhorszky, U.I.; König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972****, 11,* 45; Broxton, T.J.; McLeish, M.J. *Aust. J. Chem.* ***1983****, 36,* 1031.
[1557] Shinkai, S.; Mori, S.; Araki, K.; Manabe, O. *Bull. Chem. Soc. Jpn.* ***1987****, 60,* 3679.

19-70 Desulfurization

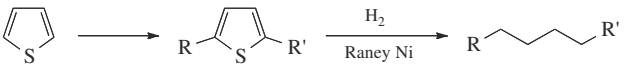
Hydro-de-thio-substitution, and so on

$$RSH \longrightarrow RH \quad RSR' \longrightarrow RH + R'H \quad RS(O)_nR' \longrightarrow RH + R'H$$

Thiols and thioethers,[1558] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[1559] The hydrogen is usually not applied externally, since Raney nickel typically contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, including disulfides, thiono esters,[1560] thioamides, sulfoxides, and thioacetals.[1561] Reduction of thioacetals is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see Reaction **19-61**), and it can also give the alkene if a hydrogen atom is present.[1562] In most of the examples given, R can also be aryl. Other reagents[1563] have also been used.[1564] Reductive cleavage of sulfones and sulfonamides occurs with organobases [e.g., bis(imidazolylidenes)].[1565]

Lithium aluminum hydride reduces most sulfur compounds with cleavage of the C–S bond, including thiols.[1566] Thioesters can be reduced with Ni_2B (from $NiBr_2/NaBH_4$).[1567] β-Ketosulfones are reduced with $TiCl_4$–Zn[1568] or $TiCl_4$–Sm.[1569]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene to **42**, followed by reduction to give the alkane.



42

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **42**) with a nickel boride catalyst prepared from $NiCl_2$ and $NaBH_4$ in CH_3OH.[1570] Only one SR group of a dithioacetal is reduced by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[1571] Phenyl selenides (RSePh) can be reduced to RH with

[1558] For a review of the reduction of thioethers, see Block, E. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.
[1559] For reviews, see Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.
[1560] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.
[1561] See Nakata, D.; Kusaka, C.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***2001***, *42*, 415.
[1562] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.
[1563] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 53–60. See Luh, T.; Ni, Z. *Synthesis* ***1990***, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.
[1564] See Ikeshita, K.-i.; Kihara, N.; Ogawa, A. *Tetrahedron Lett.* ***2005***, *46,* 8773.
[1565] Schoenebeck, F.; Murphy, J.A.; Zhou, S.-z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* ***2007***, *129,* 13368.
[1566] Smith, M.B.; Wolinsky, J. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1431.
[1567] Back, T.G.; Baron D.L.; Yang, K. *J. Org. Chem.* ***1993***, *58*, 2407.
[1568] Guo, H.; Ye, S.; Wang, J.; Zhang, Y. *J. Chem. Res. (S)* ***1997***, 114.
[1569] Wang, J.; Zhang, Y. *Synth. Commun.* ***1996***, *26*, 1931.
[1570] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.
[1571] Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 609.

Ph_3SnH[1572] and with nickel boride.[1573] Cleavage of the C−Se bond can also be achieved with SmI_2.[1574]

The exact mechanism of the Raney nickel reactions is still in doubt, although they are probably of the free radical type.[1575] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds; that is the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.[1576]

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also, OS **VII**, 124, 476.

19-71 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols or Disulfides

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

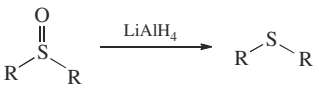
Thiols can be prepared by the reduction of sulfonyl halides[1577] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.[1578] For the reduction of sulfonyl chlorides to sulfinic acids, see Reaction **16-104**.

Disulfides (RSSR) can also be produced.[1579] Other sulfonic acid derivatives can be converted to disulfides. Esters (e.g., PhSAc) are converted to disulfides (PhS-SPh) with Clayan and microwave irradiation.[1580] Thiobenzoate derivatives (PhSBz) are similarly converted to PhS−SPh with SmI_2.[1581] In a similar manner, RS−SO_3Na is converted to RS−SR when heated with Sm metal in water.[1582]

OS **I**, 504; **IV**, 695; **V**, 843.

19-72 Reduction of Sulfoxides and Sulfones

***S*-Oxygen-detachment**



[1572] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc. Chem. Commun.* ***1978***, 41.
[1573] Back, T.G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1417.
[1574] Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* ***1998***, *39*, 6341.
[1575] For a review, see Bonner, W.A.; Grimm, R.A. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. Also see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.
[1576] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.
[1577] See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group,* pt. 2, Wiley, NY, ***1974***, pp. 216–220.
[1578] Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56,* 3802; ***1984***, *57*, 232.
[1579] See Narayana, C.; Padmanabhan, S.; Kabalka, G.W. *Synlett* ***1991***, 125.
[1580] Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1999***, *29,* 2705.
[1581] Yoo, B.W.; Baek, H.S.; Keum, S.R.; Yoon, C.M.; Nam. G.S.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2000***, *30*, 4317.
[1582] Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* ***2002***, *43*, 8141.

Sulfoxides can be reduced to sulfides by many reagents,[1583] including $LiAlH_4$, HI, Bu_3SnH,[1584] H_2-Pd-C,[1585] $NaBH_4-NiCl_2$,[1586] $NaBH_4/I_2$,[1587] catecholborane,[1588] BH_3 with a Mo catalyst,[1589] a Mo/In system,[1590] Ti compounds,[1591] and Sm/methanolic NH_4Cl with ultrasound.[1592] Sulfoxides are deoxygenated by treatment with 2,4-diphenyl-1,3-diselenadiphosphetane-2,4-diselenide.[1593] Sulfones, however, are usually more difficult to reduce, but they have been reduced to sulfides with Dibal-H.[1594] A less general reagent is $LiAlH_4$, which reduces some sulfones to sulfides, but not others.[1595] Both sulfoxides and sulfones can be reduced by heating with sulfur, which is oxidized to SO_2, although the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since ~75% of the original radioactivity of the sulfone is lost.[1596] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general method for the reduction of sulfones to sulfoxides, but an indirect method has been reported.[1597] Selenoxides can be reduced to selenides with a number of reagents.[1598]

OS **IX**, 446

E. Reduction with Cleavage

19-73 de-Alkylation of Amines and Amides

$$R'_2N-R \longrightarrow R'_2N-H$$

Certain amines can be dealkylated, usually under reductive conditions. Both *N*-allyl amines and *N,N*-dialkyl allyl amines, are converted to the corresponding amine, R_2N-H, with Dibal-H/$NiCl_2$dppp[dppp = 1, 3-bis(diphenylphosphino)propane],[1599] and with $Pd(dba)_2$dppb[dppb = 1, 4-bis(diphenylphosphino)butane].[1600] A mixture of $TiCl_3$ and

[1583] See Kukushkin, V.Yu. *Russ. Chem. Rev.* ***1990****, 59,* 844; Madesclaire, M. *Tetrahedron* ***1988****, 44,* 6537; Drabowicz, J.; Togo, H.; Mikolajczyk, M.; Oae, S. *Org. Prep. Proced. Int.* ***1984****, 16,* 171; Drabowicz, J.; Numata, T.; Oae, S. *Org. Prep. Proced. Int.* ***1977****, 9,* 63. See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.

[1584] Kozuka, S.; Furumai, S.; Akasaka, T.; Oae, S. *Chem. Ind. (London)* ***1974***, 496.

[1585] Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* ***1975***, 385.

[1586] Khurana, J.M.; Ray, A.; Singh, S. *Tetrahedron Lett.* ***1998****, 39*, 3829.

[1587] Karimi, B.; Zareyee, D. *Synthesis* ***2003***, 335.

[1588] Harrison, D.J.; Tam, N.C.; Vogels, C.M.; Langler, R.F.; Baker, R.T.; Decken, A.; Westcott, S.A. *Tetrahedron Lett.* ***2004****, 45*, 8493.

[1589] Fernandes, A.C.; Romão, C.C. *Tetrahedron Lett.* ***2007****, 48*, 9176.

[1590] Yoo, B.W.; Song, M.S.; Park, M.C. *Synth. Commun.* ***2007****, 37*, 3089.

[1591] See Yoo, B.W.; Choi, K.H.; Kim, D.Y.; Choi, K.I.; Kim, J.H. *Synth. Commun.* **2003**, 33, 53.

[1592] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, C.; Srihari, P. *Synlett* ***2001***, 854.

[1593] Hua, G.; Woollins, J.D. Te*trahedron Lett.* ***2007****, 48,* 3677.

[1594] Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* ***1973****, 51*, 1419.

[1595] See Weber, W.P.; Stromquist, P.; Ito, T.I. *Tetrahedron Lett.* ***1974***, 2595.

[1596] Kiso, S.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1967****, 40*, 1722. See also, Oae, S.; Nakai, M.; Tsuchida, Y.; Furukawa, N. *Bull. Chem. Soc. Jpn.* ***1971****, 44,* 445.

[1597] Still, I.W.J.; Ablenas, F.J. *J. Org. Chem.* ***1983****, 48,* 1617.

[1598] See Denis, J.N.; Krief, A. *J. Chem. Soc. Chem. Commun.* ***1980***, 544.

[1599] Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* ***1998****, 39*, 4679.

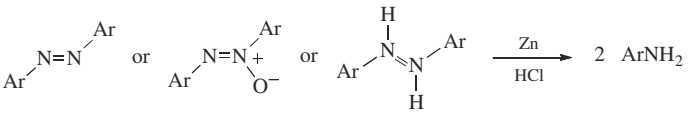
[1600] Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* ***1995****, 132*, 1157; Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* ***1995****, 36*, 1267.

Li converts *N*-benzylamines to the amine.[1601] In the case of *N,N*-dimethyl amines, $RuCl_3$ and H_2O_2 demethylate the amine ($ArNMe_2 \rightarrow ArNHMe$).[1602] Tribenzylamines are dealkylated to give the dibenzylamine with ceric ammonium nitrate in aq acetonitrile.[1603] *N*-Benzyl indoles are cleaved to indoles with O_2, DMSO/K*O-t*-Bu[1604] or with tetrabutylammonium fluoride.[1605] *N*-Demethylation of alkaloids was reported using a Fe mediated two-step procedure.[1606] *N*-Deallylation and debenzylation of amines occurs with alkali metals on silica.[1607]

The process is not limited to amines. Amides can also be dealkylated. *N*-Benzyl amides are debenzylated in the presence of NBS and AIBN.[1608] Scandium triflate removes *N-tert*-butyl from amides.[1609]

N-Alkyl sulfonamides are dealkylated with $PhI(OAc)_2$ and I_2 with ultrasound to give a primary sulfonamide.[1610] Similar results are obtained with H_5IO_6 and a Cr catalyst.[1611] *tert*-Butyl sulfonamides are cleaved to the primary sulfonamide with BCl_3.[1612]

19-74 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.[1613] Metals (notably Zn) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents, and Bu_3SnH with a Cu catalyst has been used.[1614] Borane reduces azo compounds to amines, although it does not reduce nitro compounds.[1615] Lithium aluminum hydride does not reduce hydrazo compounds or azo compounds, although with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (Reaction **19-68**). Note that azo compounds are reduced to the hydrazine by reaction with hydrazine hydrate in ethanol,[1616] or with Fe powder in ammonium chloride.[1617]

OS **I**, 49; **II**, 35, 39; **III**, 360; **X**, 327. Also see, OS **II**, 290.

[1601] Talukdar, S.; Banerji, A. *Synth. Commun.* ***1995****, 25,* 813.
[1602] Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* ***1992****, 33*, 6991.
[1603] Bull, S.D.; Davies, S.G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D.; Fenton, G. *Chem. Commun.* ***2000***, 337.
[1604] Haddach, A.A.; Kelleman, A.; Deaton-Rewoliwski, M.V. *Tetrahedron Lett.* ***2002****, 43*, 399.
[1605] Routier, S.; Saugé, L.; Ayerbe, N,; Couderet, G.; Mérour, J.-Y. *Tetrahedron Lett.* ***2002****, 43*, 589. For a related debenzylation see Meng, G.; He, Y.-P.; Chen, F.-E. *Synth. Commun.* ***2003****, 33*, 2593.
[1606] Kok, G.B.; Pye, C.C.; Singer, R.D.; Scammells, P.J. *J. Org. Chem.* ***2010****, 75,* 4806.
[1607] Nandi, P.; Dye, J.L.; Jackson, J.E. *Tetrahedron Lett.* ***2009****, 50*, 3864.
[1608] Baker, S.R.; Parsons, A.F.; Wilson, M. *Tetrahedron Lett.* ***1998****, 39*, 331.
[1609] Mahalingam, A.K.; Wu, X.; Alterman, M. *Tetrahedron Lett.* ***2006****, 47,* 3051.
[1610] Katohgi, M.; Togo, H. *Tetrahedron* ***2001****, 57*, 7481.
[1611] Xu, L.; Zhang, S.; Trudell, M.L. *Synlett* ***2004***, 1901.
[1612] Wan, Y.; Wu, X.; Kannan, M.A.; Alterman, M. *Tetrahedron Lett.* ***2003****, 44*, 4523.
[1613] See Newbold, B.T. in Patai, S. *The Chemistry of Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 629–637.
[1614] Tan, Z.; Qu, Z.; Chen, B.; Wang, J. *Tetrahedron* ***2000****, 56*, 7457.
[1615] Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* ***1960****, 82*, 681.
[1616] Zhang, C.-R.; Wang, Y.-L. *Synth. Commun.* ***2003****, 33*, 4205.
[1617] Mobinikhaledi, A.; Foroughifar, N.; Jirandehi, H.F. *Monat. Chemie* ***2007****, 138*, 755.

19-75 Reduction of Disulfides to Thiols

S-Hydrogen-uncoupling

$$\mathrm{RSSR} \xrightarrow[\mathrm{H^+}]{\mathrm{Zn}} 2\,\mathrm{RSH}$$

Disulfides can be reduced to thiols by mild reducing agents[1618] (e.g., Zn and dilute acid, In and NH_4Cl/EtOH,[1619] or Ph_3P and H_2O).[1620] The reaction can also be accomplished simply by heating with alkali.[1621] Among other reagents used have been $LiAlH_4$, $NaBH_4/ZrCl_4$,[1622] Mg/MeOH,[1623] and hydrazine or substituted hydrazines.[1624]

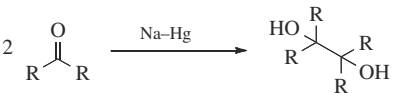
Aryl diselenides are similarly cleaved to selenols (ArSeH) with Cp_2TiH followed by $Ph_2I^+X^-$.[1625]

OS **II**, 580. Also see, OS **IV**, 295.

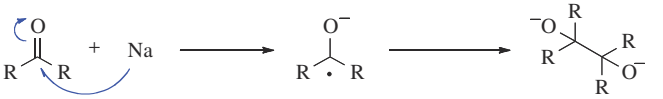
F. Reductive Coupling

19-76 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols and Imines to 1,2-Diamines

2/*O*-Hydrogen-coupling and 2/*N*-Hydrogen-coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals (e.g., Na, Mg, or Al).[1626] Aromatic ketones give better yields than aliphatic ones. The use of a $Mg-MgI_2$ mixture has been called the *Gomberg–Bachmann pinacol synthesis*.[1627] As with a number of other reactions involving Na, there is a direct electron transfer that converts the ketone or aldehyde to a ketyl, which dimerizes.



[1618] See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 220–229.
[1619] Reddy, G.V.S.; Rao, G.V.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 859.
[1620] Overman, L.E.; Smoot, J.; Overman, J.D. *Synthesis* ***1974***, 59.
[1621] See Danehy, J.P.; Hunter, W.E. *J. Org. Chem.* ***1967***, *32*, 2047.
[1622] Chary, K.P.; Rajaram, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3905.
[1623] Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.* ***1997***, *27*, 1347.
[1624] Maiti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 575.
[1625] Huang, X.; Wu, L.-L.; Xu, X.-H. *Synth. Commun.* ***2001***, *31*, 1871.
[1626] See Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1729. Also see Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synth. Commun.* ***2002***, *32*, 1169.
[1627] Gomberg, M.; Bachmann, W.E. *J. Am. Chem. Soc.* ***1927***, *49*, 236; *The Merck Index, 14th Ed.* Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p ONR-74; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley–Interscience, New Jersey, ***2005***, pp. 512–513. See Wang, J.-S.; Li, J.-T.; Lin, Z.-P.; Li, T.-S. *Synth. Commun.* ***2005***, *35*, 1419; Wang, S.-X.; Wang, K.; Li, J.-T. *Synth. Commun.* ***2005***, *35*, 2387; Li, J.-T.; Chen, Y.-X.; Li, T.-S. *Synth. Commun.* ***2005***, *35*, 2831.

Other reagents have been used,[1628] including Sm,[1629] SmI_2,[1630] Pr,[1631] Yb,[1632] In with ultrasound,[1633] $InCl_3$ catalyst with Mg,[1634] $InCl_3$/Al in H_2O,[1635] Al/$TiCl_3$,[1636] VCl_3/Zn in H_2O,[1637] activated Mn,[1638] Zn,[1639] and a low-valent Ti reagent[1640] (see Reaction **19-76**). Unsymmetrical coupling between two different ketones has been accomplished using $TiCl_3$ in aqueous solution,[1641] and coupling of two different aldehydes has been achieved by the use of a V complex.[1642] Two aldehydes have also been coupled using Mg in water.[1643] Coupling leads to a mixture of *syn*- and *anti*-diols. "Syn-selective" reagents are Cp_2TiCl_2/Mn,[1644] $TiCl_4$/Bu_4I,[1645] TiI_4,[1646] and $NbCl_3$.[1647] "Anti-selective" coupling reactions are also known: Ti–salen,[1648] Mg with a $NiCl_2$ catalyst,[1649] and Sm/$SmCl_3$.[1650] Aryl aldehydes are coupled to give the bis(trimethylsilyl) ether using Mn, Me_3SiCl and Cp_2TiCl_2.[1651]

Stereoselective pinacol coupling reactions are well known.[1652] Chiral additives with pinacol couplings lead to formation of a diol with moderate to good enantioselectivity.[1653] A crossed-pinacol coupling was reported using Et_2Zn and with a BINOL catalyst gave good enantioselectivity.[1654] Enantioselective coupling was reported using a chiral salen–Mo

[1628] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp.1111–1114.

[1629] Hélion, F.; Lannou, M.-I.; Namy, J.-L. *Tetrahedron Lett.* ***2003****, 44*, 5507. See Banik, B.K.; Banik, I.; Aounallah, N.; Castillo, M. *Tetrahedron Lett.* ***2005****, 46,* 7065.

[1630] Aspinall, H.C.; Greeves, N.; Valla, C. *Org. Lett.* ***2005****, 7,* 1919.

[1631] Drapo, J.R.; Priefer, R. *Synth. Commun.* ***2009****, 39,* 85.

[1632] Hou, Z.; Takamine, K.; Fujiwara, Y.; Taniguchi, K. *Chem. Lett.* ***1987***, 2061.

[1633] Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. *Tetrahedron Lett.* ***1998****, 39*, 4367.

[1634] Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***2001****, 74*, 1497.

[1635] Wang, C.; Pan, Y.; Wu, A. *Tetrahedron* ***2007****, 63,* 429.

[1636] Li, J.-T.; Lin, Z.-P.; Qi, N.; Li, T.-S. *Synth. Commun.* ***2004****, 34*, 4339.

[1637] Xu, X.; Hirao, T. *J. Org. Chem.* ***2005****, 70*, 8594.

[1638] Rieke, R.D.; Kim, S.-H. *J. Org. Chem.* ***1998****, 63*, 5235. See Groth, U.; Jeske, M. *Synlett* ***2001***, 129.

[1639] Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y.S.; Heravi, M.M. *Monat. Chem.* ***2001****, 132*, 689.

[1640] For a discussion of the mechanism, see Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem Soc.* ***2001****, 123*, 1503. See Duan, X.-F.; Feng, J.-X.; Zi, G.-F.; Zhang, Z.-B. *Synthesis* ***2009***, 277. Also see Li, T.; Cui, W.; Liu, J.; Zhao, J.; Wang, Z. *Chem. Commun.* ***2000***, 139; Kagayama, A.; Igarashi, K.; Mukaiyama, T. *Can. J. Chem.* ***2000****, 78*, 657.

[1641] Clerici, A.; Porta, O. *J. Org. Chem.* ***1982****, 47,* 2852; *Tetrahedron* ***1983****, 39,* 1239. See Delair, P.; Luche, J. *J. Chem. Soc. Chem. Commun.* ***1989***, 398; Takahara, P.M.; Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *Tetrahedron Lett.* ***1989****, 30,* 7177.

[1642] Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *J. Am. Chem. Soc.* ***1989****, 111,* 8014.

[1643] Zhang, W.-C.; Li, C.-J. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3131.

[1644] Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* ***1998***, 2673. Also see, Barden, M.C.; Schwartz, J. *J. Am. Chem. Soc.* ***1996****, 118*, 5484; Gansäuer, A. *Chem. Commun.* ***1997***, 457; Gansäuer, A. *Synlett* ***1997***, 363.

[1645] Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, 65, 5066.

[1646] Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***2000***, 724. For a syn-selective coupling with conjugated aldehydes see Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* ***2002****, 4*, 4097.

[1647] Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* ***1994****, 50*, 2841.

[1648] Chatterjee, A.; Bennur, T.H.; Joshi, N.N. *J. Org. Chem.* ***2003****, 68*, 5668.

[1649] Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* ***2004****, 60*, 2851. See also Luanphaisarnnont, T.; Ndubaku, C.O.; Jamison, T.F. *Org. Lett.* ***2005****, 7,* 2937.

[1650] Matsukawa, S.; Hinakubo, Y. *Org. Lett.* ***2003****, 5*, 1221.

[1651] Dunlap, M.S.; Nicholas, K.M. *Synth. Commun.* ***1999****, 29*, 1097.

[1652] For a review, see Chatterjee, A.; Joshi, N.N. *Tetrahedron* ***2006****, 62,* 12137.

[1653] Enders, D.; Ullrich, E.C. *Tetrahedron Asymmetry* ***2000****, 11*, 3861.

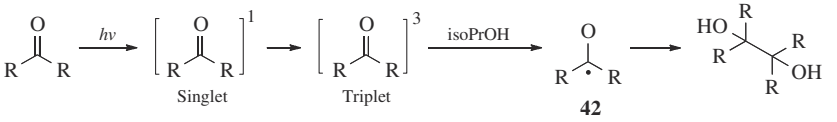
[1654] Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003****, 125*, 2169.

complex.[1655] A combination of Mg and Me_3SiCl was also used to effect a crossed-pinacol.[1656] Chiral metal complexes in conjunction with a metal leads to diol formation with good enantioselectivity.[1657]

Intramolecular pinacol coupling reactions are known, giving cyclic 1,2-diols.[1658] Dialdehydes have been cyclized by reaction with $TiCl_3$ to give cyclic 1,2-diols in good yield.[1659]

A variation of the pinacol coupling treats acyl nitriles with In metal and ultrasound to give a 1,2-diketone.[1660] Another variation couples acetals to give 1,2-diols.[1661]

The photochemical dimerization of ketones to 1,2-diols is one of the most common photochemical reactions.[1662] The substrate, which is usually a diaryl or aryl alkyl ketone, is irradiated with UV light in the presence of a hydrogen donor (e.g., isopropyl alcohol, toluene, or an amine).[1663] In the case of benzophenone, irradiated in the presence of 2-propanol, the ketone molecule initially undergoes $n \rightarrow \pi*$ excitation, and the singlet species thus formed crosses to the T_1 state with a very high efficiency.

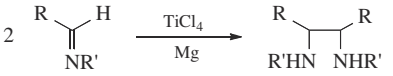


42

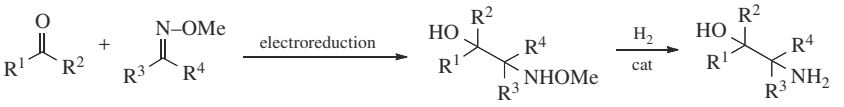
The T_1 species abstracts hydrogen from the alcohol (Sec. 7.A.vii, category 4) and then dimerizes. The *i*PrO$^{\bullet}$ radical, which is formed by this process, reacts by atom transfer of H$^{\bullet}$ to another molecule of ground-state benzophenone, producing acetone and another molecule of **51**. This mechanism[1664] predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum of light results in the conversion of 2 equiv of benzophenone to **42**. Under favorable experimental conditions, the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (although *p*-aminobenzophenone, e.g., can be dimerized in cyclohexane[1665]). The reaction has also been carried out electrochemically.[1666]

[1655] Yang, H.; Wang, H.; Zhu, C. *J. Org. Chem.* ***2007****, 72*, 10029.
[1656] Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetraheron Lett.* ***2004****, 45*, 3869.
[1657] See Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004****, 126*, 13198.
[1658] See Handa, S.; Kachala, M.S.; Lowe, S.R. *Tetrahedron Lett.* ***2004****, 45*, 253.
[1659] McMurry, J.E.; Siemers, N.O. *Tetrahedron Lett.* ***1993****, 34*, 7891. See Raw, A.S.; Pedersen, S.F. *J. Org. Chem.* ***1991****, 56,* 830; Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* ***1991****, 32,* 1125.
[1660] Baek, H.S.; Lee, S.J.; Yoo, B.W.; Ko, J.J.; Kim, S.H.; Kim, J.H. *Tetrahedron Lett.* ***2000****, 41*, 8097.
[1661] Studer, A.; Curran, D.P. *Synlett* ***1996***, 255.
[1662] See Schönberg, A. *Preparative Organic Photochemistry*; Springer, NY, ***1968***, pp. 203–217; Neckers, D.C. *Mechanistic Organic Photochemistry*, Reinhold, NY, ***1967***, pp. 163–177; Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 532–536; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 363–385; Kan, R.O. *Organic Photochemisty*, McGraw-Hill, NY, ***1966***, pp. 222–229.
[1663] See Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973****, 73,* 141.
[1664] See Huyser, E.S.; Neckers, D.C. *J. Am. Chem. Soc.* ***1963****, 85,* 3641.
[1665] Porter, G.; Suppan, P. *Proc. Chem. Soc.* ***1964***, 191.
[1666] Elinson, M.N.; Feducovich, S.K.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron* ***2000****, 56*, 9999. See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 174–180; Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 137–140; Baizer, M.M.; Petrovich, J.P. *Prog. Phys. Org. Chem.* ***1970****, 7,* 189; Baizer, M.M. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 639–689.

A coupling reaction similar to pinacol coupling has been used with imines, which dimerize to give 1,2-diamines. A number of reagents have been used, including treatment with $TiCl_4$–Mg,[1667] In/aq EtOH,[1668] Zn/aq NaOH,[1669] or SmI_2.[1670]



When electroreduction was used, it was possible to obtain cross-products by coupling a ketone to an *O*-methyl oxime[1671]: *O*-Methyl oxime ethers are coupled to give 1,2-diamines using Zn and $TiCl_4$.[1672] Aldehydes are converted to 1,2-diamines by treatment with TMS_2NH, NaH, and Li metal in 5 M $LiClO_4$ in ether, with sonication.[1673] Aldehydes are coupled with *N*-sulfinyl imines to give *N*-sulfinyl amino alcohols in the presence of SmI_2.[1674] Hemiaminals are coupled to give 1,2-diamines with TiI_4/Zn.[1675] Amides are converted to 1,2-diamines with Cp_2TiF_2 and $PhMeSiH_2$.[1676] Samarium(II) iodide was used to couple iminium salts, giving the 1,2-diamine.[1677] Ketones can be treated with Yb, and then an imine to give amino alcohols.[1678]

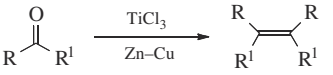


The *N*-methoxyamino alcohol could then be reduced to the amino alcohol.[1671] A photochemical coupling has also been reported.[1679] A variation of this reaction treats an imine with Yb in THF/HMPA, and then an aldehyde to give a 1,2-bis(imine).[1680]

OS **I**, 459; **II**, 71; **X**, 312; **81**, 26.

19-77 Bimolecular Reduction of Aldehydes or Ketones to Alkenes

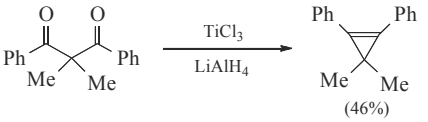
De-oxygen-coupling



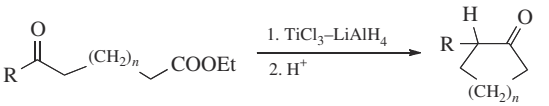
Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment with low valent Ti,[1681] initially

[1667] See Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* ***1998***, 873, 875.
[1668] Kalyanam, N.; Rao, G.V. *Tetrahedron Lett.* ***1993****, 34*, 1647.
[1669] Dutta, M.P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett* ***1998***, 857.
[1670] Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* ***2004****, 6,* 4747.
[1671] Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* ***1991****, 32*, 525.
[1672] Kise, N.; Ueda, N. *Tetrahedron Lett.* ***2001****, 42*, 2365.
[1673] Mojtahedi, M.M.; Saidi, M.R.; Shirzi, J.S.; Bolourtchian, M. *Synth. Commun.* ***2001****, 31,* 3587.
[1674] Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2005****, 127,* 11956.
[1675] Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* ***2001***, 1334.
[1676] Selvakumar, K.; Harrod, J.F. *Angew. Chem. Int. Ed.* ***2001****, 40*, 2129.
[1677] Kim, M.; Knettle, B.W.; Dahlén, A.; Hilmersson, G.; Flowers III, R.A. *Tetrahedron* ***2003****, 59*, 10397.
[1678] Su, W.; Yang, B. *Synth. Commun.* ***2003****, 33*, 2613.
[1679] Ortega, M.; Rodríguez, M.A.; Campos, P.J. *Tetrahedron* ***2004****, 60*, 6475.
[1680] Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* ***2001****, 66*, 514.
[1681] See Rele, S.; Chattopadhyay, S.; Nayak, S.K. *Tetrahedron Lett.* ***2001****, 42*, 9093.

generated with $TiCl_3$ and a Zn–Cu couple.[1682] This is called the *McMurry reaction*.[1683] The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished[1684] with low-valent Ti reagents prepared in other ways, for example, from Mg and a $TiCl_3$–THF complex;[1685] from $TiCl_4$ and Zn or Mg;[1686] from $TiCl_3$ and $LiAlH_4$;[1687] and from $TiCl_3$ and K or Li;[1688] and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, $LiAlH_4$, or an organolithium[1689] (see Reaction **17-18**). Microwave irradiation has been used to facilitate the coupling.[1690] The reaction has been used to convert dialdehydes and diketones to cycloalkenes.[1691] Rings of 3–16 and 22 members have been closed in this way, for example,[1692]



The same reaction on a keto ester gives a cycloalkanone.[1693]



Indoles have been prepared form *o*-acyl amides with Ti(powder) and Me_3SiCl[1694] or with $TiCl_3$–C_8K.[1695] Benzofurans have been prepared by a closely related reaction.[1696]

Unsymmetrical alkenes can be prepared from a mixture of two ketones in a cross-coupling reaction, if one is in excess.[1697] An aldehyde and a ketone were cross-coupled using $Yb(OTf)_3$, for example.[1698] The mechanism consists of initial coupling of two radical

[1682] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978****, 43,* 3255. For an optimized procedure, see McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* ***1989****, 54,* 3748.

[1683] See McMurry, J.E. *Chem. Rev.* ***1989****, 89*, 1513; *Acc. Chem. Res.* ***1983****, 16,* 405; Lenoir, D. *Synthesis* ***1989***, 883; Betschart, C.; Seebach, D. *Chimia* ***1989****, 43,* 39; Lai, Y. *Org. Prep. Proceed. Int.* ***1980****, 12*, 363. For related reviews, see Kahn, B.E.; Rieke, R.D. *Chem. Rev.* ***1988****, 88,* 733; Pons, J.; Santelli, M. *Tetrahedron* ***1988****, 44,* 4295. See Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* ***2006****, 71*, 9873.

[1684] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 305–308.

[1685] Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* ***1973***, 2147.

[1686] Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* ***1990****, 43,* 1439.

[1687] Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982****, 91*, 149, 311; Bottino, F.A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 77. This reagent has been reported to give capricious results; see McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976****, 41*, 896.

[1688] Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* ***2001****, 66*, 2990.

[1689] Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982****, 19*, 149, 311. See also, Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989****, 111,* 2324.

[1690] Stuhr-Hansen, N. *Tetrahedron Lett.* ***2005****, 46*, 5491.

[1691] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978****, 43*, 3255.

[1692] Baumstark, A.L.; McCloskey, C.J.; Witt, K.E. *J. Org. Chem.* ***1978****, 43,* 3609.

[1693] McMurry, J.E.; Miller, D.D. *J. Am. Chem. Soc.* ***1983****, 105*, 1660.

[1694] Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* ***1995****, 117*, 4468.

[1695] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* ***1994****, 59*, 5215.

[1696] Fürstner, A.; Jumbam, D.N. *Tetrahedron* ***1992****, 48*, 5991.

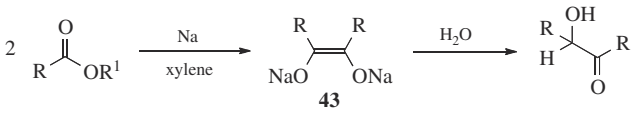
[1697] See Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989****, 111*, 2324.

[1698] Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M.C. *Eur. J. Org. Chem.* ***2003***, 1631.

species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.[1699]

OS **VII**, 1.

19-78 Acyloin Ester Condensation



43

When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α-hydroxy ketone (called an acyloin).[1700] The reaction, called the *acyloin ester condensation* (or just *acyloin condensation*),[1701] is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way (e.g., $R = C_{17}H_{35}$), but for high-molecular-weight esters, toluene or xylene is used as the solvent. Modifications to this procedure have been reported, including an ultrasound-promoted acyloin condensation in ether,[1702] which improved the yields of four-, five-, and six-membered rings, and Olah's procedure, which was also done in ether.[1703]

The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[1704] The yields are 50–60% for the preparation of 6- and 7-membered rings, 30–40% for 8- and 19-membered, and 60–95% for rings of 10–20 members. Even larger rings have been closed in this manner. Indeed, this is one of the best ways of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,[1705] although this is generally unsuccessful. For larger rings, the presence of double or triple bonds does not interfere.[1706] Even a benzene ring can be present, and many paracyclophane derivatives (**44**) with $n = 9$ or more have been synthesized in this manner.[1707]

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane (Me_3SiCl), in which case the dianion (**43**) is converted to the bis (silyl) enol ether (**45**), which can be isolated and subsequently hydrolyzed to the acyloin with aq acid.[1708] This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the *Dieckmann condensation*[1709] (Reaction **16-85**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-membered ring can be closed (note that the ring formed by a *Dieckmann condensation* is

[1699] Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H.Y. *J. Org. Chem.* ***1982****, 47*, 248. See Villiers, C.; Ephritikhine, M. *Angew. Chem,. Int. Ed.* ***1997****, 36*, 2380; Stahl, M.; Pindur, U.; Frenking, G. *Angew. Chem. Int. Ed.* ***1997****, 36*, 2234.

[1700] See Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. *Org. React.* ***1976****, 23,* 259. For a list of reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, pp. 1313–1315.

[1701] Also see Daynard, T.S.; Eby, P.S.; Hutchinson, J.H. *Can. J. Chem.* ***1993****, 71*, 1022.

[1702] Fadel, A.; Canet, J,-L.; Salaün, J. *Synlett* ***1990***, 89.

[1703] Olah, G.A.; Wu, A. *Synthesis* ***1991***, 1177.

[1704] See Finley, K.T. *Chem. Rev.* ***1964****, 64,* 573.

[1705] Bloomfield, J.J.; Irelan, J.R.S. *J. Org. Chem.* ***1966****, 31*, 2017.

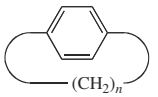
[1706] Cram, D.J.; Gaston, L.K. *J. Am. Chem. Soc.* ***1960****, 82*, 6386.

[1707] For a review, see Cram, D.J. *Rec. Chem. Prog.* ***1959****, 20*, 71.

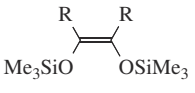
[1708] Schräpler, U.; Rühlmann, K. *Chem. Ber.* ***1964****, 97*, 1383. See Rühlmann, K. *Synthesis* ***1971***, 236.

[1709] Bloomfield, J.J. *Tetrahedron Lett.* ***1968***, 591.

always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The Me_3SiCl method is especially good for the closing of four-membered rings.[1710]

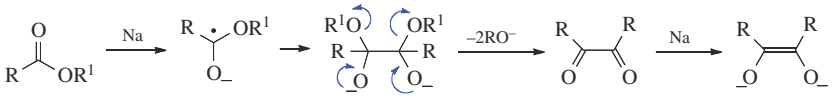


44



45

The mechanism is usually presumed to have a diketone (RCOCOR) as an intermediate,[1711] since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., *t*-Bu−COCO−*t*-Bu), it is the major product. A possible sequence (analogous to that of Reaction **19-76**) is



A large surface area for the Na is usually required for good results in this coupling, consistent with a surface reaction. In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface[1712] of the Na. Although high dilution techniques are not always necessary, effective stirring (high-speed stirrer at 2000–2500 rpm) is usually required to generate "sodium sand". Highly pure Na gives poorer results because the presence of a small percentage of K is important. Up to 50% potassium (1 : 1 Na/K)[1713] has been used in acyloin condensations.

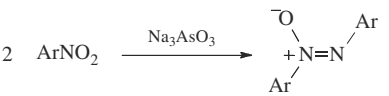
In a related reaction, aromatic carboxylic acids were condensed to α-diketones (2ArCOOH → ArCOCOAr) on treatment with excess Li in dry THF in the presence of ultrasound.[1714]

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see Sec. 3.D).[1715] This synthesis of a catenane produced only a small yield and relied on chance for threading the molecules before ring closure.

OS **II**, 114; **IV**, 840; **VI**, 167.

19-79 Reduction of Nitro to Azoxy Compounds

Nitro-azoxy reductive transformation



[1710] Bloomfield, J.J.; Martin, R.A.; Nelke, J.M. *J. Chem. Soc. Chem. Commun.* ***1972***, 96.
[1711] Another mechanism has been proposed: Bloomfield, J.J.; Owsley, D.C.; Ainsworth, C.; Robertson, R.E. *J. Org. Chem.* ***1975****, 40,* 393.
[1712] For the preparation of high-surface sodium, see Makosza, M.; Grela, K. *Synlett* ***1997***, 267.
[1713] Vogel, I.A. *A Textbook of Practical Organic Chemistry*, 3rd ed, Wiley, NY, ***1966***, p. 856.
[1714] Karaman, R.; Fry, J.L. *Tetrahedron Lett.* ***1989****, 30,* 6267.
[1715] For reviews of the synthesis of catenanes, see Sauvage, J. *Acc. Chem. Res.* ***1990****, 23,* 319; *Nouv. J. Chim.* ***1985****, 9*, 299; Dietrich-Buchecker, C.O.; Sauvage, J. *Chem. Rev.* ***1987****, 87,* 795.

Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,[1716] and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (Reaction **19-46**), and these combine (Reaction **12-51**). The combination step is rapid compared to the reduction process.[1717] Nitroso compounds can be reduced to azoxy compounds with triethylphosphite or triphenylphosphine[1718] or with an alkaline aqueous solution of an alcohol.[1719]

OS **II**, 57.

19-80 Reduction of Nitro to Azo Compounds

_N_-De-bisoxygen-coupling

$$2\,ArNO_2 \xrightarrow{LiAlH_4} Ar{-}N{=}N{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and Zn and alkali are the most common. A combination of triethylammonium formate and lead in methanol is also effective.[1720] With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (Reaction **19-79**) compound. By analogy to Reaction **19-79**, this reaction may be looked on as a combination of ArN=O and $ArNH_2$ (**13-24**). However, when the reducing agent was $NaBH_4$,[1721] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$. Dicarborane, with a catalytic amount of acetic acid, reduces aromatic nitro compounds to the amine.[1722]

Nitro compounds can be further reduced to hydrazo compounds with Zn and sodium hydroxide, with hydrazine hydrate and Raney nickel,[1723] or with $LiAlH_4$ mixed with a metal chloride (e.g., $TiCl_4$ or VCl_3).[1724] The reduction has also been accomplished electrochemically.

OS **III**, 103.

G. Reactions in which an Organic Substrate Is Both Oxidized and Reduced

Some reactions that belong in this category have been considered in earlier chapters. Among these are the *Tollens' condensation* (Reaction **16-43**), the benzil–benzilic acid rearrangement (Reaction **18-6**), and the *Wallach rearrangement* (Reaction **18-43**).

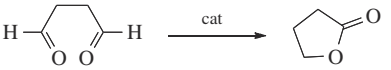
19-81 The Cannizzaro Reaction

Cannizzaro Aldehyde Disproportionation

$$2\,ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

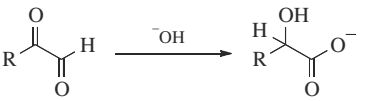
[1716] Osuka, A.; Shimizu, H.; Suzuki, H. *Chem. Lett.* ***1983***, 1373. See Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H.; Taga, T. *J. Org. Chem.* ***1989****, 54,* 4169.
[1717] Ogata, Y.; Mibae, J. *J. Org. Chem.* ***1962****, 27,* 2048.
[1718] Bunyan, P.J.; Cadogan, J.I.G. *J. Chem. Soc.* ***1963***, 42.
[1719] See Hutton, J.; Waters, W.A. *J. Chem. Soc. B* ***1968***, 191. See also, Porta, F.; Pizzotti, M.; Cenini, S. *J. Organomet. Chem.* ***1981****, 222,* 279.
[1720] Srinavasa, G.R.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2003****, 44*, 5835.
[1721] Hutchins, R.O.; Lamson, D.W.; Rufa, L.; Milewski, C.; Maryanoff, B. *J. Org. Chem.* ***1971****, 36,* 803.
[1722] Bae, J.W.; Cho, Y.J.; Lee, S.H.; Yoon, C.M. *Tetrahedron Lett.* ***2000****, 41*, 175.
[1723] Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* ***1957****, 79,* 5492.
[1724] Olah, G.A. *J. Am. Chem. Soc.* ***1959****, 81,* 3165.

Aromatic aldehydes, and aliphatic ones with no α hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[1725] Reaction with triethylamine and $MgBr_2$ gave a room temperature *Cannizzaro reaction*.[1726] The reaction is mediated by organobases.[1727] In this reaction, one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α hydrogen do not give the reaction, because when these compounds are treated with base, the aldol reaction (**16-34**) is much faster.[1728] Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. Solvent-free reactions are known.[1729] On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde.[1730] In this case, the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed-Cannizzaro reaction*.[1731] The *Tollens' condensation* (Reaction **16-43**) includes a *crossed-Cannizzaro reaction* as its last step. A *Cannizzaro reaction* with 1,4-dialdehydes (note that α-hydrogen atoms are present here) and a Rh catalyst gives ring closure, for example,[1732]



The product is the lactone derived from the hydroxy acid that would result from a normal *Cannizzaro reaction*. Chiral additives have been used, but with bis(oxazolidine) derivatives, the reaction proceeded with poor enantioselectivity.[1733]

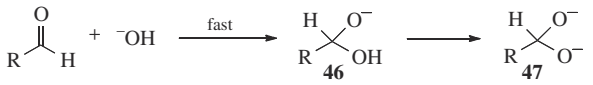
α-Keto aldehydes give internal *Cannizzaro reactions*[1734]:



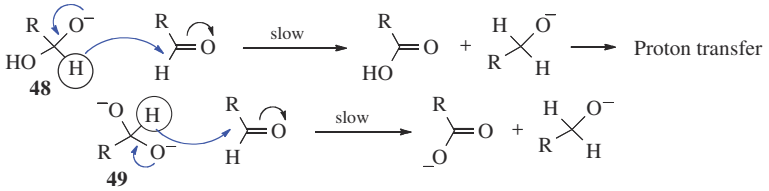
This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[1735] and γ-keto aldehydes.

The mechanism[1736] of the *Cannizzaro reaction*[1737] involves a hydride shift (an example of mechanism type 2, Sec. 19.A). First ^-OH adds to the C=O to give **46**, which may lose a proton in the basic solution to give the diion (**47**).

[1725] See Geissman, T.A. *Org. React.* ***1944****, 2,* 94.
[1726] Abaee, M.S.; Sharifi, R.; Mojtahedi, M.M. *Org. Lett.* ***2005****, 7,* 5893.
[1727] Basavaiah, D.; Sharada, D.S.; Veerendhar, A. *Tetrahedron Lett.* ***2006****, 47*, 5771.
[1728] An exception is cyclopropanecarboxaldehyde: van der Maeden, F.P.B.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1972****, 91,* 221.
[1729] Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001****, 42*, 7983.
[1730] See Thakuria, J.A.; Baruah, M.; Sandhu, J.S. *Chem. Lett.* ***1999***, 995.
[1731] See Reddy, B.V.S.; Srinivas, R.; Yadav, J.S.; Ramalingam, T. *Synth. Commun.* ***2002****, 32*, 219.
[1732] Bergens, S.H.; Fairlie, D.P.; Bosnich, B. *Organometallics* ***1990****, 9,* 566.
[1733] Russell, A.E.; Miller, S.P.; Morken, J.P. *J. Org. Chem.* ***2000****, 65*, 8381.
[1734] Russell, G.A.; Mikol, G.J. *J. Am. Chem. Soc.* ***1966****, 88,* 6498; Prey, V.; Berbdk, H.; Steinbauer, E. *Monatch. Chem.* ***1960****, 91,* 1196; ***1962****, 93,* 237.
[1735] Thompson, J.E. *J. Org. Chem.* ***1967****, 32,* 3947.
[1736] See Ashby, E.C.; Coleman, III, D.T.; Gamasa, M.P. *J. Org. Chem.* ***1987****, 52,* 4079; Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* ***1987****, 28*, 2947.
[1737] See Swain, C.G.; Powell, A.L.; Sheppard, W.A.; Morgan, C.R. *J. Am. Chem. Soc.* ***1979****, 101,* 3576; Watt, C.I. F. *Adv. Phys. Org. Chem.* ***1988****, 24*, 57, pp. 81–86.



The strong electron-donating character of O^- greatly facilitates the ability of the aldehyde hydrogen to leave with its electron pair. Of course, this effect is even stronger in **49**. Hydride is transferred to another molecule of aldehyde. The hydride can come from **48** or **49**:



If the hydride ion comes from **48**, the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is (1) The reaction can be first order in base and second order in substrate (thus going through **48**) or, at higher base concentrations, second order in each (going through **49**); and (2) when the reaction was run in D_2O, the recovered alcohol contained no α deuterium,[1738] indicating that the hydrogen comes from another equivalent of aldehyde and not from the medium.[1739]

OS **I**, 276; **II**, 590; **III**, 538; **IV**, 110.

19-82 The Tishchenko Reaction

Tishchenko aldehyde-ester disproportionation

$$2\ \mathrm{ArCHO} \xrightarrow{\mathrm{Al(OEt)_3}} \mathrm{ROOCH_2R}$$

When aldehydes, with or without an α hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another is reduced, as in Reaction **19-81**, but here they are found as the ester. The process is called the *Tishchenko reaction*.[1740] Crossed-*Tishchenko reactions* are also possible. With more strongly basic alkoxides (e.g., Mg or sodium alkoxides), aldehydes with an a hydrogen give the *aldol reaction*. Treatment of a dialdehyde [e.g., phthalic dicarboxaldehyde (phthalaldehyde) with CaO] leads to a lactone.[1741] Like Reaction **19-81**, this reaction has a mechanism that involves hydride transfer.[1742] The *Tishchenko reaction* can also be catalyzed[1743] by Ru complexes,[1744] organoactinides,[1745] alkaline earth amides,[1746] by Cp_2ZrH_2[1747] and, for aromatic

[1738] Fredenhagen, H.; Bonhoeffer, K.F. *Z. Phys. Chem. Abt. A* ***1938,*** *181*, 379; Hauser, C.R.; Hamrick, Jr., P.J.; Stewart, A.T. *J. Org. Chem.* ***1956,*** *21,* 260.

[1739] See Swain, C.G.; Powell, A.L.; Lynch, T.J.; Alpha, S.R.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1979,*** *101,* 3584. See, however, Chung, S. *J. Chem. Soc. Chem. Commun.* ***1982***, 480.

[1740] For a review, see Seki, T.; Nakajo, T.; Onaka, M. *Chem. Lett.* ***2006,*** *35*, 824.

[1741] Seki, T.; Hattori, H. *Chem. Commun.* ***2001***, 2510.

[1742] See Saegusa, T.; Ueshima, T.; Kitagawa, S. *Bull. Chem. Soc. Jpn.* ***1969,*** *42,* 248; Ogata, Y.; Kishi, I. *Tetrahedron* ***1969,*** *25,* 929.

[1743] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley–VCH, NY, ***1999***, p. 1653–1655.

[1744] Ito, T.; Horino, H.; Koshiro,Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1982,*** *55,* 504.

[1745] Andrea, T.; Barnea, E.; Eisen, M.S. *J. Am. Chem. Soc.* ***2008,*** *130*, 2454.

[1746] Crimmin, M.R.; Barrett, A.G.M.; Hill, M.S.; Procopiou, P.A. *Org. Lett.* ***2007,*** *9,* 331.

[1747] DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997,*** *62*, 6974.

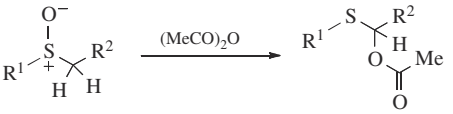
aldehydes, by disodium tetracarbonylferrate [$Na_2Fe(CO)_4$].[1748] Both CaO (noted above) and SrO have been used as catalysts.[1749] A bis(phenylenedioxy) bis(aluminum) catalyst has been used to convert aliphatic aldehydes to the corresponding ester.[1750] The bis Al(O-*i*Pr)$_2$ derivative of catechol has also been used as a catalyst.[1751]

A *Tishchenko–aldol transfer reaction* was reported using β-hydroxy ketones and an aldehydes with an $AlMe_3$ catalyst, giving a monoacyl diol.[1752]

OS **I**, 104.

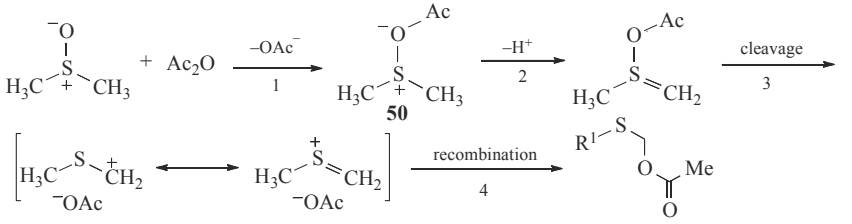
19-83 The Pummerer Rearrangement[1753]

Pummerer methyl sulfoxide rearrangement



When sulfoxides bearing an α hydrogen are treated with acetic anhydride, the product is an α-acetoxy sulfide. This is one example of *the Pummerer rearrangement*,[1754] in which the sulfur is reduced while an adjacent carbon is oxidized.[1755] The product is readily hydrolyzed (Reaction **10-6**) to the aldehyde (R_2CHO).[1756] Besides acetic anhydride, other anhydrides and acyl halides give similar products. Inorganic acids (e.g., HCl), also give the reaction, and $RSOCH_2R'$ can be converted to $RSCHClR'$ in this way. Sulfoxides can also be converted to α-halo sulfides[1757] by other reagents, including sulfuryl chloride, NBS, and NCS. Enantioselective *Pummerer rearrangements* are known.[1758] Uncatalyzed thermal rearrangements are also known.[1759]

The following 4-step mechanism has been proposed for the reaction between acetic anhydride and DMSO[1760]:



[1748] Yamashita, A.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1976****, 49,* 3597.
[1749] Seki, T.; Akutsu, K.; Hattori, H. *Chem. Commun.* ***2001***, 1000.
[1750] Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* ***1999****, 40*, 7695.
[1751] Simpura, I.; Jevalainen, V. *Tetrahedron* ***2001****, 57*, 9867.
[1752] Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* ***2001****, 42*, 3905; Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* ***2001***, 1220.
[1753] See Bur, S.K.; Padwa, A. *Chem. Rev.* ***2004****, 104*, 2401.
[1754] For a review, see Feldman, K.S. *Tetrahedron* ***2006****, 62,* 5003. Also see Smith, L.H.S.; Coote, S.C.; Sneddon, H.F.; Procter, D.J. *Angew. Chem. Int. Ed.* ***2010****, 49*, 5832.
[1755] See De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* ***1991****, 40,* 157; Warren, S. *Chem. Ind. (London)* ***1980***, 824; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–162.
[1756] See Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* ***1978***, 881.
[1757] See Dilworth, B.M.; McKervey, M.A. *Tetrahedron* ***1986****, 42,* 3731.
[1758] Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* ***1995****, 36*, 115; Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* ***1994****, 35*, 9733.
[1759] Wladislaw, B.; Marzorati, L.; Biaggio, F.C. *J. Org. Chem.* ***1993****, 58*, 6132.
[1760] See Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994****, 35,* 2569.

For DMSO and acetic anhydride, step 4 is intermolecular, as shown by ^{18}O isotopic labeling studies.[1761] With other substrates, however, step 4 can be inter- or intramolecular, depending on the structure of the sulfoxide.[1762] Depending on the substrate and reagent, any of the first three steps can be rate determining. In the case of Me_2SO treated with $(F_3CCO)_2O$, the intermediate corresponding to **50**[1763] could be isolated at low temperature, and on warming gave the expected product.[1764] There is also an abundance of other evidence for this mechanism.[1765]

A *sila-Pummerer rearrangement* has been reported.[1766]

19-84 The Willgerodt Reaction

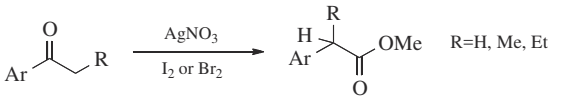
Willgerodt carbonyl transformation

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^-NH_4^+$$

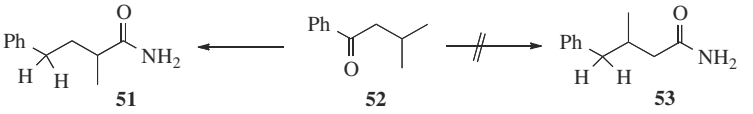
In the *Willgerodt reaction*, a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.[1767] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2CO_2H$ and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2CH_2CH_2CO_2H$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. Unlike the *Pummerer rearrangement* (Reaction **19-83**), which involves transposition of an oxygen from S to C, the *Willgerodt reaction* involves oxygen migration *and* oxidation of the organic species. The use of sulfur and a dry primary or secondary amine (or ammonia), as the reagent is called the *Kindler modification* of the *Willgerodt reaction*.[1768] The product in this case is $Ar(CH_2)_nCSNR_2$,[1769] which can be hydrolyzed to the acid. Particularly good results are obtained with morpholine as the amine. For volatile amines, the HCl salts can be used instead, with NaOAc in DMF at 100 °C.[1770] Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate (Me_2NCOO^- $Me_2NH_2^+$).[1771] The *Kindler modification* has also been applied to aliphatic ketones.[1772] Thioamides have been prepared from ketones in a base-catalyzed reaction.[1773]

[1761] Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* ***1963****, 19,* 817.
[1762] See Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983****, 56,* 266; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* ***1983****, 56,* 270.
[1763] See Marino, J.P. *Top. Sulfur Chem.* ***1976****, 1,* 1.
[1764] Sharma, A.K.; Swern, D. *Tetrahedron Lett.* ***1974***, 1503.
[1765] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–156; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980****, 5*, 45, p. 48; Wolfe, S.; Kazmaier, P.M. *Can. J. Chem.* ***1979****, 57*, 2388, 2397; Russell, G.A.; Mikol, G.J. *Mech. Mol. Migr.* ***1968****, 1,* 157.
[1766] Kirpichenko, S.V.; Suslova, E.N.; Albanov, A.I.; Shainyan, B.A. *Tetrahedron Lett.* ***1999****, 40*, 185.
[1767] For a review, see Brown, E.V. *Synthesis* ***1975***, 358.
[1768] See Mayer, R. in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 58–63; Lundstedt, T.; Carlson, R.; Shabana, R. *Acta Chem. Scand. Ser. B* ***1987****, 41,* 157, and other papers in this series. See also, Kanyonyo, M.R.; Gozzo, A.; Lambert, D.M.; Lesieur, D.; Poupaert, J.H. *Bull. Soc. Chim. Belg.* ***1997****, 106*, 39.
[1769] See Asinger, F.; Offermanns, H. *Angew. Chem. Int. Ed.* ***1967****, 6,* 907.
[1770] Amupitan, J.O. *Synthesis* ***1983***, 730.
[1771] Schroth, W.; Andersch, J. *Synthesis* ***1989***, 202.
[1772] See Dutron-Woitrin, F.; Merényi, R.; Viehe, H.G. *Synthesis* ***1985***, 77.
[1773] For a review, see Poupaert, J.H.; Bouinidane, K.; Renard, M.; Lambert, D.; Isa, M. *Org. Prep. Proceed. Int.* ***2001****, 33*, 335.

Alkyl aryl ketones can be converted to arylacetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with silver nitrate and I_2 or Br_2.[1774]



The mechanism of the *Willgerodt reaction* is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring, and then attacks it with its other end. However, this possibility is ruled out by experiments, such as the following: When isobutyl phenyl ketone (**51**) is subjected to the *Willgerodt reaction*, the product is **52**, not **53**, which would arise if the end carbon of the ketone became bonded to the ring in the product[1775]:



This also excludes a cyclic-intermediate mechanism similar to that of the *Claisen rearrangement* (Reaction **18-33**). Another important fact is that the reaction is successful for singly branched side chains (e.g., **52**), but not for doubly branched side chains, as in $PhCOCMe_3$.[1775] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$.[1776] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, although just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases, imines[1777] or enamines[1778] have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

[1774] Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 235. See also, Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1483.
[1775] King, J.A.; McMillan, F.H. *J. Am. Chem. Soc.* ***1946****, 68*, 632.
[1776] See Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* ***1967****, 98,* 825.
[1777] Asinger, F.; Halcour, K. *Monatsh. Chem.* ***1964****, 95*, 24. See also, Nakova, E.P.; Tolkachev, O.N.; Evstigneeva, R.P. *J. Org. Chem. USSR* ***1975****, 11,* 2660.
[1778] Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 229–232.

APPENDIX A

The Literature of Organic Chemistry

All discoveries in the laboratory must be published somewhere if the information is to be made available to the scientific community. A new experimental result that is not published is useless, insofar as it benefits the entire chemical world. Traditionally, the total body of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. Nowadays, books remain on library shelves, but many, if not most, chemical journals are available online. As e-books become increasingly available, however, books will be available online or for personal electronic reading devices. Anyone who wishes to learn the answer to a chemical question will access the chemical literature, both books and original articles in journals. The expressions "is known", "has been done", and so on, usually means "has been published". The contents of the scientific literature may appear formidably large, but the process of extracting information from the literature of organic chemistry is usually manageable. Appendix A examines both the print literature of organic chemistry[1] and, within reasonable limits, electronic forms of the literature.

It is quite clear that the literature can be divided into two broad categories: primary sources and secondary sources. A *primary source* publishes the original results of laboratory investigations, usually in scientific journals. Indeed, the two chief kinds of primary source are journals and patents. Books, indexes, and other publications that cover material that has previously been published in primary sources are called *secondary sources*. Electronic search engines that use primary sources as a database are also considered to be secondary sources. It is because of the excellence of the secondary sources in organic chemistry (especially *Chemical Abstracts*, *SciFinder*) that literature searching is comparatively straightforward.

[1] See Williams, S. *College Teaching* ***2005****, 53*, 137 Kennedy, M.M. *Educational Researcher* ***2007****, 36*, 139; Available at www.chemistryguide.org; Gallagher, G.J.; Adams, D.L. *J. Chem. Educ.* ***2002****, 79*, 1368. Also see Wolman, Y. *Chemical Information, 2nd ed.*, Wiley, NY, ***1988***; Maizell, R.E. *How to Find Chemical Information, 2nd ed.*, Wiley, NY, ***1987***; Mellon, M.G. *Chemical Publications, 5th ed.*, McGraw-Hill, NY, ***1982***; Skolnik, H. *The Literature Matrix of Chemistry,* Wiley, NY, ***1982***; Antony, A. *Guide to Basic Information Sources in Chemistry,* Jeffrey Norton Publishers, NY, ***1979***; Bottle, R.T. *Use of the Chemical Literature*, Butterworth, London, ***1979***; Woodburn, H.M. *Using the Chemical Literature*, Marcel Dekker, NY, ***1974***. For a three-part article on the literature of organic chemistry, see Hancock, J.E.H. *J. Chem. Educ.* ***1968****, 45*, 193, 260, 336.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.
© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

A. PRIMARY SOURCES

A.i. Journals

For well over 100 years, nearly all new work in organic chemistry (except for that disclosed in patents) has been published in journals. There are many journals that publish chemical papers, in many countries and in many languages. Nowadays, a high percentage of the journals are published in English, but not all. Some print papers cover all fields of science; some are restricted to chemistry; some to organic chemistry; and some are still more specialized. As noted above, many journals are now available in electronic form.[2] The actual article is usually offered as an html file, or a PDF file, often with links to the cited references. The vast majority of important papers in "pure" organic chemistry (as opposed to "applied") are published in relatively few journals, perhaps 50 or fewer. The concept of "pure" organic chemistry is not as useful nowadays because organic chemistry is important in many areas, and multidisciplinary research often includes organic chemistry. Literature that is important to an organic chemist is found in journals and patents that focus on bioorganic, organometallic, materials science, polymer science, separation science, medicinal chemistry, pharmaceutical sciences, and medicine to name a few. The reader is therefore cautioned that the journals listed in this section have organic chemistry as their primary focus, but are by no means the only sources of information concerning organic chemistry. The literature is vast and many journals are published weekly and some semimonthly.

Ordinary papers, usually referred to as full papers, usually include full experimental details, either as part of the paper itself or as accompanying supplemental information. Such details are the mainstay of modern research, providing a guide to what has been done, and the experimental details allow one to repeat that work. With the increase in the volume of chemical literature, and especially with the proliferation of electronic journals, and as noted above, many journals now place full experimental details into "Supplemental Information". For journals published by the American Chemical Society, a URL link is provided for each article that contains the supplemental information: experiential details, spectral data, visual reproductions of spectral data, X-ray crystallographic data, and so on. Other publishers offer similar links. Once a paper is accepted, the online version (e.g., American Chemical Society ASAP papers) can be found before the print version or the full electronic version that contains the page numbers appear.

In addition to full papers, there are two other types of publications in which original work is reported: *notes* and *communi*cation*s*. A note is a brief paper, often without a summary (nearly all papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper.[3] Some journals specialize in publishing only notes. Communications (also called *letters*) are also brief and are usually without summaries (some journals now publish summaries along with their communications), and there are journals that publish only communications or letters.

Communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details or none at all.

[2] For examples of the contents of an academic electronic library see http://lib.uconn.edu/ or http://www.chem.ox.ac.uk/cheminfo/ejournals.html. Also see eJournal Locator.

[3] In some journals, notes are called "short communications", an unfortunate practice, because they are not communications as that term is defined in this text.

2. They are often of immediate significance. Journals that publish communications make every effort to have them appear as soon as possible after they are received. With modern computer technology, communications can often be published in a matter of weeks.
3. Communications are preliminary reports, and the material in them may be republished as papers at a later date, in contrast to the material in papers and notes, which cannot be republished.

Although chemical publications are published in many languages, the vast majority of important papers in organic chemistry are published in English. For example, six prominent European journals (*Chemische Berichte, Liebigs Annalen der Chemie*, *Bulletin de la Société Chimique de France, Bulletin des Sociétés Chimique Belges, Recueil des Travaux Chimiques des Pays-Bas, and Gazzetta Chimica Italiana*) were discontinued. In their place is the *European Journal of Organic Chemistry, published in English.* Most of the articles published in other languages have summaries printed in English also. Important papers were published in German and French for >200 years, and these are generally not available in translation, so that the organic chemist was required to have at least a reading knowledge of these languages. Before ~1920, more than one-half of the important chemical papers were in these languages. In recent years, however, fewer papers in French or German have appeared without an English translation. Of course, a reading knowledge of French and German (especially German) is critical for the older literature. It must be realized that the original literature is never obsolete. With the rise of China in the scientific community, journals are published in Chinese, and there are journals and important chemical discoveries published in Japanese. Work by Chinese and Japanese scientists regularly appears in English-language journals. Secondary sources become superseded or outdated, but nineteenth century journals with primary literature are found in most chemical libraries and are still consulted. Table A.1 presents a list of important current journals that publish original papers[4] and communications in organic chemistry. Some of them also publish review articles, book reviews, and other material. In 1999, the *Journal of Organic Chemistry* stopped publishing communications, and these are now published in *Organic Letters*.

For some years, the American Chemical Society journals, including *J. Am. Chem. Soc.* and *J. Org. Chem.*, provided supplementary material for some of their papers on microfilm or microfiche. As noted above, this material is now available online, and for older literature from the Microforms and Back Issues Office at the ACS Washington office, either on microfiche, or as a photocopy. These practices have not yet succeeded in substantially reducing the total volume of the world's primary chemical literature since many new journals have appeared, and the yearly page count for most journals has doubled or tripled.

A.ii. Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures). It comes as a surprise to many to learn that a substantial proportion of the patents granted (perhaps 20–30%) have been chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents were regularly abstracted by *Chemical Abstracts* and now *SciFinder*. In addition to learning about the contents of patents

[4] In Table A.1, notes are counted as papers.

TABLE A.1 A List of the More Important *Current* Journals[a]

No.	Name	Papers or Communications	Issues per Year
1	**Angew**andte **Chem**ie (1887)[b]	C[c]	12
2	**Angew**andte **Chem**ie **Int**ernational **Ed**ition (1962)[b]	C[c]	48
3	**Aust**ralian **J**ournal of **Chem**istry (1948)	P	12
4	**Bioorg**anic **Chem**istry (1971)	P[b]	4
5	**Bioorg**anic & **Med**icinal **Chem**istry **Lett**ers (1991)	C	12
6	**Bull**etin of the **Chem**ical **Soc**iety of **Jap**an (1926)	P	12
7	**Can**adian **J**ournal of **Chem**istry (1929)	P,C	12
8	**Carbohydr**ate **Res**earch (1965)	P,C	22
9	**Chem**istry, a **Eur**opean **Journal** (1995)	P	24
10	**Chem**istry, an **Asian J**ournal (2006)	P	24
11	**Chem**istry and **Ind**ustry **(London)** (1923)	C	24
12	**Chem**istry **Lett**ers (1972)	C	12
13	**Chimia** (1947)	C[b]	12
14	**ChemPlusChem**	New	
15	**Dokl**ady **Chem**istry (1922)[b]	C	12
17.	**Eur**opean **J**ournal of **Org**anic **Chem**istry (1998)	P	12
18	**Helv**etica **Chim**ica **Acta** (1918)	P	8
19	**Heteroat**om **Chem**istry (1990)	P	6
20	**Heterocycles** (1973)	C[b]	12
21	**Ind**ian **J**ournal of **Chem**istry (Section **B**)	P	12
22	**Int**ernational **J**ournal of chemical **Kinet**ics (1969)	P	12
23	**Isr**ael **J**ournal of **Chem**istry (1963)	P[d]	4
23	**J**ournal of the **Am**erican **Chem**ical **Soc**iety (1879)	P,C	52
25	**J**ournal of **Carbohydr**ate **Chem**istry (1981)	P,C	6
26	**J**ournal of **Chem**ical **Res**earch, **Synop**ses (1977)	P	12
27	**Chem**ical **Commun**ications (1965)	C	24
28	**J**ournal of **Comb**inatorial **Chem**istry (2000)	P,C	6
29.	**J**ournal of **Comput**ational **Chem**istry (1979)	P	16
30	**J**ournal of **Fluorine Chem**istry (1971)	P,C	12
31	**J**ournal of **Heterocycl**ic **Chem**istry (1964)	P,C	12
32	**J**ournal of the **Indian** Chemical **Soc**iety (1924)	P	12
33	**J**ournal of **Lipid Res**earch (1959)	P	12
34	**J**ournal of **Med**icinal **Chem**istry (1958)	P,C	12
35	**J**ournal of **Mol**ecular **Struct**ure (1967)	P,C	16
36	**J**ournal of **Organomet**allic **Chem**istry (1963)	P,C	48
37	**J**ournal of **Org**anic **Chem**istry (1936)	P,C	26
38	**J**ournal of **Photochem**istry and **Photobiol**ogy, **A**: Chemistry (1972)	P	12
39	**J**ournal of **Phys**ical **Org**anic **Chem**istry (1988)	P	12
40	**J**ournal of **Poly**mer **Sci**ence Part **A** (1962)	P	24
41	**J**ournal für **Prakt**ische **Chem**ie (1834)	P	6
42	**Macromolecules** (1968)	P,C	26
43	**Liebigs Ann**alen der **Chem**ie (1832)	P	12
44	**Mendeleev Commun**ications (1991)	C	8
45	**Monatsh**efte für **Chem**ie (1870)	P	12
46	**New J**ournal of **Chem**istry (1977)[d]	P	11
47	**Organometallics** (1982)	P,C	12
48	**Org**anic and **Biomol**ecular **Chem**istry (2003)	P	24

49	**Org**anic **Lett**ers (1999)	C	12
50	**Org**anic **Mass Spectrom**etry (1968)	PC	12
51	**Org**anic **Prep**arations and **Proced**ures **Int**ernational (1969)	P[b]	6
52	**Org**anic **Process Res**earch & **Dev**elopment (1997)	P	6
53	**Photochem**istry and **Photobiol**ogy (1962)	P[b]	12
54	**Pol**ish **J**ournal of **Chem**istry (1921)[e]	PC	12
55	**Pure** and **Appl**ied **Chem**istry (1960)	[f]	12
56	**Res**earch on Chemical **Intermed**iates (1973)[g]	P[b]	6
57	**Russ**ian **J**ournal of **Org**anic **Chem**istry (1984)	P,C	12
58	**Sulf**ur **Lett**ers (1982)	C	6
59	**Synlett** (1989)	C[b]	12
60	**Synth**etic **Commun**ications (1971)	C	22
61	**Synthesis** (1969)	P[b]	12
62	**Tetrahedron** (1958)	P[b]	52
63	**Tetrahedron: Asymmetry** (1990)	PC	12
64	**Tetrahedron Lett**ers (1959)	C	52

[a]These journals currently publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are indicated in boldface. Also given are the year of founding, number of issues per year as of 2012, and whether the journal primarily publishes papers (P), communications (C), or both.

[b]See Ref. 5.

[c]See Ref. 6.

[d]See Ref. 7.

[e]See Ref. 8.

[f]See Ref. 9.

[g]See Ref. 10.

from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in many libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and most foreign patents were obtained at low cost from the U.S. Patent and Trademark Office, Washington, DC, 20231. Many patents can now be obtained online as well or are available as PDF files. Patents are also available via SciFinder (formerly, CAS online).

Although patents are often very useful to the laboratory chemist, and no literature search is complete that neglects relevant patents, as a rule they are not as reliable as papers. There are two reasons for this finding:

1. It is in the interest of the inventor to claim as much as possible. The patent may show, for example, that a reaction was actually carried with ethanol and with 1-propanol, but will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol that the inventor did not use may find that the reaction gives no yield at all.

[5] These journals are available in English translation.
[6] These journals also publish review articles regularly.
[7] Each issue of this journal is devoted to a specific topic.
[8] Before 1978 this journal was called ***Roczniki Chemii***.
[9] *Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.
[10] Before 1989 this journal was called ***Rev****iews of* ***Chem****ical* ***Intermed****iates*.

In general, it is safest to duplicate the actual examples given, of which most chemical patents contain one or more.

2. Although legally a patent gives an inventor a monopoly, any alleged infringements must be protected in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. A patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in every paper in a journal due to the use of proprietary catalysts or equipment not available to the public. It is not uncommon to literally purchase the world's supply of a key ingredient. Note, however, that some work is not published or patented but rather maintained within the company as a trade secret. Such work is not, of course, available to the public.

B. SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all, if there were no indexes, abstracts, review articles, and other secondary sources, the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. There are various kinds and the classification shown here is somewhat arbitrary.

B.i. Listings of Titles

The profusion of original papers is so great that publications that list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals that are not normally read. This approach using print versions containing lists or journals and articles is used sparingly nowadays. Most journals are available online with useful search engines, and most have the original papers, with supplemental material, as html and PDF[11] documents. The PDF document can be downloaded to the searcher's desktop, sometimes for a fee, shipped to other scientists electronically, and is most convenient. *Chemical Abstracts* was available online as *CAS OnLine*, but this service has been supplanted by *SciFinder* (see Appendix A.D.iii). University libraries and companies pay the appropriate fees, so access to the journals is usually quite easy if one is affiliated with these organizations. Search engines allow one to quickly scan an enormous amount of literature from office or home. In addition, most browsers have online searching capabilities via various search engines, and simply typing in an author, a topic, a chemical, or a few keywords can lead to important articles or information. "Google® searching"[12] is commonly employed for a "quick and dirty" search, but one is strongly urged to use one of the established scientific search engines for a proper search.

[11] Adobe Acrobat files.
[12] Available at www.google.com/

The more important online technology will be discussed below. However, some other resources[13] include Specialty Citation Indexes Science Citation Index Expanded™, Web of Science®, Science Citation Index®, ISI ProceedingsSM, Reaction Citation Index™, and the Derwent Innovations IndexSM. The discussion will begin with the older print versions for chemical searches.

A print-version "title" publication covering the whole of chemistry is *Current Contents Physical, Chemical & Earth Sciences*,[14] which began in 1967 and appears weekly, contains the contents pages of all issues of about 800 journals in chemistry, physics, earth sciences, mathematics, and allied sciences. Each issue contains an index of important words taken from the titles of the papers listed in that issue, and an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. An online service is available called *Current Contents Connect*® is a multidisciplinary Web resource providing access to complete bibliographic information from >8000 of the world's leading scholarly journals and >2000 books.[15]

Chemical titles is a similar publication produced by the Chemical Abstracts Service (CAS). SciFinder described below allows one to search a variety of databases, including journal titles.

B.ii. Abstracts

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. Most current journals contain a graphic abstract, as well as a title and a brief print description of the research. The graphical abstract is extremely useful for scanning the literature presented in a journal, and both the print and graphical abstracts are available online for most journals.

From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.[16] At the present time there are only two publications entirely devoted to abstracts covering the whole field of chemistry. One of these, *Referativnyi Zhurnal, Khimiya*, which began in 1953, is published in Russian and is chiefly of interest to Russian-speaking chemists. The other is *Chemical Abstracts*, which was published until 2010. Abstracts are now available online via *SciFinder*. Although out of print, knowledge of Chemical Abstracts is important to properly do a literature search that includes older literature. *Chemical Abstracts* appeared weekly and printed abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world.[17] More than 18,000 journals were covered, in many languages. In addition, *CA* published abstracts of every patent of chemical interest from 18 countries, as well as many patents from additional countries. The abstracts currently appeared in 80 sections, with sections 21–34 devoted to organic chemistry, under such headings as Alicyclic Compounds, Alkaloids, Physical Organic Chemistry, Heterocyclic Compounds (One Heteroatom),

[13] See http://scientific.thomson.com/products/categories/citation/

[14] Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

[15] Available at http://scientific.thomson.com/products/ccc/

[16] For example, *Chem. Ind. (London)* publishes abstracts of papers that appear in other journals. In the past, journals, such as *J. Am. Chem. Soc., J. Chem. Soc.,* and *Ber*. also did so.

[17] For a guide to the use of *CA*, see Schulz, H. *From CA to CAS ONLINE*; VCH: NY, 1988.

and so on. Each abstract of a paper had a heading that gave (1) the abstract number;[18] (2) the title of the paper; (3) the authors' names as given in the paper; (4) the authors' address; (5) the abbreviated name of the journal (see Table A.1);[19] (6) the year, volume, issue, and page numbers; and (7) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents showed the abstract number, title, inventor and company (if any), patent number, patent class number, date patent issued, country of priority, patent application number, date patent applied for, and number of pages in the patent. The body of the abstract contained a concise summary of the information in the paper. For many common journals, the author's summary (if there is one) was used in *CA* as it appeared in the original paper, with perhaps some editing and additional information. Each issue of *CA* contained an author index, a patent index, and an index of keywords taken from the titles and the texts or contexts of the abstracts. The patent index listed all patents in order of number. The same compound or method is often patented in several countries. *Chemical Abstracts* abstracted only the first patent, but listed the patent numbers of the duplicated patents in the patent index along with all previous patent numbers that correspond to it. Before 1981 there were separate Patent Number Indexes and Patent Concordances (the latter began in 1963).

At the end of each section of *CA* a list of cross-references to related papers in other sections is given.

Chemical Abstracts is useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases to ascertain quickly where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes. After 1962 there were two volumes published each year, and a separate index is issued for each volume. Each volume contained an index of subjects, authors, formulas, and patent numbers. Beginning in 1972, the subject index was issued in two parts, a chemical substance index and a general subject index, which included all entries that are not the names of single chemical substances. However, the indexes to each volume were essentially superseded by each collective index. The first collective indexes were 10-year (decennial) indexes, but the volume of information made 5-year indexes necessary since 1956. Collective indexes so far published are shown in Table A.2.

As noted above, the print form of Chemical Abstracts has been superseded by SciFinder (see Appendix A.D.iii)

Beginning with the Eighth collective index period, *CA* has published an *Index Guide*. This publication gave structural formulas and/or alternate names for thousands of compounds, as well as many other cross-references. It was designed to help the user efficiently and rapidly to find *CA* references to subjects of interest in the general subject, formula, and chemical substance indexes. Each collective index contained its own *Index Guide*. The *Index Guide* was necessary because the *CA* general subject index was a "controlled index", meaning it restricted its entries only to certain terms.

For example, anyone looking for the term "refraction" in the printed general subject index will not find it. The *Index Guide* included this term, and directed the reader to "Electromagnetic wave, refraction of", "Sound and ultrasound, refraction of", and other terms, all of which were found in the general subject index. Similarly, the chemical substance index usually listed a compound only under one name - the approved *CA* name.

[18] Began in 1967. See Appendix A.B.ii.

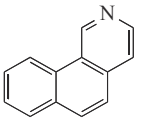
[19] These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

TABLE A.2 *CA* Collective Indexes So Far Published

Collective Index	Subject General Subject	Chemical Substance	Author	Formula	Patents
1	1907–1916		1907–1916		
2	1917–1926		1917–1926		1907–1936
3	1927–1936		1927–1936	1920–1946	
4	1937–1946		1937–1946		1937–1946
5	1947–1956		1947–1956	1947–1956	1947–1956
6	1957–1961		1957–1961	1957–1961	1957–1961
7	1962–1966		1962–1966	1962–1966	1962–1966
8	1967–1971		1967–1971	1967–1971	1967–1971
9	1972–1976	1972–1976	1972–1976	1972–1976	1972–1976
10	1977–1981	1977–1981	1977–1981	1977–1981	1977–1981
11	1982–1986	1982–1986	1982–1986	1982–1986	1982–1986
12	1987–1991	1987–1991	1987–1991	1987–1991	1987–1991
13	1992–1996	1992–1996	1992–1996	1992–1996	1992–1996
14	1997–2001	1997–2001	1997–2001	1997–2001	1997–2001
15	2002–2006	2002–2006	2002–2006	2002–2006	2002–2006

Trivial and other names were found in the *Index Guide*. For example, the term "methyl carbonate" is not in the chemical substance index, but the *Index Guide* does have this term, and directs the reader to the chemical substance index under the headings "carbonic acid, esters, dimethyl ester" (for Me_2CO_3) and "carbonic acid, esters, monomethyl ester" (for $MeHCO_3$). Furthermore, the *Index Guide* gives terms related to the chosen term, helping users to broaden a search. For example, one who looks for "Atomic orbital" in the *Index Guide* will find the terms "Energy Level", "Molecular orbital", "Atomic integral", and "Exchange, quantum mechanical, integrals for", all of which are controlled index terms.

Each index (annual, semiannual, or collective) also provided an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names. For example, someone wishing to determine whether any compounds



Benz(*h*)isoquinoline

containing the benz(*h*)isoquinoline ring system are reported in the 1982–1986 collective index would locate, under the heading "3-ring systems", the listing **6**, **6**, **6** (since the compound has three rings of six-members each), and would find the sublisting C_5N–C_6–C_6 (since one ring contains five carbons and a nitrogen while the others are all-carbon), under which is listed the name benz(*h*)isoquinoline, as well as the names of 30 other systems C_5N–C_6–C_6. A search of the chemical substance index under these names will give all references to these ring systems that appeared in *CA* from 1982 to 1986.

Nowadays, the drawing tools of SciFinder (sec. Appendix A.D.iii) are used to draw this structure, and then perform the search.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years, superscript numbers (e.g., 4327^5) were used in a similar manner. In very early years, these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered and column numbers are discarded. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter that serves as a check character to prevent miscopying errors in computer handling. To use the *CA* general subject, chemical substance, and formula indexes intelligently requires practice, and the student should become familiar with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

In the *CA* formula indexes, formulas were listed in order of (1) number of carbon atoms; (2) number of hydrogen atoms; (3) other elements in alphabetic order. Thus, all C_3 compounds are listed before any C_4 compound; all C_5H_7 compounds before any C_5H_8 compound; $C_7H_{11}Br$ before $C_7H_{11}N$; $C_9H_6N_4S$ before C_9H_6O, and so on. Deuterium and tritium are represented by D and T and treated alphabetically (e.g., C_2H_5DO after C_2H_5Cl and before C_2H_5F or C_2H_6).

Since 1965, *CA* has assigned a Registry Number[20] to each unique chemical substance. This is a number of the form [766-51-8] that remains invariant, no matter what names are used in the literature. More than 64 million numbers have already been assigned and thousands are added each week. Registry Numbers are primarily for computer use, but chemical suppliers use CAS registry numbers to identify chemicals that are available for sale.

There were a number of earlier abstracting publications now defunct. The most important are *Chemisches Zentralblatt* and *British Abstracts*. These publications are still valuable because they began before *CA* and can therefore supply abstracts for papers that appeared before 1907. Furthermore, even for papers published after 1907, *Zentralblatt* and *British Abstracts* are often more detailed. *Zentralblatt* was published, under various names, from 1830 to 1969.[21] *British Abstracts* was a separate publication from 1926 to 1953, but earlier abstracts from this source are available in the *Journal of the Chemical Society* from 1871 to 1925.

B.iii. Beilstein

This publication has been so important to organic chemistry that it deserves a section by itself. Beilstein's *Handbuch der Organischen Chemie*, usually referred to as *Beilstein*, lists all the known organic compounds reported in the literature during its period of coverage. The print version will be described first, as it is particularly important for older literature.

For each compound in *Beilstein*, the following data are given: all names; the molecular formula; the structural formula; all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"); physical constants (melting point, refractive index, etc.); other physical properties; chemical properties including reactions; occurrence in nature (i.e., which species it was isolated from); biological properties, if any; derivatives

[20] See http://www.cas.org/expertise/cascontent/registry/regsys.html

[21] An "obituary" of *Zentralblatt* by Weiske, C., gives its history and statistical data about its abstracts and indexes, and was published in the April 1973 issue of *Chem. Ber.* (pp. I–XVI).

with melting points; analytical data, and any other information that has been reported in the literature.[22] Equally important, for every piece of information, a reference is given to the original literature. Furthermore, the data in Beilstein have been critically evaluated. That is, all information is carefully researched and documented, and duplicate and erroneous results are eliminated. Some compounds are discussed in two or three lines and others require several pages.

The print editions are invaluable for searching older literature, but even today provide valuable data for many compounds used every day. A discussion of using *Beilstein* is therefore essential.

The first three editions of Beilstein are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk*, consists of 27 volumes. The compounds are arranged in order of a system too elaborate to discuss fully here.[23] The compounds are divided into three divisions that are further subdivided into "systems":

Division	Volumes	System Numbers
I. Acyclic Compounds	1–4	1–499
II Carbocyclic Compounds	5–16	450–2359
III. Heterocyclic Compounds	17–27	2360–4720

Das Hauptwerk is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements that have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes Ergänzungswerk*) covers 1910–1919; the second supplement (*zweites Ergänzungwerk*) covers 1920–1929; the third supplement (*drittes Ergänzungswerk*) covers 1930–1949; the fourth supplement (*viertes Ergänzungswerk*) covers 1950–1959, and the fifth supplement covers 1960–1979. Like *das Hauptwerk*, each supplement contains 27 volumes,[24] except that supplements 3 and 4 are combined for Vols. 17–27, so that for these volumes the combined third and fourth supplement covers the years 1930–1959. Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in Vol. 3, system number 199 of *das Hauptwerk* will also be found in Vol. 3, system number 199 of each supplement. To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound can be found in the earlier books. Thus, on page 554 of Vol. 6 of the fourth supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142; E III 545) indicating that earlier information on phenetole is given on page 140 of Vol. 6 of *das Hauptwerk*, on page 80 of the first, page 142 of the second, and

[22] For a discussion of how data are processed for inclusion in Beilstein, see Luckenbach, R.; Ecker, R.; Sunkel, J. *Angew. Chem. Int. Ed. Engl.* ***1981****, 20,* 841 [*Angew. Chem. 93*, 876].

[23] For descriptions of the Beilstein system and directions for using it, see Sunkel, J.; Hoffmann, E.; Luckenbach, R. *J. Chem. Educ.* ***1981****, 58*, 982; Luckenbach, R. *CHEMTECH* ***1979***, 612. The Beilstein Institute has also published two English language guides to the system. One, available free, is *How to Use Beilstein*, Beilstein Institute, Frankfurt/Main, ***1979***. The other is by Weissbach, O. *A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*, Springer, NY, ***1976***. An older work, which many students will find easier to follow, is by Huntress, E.H. *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie,* 2nd ed., Wiley, NY, ***1938***.

[24] In some cases, to keep the system parallel and to avoid books that are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

page 545 of the third supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all six series, location of a compound in any one series gives its location in the other five. If a compound is found, for example, in Vol. 5 of *das Hauptwerk*, one has but to note the page number and scan Vol. 5 of each supplement until that number appears in the top center of the page (the same number often covers several pages). Of course, many compounds are found in only one, two, three, four, or five of the series, since no work may have been published on that compound during a particular period covered.

From *das Hauptwerk* to the fourth supplement, Beilstein is in German, but it is not difficult to read since most of the words are the names of compounds (a Beilstein German–English Dictionary, available free from the publisher, is in many libraries). For the fifth supplement (covering 1960–1979), which is in English, publication of Division III began before the earlier divisions. Volumes 17–22 (totaling 70 separate parts exclusive of index volumes) of this supplement have been published, as well as a combined index for volumes 17–19. This index covers only the fifth supplement. The subject portion of this index, which lists compound names only, gives these names in English.

Volumes 28 and 29 of Beilstein are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement and covers only *das Hauptwerk* and the first two supplements (though complete indexes covering *das Hauptwerk* and the first four supplements have been announced to appear in the next few years). For Vol. 1, there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and the first four supplements.[25] Similar index volumes, covering all four supplements, have been issued for the other volumes, 2–27. Some of these are combined (e.g., 2–3, 12–14, and 23–25). For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course (except for the fifth supplement indexes), one must still know some German, because most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers (e.g., **1**, 501). Roman numbers are used to indicate the supplements (e.g., **26**, 15, I 5, **II** 7). Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first four supplements. The Beilstein formula indexes are constructed the same way as the *CA* indexes (Appendix A.B.ii).

There is also a fourth division of Beilstein (systems 4721–4877) that covers natural products of uncertain structure: rubbers, sugars, and so on. These are treated in Vols. 30 and 31, which do not go beyond 1935 and that are covered in the collective indexes. These volumes will not be updated. All such compounds are now included in the regular Beilstein volumes.

In recent years, Beilstein was available online, with the useful search engine *CrossFire*. However, this database is now incorporated into *Reaxys (see Appendix A.D.vi)*.

B.iv. Tables of Information

In addition to Beilstein, there are many other print reference works in organic chemistry that are essentially compilations of data. These books are very useful and often save the

[25] Most page number entries in the combined indexes contain a letter (e.g., $CHBr_2Cl$ 67f, **II** 33a, **III** 87d, **IV**, 81). These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter "a" means the compound is the first on its page, "b" is the second, and so on. No letters are given for the fourth supplement.

research worker a great deal of time. In this section, we discuss some of the more important of such works.

1. The sixth edition of *Heilbron's Dictionary of Organic Compounds*, J. Buckingham, Ed., 9 vols., Chapman and Hall, London, ***1996***, contains brief listings of >150,000 organic compounds, giving names, structural formulas, physical properties, and derivatives, with references. For many entries, additional data concerning occurrence, biological activity, and toxicity hazard information are also given. The arrangement is alphabetical. The dictionary contains indexes of names, formulas, heteroatoms, and *CA* Registry Numbers. Annual supplements, with cumulative indexes, have appeared since 1983. A similar work, devoted to organometallic compounds, is the 2nd edition of the *Dictionary of Organometallic Compounds*, 6 vols. in its 5th supplement, published by Chapman and Hall in ***1989***. Another, *Dictionary of Steroids*, 2 vols., 1991, is also published by Chapman and Hall.
2. A multivolume compendium of physical data is *Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik, 6th ed.,* by H. Landolt and R. Börnstein, Springer, Berlin, 1950. There is also a "New Series", for which the volumes are given the English title *Numerical Data and Functional Relationships in Science and Technology*, as well as the German title. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists (e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data). Literature references are given for all data.
3. *The Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL (called the "rubber handbook"), which is revised annually (92nd ed., 2011–2012), is a valuable repository of data quickly found. For organic chemists an important table is *Physical Constants of Organic Compounds*, which lists names, formulas, color, solubility, and physical properties of thousands of compounds. However, there are many other useful tables. A similar work is *Lange's Handbook of Chemistry*, 16th ed., McGraw-Hill, New York, 2004. Another such handbook, but restricted to data of interest to organic chemists, is *Dean's Handbook of Organic Chemistry, 2nd ed.,* McGraw-Hill, New York, 2003. This book also contains a long table of *Physical Constants of Organic Compounds*, and has much other information including tables of thermodynamic properties, spectral peaks, pK_a values, bond distances, and dipole moments.
4. A list of most of the known natural compounds (e.g., terpenes, alkaloids, carbohydrates) to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in T.K. Devon and A.J. Scott, *Handbook of Naturally Occurring Compounds*, 3 vols., Academic Press, New York, ***1972***.
5. R.R. Dreisbach, *Physical Properties of Chemical Compounds*, Advances in Chemistry Series Nos. 15, 22, 29, American Chemical Society, Washington, 1955–1961 lists many physical properties of >1000 organic compounds.
6. Physical properties of thousands of organometallic compounds, with references, are collected in five large compendia: the *Dictionary of Organometallic Compounds*, mentioned under item 1, above; M. Dub, *Organometallic Compounds, 2nd ed*., 3 vols. with supplements and index, Springer, New York, 1966–1975; N. Hagihara, M. Kumada, and R. Okawara, *Handbook of Organometallic Compounds*,

W.A. Benjamin, New York, ***1968***; and H.C. Kaufman, *Handbook of Organometallic Compounds*, Van Nostrand, Princeton, NJ, ***1961***; *Comprehensive Organometallic Chemistry II*, 14 vols, Pergamon, 1995.

7. The *Merck Index, 14th ed.*, Merck and Company, Rahway, NJ, ***2006*** is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: chemical *name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names,* which are different for each company that markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine is chlorcyclazine. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazyl, and Alergicide. The *Merck Index* is especially valuable because it gives all known names of all three types for each compound and the names are cross-indexed. Also given, for each compound, are the structural formula, *CA* preferred name and Registry Number, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. There are indexes of formulas and Registry Numbers, and miscellaneous tables. The "Merck Index" also includes a lengthy list of organic name reactions, with references.
8. There are two publications that list properties of azeotropic mixtures. J. Timmermans, *The Physico-chemical Constants of Binary Systems in Concentrated Solutions,* 4 vols., Interscience, New York, ***1959–1960***, is by far the more comprehensive. The other is *Azeotropic Data*, 2 vols., Advances in Chemistry Series No. 6 and No. 35, American chemical Society, Washington, ***1952***, ***1962***.
9. Thousands of dipole moments, with references, are collected in V.A.L. McClellan, *Tables of Experimental Dipole Moments, Vol. 1*, W.H. Freeman, San Francisco, CA, ***1963***; *Vol. 2*, Rahara Enterprises, El Cerrita, CA, ***1974***.
10. *Tables of Interatomic Distances and Configurations in Molecules and Ions*, London Chemical Society Special publication no. 11, ***1958***, and its supplement, Special publication no. 18, ***1965***, include bond distances and angles for hundreds of compounds, along with references.
11. The *Ring Systems Handbook*, published in 1988 by the chemical Abstracts Service, provides the names and formulas of ring and cage systems that have been published in *CA*. The ring systems are listed under a system essentially the same as that used for the *CA* index of ring systems (sec. Appendix A.B.i, A.B.ii). Each entry gives the *CA* index name and Registry Number for that ring system. In many cases a *CA* reference is also given. There is a separate Formula Index (for the parent ring systems) and a *Ring Name Index*. Cumulative supplements are issued twice a year. The *Ring Systems Handbook* supersedes earlier publications called *The Parent Compound Handbook* and *The Ring Index*.
12. The Sadtler Research Laboratories published large collections of IR, UV, NMR, and other spectra, in loose-leaf form. Indexes are available.
13. Infrared, UV, NMR, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility, density, and other data for >30,000 organic compounds are collected in the *CRC Handbook of Data on Organic Compounds, 2nd ed.,* 9 vols., CRC Press, Boca Raton, FL, 1988, edited by R.C. Weast and J.G. Grasselli. It differs from the Sadtler collection in that the data are given in tabular form (lists of peaks)

rather than reproduction of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear at one place. References are given to the Sadtler and other collections of spectra. Volumes 7–9 contain indexes of spectral peaks for IR, UV, NMR, ^{13}C NMR, mass, and Raman spectra, as well as indexes of other names, molecular formulas, molecular weights, and physical constants. Annual updates began appearing in 1990 (the first one is called volume 10).

14. The *Aldrich Library of Infrared Spectra, 3rd ed.*, Aldrich Chemical Company, Milwaukee, WI, ***1981***, by Pouchert contains >12,000 IR spectra so arranged that the user could readily see the change that takes place in a given spectrum when a slight change is made in the structure of a molecule. The same company also publishes the *Aldrich Library of FT-IR Spectra* and the *Aldrich Library of NMR Spectra*, both also by C. Pouchert. A similar volume, which has IR and Raman spectra of ∼1000 compounds, is *Raman/Infrared Atlas of Organic Compounds, 2nd ed.,* VCH, New York, ***1989***, by B. Schrader.
15. An extensive list of visible and uv peaks is given in *Organic Electronic Spectral Data,* Wiley, New York. Twenty-six volumes have appeared so far, covering the literature through 1984.
16. A collection of 500 ^{13}C NMR spectra is found in L.F. Johnson and W.C. Jankowski, *Carbon-13 NMR Spectra*, Wiley, New York, ***1972***.

C. REVIEWS

A review article is an intensive survey of a rather narrow field. For example, the titles of some recent reviews are "Metathesis of Alkanes and Related Reactions"[26], "Potassium Organotrifluoroborates: New Perspectives in Organic Synthesis"[27], and "Asymmetric Addition of Allylic Nucleophiles to Imino Compounds".[28] A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though most are not exclusively devoted to organic chemistry) are shown in Table A.3. Some of the journals listed in Table A.1, for example, *Chemical Reviews, Accounts of Chemical Research, and Synlett, Tetrahedron, Synthesis, Organic Preparations and Procedures International,* and *J. Organomet. Chem.* also publish occasional review articles. As with other journals, journals that contain reviews are available online.

There are several open-ended serial publications that are similar in content to the review journals but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; some specialize further. The coverage is indicated by the titles. Table A.4 shows some of the more important such publications, with *CA* abbreviations.

Another publication is the *Index of Reviews in Organic Chemistry*, complied by Lewis, Chemical Society, London, a classified listing of review articles. The first volume, published in 1971, lists reviews from ∼1960 (in some cases much earlier) to ∼1970 in alphabetical

[26] Basset, J.-M.; Copret, C.; Soulivong, D.; Taoufik, M.; Cazat, J.T. *Acc. Chem. Res.* ***2010****, 43*, 323.
[27] Darses, S.; Genet, J.-P. *Chem. Rev.* ***2008****, 108*, 288.
[28] Ding, H.; Friestad, G.K. *Synthesis* ***2005***, 2815.

TABLE A.3 Review Journals, with Year of Founding and Issues per Year

Journal	Issues
Accounts of **Chem**ical **Res**earch (1968)	12
Aldrichimica **Acta** (1968)	4
Angewandte **Chem**ie (1888)	12
and its English Translation:	
Angewandte **Chem**ie, **Int**ernational **Ed**ition (1962)	12
Chemical **Rev**iews (1924)	8
Chemical **Soc**iety **Rev**iews (1947)[a]	4
Heterocycles (1973)	12
Natural **Prod**uct **Rep**orts (1984)	6
Organic **Prep**arations and **Proc**edures **Int**ernational (1969)	6
Soviet **Sci**entific **Rev**iews, **Sect**ion **B, Chem**istry **Rev**iews (1979) Irreg.	
Sulfur Reports (1980)	6
Synlett (1989)	12
Synthesis (1969)	12
Tetrahedron (1958)	52
Topics in **Curr**ent **Chem**istry (1949)[b]	Irreg.
Uspekhi **Khim**ii (1932)	12
and its English translation: **Russ**ian chemical **Rev**iews (1960)	12

[a]See Ref. 29.

[b]See Ref. 30.

TABLE A.4 Irregularly Published Serial Publications

Advances in **Carbo**cation **Chem**istry
Advances in **Carbohydr**ate **Chem**istry and **Biochem**istry
Advances in **Catal**ysis
Advances in **Cycloadd**ition
Advances in **Free Radical Chem**istry
Advances in **Heterocycl**ic **Chem**istry
Advances in **Met**al-**Org**anic **Chem**istry
Advances in **Mol**ecular **Model**ing
Advances in **Organomet**allic **Chem**istry
Advances in **Oxygenated Processes**
Advances in **Photochem**istry
Advances in **Phy**sical **Org**anic **Chem**istry
Advances in **Protein Chem**istry
Advances in **Theor**etically **Interesting Mol**ecules
Fluorine Chemistry **Rev**iews
Fortshritte der **Chem**ie **Org**anischer **Naturst**offe
Isotopes in **Org**anic **Chem**istry
Molecular **Struct**ure and **Energ**etics
Organic **Photochem**istry
Organometallic **React**ions
Organic **React**ions
Organic **Synth**esis: **Theory** and **Appl**ications

[29] Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).
[30] Formerly called ***Fortschr****itte der* ***Chem****ischen* ***Forsch****ung*.

Progress in **Heterocycl**ic **Chem**istry
Progress in **Macrocyclic Chem**istry
Progress in **Phy**sical **Org**anic **Chem**istry
Reactive **Int**ermediates (Plenum)
Reactive **Int**ermediates (Wiley)
Survey of **Prog**ress in **Chem**istry
Topics in **Phy**sical **Organomet**allic **Chem**istry
Topics in **Stereochem**istry

order of topic. Thus four reviews are listed under "Knoevenagel condensation", five under "Inclusion compounds", and one under "Vinyl ketones". There is no index. A second volume (1977) covers the literature to 1976. Annual or biannual supplements appeared from 1979 until the publication was terminated in 1985. Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton[31] and by Bruce.[32] A similar list for heterocyclic chemistry is found in articles by A. Katritzky and others.[33] See also the discussion of the *Index of Scientific Reviews* in Appendix A.D.iv.

C.i. Annual Reviews

The review articles discussed in Table A.3 are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication that covers a broad area but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication still publishing is *Annual Reports on the Progress of Chemistry*, published by the Royal Society of Chemistry (formerly the chemical Society), which began in 1905 and which covers the whole field of chemistry. Since 1967 it has been divided into sections. Organic chemistry is found in Section B.
2. Because the number of papers in chemistry has become so large, the Royal Society of Chemistry publishes annual-review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are *Carbohydrate Chemistry* (Vol. 22 covers 1988); *Photochemistry* (Vol. 21 covers 1988–1989); and *General and Synthetic Methods* (Vol. 12 covers 1987).
3. *Organic Reaction Mechanisms*, published by Wiley, New York, is an annual survey that covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.
4. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, *Synthetic Methods of Organic Chemistry*, S. Karger, Verlag, Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closing and bond breaking reactions. Equations, brief procedures, yields, and literature references are given. Volume 44 was issued in 1990. Volumes 3 and 4 are available only in

[31] Smith, J.D.; Walton, D.R.M. *Adv. Organomet. Chem.* ***1975****, 13,* 453.
[32] Bruce, M.I. *Adv. Organomet. Chem.* ***1972****, 10,* 273, ***1973****, 11,* 447, ***1974****, 12,* 380.
[33] Belen'kii, L.I. *Adv. Heterocycl. Chem.* ***1988****, 44,* 269; Katritzky, A.R.; Jones, P.M. *Adv. Heterocycl. Chem.* ***1979****, 25,* 303; Katritzky, A.R.; Weeds, S.M. *Adv. Heterocycl. Chem.* ***1966****, 7*, 225.

German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is *Annual Reports in Organic Synthesis,* Academic Press, New York, which has covered the literature of each year since 1970. Equations are listed with yields and references according to a fairly simple system.

C.ii. Awareness Services

Besides the annual reviews and the title and abstract services previously mentioned, there exist a number of publications designed to keep readers aware of new developments in organic chemistry or in specific areas of it.

1. *Chemtracts: Organic Chemistry* is a bimonthly Periodical, begun in 1988, that prints abstracts of certain recently published papers (those that the editors consider most important), with commentaries on these papers by distinguished organic chemists. Important current research in bioorganic, organometallic, synthesis, physical-organic and theoretical chemistry, and pharmaceutical/medicinal chemistry is covered in each issue, giving readers updates on the newest trends and developments in organic chemistry by summarizing and commenting on current and past research.
2. The Institute for Scientific Information (ISI), besides publishing *Current Contents* (sec. Appendix A.B.i) and the *Science Citation Index* (sec. Appendix A.B.i), also publishes *Index Chemicus* (formerly called *Current Abstracts of Chemistry and Index Chemicus*). This publication, begun in 1960 and appearing weekly, is devoted to printing structural formulas of all new compounds appearing in >100 journals, along with equations to show how they were synthesized and an author's summary of the work. Each issue contains five indexes: author, journal, biological activity, labeled compounds, and intermediates that were not isolated. These indexes are cumulated annually.
3. Theilheimer and the *Annual Reports on Organic Synthesis*, mentioned in the previous section, list new synthetic methods once a year. There are several publications that do this monthly. Among these are *Current Chemical Reactions* (begun in 1979 and published by ISI), *Journal of Synthetic Methods* (begun in 1975 and published by Derwent publications), and *Methods in Organic Synthesis*, begun in 1984 and published by the Royal Society of Chemistry. *Methods in Organic Synthesis* also lists books and review articles pertaining to organic synthesis.
4. *Natural Product Updates,* a monthly publication begun in 1987 and published by the Royal Society of Chemistry, lists recent results in the chemistry of natural products, along with structural formulas. It covers new compounds, structure determinations, new properties and total syntheses, among other topics.

C.iii. General Treatises

There are a number of large-scale multivolume treatises that cover the whole field of organic chemistry or large areas of it.

1. *Rodd's Chemistry of Carbon Compounds*, edited by S. Coffey, Elsevier, Amsterdam, is a treatise consisting of five main volumes, each of which contains several

parts. Publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to many of the volumes have appeared. An earlier edition, called *Chemistry of Carbon Compounds,* edited by E.H. Rodd, was published in 10 parts from 1951 to 1962.

2. Houben–Weyl's *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 20 volumes, most of them in several parts, is edited by E. Muller. The series includes supplementary volumes. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the synthesis of specific types of compounds (hydrocarbons, oxygen compounds, nitrogen compounds, etc.). Beginning in 1990 parts of the series have appeared in English.
3. *Comprehensive Organic Chemistry*, Pergamon, Elmsford, NY, ***1979***, is a six-volume treatise on the synthesis and reactions of organic compounds. The first three volumes cover the various functional groups, Vol. 4, heterocyclic compounds, and Vol. 5, biological compounds (e.g., proteins, carbohydrates, and lipids). Probably the most useful volume is Vol. 6, which contains formula, subject, and author indexes, as well as indexes of reactions and reagents. The last two of these not only refer to pages within the treatise, but directly give references to review articles and original papers Several similar treatises, including the nine-volume *Comprehensive Organometallic Chemistry* (1982), the eight-volume *Comprehensive Heterocyclic Chemistry* (1984), and the six-volume *Comprehensive Medicinal Chemistry* (1989) are also published by Pergamon. The indexes to these works also include references.
4. A major treatise devoted to experimental methods of chemistry is *Techniques of Chemistry*, edited first by A. Weissberger and then by J.K.M. Saunders, Wiley, New York. This publication, which began in 1970, so far consists of 21 volumes, most of them in several parts, covering such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. *Techniques of Chemistry* is a successor to an earlier series, called *Techniques of Organic Chemistry*, which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969.
5. *Comprehensive Chemical Kinetics,* edited by C.H. Bamford and C.F.H. Tipper, ***1969***, Elsevier, Amsterdam, is a multivolume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.
6. Three multivolume treatises that cover specific areas are R.C. Elderfield, *Heterocyclic Compounds,* Wiley, New York, ***1950***; R.H.F. Manske and H.L. Holmes, *The Alkaloids*, Academic Press, New York, ***1950***; and J.L. Simonson, L.N. Owen, D.H. R. Barton, and W.C.J. Ross, *The Terpenes*, Cambridge University Press, London, 1947–1957.
7. *Encyclopedia of Reagents for Organic Synthesis,* edited by L. Paquette, Wiley, New York, was published in 1995. It is an 8 volume, alphabetic listing of reagents used in organic chemistry with descriptions of the preparation, use and chemistry, with references. Each reagent was researched by organic chemists active in research, who contributed to the total publication.

This latter work is available online as **eEROS.** The *Encyclopedia of Reagents for Organic Synthesis*, e-EROS, provides updated information on ~3800 reagents with a database of close to 50,000 reactions. Each reagent entry includes properties (e.g., physical data, solubility, form supplied in, purification, and preparative methods); examples of use in reactions; and literature references. Search options include: name, CAS number, structure and reaction.

8. *Comprehensive Organic Synthesis*, edited by B.M. Trost and I. Fleming, Pergamon, was published in 1991. It is a 9 volume compilation.
9. *Comprehensive Organic Functional Group Transformations,* edited by A.R. Katritzky, O. Meth-Cohn, and C.W. Rees, Pergamon, was published in 1995. It is a 7 volume compilation.

C.iv. Monographs and Treatises on Specific Areas

There are many books devoted to organic chemistry that provide a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some are comprised of a series of articles, edited by an organic chemist for a specific area of research. Some of the books are by a single author, and others have chapters by different authors. All, however, are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. There have been several series of monographs, one of which is worth special mention: *The Chemistry of Functional Groups,* under the general editorship of Z. Rappoport (S. Patai was the original editor), published by Wiley, New York. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. There are >130 volumes in the series, covering functional groups have appeared so far, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, quinones, and so far. Since 2003, the series has appeared both in print and online.

C.v. Textbooks

There are many excellent textbooks in the field of organic chemistry. We restrict ourselves to listing only a few of those published, mostly since 1985. Some of these are first-year texts and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are not only good textbooks and the advanced books are valuable reference books for graduate students and practicing chemists.

Bruckner, *Advanced Organic Chemistry: Reaction Mechanisms*, Academic Press, ***2001***.

Bruice, *Organic Chemistry, 6th ed.*, Prentice-Hall, NJ, ***2010***.

Carey, *Organic Chemistry, 8th ed.*, McGraw-Hill, New York, ***2010***.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part A), 4th ed.*, Springer, ***2004***.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part B), 4th ed.*, Springer, ***2001***.

Carruthers and Coldham, *Some Modern Methods of Organic Synthesis, 4th ed.,* Cambridge University Press, Cambridge, ***2004***.

Ege, *Organic Chemistry: Structure and Reactivity, 5th ed.*, D.C. Houghton Mifflin, Boston ***2003***.

Fox and Whitesell, *Organic Chemistry, 3rd ed,* Jones and Bartlett, Sudbury, MA, ***2004***.

Grossman *The Art of Writing Reasonable Organic Reaction Mechanisms, 2nd ed*, Springer, ***2005***.

House, *Modern Synthetic Reactions, 2nd ed.,* W.A. Benjamin, New York, ***1972***.

Ingold, *Structure and Mechanism in Organic Chemistry, 2nd ed.*, Cornell University Press, Ithaca, NY, ***1969***.

Isaacs, *Physical Organic Chemistry,* Wiley, New York, ***1987***.

Jones, *Organic Chemistry, 4th ed.* W.W. Norton, New York, ***2009***.

Klein, *Organic Chemistry*, Wiley, New York, ***2011***.

Loudon, *Organic Chemistry, 5th ed.*, Oxford University Press, ***2009***.

Lowry and Richardson, *Mechanism and Theory in Organic Chemistry, 3rd ed.*, Harper and Row, New York, ***1987***.

McMurry, *Organic Chemistry, 8th ed.*, Brooks/Cole, Monterey CA, ***2012***.

Maskill, *The Physical Basis of Organic Chemistry,* Oxford University Press, Oxford, ***1985***.

Mundy, Ellerd and Favaloro, Jr. *Name Reactions and Reagents in Organic Synthesis, 2nd ed,* Wiley, ***2005***.

Ritchie, *Physical Organic Chemistry, 2nd ed.,* Marcel Dekker, New York, ***1989***.

Solomons and Fryhle, *Organic Chemistry, 10th ed.*, Wiley, New York, ***2011***.

Smith, *Organic Synthesis, 3rd ed.* Wavefunction Inc. and Elsevier, New York/London, ***2010***.

Smith, *Organic Chemistry: An Acid–Base Approach,* CRC Press, Boca Raton, FL, ***2011***.

Streitwieser, Heathcock and Kosower, *Introductory Organic Chemistry, 4th ed.,* Prentice Hall, ***1998***.

Sykes, A *Guidebook to Mechanism in Organic Chemistry, 6th ed.,* Longmans Scientific and Technical, Essex, ***1986***.

Vollhardt and Schore, *Organic Chemistry, 6th ed.,* W.H. Freeman, New York, ***2010***.

Wade, *Organic Chemistry, 7th ed.,* Prentice-Hall, Upper Saddle River, NJ, ***2009***.

C.vi. Other Books

In this section, we mention several books that do not fit conveniently into the previous categories. All but the last have to do with laboratory synthesis.

1. *Organic Syntheses*, published by Wiley, New York is a collection of procedures for the preparation of specific compounds. *Organic Syntheses* is currently available online.[34] The thin annual volumes have appeared each year since 1921. For the first

[34] Available at http://www.orgsyn.org/

59 volumes, the procedures for each 10- (or 9-) year period are collected in cumulative volumes. Beginning with Vol. 60, the cumulative volumes cover 5-year periods. The cumulative volumes published so far are

Annual Volumes	Collective Volumes
1–9	**I**
10–19	**II**
20–29	**III**
30–39	**IV**
40–49	**V**
50–59	**VI**
60–64	**VII**
65–69	**VIII**
70–74	**IX**
75–80	**X**
81–84	**XI**

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in Beilstein and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS **69**); the indexes in *Organic Syntheses* itself; R. Shriner and R. Shriner, "*Organic Syntheses* Collective Volumes **I**, **II**, **III**, **IV**, **V** Cumulative Indices", Wiley, New York, ***1976***, or S. Sugasawa and S. Nakai; "Reaction Index of *Organic Syntheses*", Wiley, New York, ***1967*** (through OS **45**). Another book classifies virtually all the reactions in *Organic Syntheses* (collective vols. **I–VII** and annual vols. 65–68) into 11 categories: annulation, rearrangement, oxidation, reduction, addition, elimination, substitution, C—C bond formation, cleavage, protection/deprotection, and miscellaneous. This is *Organic Syntheses: Reaction Guide*, by D. Liotta and M. Volmer, published by Wiley, New York, in ***1991***. Some of the categories are subdivided further, and some reactions are listed in more than one category. What is given under each entry are the equation, the volume, and page reference to *Organic Syntheses*.

2. Volume 1 of *Reagents for Organic Synthesis*, by L. Fieser and M. Fieser, Wiley, New York, ***1967***, is a 1457–page volume that discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. There are now a total of 25 volumes published as of 2009, which continue the format of Vol. 1 and add more recent material. A cumulative index for Vols. 1–12, by J. Smith and M. Fieser, was published in ***1990***. A cumulative index for volumes 1–22 was published in ***2005***, by M.B. Smith. The series included volumes 1–18 with Mary Fieser.

   After the death of Mary Fieser, the series was resumed by T.-L. Ho and now includes volumes 19–25.

3. *Comprehensive Organic Transformations, 2nd ed.* by R.C. Larock, Wiley–VCH, New York, ***1999***, has been frequently referred to in footnotes in Part 2 of this book. This compendium is devoted to listings of methods for the conversion of one functional group into another, and covers the literature through 1987. It is divided into nine sections covering the preparation of alkanes and arenes, alkenes, alkynes, halides, amines, ethers, alcohols and phenols, aldehydes and ketones, and nitriles, carboxylic acids and derivatives. Within each section are given many methods for synthesizing the given type of compound, arranged in a logical system. A schematic equation is given for each method, and then a list of references (without author names, to save space) for locating examples of the use of that method. When different reagents are used for the same functional group transformation, the particular reagent is shown for each reference. There is a 164 page index of group transformations. The 2nd edition has only recently been published and is *not* referenced in this edition, and a CD–ROM version is now available.
4. *Survey of Organic Synthesis*, by C.A. Buehler and D.E. Pearson, Wiley, New York, 2 vols., ***1970***, ***1977***, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group (ketones, acyl halides, amines, etc.). Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.
5. A similar publication is S. Sandler and W. Karo, *Organic Functional Group Preparations, 2nd ed.,* 3 vols., Academic Press, New York, 1983–1989. This publication covers more functional groups than Buehler and Pearson.
6. *Compendium of Organic Synthetic Methods,* Wiley, New York, contains equations describing the preparation of thousands of monofunctional and difunctional compounds with references. Twelve volumes have been published so far (Vols. 1–2, edited by I.T. Harrison and S. Harrison; Vol. 3, edited by L. Hegedus and L.G. Wade, Jr.; Vol. 4–5, edited by L.G. Wade, Jr.; Vols. 6–12, edited by M.B. Smith). Volume 13 will appear in 2014.
7. *The Vocabulary of Organic Chemistry,* by M. Orchin, F. Kaplan, R.S. Macomber, R. M. Wilson, and H. Zimmer, Wiley, New York, ***1980***, presents definitions of >1000 terms used in many branches of organic chemistry, including stereochemistry, thermodynamics, wave mechanics, natural products, and fossil fuels. There are also lists of classes of organic compounds, types of mechanism, and name reactions (with mechanisms). The arrangement is topical rather than alphabetical, but there is a good index. *Compendium of Chemical Terminology,* by V. Gold, K.L. Loening, A. D. McNaught, and P. Sehmi (the "Gold book"), published by Blackwell Scientific Publications, Oxford, in ***1987***, is an official IUPAC list of definitions of terms in several areas of chemistry, including organic.

D. LITERATURE SEARCHING

Until recently, searching the chemical literature meant looking only at printed materials (some of which might be on microfilm or microfiche). Now, however, virtually all of the literature can be searched online. Whether the search is online or uses only the printed material, there are two basic types of search, (1) searches for information about one or more specific compounds or classes of compounds, and (2)

other types of searches. First, we will discuss searches using only printed materials, and then online searching.[35]

D.i. Literature Searching Using Printed Materials

Searching for Specific Compounds. Organic chemists often need to know if a compound has ever been prepared and if so, how, and/or they may be seeking a melting point, an ir spectrum, or some other property. Someone who wants all the information that has ever been published on any compound begins by consulting the formula indexes in Beilstein (sec. Appendix A.B.iii). At this time there are two ways to do this. (1) The formula index to the second supplement (Vol. 29, see Appendix A.B.iii) will quickly show whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. Use of the page heading method described in Appendix A.B.iii will then show the locations, if any, in the third and later supplements. (2) If one has an idea what volume of Beilstein the compound is in (and the tables of contents at the front of the volumes may help), one may search the cumulative index for that volume. If not sure, one may consult several indexes. One of these two procedures will locate all compounds mentioned in the literature through 1959. If the compound is heterocyclic, it may be in the fifth supplement. If it is in Vols. 17–19 (or in a later volume whose index has been published), the corresponding indexes may be consulted. If not, the page heading method will find it, if it was reported before 1960.[36] There is a way by which all of the above can be avoided. At this point, the investigator will know (1) all information published through 1959 or 1979,[35] or (2) that the compound is not mentioned in the literature through 1959 or 1979.[37] In some cases, scrutiny of Beilstein will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search to more recent articles, the chemist turned to the collective formula indexes of *Chemical Abstracts* and such later collective indexes as have appeared; and the semiannual indexes thereafter. *However, such searches now would use SciFinder*.

If the compound has not been reported, the investigator will know that. Indeed, this is perhaps the most important consideration when considering a new area of research. It should be pointed out that for common compounds (benzene, ether, acetone, etc.), trivial mentions in the literature are not indexed (so they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluant in a common procedure.

[35] For a monograph that covers both online searching and searching using printed materials, see Wiggins, G. *Chemical Information Sources*, McGraw-Hill, NY, ***1991***.

[36] Compounds newly reported in the fifth supplement that are in a volume whose index has not yet been published will not be found by this procedure. To find them in Beilstein, it is necessary to know something about the system, but they may also be found by consulting *SciFinder*.

[37] For those heterocyclic compounds that would naturally belong to a volume for which the fifth supplement has been published.

While online searching is extraordinarily powerful, it should be pointed out that there are two problems with computer searches. First of all, far too many "hits" may be returned. For example, a 2011 research topic search (see Appendix A.D.iii) of the topic "macrolactones from hydroxy acids" gave the results:

Research Topic Candidates	References
159 references were found containing the two concepts "macrolactones" and "hydroxy acids" closely associated with one another	159
474 references were found where the two concepts "macrolactones" and "hydroxy acids" were present anywhere in the reference	474
35157 references were found containing the concept "macrolactones"	35157
193323 references were found containing the concept "hydroxy acids"	193323

Clearly, only examining the first few hundred references is practical. The search can, and must be refined. Depending on the scope of the search, this fact can be a limitation. The second problem relates to the search words used (the keywords). If they are too broad, little useful information is returned. If the keywords are too narrow in scope, many useful references may be missed. The point of these two cautions is to take care in choosing keywords. On the other hand, using many related keywords and doing multiple searches is very easy using SciFinder, and is probably a good strategy.

Often, all the information one needs about a compound will be found in one of the handbooks (Appendix A.C.i), in the *Dictionary of Organic Compounds* (Appendix A.C.i), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches. There is no definite procedure for making other literature searches using only printed materials. Any chemist who wishes to learn all that is known about the mechanism of the reaction between aldehydes and HCN, or which compounds of the general formula Ar_3CR have been prepared, or which are the best catalysts for *Friedel–Crafts acylation* of naphthalene derivatives with anhydrides, or where the group —$C(NH_2)$=N— absorbs in the IR, is dependent on ingenuity and knowledge of the literature. If a specific piece of information is needed, it may be possible to find it in one of the compendia mentioned previously. If the topic is more general, the best procedure is often to begin by consulting one or more monographs, treatises, or textbooks that will give general background information and often provide references to review articles and original papers. In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, and also *SciFinder*, where the ingenuity of the investigator is most required, for now it must be decided which words to look under. This statement relates to the keyword used for a computer search, as indicated above. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under "aldehydes", or "hydrogen cyanide", or even under "acetaldehyde" or "benzaldehyde", and so on, but then the search is likely to prove long. A better choice in this case would be "cyanohydrin", since these are the normal products and references there would be fewer. It would be a waste of time to look under "mechanism". In any case, many of the abstracts would not prove helpful. If it is necessary to search before 1907

(and even before 1920, since *CA* was not very complete from 1907 to ~1920), recourse may be made to *Chemisches Zentralblatt* and the abstracts in the *Journal of the Chemical Society*.

D.ii. Literature Searching Online[20]

Most of the *Chemical Abstracts* literature can be accessed online via *CAS*, using *SciFinder* in Appendix A.D.iii, the largest and most current database of chemical substance information in the world. *CAS* is located in Columbus, Ohio and is a division of the American Chemical Society. *CAS* can be contacted at Chemical Abstracts Service, 2540 Olentangy River Road, P.O. Box 3012, Columbus, Ohio 43210 (e-mail: help@cas.org). *CAS* is a team of scientists who provide digital information environment for scientific research and discovery. *CAS* provides pathways to published research in the world's journal and patent literature back to the beginning of the 20th century. Since 1907, *CAS* has indexed and summarized chemistry-related articles from >40,000 scientific journals, in addition to patents, conference proceedings and other documents pertinent to chemistry, life sciences, and many other fields. Through the printed *CA* (*Chemical Abstracts*), *CA* on CD, STN, the *CAS* files distributed through licensed vendors, the *SciFinder* and *SciFinder Scholar* desktop research tools, and the *STN Easy* or *STN* on the Web services, data produced by *CAS* is accessible to virtually any scientific researcher worldwide in industry, governmental research institutions, and academia.

Substance identification is a special strength of *CAS*. It is widely known as the *CAS Registry*, the largest substance identification system in existence. When a chemical substance, newly encountered in the literature, is processed by *CAS*, its molecular structure diagram, systematic chemical name, molecular formula, and other identifying information are added to the Registry and it is assigned a unique *CAS Registry* Number.

The *CAS REGISTRY* mostly covers substances identified from the scientific literature from 1957 to the present with some classes (fluorine- and silicon-containing compounds) going back to the early 1900s. An important piece of information that assists in such a search is the *CAS* registry number. Each substance in *REGISTRY* is identified by a unique numeric identifier called a CAS Registry Number.[38] "The CAS Registry number is a unique number assigned to a chemical by the Chemical Abstracts Service.[39] A fairly large collection of *CAS* numbers, with links to safety data for many chemicals, can be found at the listing of chemicals by *CAS* number at the Safety Home Page of the Physical and Theoretical Chemistry Laboratory at Oxford University".[40] The CAS Registry Number is a unique numeric identifier that designates only one substance, has no chemical significance, and is a link to finding information about a specific chemical substance. A *CAS* Registry Number includes up to 9 digits that are separated into 3 groups by hyphens. The first part of the number, starting from the left, has up to 6 digits; the second part has 2 digits. The final part consists of a single check digit.[41]

Online searching means using a computer terminal to search a *database*. Although databases in chemistry are available from several organizations, STN International (The

[38] Available at http://www.cas.org/EO/regsys.html
[39] Available at http://www.cas.org/
[40] Available at http://ptcl.chem.ox.ac.uk/MSDS/glossary/casnumber.html
[41] Available at http://www.cas.org/EO/checkdig.html

Scientific & Technical Information Network) is important because it is comprehensive and available in many countries. STN has dozens of databases, including many that cover chemistry and chemical engineering. To access these databases a chemistry department, a library, or an individual subscribes to STN (for a nominal fee), and receives code numbers that will permit access to the system, usually via a desktop computer.

D.iii. SciFinder—the CAS database[42]

Tutorials are available to help use Sci-Finder.[43] SciFinder can search a research topic[44] or a compound can be searched by structure[45] The search engine is known as STN Express with Discover![46] and can easily and efficiently search >200 scientific and technical databases online through STN®.[47] The Analysis Edition of STN Express with Discover! allows one to search, analyze, visualize, and discover sci-tech information by the ability to create a table for substance analysis that identifies the common substructure for an answer set of structurally related substances: Group related author/inventor names and company names for better analysis and visualization results; Analyze and tabulate data from single- or multi-file search results, and create a data table and 3D chart; Save an answer set from databases (e.g., CAplusSM, PCTFULL, and USPATFULL) with the Save for STN AnaVist Wizard, and then import and open it in STN® AnaVistTM; Create an interactive spreadsheet from all or only hit CAS Registry Numbers and their corresponding CAS Roles through the CAS Registry Number®; Upload lengthy genetic sequences automatically for searching in DGENE and PCTGEN via the Upload Query Wizard. STN Express was developed in collaboration with Hampden Data Services.

To illustrate how STN is used, an online tutorial is available.[48] A few online windows from a *SciFinder* search are provided to illustrate how searches can be done. This presentation is by no means complete or intended as an alternative to the actual tutorial. Indeed, one could *not* use *SciFinder* properly after simply reading this discussion. The intent is to illustrate some features that are available and to present an overview of the use of this important tool.

Using *SciFinder*®, a search can be done in one of several different ways. Searches can be done by research topic, by substances, or by reactions. The latter two searches use drawing tools that are part of *SciFinder*. An example is shown of a search done by research topic:[49] The example shown in Fig. A.3. shows a search for intramolecular hydroamination of aminoalkenes. To begin, click Explore by research topic and enter the appropriate information.

It is possible to use filters (see Fig. A.1) in order to refine the search by year, document type (journal, patent, review, etc.), author or company. A window is returned that contain references categorized by their relationship to the search phrase, as shown in Fig. A.2. One simply checks those reference lists that appear closest to those of interest.

[42] Available at http://www.cas.org/
[43] Available at http://www.cas.org/SCIFINDER/SCHOLAR/interact/
[44] Available at http://www.cas.org/SCIFINDER/SCHOLAR/page2a.html
[45] Available at http://www.cas.org/SCIFINDER/SCHOLAR/scholstruc.html
[46] Available at http://www.cas.org/ONLINE/STN/discover.html
[47] Available at http://www.cas.org/stn.html
[48] Available at http://www.cas.org/ONLINE/STN/expressmac.pdf
[49] Available at http://www.cas.org/SCIFINDER/topic.html

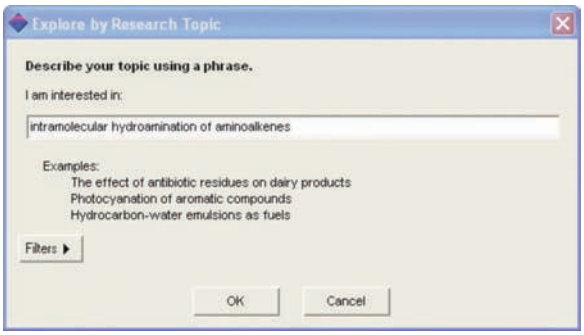


FIG. A.1. Explore by research topic.

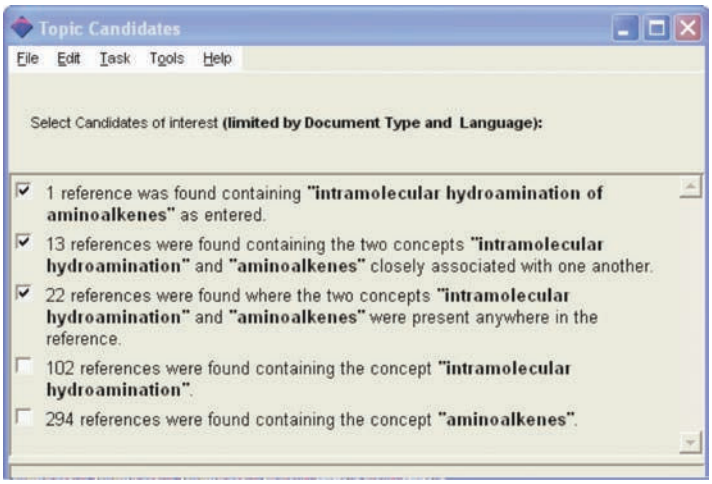


FIG. A.2. Selection of candidates of interest for search by research topic.

After clicking on "get references," a screen is returned (Fig. A.3) that has the original references, as shown in the window. One is given the option of refining this list further, and for each reference, most browsers allow viewing the abstract or the full references as an HTML or a PDF file. However, your library must have paid the appropriate fees so the journal and volumes of interest are available online. Otherwise, interlibrary loan or direct ordering of the article may be necessary.

Other examples of typical searches allowed by SciFinder include search by author's name,[50] as with the example of Professor K. Barry Sharpless shown in Fig. A.4. Search by structure is also possible,[51] such as the example shown in Fig. A.5, using SciFinder drawing tools. Once a structure is drawn, SciFinder searches to find matches based on that structure. The drawing tools can be used to show a reaction, and reaction information is returned, as shown in Fig. A.6. Ultimately, journal article and/or patents are returned that provide direct access to the literature of interest.

[50] Available at http://www.cas.org/SCIFINDER/author.html
[51] Available at http://www.cas.org/SCIFINDER/structure.html

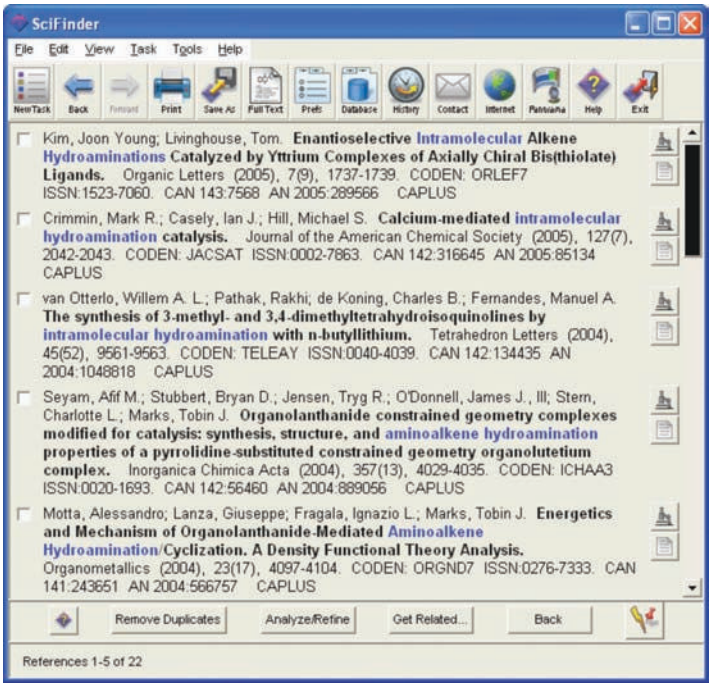


FIG. A.3. Original literature references returned for search by research topic.

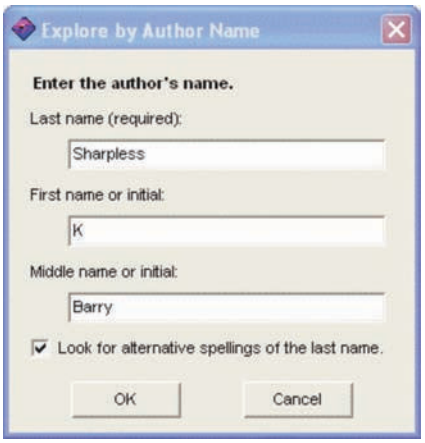


FIG. A.4. Screen shot for beginning a search by author.

D.iv. Science Citation Index

As seen in the SciFinder search tutorials, it is possible to track papers that have cited a particular article or author. A publication that can greatly facilitate literature searching is *Science Citation Index(*SCI*)*, begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year that have cited a

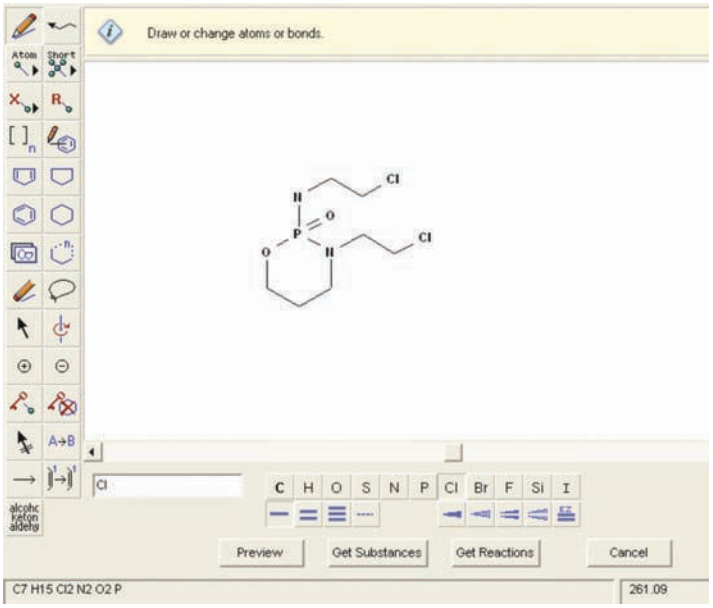


FIG. A.5. Screen shot for beginning a search by structure, using the drawing tools.

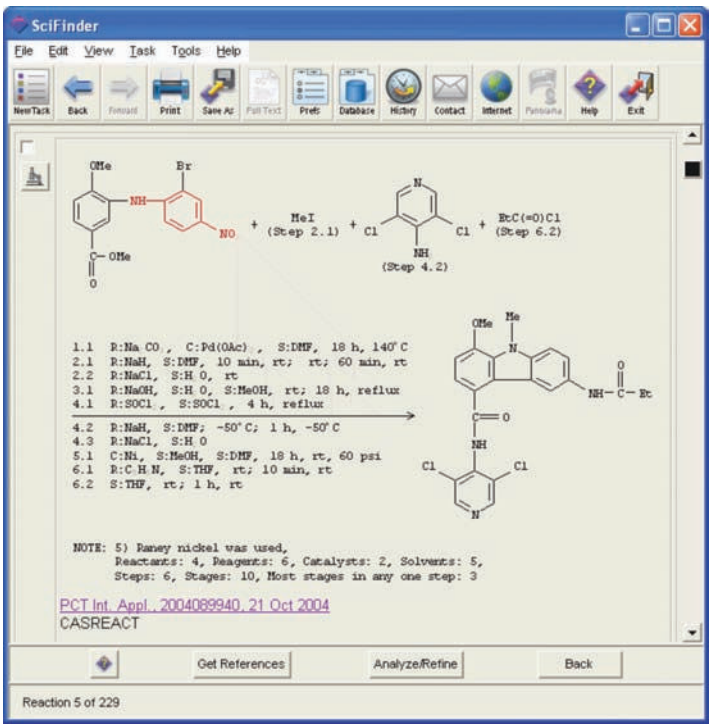


FIG. A.6. Screen shot of results for a search by reaction, using the drawing tools.

given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by W.P. Jencks and M. Gilchrist (*J. Am. Chem. Soc.,* ***1968***, *90*, 2622) entitled "Nonlinear Structure–Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters". The chemist is easily able to begin a search for earlier papers by using references supplied in this paper and can then go further backward with the aid of references in those papers, and so on. But for obvious reasons the paper itself supplies no way to locate *later* papers. *Science Citation Index* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or 2-month period (by first author only) and then gives a list of papers that have done the citing. The index is published bimonthly and cumulated annually. For example, column 43901 of the 1989 citation index shows that the Jencks paper mentioned above was cited as a footnote in 16 papers published in 1989. It is reasonable to assume that most of the papers that cited the Jencks paper were on closely related subjects. For each of the 16 papers are listed the first author, journal abbreviation, volume and page numbers, and year. In a similar manner, if one consulted *SCI* for all the years from 1968 to date, one would have a complete list of papers that cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1989 on) for papers that cited these 16 papers, and so on. Papers, patents, or books listed (e.g., in the 1989 *SCI*) may go back many years (e.g., papers published by A. Einstein in 1905 and 1906 are included). The only requirement is that a paper published in 1989 (or late 1988) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. Cited patents are listed in a separate table, in order of patent number, though the inventor and country are also given.

SCI covers ~3200 journals in the physical and biological sciences, as well as in medicine, agriculture, and technology. In addition to the citation index, each bimonthly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, volume, issue, page numbers, and year of all papers published by a given author during that 2-month period or year. All authors are listed; not just first authors. The second, called the *Corporate Index*, lists all publications that have been published from a given institution during that period, by first author. Thus, the corporate index for 1989 lists 63 papers by 45 different first authors emanating from the Department of Chemistry of Rutgers University, New Brunswick, NJ. The main section of the corporate index (the Geographic Section) lists institutions by country or (for the US) by state. There is also an Organization Section, which lists the names of institutions alphabetically, and for each gives the location, so it can be found in the geographic section. The third index included in *SCI* is the *Permuterm*[52] *Subject Index*. This index alphabetically lists every significant word in the titles of all papers published in that year or bimonthly period, paired with all other significant words in the same title. Thus, for example, a title with seven significant words appears at 42 separate places in the index. Each of the seven words appears six times as the main word, each time paired with a different word as the coword. The user is then led to the *Source Index*, where the full reference is given. *Science Citation Index* is also available online (though not through STN) and on CD–ROM discs. A version of *SCI* that is restricted to chemistry but also includes searchable abstracts, is available only in the CD–ROM format.

[52] Registered trade name.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews* that appears semiannually. This publication, which began in 1974, is very similar to *SCI*, but confines itself to listing citations to review articles. The citations come from ~2500 journals in the same general areas as are covered by *SCI*. The review articles cited appeared in ~215 review journals and books, as well as in those journals that publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and Permuterm indexes. It also contains a "Research Front Specialty Index", which classifies reviews by subject.

D.v. How to Locate Journal Articles

Having obtained a reference from various sources or searches, one often needs to consult the original journal (patents are discussed in Appendix A.A.ii). The first step is to ascertain the full name of the journal, since it is the abbreviation that is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals (*J. Org. Chem.*, *Chem. Ber.*, etc.), but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the *Chemical Abstracts Service Source Index(*CASSI*)*, 1989 edition, which contains the names of all the journals covered by *CA* from 1907 to 1989 (even those no longer published), with the most recent abbreviations in bold print. *Chemical Abstracts Service Source Index* also lists journals covered by *Chemisches Zentralblatt* and its predecessors from 1830 to 1969, and journals cited in Beilstein before 1907. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and *CASSI* also contains all former names, with cross-references to the current names. Quarterly supplements, cumulated annually, to *CASSI* have appeared since 1990 listing new journals and recent changes in journal titles. Note that while many publications use the *CA* abbreviations, not all do. Usage will vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations have changed from time to time. This latter point is particularly important when doing keywords searches. Using a structure search in SciFinder may get around this problem.

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist, or if that journal is available in electronic form. If not, one must use another library. The next step is to find out which libraries carry the journal and *CASSI* answers this question too, since it carries a list of some 360 libraries in the United States and other countries. *For each journal it tells which of these libraries carries it*, and furthermore, if the holdings are incomplete, which volumes of that journal are carried by each library. However, most libraries have an inter-library loan service that will provide access to such journal articles. It may be possible to visit the closest library personally and *CASSI* also includes lists of journal publishers, sales agents, and document depositories. Photocopies of most documents cited in *CA* can be obtained from chemical Abstracts Document Delivery Service, Customer Services, 2540 Olentangy River Road, Columbus OH, 43210, USA. Orders for documents can be placed by mail, telephone, Telex, fax, or online through STN or other services.

These latter comments are largely out of date given the online status of most journals. As mentioned above, PDF files of an article can be downloaded, or they can be read directly via the HTML file using any current browser. The reader is encouraged to contact the library person in your establishment that is responsible for chemical literature and to learn which online services are available through your local library.

D.vi. REAXYS® [53]

Launched in 2009, "Reaxys was created through the merger of the existing *CrossFire* databases (AppendixA.B.iii.) into a single database with a new and intuitive user interface. Reaxys is a fully integrated content source providing in-depth coverage of inorganic, organic, and organometallic small molecule chemistries excerpted from appropriate journal and patent literature".[54] Reaxys is available online with drawing tools that allows entry of a structure, or multiple structures as part of a reaction. Once the structure is drawn, Reaxys offers several options for the search:

Reaxys is a unique workflow solution for research chemists providing in depth coverage of inorganic, organic, and organometallic small molecule chemistries. The database consists of chemical compounds and related factual properties; chemical reaction and synthesis information; related bibliographic data, all of which have been excerpted from a carefully selected list of journals and patents: The latter is sourced from carefully selected patent classes and patent offices. This content is delivered through a web-based interface, designed for chemists, with powerful functionality that delivers the content in a flexible and intuitive way and helps a chemist with his/her major information tasks.

At the heart of Reaxys is the concept of "Chemistry as the organizing principle". This means that the chemical compound or reaction is central to the way in which the data is organized in the database. This is fundamentally different from bibliographic databases in which a journal or patent record is at the center. This chemically focused approach allows all data from multiple sources to be combined together in one de duplicated record for a given compound or reaction (i.e., a single compound or reaction can have multiple source citations, whereas a bibliographic database will have one record per published item, so the same compound or reaction may be found in multiple records).

The value of Reaxys to organic chemists may be understood best in relation to the synthesis of compounds, which is at the core of organic chemistry. Devising new routes to unique and artificial scaffolds requires the skills of planning and executing multistep syntheses and having a toolbox of methodologies at one's disposal. However, even the best conceived synthesis plans may require modifications, fine-tuning or entire rerouting, and chemists are faced with the daily challenge of choosing the right combination of reagents and building blocks for a whole set of problems: Which building blocks are optimal? In which sequence should they be assembled? Which reactions accomplish the task best? The Reaxys synthesis planning tool has been designed to make these choices as painless as possible using information and data from the journal and patent literature to investigate a number of possible alternative synthetic routes.

As an example, searching for papers that have reported direct arylation of indoles at the C-3 position. Construct a graphical search query (using one of the common graphical chemical structure editors, e.g., ChemDraw), with GH on indole nitrogen and also at the 5- and 6-positions of indole. The screen in Fig. A.7. shows the entry information required for the search. This query, retrieved 164 reactions from 45 citations (search results obtained in February 2012):

[53] Available at https://www.reaxys.com/info/
[54] Available at Reaxys_whitepaper_2011_whatsinReaxys.pdf

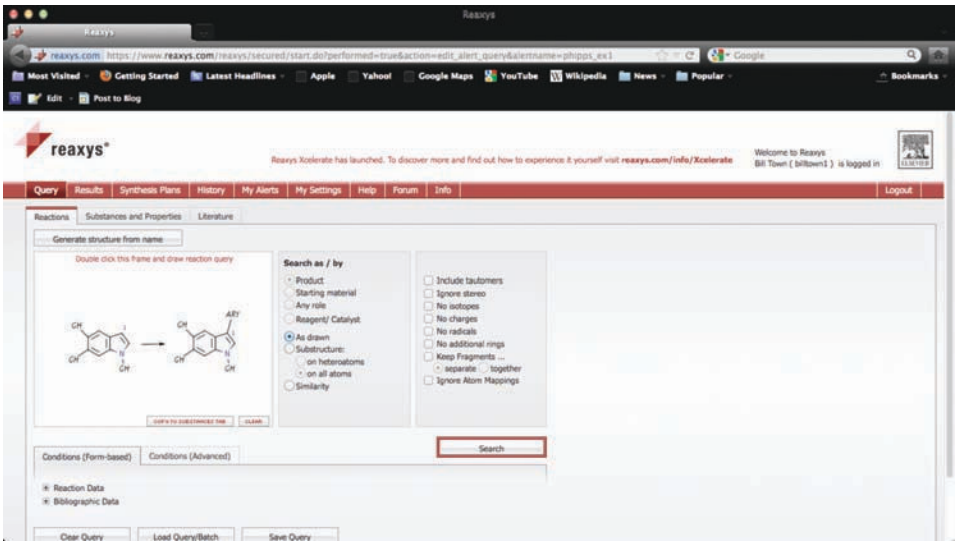


FIG. A.7. Search for direct arylation of indoles at C-3.

The Reaxys Version used in the above example is Application version: 1.0.9619; Content last updated: February 2012; Reactions: 31.681.788; Substances: 20.286.045; Citations: 4.504.504. Figure A.8 shows details for one of the reactions returned for this search. Also shown on this screen are various parameters that are available to search for this example. The original publication from which the reaction was taken is readily available.

It is also possible to expand the literature review by viewing the details of any recent articles that cite articles of interest. This is easily achieved by clicking on the 'view citing

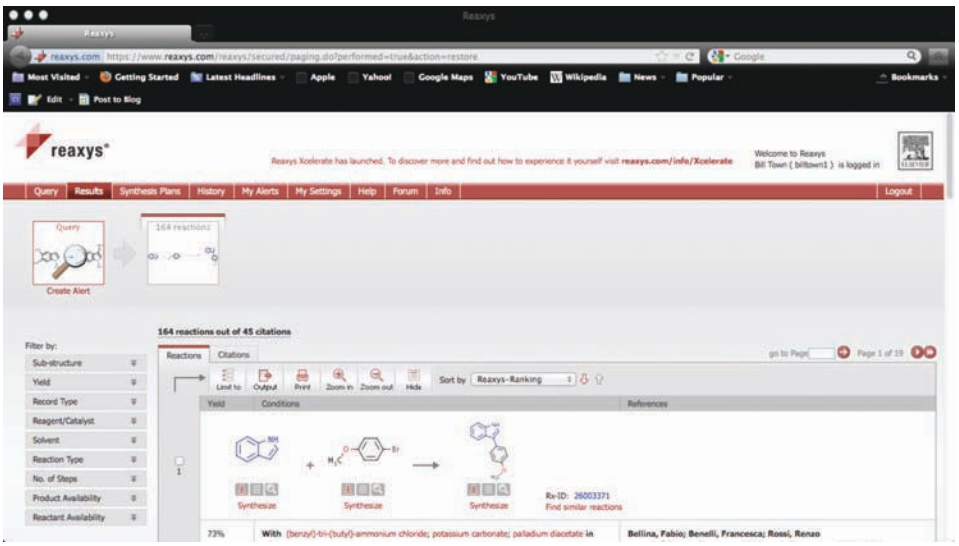


FIG. A.8. One reaction returned for this search.

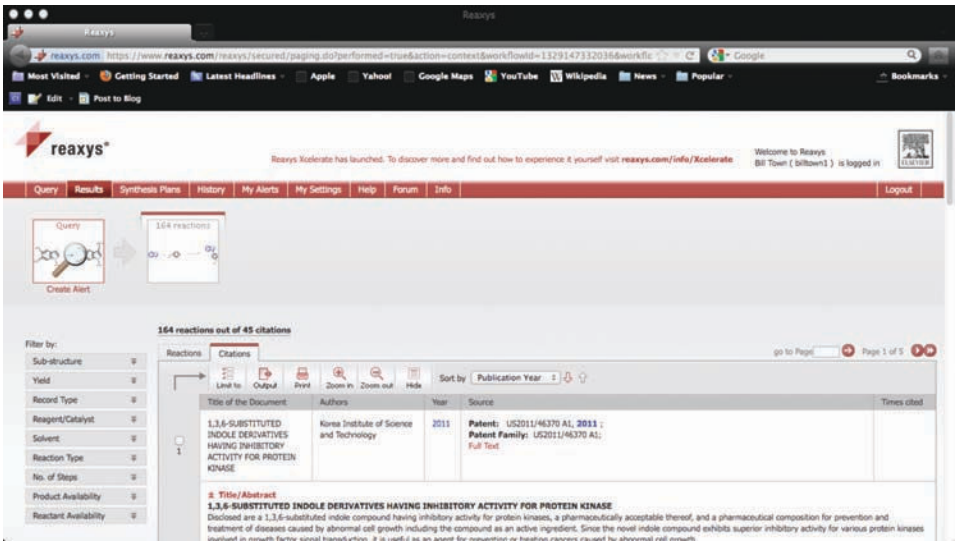


FIG. A.9. Papers that cited the work in Fig. A.8.

articles' hyperlink. The reaction shown in Fig. A.8 was cited in the patent literature and also in the *Journal of Organic Chemistry*, as shown in Fig. A.9. In this manner, relevant, more recent articles may be identified and explored using citation data from Scopus. A few of such citations are shown in Fig. A.10.

The synthesis planning tool allows a more in depth investigation. The Reaxys synthesis tool makes it easy to add more steps to the synthesis plan by searching the journal and patent literature for reactions designed to prepare the precursor molecules in any reaction step. Figure A.11 illustrates how a synthesis of a target that is consistent with the original

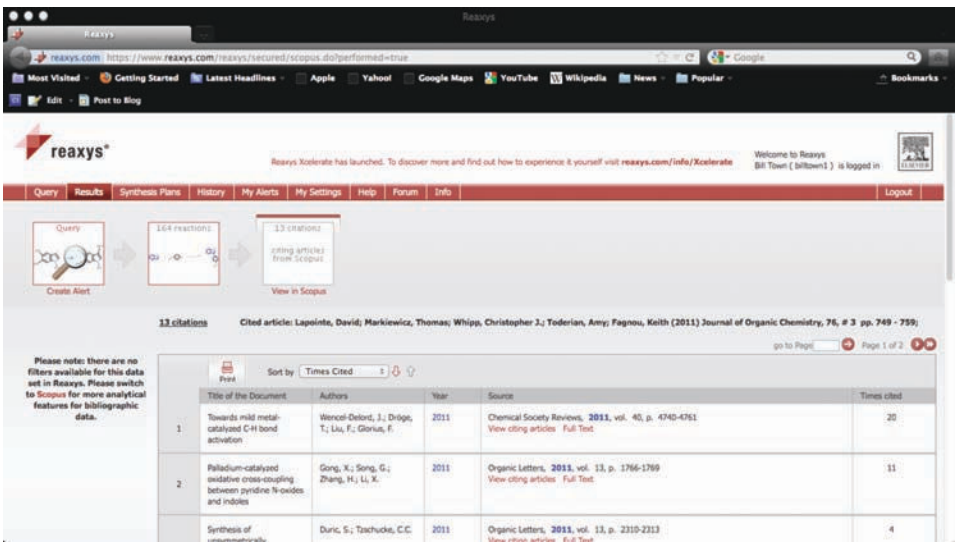


FIG. A.10. Other potentially relevant papers based on an expanded search.

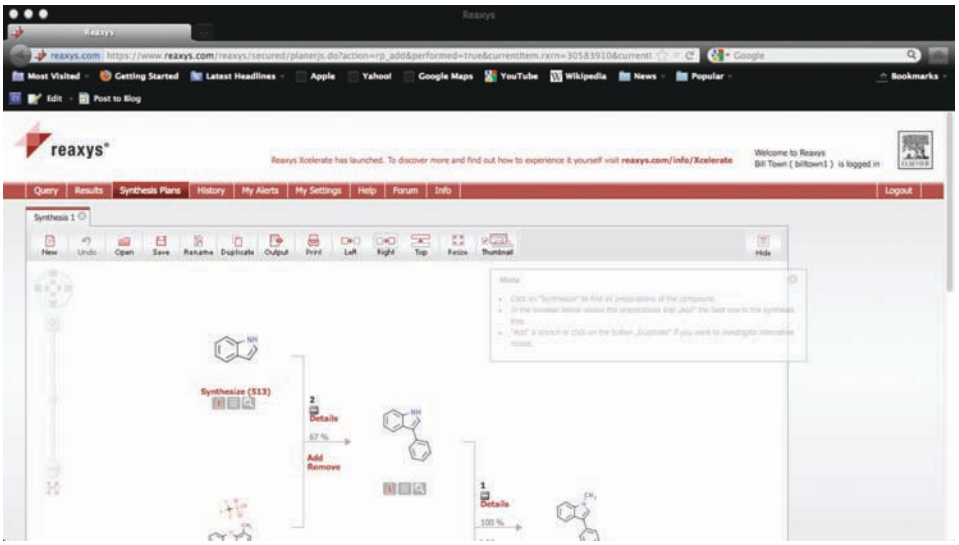


FIG. A.11. Synthesis plan for 3-phenylindole.

search parameters may be constructed. Extensive property data for chemical substances is available at every stage in the process. Reaxys is a valuable addition to the information resources used by synthetic chemists.

Note that Reaxys and the Reaxys® trademark are owned by Elsevier Properties SA and used under license. All rights reserved.

APPENDIX B

Classification of Reactions by Type of Compounds Synthesized

ACETALS

acetals + RM **10-64**
aldehydes + alcohols **16-05**
by transetherification **10-13**
from dihalides **10-08**
from hydroxy-ethers **14-06**
ortho esters + RM **10-64**
reductive cleavage of ortho esters **19-56**

ACYLALS (DIESTERS)

aldehydes + anhydrides **16-06**

ACYLOINS: See hydroxy-ketones

ALCOHOLS

addition of other organometallics to carbonyls **16-25**
aldehydes + allylic silanes **16-51**
alkenes + alcohols **15-33**
alkenes + aldehydes or ketones **16-54**
alkenes-oxymercuration **15-03**
amides + organometallic compounds **16-82**
amines + KOH **10-23**
anhydrides + organometallic compounds **16-82**
aromatics + carbonyls **11-12**
arylation of ketones **11-12**
boranes + CO; oxidation **18-23**
boranes + CO; reduction **18-24**
by the Cannizzaro reaction **19-81**
by Wittig rearrangement **18-22**
carboxylic esters + organometallics **16-82**
cleavage of ethers **10-49**
condensation of aldehydes **19-81**
conjugate reduction **15-14**
epoxides + organometallics **10-65**
epoxides + silanes **10-55**
from alcohols **10-17**
from amines **10-23**
from boranes **10-01**
from boranes **12-27**
from boranes **18-23**
from boronates **18-23**
from epoxides **10-65**
from ethers **10-13**
from silanes **10-16**
Grignard addition to aldehydes or ketones **16-24**
hydration of alkenes **15-03**
hydrolysis of acetals and ketals **10-06**
hydrolysis of alkyl halides **10-01**
hydrolysis of inorganic esters **10-04**
hydrolysis of sulfonate esters **10-04**
hydrolysis of vinyl ethers **10-06**
hydroxylation at aliphatic carbon **19-14**
hydroxymethylation of arenes **11-12**
organolithium addition to aldehydes or ketones **16-24**
organometallics + oxygen **12-25**
oxidation of boranes **12-27**
oxidation of boranes **15-16**
oxidation of boranes **18-23**

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition. Michael B. Smith.

© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

oxidation of methylene **19-15**
oxidation of silanes **10-16**
radical addition to carbonyl compounds **16-56**
rearrangement of ethers **18-22**
rearrangement of peroxides **18-20**
reduction of acyl halides **19-63**
reduction of aldehydes or ketones **19-36**
reduction of carbonyls with Grignard reagents **16-24**
reduction of carboxylic acids **19-37**
reduction of carboxylic esters **19-38**
reduction of carboxylic esters **19-65**
reduction of conjugated ketones **15-44**
reduction of epoxides **19-35**
reduction peroxides **19-60**
ring expansion of amines **18-03**
silanes + aldehydes or ketones **16-26**

ALCOHOLS, ALLYLIC
addition of allylic organometallics to carbonyls **16-25**
alkenes + formaldehyde **16-54**
allylic silanes + aldehydes or ketones **16-26**
deprotonation of epoxides **17-03**
rearrangement of alkene-sulfoxides **18-35**

ALDEHYDES
alkenes + aldehydes **15-33**
alkyl halides + organoiron compounds **10-76**
alkylation of aldehydes **10-68**
alkylation of imines **10-68**
alkylation reactions **10-67**
and keto–enol tautomerism **12-03**
aromatic compounds: Friedel–Crafts **11-18**
arylation of aldehydes **13-14**
boranes + $MeO(ArS)CH_2Li$ **18-24**
by decarboxylation **12-40**
by rearrangement of aldehydes **18-04**
by the Wacker process **19-25**
carbonylation of alkenes **15-37**
carbonylation of aromatic compounds **11-18**
carbonylation of hydrocarbons **12-33**
formylation of aromatic compounds **11-18**
from alkyl halides **10-64**
from alkyl halides **10-76**
from aryl imines **11-18**
from dihydrooxazines **10-72**
from dithianes **10-71**
from dithioaldehydes **16-11**
from organometallics **12-33**
from oxazines **10-72**
hydration of alkynes **15-04**
hydroformylation **15-37**
hydrolysis of acetals **10-05**
hydrolysis of C=N compounds **16-02**
hydrolysis of *gem*-dihalides **10-02**
hydrolysis of nitro compounds **16-03**
hydrolysis of vinyl ethers **10-06**
hydrolysis of vinyl halides **10-04**
Michael addition **15-24**
oxidation of alcohols **19-03**
oxidation of aryl methyl groups **19-18**
oxidation of nitro compounds **19-21**
oxidation of primary alkyl halides **19-20**
oxidative cleavage of diols **19-07**
oxidative cleavage of epoxides **19-07**
ozonolysis of alkenes **19-09**
reduction anhydrides **19-40**
reduction nitriles **19-44**
reduction of acid anhydrides **19-40**
reduction of acyl halides **19-39**
reduction of amides **19-41**
reduction of carboxylic acids **19-40**
reduction of carboxylic esters **19-40**

ALDEHYDES, CONJUGATED
by aldol condensation **16-34**

ALKANES
alcohols + RM **10-63**
alkane addition to alkenes **15-18**
alkenes + alkyl radicals **15-29**
alkenes + diimide **15-12**
alkenes + metals **15-12**
alkenes + organometallics **15-21**
alkyl halides + metals **10-56**
alkyl halides + metals **10-57**
alkyl halides + organocuprates **10-58**
alkyl halides + RM (Li, Na, K) **10-57**
alkyl halides + RM (other metals) **10-59**

alkyl halides + silanes **10-55**
Barton–McCombie reaction **19-58**
by [2 + 2]-cycloaddition **15-63**
by [3 + 2]-cycloaddition **15-59**
by decarboxylation **12-40**
cleavage of alkanes **12-47**
cleavage of ketones **12-46**
coupling of boranes **14-26**
coupling of carboxylate salts **14-29**
coupling of Grignard reagents **14-24**
coupling of organocuprates **14-25**
coupling of two alkanes **14-15**
decarbonylation of aldehydes **14-32**
decyanation **12-48**
from alcohols **10-63**
from alcohols **19-58**
from alkanes **12-20**
from alkanes **12-21**
from alkyl halides **10-55–10-59**
from alkyl halides **12-24**
from alkylborates **10-59**
from boranes **10-59**
from nitriles **12-48**
from organometallics **12-22**
from organometallics **12-23**
from organometallics **12-24**
from S compounds **10-61**
from S compounds **14-27**
from silanes **10-55**
Grignard reagents with metal compounds **14-24**
homocoupling of organocuprates **14-24**
hydrogen exchange **12-01**
hydrogenation of alkenes **15-11**
hydrogenation of alkynes **15-11**
hydrogenation of aromatic compounds **15-13**
inorganic esters + RM **10-61**
insertion by carbenes **12-21**
Kolbe reaction **14-29**
pyrolysis of peroxides **17-37**
radical addition to alkenes **15-29**
radical coupling of alkanes **14-14**
radical cyclization of alkenes **15-30**
reduction dithianes **10-71**
reduction of acyl halides **19-59**
reduction of alcohols **19-54**
reduction of alkenes and alkynes **15-12**
reduction of alkyl halides **19-53**
reduction of anhydrides **19-65**
reduction of carbonyls to methylene **19-61**
reduction of carboxylic esters **19-65**
reduction of nitriles **19-66**
reduction of nitro compounds **19-67**
reduction of silanes **19-52**
reduction of sulfonate esters **19-57**
reduction of sulfur compounds **19-70**
reduction of thioethers **14-27**
reduction of thiols **14-27**
reduction of thiols **19-70**
reduction of xanthate esters **19-58**
reductive cleavage of cyclopropanes **15-15**
reductive cleavage of ethers **19-56**
replacement of metals in RM by hydrogen **12-24**
σ-bond rearrangements **18-38**
sulfonate esters + metals **10-56**
sulfonate esters + organocuprates **10-58**
sulfur compounds + organometallics **10-61**
via transmetallation **12-22**

ALKENE-ALCOHOLS
rearrangement of alkene-ethers **18-35**

ALKENE-ALDEHYDES
Claisen rearrangement **18-33**
Cope rearrangement **18-32**
rearrangement of allyl vinyl ethers **18-33**

ALKENE-ALKYNES
addition of alkynes to alkynes **15-20**

ALKENE-AMINES
rearrangement of alkene-ammonium salts **18-35**

ALKENE-CARBOXYLIC ACIDS
Claisen rearrangement **18-33**
rearrangement of alkene-esters **18-33**

ALKENE-KETONES
Claisen rearrangement **18-33**
rearrangement of allyl vinyl ethers **18-33**

ALKENE-THIOETHERS
rearrangement of alkene sulfonium salts **18-35**

ALKENES
aldehydes or ketones + active H compounds **16-38**
alkane addition to alkynes **15-18**
alkene addition\to alkenes **15-20**
alkene metathesis **18-37**
alkenes + aryl halides **13-10**
alkenes + arylboronic acids **13-10**
alkenes + aryldiazonium compounds **13-10**
alkenes + carbenes **15-64**
alkenes + carbocations **12-20**
alkynes + alkyl halides + RM (M = metal) **15-22**
alkynes + metals or metal hydrides **15-12**
allylic esters + RM **10-60**
allylic halides + metals **10-56**
allylic silanes + esters **10-60**
aryldiazonium salts + alkenes **13-26**
base induced elimination of halosulfones **17-20**
bis(decarboxylation) of dicarboxylic acids **19-13**
by [2 + 2]-cycloaddition **15-63**
by [3 + 2]-cycloaddition **15-59**
by decarboxylation **12-40**
by McMurry coupling **19-77**
by migration of double bonds **12-02**
by Peterson alkenylation **16-41**
by the Diels–Alder reaction **15-60**
by the ene reaction **15-23**
by the Heck reaction **13-10**
by the heteroatom Diels–Alder reaction **15-61**
by the Horner–Wadsworth–Emmons reaction **16-44**
by the Knoevenagel reaction **16-38**
by the Ramberg–Bäcklund reaction **17-20**
by the Sakurai reaction **15-26**
by the Wittig reaction **16-44**
cleavage of ethers **17-02**
cleavage of vinyl ethers **17-02**
conjugated addition of allylsilanes **15-26**
deacyloxylation **19-59**
decarbonylation of acyl halides **17-17**
decarboxylation of hydroxy-carboxylic acids **17-26**
dehydration of alcohols **17-01**
dehydrogenation **19-02**
deoxygenation of 1,2-diols **17-18**
deprotonation of episulfides (thiiranes) **17-03**
deprotonation of epoxides (oxiranes) **17-03**
diazoalkanes + aldehydes **15-64**
dimerization of alkyl halides **19-32**
elimination (1,3-) of diols **17-25**
elimination (1,3-) of haloamines **17-25**
elimination (1,3-) of halohydrins **17-25**
elimination (base) of ammonium salts **17-07**
elimination (base) of ammonium salts **17-08**
elimination (base) of halides **17-13**
elimination (base) of sulfonate esters **17-06**
elimination (base) of sulfonyl halides **17-14**
elimination (base) of sulfonyl hydrazones **17-11**
elimination of 1,2-dihalides **17-22**
elimination of boranes **17-15**
elimination of haloethers **17-24**
enamines + boranes **15-16**
esters + organometallics **10-60**
extrusion from oxathiolanes **17-38**
extrusion of CO from cyclic ketones **17-35**
from alcohols **10-63**
from alkenes **13-26**
from alkyl halides **10-55**
from allylic esters **10-60**
from bis(xanthates) **17-18**
from boranes **10-59**
from carbenes **12-21**
from dienes **18-37**
from episulfones **16-48**
from epoxides or thiiranes **17-03**
from imines **16-44**
from selenones **10-71**
from silanes **10-55**
hydroboration of alkynes **18-25**
hydrogenation of alkynes **15-11**

hydrogenation of aromatic compounds **15-13**
isomerization of double bonds **15-01**
ketones or aldehydes + bis(Grignards) **16-24**
migration of boranes **12-02**
migration of double bonds **12-02**
nitrosation of aziridines **17-21**
organometallics + ketones **16-25**
organometallics + tosylhydrazones **16-38**
other cycloaddition reactions **15-66**
oxidative decarboxylation of carboxylic acids **19-12**
Petasis alkenylation **16-45**
protonolysis of vinyl boranes **18-25**
protonolysis of vinyl boranes **18-26**
pyrolysis of amine oxides (Cope) **17-09**
pyrolysis of ammonium salts (Hofmann) **17-07**
pyrolysis of esters **17-04**
pyrolysis of hydroxy-alkenes **17-32**
pyrolysis of sulfones **17-12**
pyrolysis of sulfoxides **17-12**
pyrolysis of thionocarbonates **17-19**
pyrolysis of xanthates (Chugaev) **17-05**
pyrolysis of β-lactones **17-26**
rearrangement of dienes **18-39**
reduction of enamines **19-67**
reduction of hydrazones **19-61**
reduction of thiiranes **19-35**
reduction of thiophene derivatives **19-70**
reduction of vinyl halides **19-53**
reduction of vinyl imines **19-61**
reductive coupling of aldehydes or ketones **19-77**
reductive coupling of epoxides **19-35**
sigmatropic carbon migration **18-30**
sigmatropic H migration **18-29**
silyl-organometallics + aldehydes or ketones **16-41**
Tebbe alkenylation **16-45**
vinyl boranes + halogen/base **18-25**
vinyl halides + arylboronic acids **13-10**
vinyl-cyclopropane rearrangement **18-31**
vinyl-X + alkyl(aryl)boronic acids **12-15**
Wagner–Meerwein rearrangement of alcohols **18-01**
Wagner–Meerwein rearrangement of halides **18-01**

ALKYNE-ALCOHOLS
addition of alkynes to carbonyls **16-25**

ALKYNES
alkyl halides + alkyne anions **10-74**
alkyl halides + propargylic RM **10-57**
alkynes + aryliodonium salts **13-13**
alkynes + boranes **18-26**
aryl halides + alkyne-M (M = a metal) **13-13**
aryl halides + alkynes **10-74**
base-induced isomerization alkynes **12-02**
dimerization of dihalides **19-32**
elimination of alkenes **17-16**
elimination of dihalo compounds (by base) **17-16**
elimination of halides (by base) **17-13**
from alkyl halides **10-74**
from alkynes **10-74**
hypervalent iodine + alkyne-M (M = a metal) **12-26**
metathesis of alkynes **18-37**
pyrolysis of bis(ammonium)salts **17-07**
pyrolysis of thiirene dioxides **17-20**
pyrolysis of ylids **17-10**
Sonogashira coupling **13-13**
Stephens–Castro coupling **13-13**

ALLENES
base-induced rearrangement of halocyclopropanes **18-03**
by Claisen rearrangement **18-33**
by the Wittig reaction **16-44**
Cope rearrangement of diynes **18-32**
elimination of dihalides **17-22**
propargylic esters + organocuprates **10-60**
reduction of alkynes **19-53**

ALLOPHANATES
carbamates + isocyanates **16-08**

AMIDE–ESTERS
aziridines + amides **10-14**

AMIDES
acyl halides + ammonia or amines **16-72**

addition of organometallics to isocyanates **16-33**
alcohols + cyanogen halides **16-09**
aldehydes + ammonia + oxidant **14-11**
alkanes + nitriles **14-12**
alkenes + amides **15-09**
alkenes + nitriles **16-91**
alkyl halides + amides **10-41**
amides + aldehydes **10-41**
amides + amines **16-76**
amines + CO + alkenes **15-36**
amines + CO **12-53**
amines + haloformates **10-53**
amines + organoiron compounds **10-77**
amines + vinyl esters **16-75**
anhydrides + ammonia or amines **16-73**
aromatic compounds + amides **11-22**
aromatic compounds + hydroxamic acids **11-06**
aromatic compounds + isocyanates **11-21**
aryl halides + amides **10-41**
aryl halides + amides **13-05**
aryl halides, DMF and $POCl_3$ **11-21**
by Beckmann rearrangement **18-17**
by Michael addition **15-24**
by Mitsunobu reaction **10-41**
by reaction with nitrenes **12-13**
by the Haller–Bauer reaction **12-46**
by the Willgerodt reaction **19-84**
carboxylic acids + amino-boranes **16-74**
carboxylic acids and ammonia or amines **16-74**
carboxylic esters + ammonia or amines **16-75**
cleavage of ketones **12-46**
condensation of methyl ketones **19-84**
dealkylation of amides **19-73**
from alcohols **10-41**
from aromatic compounds **11-19**
from *N*-halo amides **11-31**
hydrolysis of isonitriles **16-97**
hydrolysis of nitriles **16-04**
imines + borane + CO **12-33**
insertion of acyl nitrenes **12-13**
insertion of diazo amides **12-21**
ketenes + amines **15-08**
ketones + HN_3 **18-16**
ketones + $^{-}NH_2$ **12-46**
N-alkylation **10-41**
N-arylation **10-41**
nitriles + alcohols **16-91**
nitriles + amines **16-21**
oxidation of methylene in amines **19-17**
oximes + halogenating or oxidizing agents **18-17**
pyrolysis of imino esters **18-42**
rearrangement of oximes **18-17**
reduction of imides **19-64**
Ritter reaction **16-91**
transamidation **16-70**

AMIDES, CONJUGATED
isocyanates + vinyl-M (metal) **15-22**

AMIDINES
ketenimines + amines **15-08**
nitriles + ammonia or amines **16-21**

AMIDO-ALCOHOLS
alkenes + amides **15-52**

AMINE OXIDES
oxidation of amines **19-29**

AMINES
addition of organometallics to C=N compounds **16-31**
addition of silanes to C=N **16-31**
alkenes + amines or ammonia **15-08**
alkyl halides + amines **10-31**
alkylation of amines **10-31**
alkylation of formamidines **10-71**
alkylation of nitroso amines **10-71**
allylic amination **12-12**
amides + organometallic compounds **16-82**
amination of active methylene compounds **12-12**
amination of alkanes **10-39**
amination of alkanes **12-12**
amination of heterocycles **13-18**
amination of methylene **19-16**
amines + aryl halides **13-05**
amines + diaryliodonium compounds **11-06**
amines + diazo compounds **10-34**

aminomethylation of aromatic compound **11-22**
aromatic compounds + amide bases **13-18**
aromatic compounds + aryl azides **11-06**
aromatic compounds + haloamines **11-06**
aromatic compounds + hydrazoic acid **11-06**
aryl halides + amines **13-05**
aryl halides + hydroxylamine-*O*-sulfonic acid **18-15**
azides + haloboranes **12-32**
aziridines + RM **10-66**
boranes + ammonia + NaOCl **12-32**
boranes + chloramine **12-32**
by amidomethylation **11-22**
by reaction with nitrenes **12-13**
by the Stevens rearrangement **18-21**
by transamination **10-33**
Curtius rearrangement **18-14**
cyclization of haloamines **18-40**
dealkylation of amines **19-73**
dehydrogenation **19-02**
displacement of cyano **10-62**
diynes + amines **15-08**
enamines + boranes **15-16**
from alcohols **10-31**
from alcohols **10-32**
from alkanes **10-39**
from amides **18-13**
from amines **10-31**
from amines **10-33**
from amines **10-34**
from amines **10-71**
from amino-ethers **10-64**
from amino-nitriles **10-62**
from ammonium salts **11-32**
from boranes **10-31**
from cyanohydrins **10-32**
from ethers **10-32**
from haloamines **10-31**
from hydrazones **10-71**
from hydroxylamines **13-32**
from nitroamines **11-28**
from nitrosamines **11-29**
from organometallics **12-32**
from phenols **11-22**
from phenols **13-06**
Hofmann rearrangement **18-13**
Hofmann–Löffler reaction **18-40**
hydrolysis of isocyanates **18-13**
hydrolysis of isocyanates **18-15**
hydrolysis of isocyanates **18-16**
hydroxylamines + alkyl organometallics **12-32**
imines + allylic silanes **16-51**
insertion of nitrenes **12-13**
Lossen rearrangement **18-15**
Michael addition with N nucleophiles **15-31**
phenols + amines or ammonia **13-06**
Pictet–Spengler reaction **10-13**
radical addition to C=N compounds **16-56**
rearrangement of ammonium salts **13-31**
rearrangement of ammonium salts **18-21**
rearrangement of aryl hydroxylamines **13-32**
reduction nitroso compounds **19-47**
reduction of amides **19-64**
reduction of amine oxides **19-68**
reduction of amines **19-64**
reduction of azides **19-50**
reduction of azo compounds **19-74**
reduction of azoxy compounds **19-74**
reduction of C=N compounds **19-42**
reduction of hydrazines **19-74**
reduction of hydroxylamines **19-47**
reduction of isocyanates **19-51**
reduction of isothiocyanates **19-51**
reduction of lactams **19-64**
reduction of nitriles **19-43**
reduction of nitro compounds **19-45**
reduction of nitrosoamines **19-51**
reduction oximes **19-48**
reductive alkylation of aldehydes or ketones **16-17**
Schmidt reaction **18-16**
Sommelet–Hauser rearrangement **13-31**
Stevens rearrangement **13-31**
transamination **10-33**

AMINO ACIDS
lactones + ammonia or amines **16-75**

AMINO ALCOHOLS
alkenes + amines **15-52**
epoxides + amines or ammonia **10-35**
from amino epoxides **10-36**
from isonitriles **10-40**
from nitroalcohols **10-35**
oxetanes + amines or ammonia **10-37**
rearrangement of haloamines **18-10**
reductive coupling of C=N with C=O **19-76**

AMINO ALDEHYDES
aldehydes + C=N compounds **16-31**

AMINO ESTERS
diazoesters + amines **15-64**

AMINO ETHERS
aziridines + alcohols **10-14**

AMINO KETONES
base-induced rearrangement of sulfonyl oximes **18-12**
ketones + HCHO + amines **16-19**
Mannich reaction **16-19**

AMINO NITRILES
from amines **12-19**
from cyanohydrins **10-32**
HCN or cyanide + C=N compounds **16-53**

AMINO THIOETHERS
alkenes + sulfonamides **15-55**
alkenes + sulfonium salts + amines **15-55**

AMINO THIOLS
episulfides + amines or ammonia **10-35**

AMMONIUM SALTS
alkyl halides + amines **10-31**

ANHYDRIDES
acyl halides + carboxylic acids **16-66**
aldehydes + acyl peroxides **14-09**
carboxylic acids + vinyl esters **16-67**
dehydration of carboxylic acids **16-67**
dehydration of dicarboxylic acids **16-67**

ANHYDRIDES, ORGANIC–INORGANIC
anhydrides + mineral acids **16-68**

ARENES
alkyl halides + ArM (Li, Na, K) **10-57**
alkyl halides + aryl organometallics **10-57**
alkyl halides + arylboronic acids **13-09**
alkyl halides + organocuprates **10-58**
alkyl halides + organometallics **13-17**
aromatic compounds + active H compounds **13-17**
aromatic compounds + acylperoxides **14-17**
aromatic compounds + alcohols **11-11**
aromatic compounds + alkenes **11-11**
aromatic compounds + alkyl halides **11-11**
aromatic compounds + carboxylic acids **14-19**
aromatic compounds + ketones **11-12**
aromatic compounds + peroxides **14-17**
aryl halides + active methylene compounds **13-14**
aryl halides + alkenes **13-10**
aryl halides + alkenes **15-21**
aryl halides + alkynes **15-21**
aryl halides + organocuprates **10-58**
aryl halides + RM (other metals) **10-59**
aryl halides + trifluoroborates **13-09**
aryl halides + vinylboronic acids **13-09**
aryldiazonium salts + alkenes **13-26**
aryldiazonium salts + alkyl organometallics **13-25**
aryldiazonium salts + organometallics **13-25**
by decarboxylation **12-40**
by radical cyclization **15-30**
coupling of aromatic compounds **11-15**
cyclodehydration of carbonyl compounds **11-13**
Friedel–Crafts alkylation **11-11**
from alkylborates **10-59**
from boranes **10-59**
from ketones **11-13**
hydrogen exchange **11-01**
rearrangement of *N*-alkyl aryl amines **11-32**

replacement of aryl nitro **13-29**
α-halo ketones + organocuprates **10-58**

AROMATIC COMPOUNDS
alkylation of heteroaryls **14-19**
aromatic compounds + carbenes **15-64**
aromatization of six-membered rings **19-01**
cleavage of arenes **11-33**
cleavage of aryl alkyl ethers **11-37**
cyclization of ene–diynes **18-27**
cyclotrimerization of alkynes **15-65**
deamination of aromatic compounds **19-69**
decarbonylation of aryl aldehydes **11-34**
decarboxylation of aryl carboxylic acids **11-35**
dehalogenation of aryl halides **11-39**
dehydrogenation of cyclic alkanes **19-01**
deoxygenation of aryl ethers **11-37**
desulfonylation of aryl sulfonic acids **11-38**
from aldehydes **11-34**
from aromatic compounds **11-33**
from aromatic compounds **18-28**
hydrolysis of aromatic organometallics **11-41**
protonation of aryl organometallics **11-41**
pyrolysis of bicyclic dienones **17-28**
reduction aryl diazonium salts **19-69**
reduction of aryl halides **11-39**
reduction of phenols **19-55**
reduction of quinones **19-01**

AZIDES
aldehydes + metal azides **16-78**
alkenes + hydrazoic acid **15-10**
alkenes + metal azides **15-53**
amides + sulfonyl azides **12-11**
from acyl halides **10-43**
from alkyl halides **10-43**
hydrazines + HONO or nitrosyl compounds **12-49**

AZIDO ALCOHOLS
from epoxides **10-43**

AZIDO AMIDES
from amides **12-11**

AZIDO AMINES
from aziridines **10-38**

AZIRIDINES
alkenes + alkyl azides **15-54**
alkenes + halogen + haloamines **15-54**
C=N compounds + sulfur ylids **16-47**
extrusion of nitrogen from triazolines **17-34**
form haloamines **10-31**
from allene amides **15-09**
from azido alcohols **10-43**
from epoxides **10-36**
from halo-azides **15-45**
from hydroxy-amines **10-32**
from imines **16-32**
from triazolines **15-58**
imines + diazo compounds **16-32**

AZIRINES
alkynes + amino nitrenes **15-54**

AZO COMPOUNDS
aryl amines + nitroso compounds **13-24**
aryl diazonium salts + aromatic compounds **11-04**
from aryldiazonium salts **13-28**
oxidation of hydrazines **19-05**
rearrangement of aryl triazenes **11-30**
rearrangement of azoxy compounds **18-43**
reduction of azoxy compounds **19-68**
reduction of nitro compounds **19-80**
Wallach rearrangement **18-43**

AZOXY COMPOUNDS
from alkyl halides **10-45**
nitroso compounds + hydroxylamines **12-51**
reduction of nitro compounds **19-79**

BIARYLS
aromatic compounds + aryl halides (*hν*) **14-18**
aromatic compounds + aryl organometallics **11-16**

aromatic compounds + aryl organometallics **14-17**
aromatic compounds + arylboronates **11-16**
aryl halides + alkyl or aryl organometallics **13-09**
aryl halides + arylboronic acids **13-09**
aryl halides + arylboronic acids **13-12**
aryl halides + metals **13-11**
aryl halides + trifluoroborates **13-12**
aryldiazonium salts + aromatic compounds **13-27**
aryldiazonium salts + metal salts **13-28**
arylsulfonic acid + arylboronic acids **13-05**
by benzidine rearrangement **18-36**
coupling 2 aryldiazonium salts **13-28**
coupling aryl halides **13-11**
coupling of aromatic compounds **11-15**
coupling of aryl sulfonates **13-12**
Scholl Reaction **11-15**
Suzuki–Miyaura coupling **13-12**
Ullmann coupling **13-11**

BIS(AMINES)
by benzidine rearrangement **18-36**

BIS(AMIDES)
aldehydes + amides **16-18**

BISULFITES
metal bisulfite + carbonyl compounds **16-12**

BORANES
alkenes + borane or alkyl boranes **15-16**
thermal migration of boron in boranes **18-11**

BORATES (TRIFLUORO)
boranes + KHF_2 **12-28**

BORATES
alcohols + boranes **12-28**
oxidation of boranes **12-27**

BORONIC ACIDS
alkyl borates + alkyl organometallics **12-28**

BUNTE SALTS
from alkyl halides **10-28**

CARBAMATES
alkyl halides + amines **10-17**
amines + alkyl halides + CO_2 **12-53**
amines + CO_2 **12-53**
from aziridines **12-53**
haloformates + amines **16-72**
isocyanates + alcohols **16-08**

CARBONATES
alcohols + phosphine **16-10**

CARBOXYLIC ACIDS
acyl halides + diazo compounds **18-08**
acyl peroxides + alkyl organometallics **12-26**
alkylation of carboxylic acids **10-70**
aromatic compounds + CO_2 **11-20**
aromatic compounds + CO_2 **11-20**
aromatic compounds-carboxylation **11-19**
aryl nitro compounds + cyanide **13-30**
Barbier–Wieland procedure **19-10**
boranes + ether-acids **18-24**
by decarboxylation **12-40**
by Favorskii rearrangement **18-07**
by malonic ester synthesis **10-67**
by Michael addition **15-24**
by the Cannizzaro reaction **19-81**
carboxylation of alkenes **15-35**
cleavage of diketones **12-43**
cleavage of ketoesters **12-43**
cleavage of ketones **12-45**
cleavage of methyl ketones **12-44**
deacyloxylation **19-59**
esters + metal halides **10-51**
from carboxylic acids **10-70**
from lactones **10-51**
from oxazolones **10-72**
from RM + arenes **10-57**
haloform reaction **12-44**
hydrolysis of acyl halides **16-57**
hydrolysis of amides **16-60**
hydrolysis of anhydrides **16-58**
hydrolysis of carboxylic esters **16-59**
hydrolysis of diazo ketones **18-08**
hydrolysis of nitriles **16-04**

hydrolysis of ortho esters **10-06**
hydrolysis of trihalide **10-03**
ketones + peroxy acids **18-19**
organometallics + CO_2 **16-30**
oxidation of aldehydes **19-23**
oxidation of aromatic rings **19-10**
oxidation of aromatic side chains **19-11**
oxidation of organoiron compounds **10-77**
oxidation of primary alcohols **19-22**
oxidative cleavage of alkenes **19-10**
oxidative cleavage of alkynes **19-10**
ozonolysis of alkenes **19-09**
phenoxides + CO_2 **11-20**
phosphoranes + CO_2 **16-44**
pyrolysis of esters **17-04**
rearrangement of ketones **18-19**

CARBOXYLIC ACIDS, CONJUGATED
aldehydes + anhydrides **16-39**
by the Knoevenagel reaction **16-38**
CO_2 + vinyl-M (metal) **15-22**

CARBOXYLIC ESTERS
acyl halides + alcohols **16-61**
acyl halides + ethers **16-61**
alcohols + CO + alkenes **15-36**
alcohols + CO + alkyl halides **10-77**
alcohols + ketenes **15-05**
alcohols + organoiron compounds **10-77**
alcoholysis of acyl oxazolidinones **16-65**
alcoholysis of amides **16-65**
alcoholysis of nitriles **16-09**
alcoholysis of trihalides **10-03**
alkenes + acyl peroxides **14-09**
alkenes + carboxylic acids **15-06**
alkenes + carboxylic esters **15-33**
alkyl halides + carboxylate anions **10-17**
alkylation of oxazolidines **10-72**
allylic carbonates + malonates **10-60**
allylic esters + malonates **10-60**
anhydrides + alcohols **16-62**
aryl halides + alcohols + CO **13-15**
aryl halides + alcohols + metal carbonyls **13-15**
Baeyer–Villiger rearrangement **18-19**
by Favorskii rearrangement **18-07**
by Michael addition **15-24**
by the Tishchenko reaction **19-82**
carbonylation of alkyl halides and alcohols **10-77**
carboxylic acids + diazo compounds **10-19**
cleavage of keto-esters **12-43**
condensation of aldehydes **19-82**
condensation of ketones **19-84**
conjugate addition of allylic silanes **15-26**
esterification of carboxylic acids **16-63**
esters + ethers **10-18**
ethers + anhydrides **10-18**
from alcohols **10-77**
from alkanes **14-09**
from alkyl halides **10-17**
from alkyl halides **10-77**
from alkyl halo sulfites **10-17**
from carboxylate salts **10-17**
from coupling of activated esters **10-61**
from onium salts **10-17**
from peroxides **14-09**
from tosyl amides **10-17**
hydrolysis of ortho esters **10-06**
insertion of diazo esters **12-21**
ketones + peroxides **18-19**
oxidation of aldehydes **19-23**
oxidation of methylene in ethers **19-17**
oxidation of primary alcohols **19-22**
oxidation of vinyl ethers **19-25**
oxidative decarboxylation **19-12**
oxygenation of organometallics **12-29**
Pinner synthesis **16-09**
rearrangement of haloketones **18-07**
ring contraction of diazoketones **18-08**
Sakurai reaction **15-26**
transesterification **16-64**
via Mitsunobu coupling **10-17**

CARBOXYLIC ESTERS, CONJUGATED
Baylis–Hillman reaction **16-27**
by the Knoevenagel reaction **16-38**
Claisen condensation **16-36**

COUMARINS
from phenols **11-11**

CUMULENES
elimination of propargylic halides **17-22**

CYANAMIDES
amines + cyanogen halides **10-54**

CYANATES, ARYL
phenols + cyanogen halides **10-08**

CYANIDES, ACYL
acyl halides + metal cyanides **16-88**

CYANO IMINES
nitroso compounds + nitriles **16-42**

CYANOAMINES
see amino nitriles

CYANOHYDRINS
aldehydes or ketones + HCN **16-52**
aldehydes or ketones + R_3SiCN **16-52**

CYCLOBUTANES
by [2 + 2]-cycloaddition **15-63**
extrusion of SO_2 **17-36**

CYCLOBUTENES
ring closure of dienes **18-27**

CYCLOPROPANES
alkenes + carbenes **15-64**
alkenes + diazo esters **15-58**
by the Simmons–Smith reaction **15-64**
conjugated carbonyls + sulfur ylids **16-49**
extrusion of nitrogen from pyrazolines **17-34**
extrusion off CO from cyclobutanones **17-35**
from pyrazoles **17-34**
from pyrazolines **15-58**
rearrangement of dienes **18-39**

DIACETATES
oxidation of dicarboxylic acids **19-13**

DIALDEHYDES
alkylation reactions **10-67**

DIAMINES
aziridines + amines or ammonia **10-38**
diamination of alkenes **15-53**
from azido amines **10-38**
reductive coupling of imines **19-76**

DIAZO COMPOUNDS
acyl halides + diazomethane **16-89**
base-induced elimination of *N*-nitroso compounds **17-33**
from active methylene compounds **12-10**
oxidation of hydrazones **19-06**

DIAZONIUM COMPOUNDS
active methylene compounds + sulfonyl azides **12-10**
aldehydes + sulfonyl azides **12-10**
aromatic compounds + HONO **11-05**
aryl amines + HONO **13-19**

DICARBOXYLIC ACIDS
by Michael addition **15-24**
from aryl isothiocyanates **11-21**
oxidative cleavage of cyclic alkenes **19-10**
oxidative cleavage of ketones **19-08**

DIACIDS, CONJUGATED
by the Knoevenagel reaction **16-38**

DIENES
addition of alkenes to dienes **15-20**
addition of alkynes to alkynes **15-20**
allylic halides + metals **10-56**
by Stille coupling **12-15**
by the Diels–Alder reaction **15-60**
by the Wittig reaction **16-44**
cleavage of cyclobutanes **15-63**
Cope rearrangement **18-32**
coupling of alkynes and allenes **15-20**
coupling vinyl boranes **14-26**
cycloaddition of dienes **15-66**
dehydration of alkyne-alcohols **17-01**
dienes + acyl metal compounds **12-16**
elimination of halides **17-22**
from aromatic compounds **18-27**
from vinyl compounds **12-15**
hydrogenation of aromatic compounds **15-13**
hydrogenation of diynes **15-11**

metathesis of alkenes **18-37**
other cycloaddition reactions **15-66**
pyrolysis of bicyclic alkene-ketones **17-28**
pyrolysis of sulfoxides **17-20**
rearrangement of dienes **18-32**
ring closure of trienes **18-27**
ring opening of cyclic alkenes **18-27**
sigmatropic carbon migration **18-30**
sigmatropic H migration **18-29**
vinyl halides + metals **10-56**
vinyl halides + RM (other metals) **10-59**
vinyl-X + vinyl-M **12-15**

DIESTERS
active methylene compounds + alkyl halides **10-67**
alkenes + acyloxy salts **15-56**
alkylation reactions **10-67**
arylation **13-14**
dimerization of acetals **10-64**

DIHALIDES (GEMINAL)
alkenes + halogenating agents **16-23**
ketones + halogenating agents **16-23**

DIHALIDES
alkynes + HX **15-02**
dihalogenation of alkenes **15-39**
from alkyl halides + trihalides **10-57**

DIIMIDES
isocyanates + phosphine oxides **16-93**

DIKETONES
acyl halides + active H compounds **16-84**
acylation of enamines **10-69**
alkylation reactions **10-67**
arylation **13-14**
by Michael addition **15-24**
conjugate addition of acyl halides **15-32**
conjugate addition of RM with metal carbonyls **15-32**
conjugated ketones + metals **10-56**
coupling acyl halides **16-83**
dimerization of silyl enol ethers **19-33**
esters + ketones **16-86**
from dithioketals **16-86**
hydrolysis of furans **10-06**
ketones + diazoketones **12-21**
oxidation of alkynes **19-26**
oxidation of methylene **19-17**
oxidative cleavage of cyclic alkenes **19-10**

DIKETONES, CONJUGATED
by the Knoevenagel reaction **16-38**

DINITRILES
alkylation reactions **10-67**
arylation **13-14**

DIOLS
alkenes + formaldehyde **16-54**
alkenes + halogens + metal carboxylates **15-48**
by the Tollens reaction **16-43**
dihydroxylation of alkenes **15-48**
from halo-esters **15-48**
hydride shifts of epoxides **18-41**
hydrolysis of epoxides **10-07**
ketones + formaldehyde **16-43**
oxidation of aromatic compounds **15-49**
pinacol coupling **19-76**
reduction of lactones **19-38**
reductive coupling of aldehydes or ketones **19-76**

DISULFIDES
aryl halides + sulfides **13-04**
from alkyl halides **10-27**
oxidation of thiols **19-34**
reduction of sulfonyl halides **19-71**

DITHIOACETALS
aldehydes + thiols **16-11**
from dihalides **10-26**

DITHIOCARBAMATES
amines + carbon disulfide **16-22**

DITHIOKETALS
alkylation of dithioketals **10-71**
from dithioketals **10-13**
from dithiols **10-13**
ketones + CS_2 **16-42**
ketones + thiols **16-11**
vinyl sulfides + thiols **15-07**

DITHIOLS
alkenes + sulfur reagents **15-51**

DIYNES
by Cadiot–Chodkiewicz coupling **14-16**
by Glaser coupling **14-16**
by Sonogashira coupling **14-16**
from alkynyl boronates **14-16**
metal coupling of alkynes **13-13**
metal coupling of alkynes **14-16**

ENAMIDES
amines + vinyl halides **12-32**

ENAMINES
alkylation of enamines **10-71**
alkynes + amines **15-08**
from hydroxy-amines **16-13**

ENOL ETHERS: See vinyl ethers

ENOLS
and keto–enol tautomerism **12-03**

EPISULFIDES: See thiiranes

EPOXIDES (Oxiranes)
aldehydes or ketones + haloorganometallics **16-24**
diazonium compounds + aldehydes or ketones **16-46**
epoxidation of alkenes **15-50**
from halohydrins **10-09**
ketones + alkenes **16-95**
sulfur ylids + aldehydes or ketones **16-46**

EPOXY ALCOHOLS
allylic alcohols + peroxides **15-50**
from epoxy alcohols **10-14**

EPOXY AMIDES
epoxidation of conjugated esters **15-50**

EPOXY CARBOXYLIC ACIDS
epoxidation of conjugated acids **15-50**

EPOXY ESTERS
diazo esters + aldehydes **15-64**
epoxidation of conjugated esters **15-50**
halo esters + aldehydes or ketones **16-40**

EPOXY KETONES
epoxidation of conjugated ketones **15-50**

EPOXY NITRILES
epoxidation of conjugated nitriles **15-50**

ESTER AMIDES
isonitriles + carboxylic acids + aldehydes **16-98**
isonitriles + carboxylic acids + ketones **16-98**

ESTER SULFIDES
by the Pummerer rearrangement **19-83**
rearrangement of sulfoxides **19-83**

ESTERS: See Carboxylic Esters

ESTERS, INORGANIC
from alcohols **10-22**
from sulfonyl halides **10-22**
phosphites + alkyl halides **16-44**

ESTERS, SULFONIC (see SULFONATE)

ETHER AMINES
rearrangement of halo-amines **18-18**

ETHER ESTERS
conjugated esters + alcohols **15-05**

ETHER KETONES
acetals + vinyl ethers **10-64**
oxidation of methylene **19-15**

ETHERS
acyl peroxides + alkyl organometallics **12-26**
alcohols + diazo compounds **10-11**
alcohols + ethers **10-13**
alcohols + onium salts **10-15**

alcohols + sulfonate esters **10-10**
aldehydes + alcohols **16-07**
alkenes + alcohols **15-05**
alkenes-alkoxymercuration **15-05**
alkylation of ethers **10-71**
aryl halides + alkoxides **13-03**
cleavage of oxonium salts **10-49**
coupling of silanes **14-15**
dehydration of alcohols **10-12**
from alcohols (Williamson ether synthesis) **10-08**
from alcohols + phenols **10-12**
from alcohols **14-06**
from alkyl halides (Williamson ether synthesis) **10-08**
from alkyl halides **10-10**
from alkyl sulfates **10-10**
from carboxylic esters **10-10**
from dihalides **10-10**
from ethers **10-13**
from haloethers **10-08**
from halohydrins **10-09**
from lactones and organometallics **16-30**
from phenols **13-33**
from trichloroimidates **10-10**
ketones + alcohols **16-07**
Michael addition with O nucleophiles **15-31**
Organometallics + peroxides **12-26**
oxidative cyclization of alcohols **14-06**
phenols + diazo compounds **10-11**
rearrangement of aryl sulfones **13-33**
reduction of esters **19-62**
reduction of lactones **19-62**
reductive cleavage of acetals or ketals **19-56**
Smiles rearrangement **13-33**
transetherification **10-13**

ETHERS, SILYL
Brook rearrangement **18-44**
cleavage of ethers **10-49**
from alcohols and silyl halides **10-08**
rearrangement of hydroxy-silanes **18-44**

FORMAMIDES
amines + trihalides **10-40**

GLYCIDIC ESTERS: See epoxy esters

HALIDES, ACYL
acyl halides + HF **16-80**
aldehydes + halogens **14-04**
anhydrides + HF **16-80**
carboxyl acids + halogenating agents **16-79**
oxidation of primary alcohols **19-22**

HALIDES, ALKYL
alcohols + HX **10-48**
alcohols + inorganic acid halides **10-48**
aldehydes + halo-boranes **16-23**
alkanes + halogenating reagents **14-01**
alkenes + alkyl halides **15-46**
alkenes + halogenating agents **14-03**
alkenes + HX **15-02**
carboxylate salts + halogens **14-30**
cleavage of amides **10-53**
cleavage of amines **10-53**
cleavage of ethers **10-49**
cleavage of oxonium salts **10-49**
from alcohols **10-48**
from aldehydes + aromatics **10-14**
from alkyl halides **10-46**
from amines **10-53**
from esters **10-51**
from inorganic esters **10-47**
from silyl ethers **10-48**
from sulfonate esters **10-47**
halide exchange with alkyl halides **10-46**
halo-decarboxylation of acids **16-71**
halogens + alkyl organometallics **12-31**
halogens + boranes **12-31**
halo-methylation of arenes **11-14**
Hunsdiecker reaction **14-30**

HALIDES, ALLYLIC
alkanes + halo-succinimides **14-03**
alkenes + halogens **14-03**

HALIDES, ARYL
aromatic compounds + halogen **11-10**
aromatic compounds + halo-succinimides **11-10**
aryl ammonium salts + halide ion **11-32**
aryl halides + halogenating agent **13-07**

aryldiazonium salts + metal halides **14-20**
aryldiazonium salts + metal iodides **13-22**
by Sandmeyer reaction **14-20**
from aryl amines **14-20**
from phenols **13-22**
heating aryldiazonium tetrafluoroborates **13-23**
phenols + phosphonium halides **13-07**
rearrangement of *N*-haloamides **11-31**
sulfonyl halides + transition metal halides **11-38**

HALIDES, Silyl
From silanes **14-02**

HALIDES, SULFONYL
alkanes + SO_2 + halogens **14-10**
aromatic compounds + sulfonyl halides **11-08**
aryldiazonium salts + sulfur dioxide **14-22**
sulfonic acids + halogenating agents **16-103**

HALIDES, VINYL
elimination of dihalides **17-22**
elimination of halides (by base) **17-13**
from aldehydes or ketones **11-23**
from alkynes **12-31**
halide exchange with vinyl halides **10-46**
halogens + vinyl boranes **12-31**
halogens + vinyl-M (M = a metal) **12-31**

HALOALCOHOLS (Halohydrins)
cleavage of cyclic ethers **10-49**
from aldehydes or ketones **16-24**

from alkenes **15-40**

HALOALDEHYDES
aldehydes + halogen **12-04**
aldehydes + halogenating agent **12-04**
alkenes + formamides **15-47**

HALOALKYNES
from alkynes **12-31**

HALOAMIDES
from amides **12-53**
from aziridines **10-50**

HALOAMINES
alkenes + *N*-haloamines **15-43**
from amines **12-52**

HALOAZIDES
alkenes + X-N_3 **15-45**

HALOCARBOXYLIC ACIDS
carboxylic acid + halogen **12-05**
carboxylic acid + halogenating agents **12-05**
from amino acids **10-52**

HALOESTERS
from epoxides **10-50**

HALOETHERS
from alkene-alcohols **15-51**

HALOKETONES
alkenes + acyl halides **15-47**
from diazoketones **10-52**
from enol borinates **12-04**
ketone + halogen **12-04**
ketone + halogenating agents **12-04**

HALOLACTAMS
halolactamization **15-41**

HALOLACTONES
halolactonization **15-41**

HALONITRO COMPOUNDS
alkenes + NOX **15-44**

HALONITROSO COMPOUNDS
alkenes + NOX **15-44**

HALOSILANES
from silanes **10-16**
silanes + halogens **14-02**

HALOSULFONES
sulfones + halogenation agents **12-06**

HALOSULFOXIDES
sulfoxides + halogenating agents **12-06**

HALOHYDRINS
alkenes + alcohols + halogens **15-40**
alkenes + hypohalous acids **15-40**
from epoxides **10-50**

HETEROCYCLES
acylation of amines **16-77**
aromatization of six-membered rings **19-01**
by [3 + 2]-cycloaddition **15-58**
by the heteroatom Diels–Alder reaction **15-61**
by the Paterno–Büchi reaction **15-63**
condensation of aldehydes **16-92**
cyclization of amino-ketones or aldehydes **16-13**
cyclization of haloamines **18-40**
dehydrogenation reactions **19-02**
dinitriles + ammonia or amines **16-21**
rearrangement of acyl aziridines **18-31**
thermal rearrangement of azides **18-14**
furans: from diketones **16-05**
indoles: Fischer indole synthesis **18-34**
oxetanes: alkenes + aldehydes or ketones **16-95**
oxetanes: Paterno–Büchi reaction **16-95**
oxetanes: alkenes + ketones **15-63**
pyrans: from diketones **16-05**
pyrazoles: hydrazines + diketones **16-14**
pyrazolines: alkenes + diazoalkanes **15-58**
pyrazolines: hydrazines + keto-esters **16-14**
pyridine derivatives: by the heteroatom Diels–Alder reaction **15-61**
pyrrazolidines: alkenes + azomethine imines **15-58**
pyrrolidines: cleavage of aziridines **15-58**
pyrrolines: rearrangement of cyclopropyl imines **18-31**
quinolines (dihydro): cyclodehydration of imines **11-13**
quinolines (dihydro): from amines **11-13**
quinolines (tetrahydro): cyclodehydration of amides **11-13**
quinolines (tetrahydro): from amines **11-13**

HYDRATES
from ketones or aldehydes **16-01**

HYDRAZIDES
Imides + hydrazine **10-41**
carboxylic esters + hydrazine **16-75**

HYDRAZINES
reduction of azo compounds **19-51**
reduction of diazo compounds **19-51**

HYDRAZONES
active methylene compounds + aryldiazonium **12-07**
exchange of hydrazine + hydrazones **16-14**
from azo compounds **12-07**
from ketones **12-07**
hydrazines + aldehydes or ketones **16-14**

HYDROXAMIC ACIDS
carboxylic esters + hydroxylamine **16-75**

HYDROXY-ALDEHYDES
aldol condensation **16-34**
dihydrooxazines + epoxides **10-72**
imines + ketones **16-34**
Mukaiyama aldol **16-35**
oxidation of epoxides **19-20**
silyl enol ethers + aldehydes **16-35**

HYDROXY-AMIDES
aldehydes + amides **16-18**
alkenes + amides **15-52**
alkenes + sulfonyl amines **15-52**

HYDROXY-AMINES: See amino alcohols

HYDROXY-AZIRIDINES
from amino epoxides **10-36**

HYDROXY-CARBOXYLIC ACIDS
by the Cannizzaro reaction **19-81**
rearrangement of 1,2-diketones **18-06**

HYDROXY-ESTERS
Baylis–Hillman reaction **16-27**

Claisen condensation **16-36**
epoxides + carboxylate anions **10-14**
from epoxides and RCOOH **10-18**
Reformatsky reaction **16-28**
transesterification of lactones **16-64**

HYDROXY-ETHERS
epoxides + alcohols **10-14**

HYDROXY-KETONES
acyloin condensation **19-78**
aldehydes + cyanide **16-55**
aldehydes and cyanide **15-32**
Baylis–Hillman reaction **16-27**
by aldol condensation **16-34**
by rearrangement of hydroxy ketones **18-04**
by the Tollens reaction **16-43**
coupling of carboxylic esters **19-78**
hydrolysis of diazo ketones **10-05**
ketones + formaldehyde **16-43**
Mukaiyama aldol **16-35**
oxidation epoxides **19-20**
oxidation of methylene **19-15**
photolysis of epoxy ketones **10-07**
rearrangement of silyloxy epoxides **18-02**
reduction of epoxy ketones **19-35**
silyl enol ethers + ketones **16-35**

HYDROXY-NITRILES: See cyanohydrins

HYDROXY-NITRO COMPOUNDS
from epoxides **10-35**
Henry reaction **16-37**

HYDROXY-PHOSPHONATES
phosphonate esters + carbonyl compounds **16-44**

HYDROXY-PHOSPHORAMIDES
phosphoramides + carbonyl compounds **16-44**

HYDROXY-THIOCYANATES
epoxides + thiocyanate **10-14**

HYDROXY-THIOETHERS
alkenes + disulfides + carboxylic acids **15-51**
Claisen condensation **16-36**
from epoxides **10-26**

HYDROXYLAMINES
addition of organometallics to oximes **16-31**
oxidation of amines **19-27**
rearrangement of amine oxides **18-21**
reduction of nitro compounds **19-46**

IMIDES
acylation of amines **16-77**
alkyl halides + imides **10-41**
anhydrides + ammonia or amines **16-73**
from alcohols **10-41**
from aryl acyl isothiocyanates **11-21**
isocyanates + phosphine oxides **16-93**

IMIDINES
dinitriles + ammonia or amines **16-21**

IMINES
active methylene compound + nitroso compound **12-08**
addition of organometallics to nitriles **16-33**
aldehydes + amines or ammonia **16-13**
alkynes + amines **15-08**
dehydrogenation of amines **19-05**
from imines + RMgX **10-69**
ketones + amines or ammonia **16-13**
oxidation of primary amines **19-21**
rearrangement of cyclopropyl **18-31**
reductive alkylation of aldehydes or ketones **16-17**
thermal rearrangement of alkyl azides **18-14**
via Bischler–Napieralski reaction **10-13**

IMINO ESTERS
haloimines + aroxides **18-42**

ISOCYANATES
amides + hypohalites **18-13**
amines + CO **12-53**
base induced rearrangement of hydroxamic acids **18-15**
carboxylic acids + HN_3 **18-16**

Curtius rearrangement **18-14**
from acyl halides **10-44**
from alkyl halides **10-44**
from nitrile oxides **18-44**
Hofmann rearrangement **18-13**
phosgene + amines **16-72**
the Schmidt reaction **18-16**
thermal rearrangement of acyl azides **18-14**

ISONITRILES (ISOCYANIDES)
alkyl halides + cyanide **10-75**
amines + trihalides **10-40**
dehydration of formamides **17-31**
from oxetanes **10-40**

ISOTHIOCYANATES
from acyl halides **10-44**
from alkyl halides **10-44**

ISOTHIOURONIUM SALTS
from alkyl halides **10-25**

KETALS
ketals + RM **10-64**
ketones + alcohols **16-05**
reductive cleavage of ortho esters **19-56**

KETENES
base-induced elimination of acyl halides **17-14**
dehydration of carboxylic acids **17-01**
elimination of haloacyl halides **17-23**

KETENIMINES
by the Wittig reaction **16-44**
dehydration of amides **17-01**

KETO-ALDEHYDES
ketals + formamides **12-16**

KETO-ALKYNES
elimination of epoxy-hydrazones **17-27**

KETO-AMIDES
alkenes + acyloxy salts + nitriles **15-56**
amino acids + anhydrides **12-42**

KETO-CARBOXYLIC ACIDS
active H compounds + CO_2 or CS_2 **16-42**
carboxylic acids + esters **16-87**

KETO-ESTERS
acyl halides + active H compounds **16-84**
aldehydes + diazoketones **12-18**
alkenes + acyloxy salts **15-56**
alkylation reactions **10-67**
Claisen condensation **16-85**
haloesters + esters **16-28**
haloesters + nitriles **16-28**

KETO-ESTERS, CONJUGATED
by the Knoevenagel reaction **16-38**

KETO-NITRILES
acyl halides + active H compounds **16-84**
by the Thorpe reaction **16-50**
condensation of nitriles **16-50**
esters + nitriles **16-86**
from ketones **12-19**

KETO-SULFIDES
Ketones + disulfides **12-14**

KETO-SULFONES
acyl halides + active H compounds **16-84**

KETO-SULFONIC ACIDS
ketones + sulfur trioxide **12-14**

KETONES
acyl halides + aromatic compounds **11-17**
acyl halides + organometallic compounds **16-81**
addition of organometallics to nitriles **16-33**
aldehydes + alkenes **15-34**
aldehydes + boranes **12-18**
aldehydes + heterocycles **14-19**
aldehydes + transition metal complexes **12-18**
alkenes + aldehydes **15-34**
alkenes + alkenes + CO **15-36**
alkenes + ketones **15-33**
alkyl halides + organoiron compounds **10-76**

alkylation of enamines **10-69**
alkylation of hydrazones **10-68**
alkylation of ketones **10-68**
alkylation reactions **10-67**
amines + HONO **12-50**
and keto–enol tautomerism **12-03**
aromatic compounds + acyl halides **11-17**
aromatic compounds + aldehydes **14-19**
aromatic compounds + anhydrides **11-17**
aromatic compounds + carboxylic acids **11-17**
aromatic compounds + nitriles **11-24**
aryl diazonium salts + oximes **14-23**
arylation of ketones **13-14**
arylation **13-14**
by cleavage of alkoxides **12-41**
by decarboxylation **12-40**
by Michael addition **15-24**
carbonyl transposition **12-14**
carbonylation of metal alkyls **13-15**
carboxylic acids + organolithium reagents **16-29**
cleavage of diketones **12-43**
conjugate addition of alkyl halides **15-28**
conjugate addition of allylic slanes **15-26**
conjugate addition of boranes **15-27**
conjugate addition of boranes **15-27**
conjugate addition of organometallics **15-25**
cyanoboranes + anhydrides **18-23**
decarboxylative alkylation **14-31**
decarboxylative coupling of 2 acids **16-90**
diazo ketones + boranes **10-73**
elimination (1,3) of halo-amines **17-25**
elimination (1,3) of diols **17-25**
elimination (1,3) of halohydrins **17-25**
Friedel–Crafts acylation **11-17**
Fries rearrangement **11-27**
from aldehydes **12-18**
from alkyl halides **10-76**
from anhydrides **11-17**
from aryl halides **13-15**
from boranes **10-73**
from cyanohydrins **10-68**
from diazoketones **10-73**
from dihaloalkenes **10-02**
from dihydrooxazines **10-72**
from dithianes **10-71**
from dithioketals **10-06**
from dithioketals **16-11**
from enamines **10-69**
from halo-ketones **10-73**
from imines **10-69**
from ketones **10-68**
from keto-sulfoxides **10-67**
from nitriles **11-24**
from organometallics **12-33**
haloketones + boranes **10-73**
homologation of ketones **18-09**
hydration of alkynes **15-04**
hydration of allenes **15-04**
hydrolysis of C=N compounds **16-02**
hydrolysis of dithioketals **10-06**
hydrolysis of dithioketals **10-71**
hydrolysis of enol ethers **10-06**
hydrolysis of furans **10-06**
hydrolysis of *gem*-dihalides **10-02**
hydrolysis of imines **16-33**
hydrolysis of ketals **10-05**
hydrolysis of nitro compounds **16-03**
hydrolysis of orthoesters **10-06**
hydrolysis of vinyl ethers **10-06**
hydrolysis of vinyl halides **10-01**
imines + RM **10-69**
insertion of diazo ketones **12-21**
ketenes + alkenes **15-63**
keto esters + alkyl halides **10-67**
ketones + diazomethane **18-09**
Nef reaction **16-03**
oxidation alkenes **19-25**
oxidation of alcohols **19-03**
oxidation of dicarboxylic acids **19-13**
oxidation of methylene **19-17**
oxidation of nitro compounds **19-21**
oxidation of primary amines **19-21**
oxidation of vinyl boranes **18-26**
oxidative cleavage of alkenes **19-10**
oxidative cleavage of diols **19-07**
oxidative cleavage of enamines **19-10**
ozonolysis of alkenes **19-09**
pinacol rearrangement **18-02**
pyrolysis of hydroxy-alkenes **17-32**
radical addition to conjugated ketones **15-28**
rearrangement of aryl esters **11-27**
rearrangement of diols **18-02**

rearrangement of epoxides **18-02**
rearrangement of ketones **18-04**
rearrangement of peroxides **18-20**
ring expansion of amino alcohols **18-03**
ring expansion of halohydrins **18-03**
Sakurai reaction **15-26**
silyl enol ethers + alkyl halides **10-68**
tautomerization of enols **12-03**
transesterification of vinyl esters **16-64**
transition metal carbonyls + RM (M = metal) **12-33**
Wacker process **19-25**
Weinreb amides + organometallic compounds **16-82**

KETONES, CONJUGATED
aldol condensation **16-34**
alkenes + acyl halides **12-16**
carbonylation of vinyl-M (M = metal) **12-33**
coupling of dienones **15-20**
oxidation of methylene **19-17**
Pauson–Khand reaction **15-36**

LACTAMS
alkyl halides from amides **10-41**
and Michael addition **15-31**
by Beckmann rearrangement **18-17**
cyclic ketones + HN_3 **18-16**
cyclic ketones + silyl azides **18-16**
from amino carboxylic acids **16-74**
from haloamides **10-41**
lactams + amines **16-76**
lactones + ammonia or amines **16-75**
N-arylation **10-41**
N-vinylation **10-41**
oxidation of methylene in amines **19-17**
rearrangement of oximes **18-17**
reduction of imides **19-64**
Schmidt reaction **18-16**

LACTAMS, β
diazo-[2 + 2]-cycloaddition **15-63**
enamines + ketenimines **16-96**
ketenes + C=N compounds **16-96**
ketones + C=N compounds **16-96**
rearrangement of hydroxy-haloamines **18-18**

LACTONES
alkenes + carboxylic acids **15-57**
and Michael addition **15-31**
Baeyer–Villiger rearrangement **18-19**
condensation of dialdehydes **19-81**
cyclization of allene carboxylic acids **15-06**
from halocarboxylic acids **10-17**
from hydroxy-carboxylic acids **16-63**
oxidation of methylene in ethers **19-17**
photolysis of halo-amides **18-40**
rearrangement of cyclic ketones **18-19**
rearrangement of lactones **18-44**
reduction of anhydrides **19-63**

LACTONES, β
ketones + aldehydes or ketones **16-95**

NITRATES: See inorganic esters

NITRILES
aldehydes + hydroxylamines **16-16**
alkenes + HCN **15-38**
alkyl halides + cyanide **10-75**
aromatic compounds + trihalo nitriles **11-25**
aryl diazonium salts and metal cyanides **14-20**
aryl halides + metal cyanides **13-08**
aryl triflates + metal cyanides **11-25**
by decarboxylation **12-40**
by Sandmeyer reaction **14-20**
carboxylic acids + cyanogen halides **16-94**
cyanation α to active hydrogen compounds **12-19**
cyanation α to nitrogen **12-19**
cyanoborates + metal cyanide **12-34**
dehydration of amides **17-30**
dehydration of oximes **17-29**
dehydrogenation of amines **19-05**
elimination (base) of hydrazones **17-29**
from iminium salts **11-25**
from aldehydes **17-29**
from alkyl halides **10-75**
metal cyanides + alkyl organometallics **12-34**
metal cyanides + aryl organometallics **13-08**

Michael addition **15-24**
oxidation of hydrazones **19-06**
rearrangement of isonitriles **18-21**
reduction of nitro compounds **19-49**

NITRILES, CONJUGATED
by the Knoevenagel reaction **16-38**

NITRITES: See inorganic esters

NITRO COMPOUNDS
alkanes + alkyl nitrates **12-09**
alkanes + nitronium salts **12-09**
alkenes + nitric acid **12-09**
aryldiazonium salts + metal nitrites **14-21**
by Michael addition **15-24**
from alcohols **10-42**
from alkyl halides **10-42**
from aromatics **11-02**
from aromatics **14-20**
from conjugated carboxylic acids **14-13**
nitration of aromatic rings **11-02**
oxidation of amines **19-28**
oxidation of isocyanates **19-28**
oxidation of oximes **19-28**
rearrangement of nitroamines **11-28**

NITROALCOHOLS: See hydroxy-nitro compounds

NITRONES
from oximes **10-24**
oxidation of hydroxylamines **19-06**

NITROSO COMPOUNDS
Barton reaction **18-40**
from active methylene compounds **12-08**
nitrosation of aromatic rings **11-03**
oxidation of amines **19-27**
rearrangement of nitroso-amines **11-29**

NITROSOAMINES
amines + HONO **12-50**

ORGANOMETALLICS
alkanes + alkyl organometallics **12-22**
alkanes + metals **12-23**
alkenes + alkyl organometallics **15-21**
alkenes + metal hydrides **15-17**
alkyl halides + alkyl organometallics **12-39**
alkyl halides + metals **12-38**
alkynes + metal hydrides **15-17**
aryl halides + metals **11-40**
aryl halides + R-M (M = a metal) **11-40**
formation of enolate anions **12-23**
isonitriles + organolithium reagents **16-99**
metal halides + RM (where M = metals) **12-36**
metalation of aromatic compounds **13-17**
metals + RM (where M = metals) **12-35**
thioethers + organometallics **14-28**
transmetalation **12-35–12-37**

ORTHO ESTERS
by transetherification **10-13**
carboxylic acids + alcohols **16-05**
from trihalides **10-08**

OSAZONES
hydrazines + hydroxy aldehydes or ketones **16-14**

OXIMES
alcohols + NOCl **18-40**
aldehydes or ketones + hydroxylamine **16-15**
alkenes + NOX **15-44**
aryldiazonium salts + oximes **14-23**
Barton rearrangement **18-40**
carbonyl compounds + nitrous acid **12-08**
O-alkylation of oximes **10-24**
reduction of nitro compounds **19-49**

OXONIUM SALTS
alkyl halides + ethers **10-20**

OXIRANES: See Epoxides

PEROXIDES
acid halides + alkyl hydroperoxides **10-21**
acid halides + hydrogen peroxide **10-21**
alkanes + oxygen **14-07**
alkanes + peroxides **14-08**
alkenes + oxygen **15-62**
alkyl halides + hydroperoxide anion **10-21**

alkyl halides + hydroperoxide anion **10-21**
anhydrides + hydrogen peroxide **10-21**
dienes + oxygen **15-62**
from organometallics **12-29**
oxidation of carboxylic acids **19-24**
oxygen + alkyl organometallics **12-25**
oxygen + organoboranes **12-25**
photooxidation of dienes **15-62**

PHENOLS
aromatic compounds + peroxides **14-05**
aromatic compounds + peroxyacids **11-26**
aryl halides + hydroxide **13-01**
aryl sulfonic acids + hydroxide **13-02**
aryldiazonium salts + water **13-20**
Claisen rearrangement **18-33**
Fries rearrangement **11-27**
oxidation of aromatic compounds **11-26**
oxidation of aryl borates **13-01**
oxidation of arylboronic acids **13-01**
rearrangement of allyl aryl ethers **18-33**
rearrangement of aryl esters **11-27**
rearrangement of aryl hydroxylamines **13-32**
rearrangement of dienones **18-05**
Wallach rearrangement **18-43**

PHOSPHINES
alkenes + phosphines **15-08**
phosphines + aryl halides **13-05**
reduction of phosphine oxides **19-68**

PHOSPHONATE ESTERS: See inorganic esters

PHOSPHONIUM SALTS
alkyl halides + amines **10-31**
phosphines + ammonium salts **10-31**

PHOSPHORANES
and the Wittig reaction **16-43**

QUINONES
dyotropic rearrangement **18-44**
oxidation of aromatic compounds **19-04**
oxidation of aromatic compounds **19-19**
oxidation of phenols **19-04**

SELENIDES
aryl halides + selenide **13-04**
from alkyl halides **10-26**

SELENOCARBONATES
from isocyanates **16-08**

SELENOETHER-ALDEHYDES
aldehyde + diselenide **12-14**

SELENOETHER-KETONES
ketone + diselenide **12-14**

SELENOXIDES
alkylation of selenoxides **10-71**

SILANES
addition of silanes to alkenes **15-19**
and dyotropic rearrangement **18-44**
aryl halides + silanes **13-16**
from metallated aryls **10-55**

SULFIDES: See Thioethers

SULFINIC ACIDS
RM (M = a metal) + sulfonating agents **12-30**

SULFONAMIDES
addition or arylboronates to C=N **16-31**
dealkylation of sulfonamides **19-73**
reduction of acyl sulfonamides **19-64**
reduction of sulfonyl azides **19-50**
sulfonyl halides + ammonia or amines **16-102**

SULFONATE ESTERS
alkenes + sulfonic acids **15-06**
from ethers **10-22**
sulfonamides + alcohols **16-101**
sulfonyl halides + alcohols **16-101**

SULFONES
alkenes + sulfonyl halides **15-42**
alkyl halides + sulfinic acid salts **10-29**
alkyl halides + sulfonyl halides **10-29**
alkylation of sulfones **10-67**
alkylation of sulfones **10-71**

and Michael addition **15-31**
aromatic compounds + sulfonic acids **11-09**
aromatic compounds + sulfonyl halides **11-09**
aryl halides + sulfonate **13-04**
oxidation of sulfoxides **19-31**
oxidation of thioethers **19-31**
sulfones + organometallics **10-61**
sulfonyl halides + arylboronic acids **16-105**
sulfonyl halides + organometallics **16-105**

SULFONIC ACIDS
aromatic compounds + sulfuric acid **11-07**
aromatic compounds + sulfuric acid **11-36**
aryl halides + sulfonates **13-04**
hydrolysis of sulfonyl halides **16-100**
oxidation of sulfur compounds **19-30**
oxidation of thiols **19-30**
rearrangement of aryl sulfones **13-33**
reduction of sulfonyl halides **16-104**
sulfonation of aromatic compounds **11-07**
sulfonation of aromatic compounds **11-36**
sulfonation of methylene **19-16**

SULFONIUM SALTS
alkyl halides + thioethers **10-26**

SULFONYL IMINES: See halides, sulfonyl

SULFONYL IMINES
sulfonamides + aldehydes **16-18**

SULFOXIDES
alkylation of sulfoxides **10-67**
aromatic compounds + sulfonyl halides **11-09**
oxidation of thioethers **19-31**

TELLURIDES
from alkyl halides **10-26**

THIIRANES (EPISULFIDES)
diazo compounds + sulfur **16-48**
alkenes + sulfur reagents **15-50**
from epoxides **10-26**
from halo-alcohols **10-09**
from halo-ketones **10-09**
thioketones + sulfur ylids **16-48**

THIOAMIDES
amides + sulfur reagents **16-11**
amides + sulfur reagents **16-70**
from nitriles **16-04**

THIOCARBAMATES
from isocyanates **16-08**
hydrolysis of thiocyanates **16-04**

THIOCARBOXYLIC ACIDS
acyl halides + sulfur reagents **16-69**

THIOCYANATES
aryl halides + thiocyanate **13-04**
aryldiazonium salts + thiocyanate **13-21**
from alkyl halides **10-30**
from alkenes **15-42**
from amines **10-30**

THIOESTERS
acyl halides + thiols **16-69**
esters + sulfur reagents **16-11**

THIOETHER-ALDEHYDES
aldehyde + disulfides **12-14**

THIOETHER-KETONES
enol ethers + disulfides **12-14**
ketone + disulfides **12-14**

THIOETHERS (SULFIDES)
alcohols + thiols **10-26**
alkenes + thiols **15-07**
alkyl halides + thiolate anions **10-26**
aromatic compounds + sulfones **11-23**
aryl halides + alkyl sulfides **13-04**
aryldiazonium salts + sulfide **13-21**
aryldiazonium salts + thiols **13-21**
from alcohols **10-26**
from alkyl halides **10-26**
from ammonium salts **10-26**
from dihalides **10-26**

from organometallics **12-30**
from phenols **11-23**
Michael addition with S-nucleophiles **15-31**
rearrangement of sulfonium salts **18-21**
reduction of sulfones **19-72**
reduction of sulfoxides **19-72**
sulfur + alkyl organometallics **12-30**
thiols + arylboronic acids **13-04**
thiomethylation of aromatics **11-23**
thiophenols + aromatic compounds **13-04**

THIOKETONES
ketones + sulfur reagents **16-11**

THIOLACTAMS
lactam + sulfur reagents **16-11**
lactone + sulfur reagents **16-11**

THIOLS
alkyl halides + hydrogen sulfide or HS^- **10-25**
aryl halides + sulfide **13-04**
aryldiazonium salts + H_2S **13-21**
from alcohols **10-25**
from Bunte salts **10-28**
hydrolysis of Bunte salts **10-28**
reduction of disulfides **19-75**
reduction of sulfonyl halides **19-71**
sulfur + alkyl organometallics **12-30**

THIOUREAS
amines + CS_2 **16-22**
isothiocyanates + amines **16-20**

TRIAZOLES
alkenes + alkyl halides **15-58**

TRIAZOLINES
alkenes + alkyl azides **15-58**

TRIENES
aromatic compounds + carbenes **15-64**
cycloaddition of dienes **15-66**
ring opening of cyclic dienes **18-27**

TRIHALIDES
acyl halides + halogenating agents **16-23**
cleavage of methyl ketones **12-44**

TRIOXANES
from aldehydes **16-92**

UREAS
amines + CO_2 **16-22**
isocyanates + amines **16-20**

VINYL ETHERS (including silyl enol ethers)
alcohol + alkyne **15-05**
alcohol + enol ester **10-13**
alcohol + enol ether **10-13**
by the Wittig reaction **16-44**
cleavage of acetals or ketones **17-02**
from aldehydes **12-17**
from enol esters or enol ethers **10-13**
from esters **16-45**
from ketones **12-17**
from phenols **10-08**
peroxides + vinyl-M (M = a metal) **12-26**
Petasis alkenylation **16-45**
Tebbe alkenylation **16-45**

VINYL PHOSPHINES
alkynes + phosphines **15-08**

VINYL SILANES
addition of silanes to alkynes **15-19**

VINYL SULFIDES
alkynes + thiols **15-07**
ketones + thiols **16-11**

VINYL SULFONES
alkynes + sulfonyl halides **15-42**
from sulfinic acid salts **10-29**

XANTHATES
carbon disulfide + alcohols **16-10**

AUTHOR INDEX

Note that only initials are used with each surname. Therefore, several different authors may be represented by a single entry. There are several authors named Smith, M.B., for example, and citations for all are listed after the single entry.

Entries in the index refer to chapter number (**boldface**) and reference number.

Aalbersberg, W.G.L. **17**-229
Aalten, H.L. **11**-654
Aamouche, A. **4**-115
Aaron, H.S. **1**-94, **3**-42
Aarts, G.H.M. **15**-12
Abad, A. **19**-128
Abaee, M.S. **19**-1726
Abarbri, M. **10**-1883, **12**-281, **12**-307
Abazi, S. **15**-1341
Abbadi, A. **16**-424
Abbas S. **19**-1320
Abbas, A.A. **3**-152
Abbasi-Ghadim, H. **19**-36
Abbassi, M. **19**-834
Abbiati, G. **15**-2633
Abbott, D.E. **10**-1258
Abbott, S.J. **4**-32
Abbotto, A. **5**-122, **5**-203
Abboud, J.L.M. **8**-245, **10**-879
Abboud, J.M. **2**-414, **3**-19, **8**-252, **10**-474
Abboud, K.A. **10**-1534, **15**-1613, **16**-825
Abdel-Hadi, M. **10**-1309
Abdel-Magid, A.F. **16**-340, **16**-1069, **19**-879, **19**-927
Abdel-Malik, M.M. **10**-306
Abdi, S.H.R. **15**-1979
Abduljaber, M.H. **10**-209
Abdulla, N.I. **18**-431
Abdulla, R.F. **10**-1684
Abe, H. **11**-325, **12**-529, **13**-145, **13**-159, **19**-1146
Abe, M. **14**-356, **15**-1926, **16**-2214
Abe, S. **10**-1878
Abe, T. **10**-479
Abe, Y. **10**-405
Abe, Y. **15**-223, **15**-1476
Abedi, V. **10**-956
Abel, E.W. **12**-287
Abela, A.R. **13**-494, **13**-495
Abele, E. **10**-796
Abell, A.D. **10**-1598, **16**-1400, **18**-850
Abell, C. **16**-1905
Abell, P.I. **15**-51, **15**-55, **15**-59
Abella, C.A.M. **11**-462
Abelman, M.M. **17**-174
Aben, R.W. **16**-2203
Abeywickrema, A.N. **13**-791, **13**-799
Abidi, S. **10**-1262
Abidi, S.L. **17**-327
Abiko, A. **16**-1030, **16**-1189, **16**-1373
Abiko, S. **18**-484
Abiraj, K. **19**-1140, **19**-1196, **19**-1720
Abis, L. **18**-202
Ablenas, F.J. **19**-1597
About-Jaudet, E. **19**-487
Abraham, L. **18**-436, **18**-703, **18**-738
Abraham, M.H. **3**-4. **3**-19, **4**-346, **8**-113, **8**-145, **8**-146, **10**-460, **10**-463, **10**-474, **10**-479, **12**-2, **12**-20, **12**-21, **12**-23, **12**-24, **12**-38, **12**-40, **12**-448, **12**-455, **12**-505, **12**-533, **12**-579
Abraham, R.J. **4**-296, **4**-326, **4**-345, **4**-358, **4**-397
Abraham, S. **10**-1003
Abraham, W. **2**-176
Abraham, W.D. **15**-1187, **18**-245
Abrahams, S.C. **1**-89
Abrahamson, E.W. **18**-511
Abrahamsson, P. **16**-1024
Abraitys, V.Y. **15**-2446
Abram, T.S. **5**-68
Abramov, A.I. **16**-1567
Abramovitch, A. **18**-481
Abramovitch, R.A. **5**-427, **5**-438, **5**-443, **11**-72, **13**-825, **14**-372
Abrams, S.R. **12**-76, **19**-714
Abreu, A.R. **15**-185
Abrunhosa-Thomas, I. **10**-922
Abu Bakar M.D. **16**-1507
Abu-Hasanayn, F. **5**-202
Abu-Omar, M.M. **15**-1898
Abu-Omar, M.M. **19**-980
Abu-Raqabah, A. **5**-298
Aburel, P.S. **15**-1036
Acemoglu, M. **15**-2155
Acerete, R. **19**-70
Acevedo, O. **13**-3, **17**-263
Achab, S. **19**-800
Achard, M. **15**-2674
Achard, T.J.R. **16**-1284, **16**-1285
Acharya, J. **10**-859
Achiwa, K. **15**-2105, **19**-1345
Achmatowicz Jr., O. **16**-1569
Achmatowicz, O. **15**-1018
Ackerman, J.H. **4**-529
Ackerman, J.J.H. **10**-1855
Ackermann, L. **15**-332, **15**-372, **15**-382, **18**-849
Acton, N. **4**-461
Adachi, K. **12**-178
Adachi, M. **10**-875, **11**-391, **11**-558, **11**-564
Adachi, S. **11**-314, **15**-1132, **16**-1173
Adair, G.R.A. **15**-530, **19**-116
Adak, A.K. **19**-620
Adak, L. **10**-1719, **14**-425
Adam, G. **10**-1079
Adam, J. **14**-206
Adam, M. **19**-1201

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.

© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

Adam, W. **5**-270, **7**-49, **7**-52, **7**-58, **11**-600, **12**-459, **14**-252, **15**-1029, **15**-1883, **15**-1888, **15**-1912, **15**-1916, **15**-1924, **15**-1927, **15**-1976, **15**-1980, **15**-1987, **15**-1994, **15**-1998, **15**-2002, **15**-2358, **15**-2362, **15**-2364, **15**-2366, **16**-1761, **16**-2210, **16**-2211, **17**-421, **17**-502, **18**-522, **18**-70, **18**-912, **19**-10, **19**-200, **19**-230, **19**-255, **19**-474, **19**-476, **19**-477, **19**-514
Adamo,† C. **13**-545
Adams, A.D. **19**-59
Adams, C. **19**-1001
Adams, C.M. **18**-805, **18**-963, **19**-975
Adams, D.B. **4**-36
Adams, D.G. **5**-178
Adams, D.J. **9**-120
Adams, D.L. appendixa-1
Adams, D.R. **16**-1545
Adams, H. **3**-75, **3**-85, **4**-385, **16**-1448
Adams, J. **3**-22, **15**-2505, **16**-1443
Adams, J.P. **10**-1783, **12**-269
Adams, J.S. **5**-313
Adams, J.T. **16**-2126
Adams, N.D. **16**-684
Adams, R. **4**-14, **4**-58, **4**-59, **16**-1991
Adams, R.D. **4**-540
Adams, R.M. **4**-101
Adams, W.R. **14**-250
Adamsky, F. **18**-596
Adapa, S.R. **14**-228, **15**-1067, **16**-73, **18**-384
Adarsh, N.N. **13**-495
Adcock, J.L. **10**-340, **14**-150
Adcock, W. **4**-353, **5**-96, **16**-1390
Addadi, L. **4**-104, **4**-195
Addess, K.J. **10**-1219
Addis, D. **17**-472, **17**-473, **19**-1161, **19**-1478
Adema, E.H. **11**-382
Ader, J.C. **10**-1060
Adeuya, A. **13**-53
Adewuyi, Y.G. **7**-89
Adger, B.M. **19**-1216
Adhikari, R.M. **2**-343
Adibi, H. **16**-72, **19**-247
Adickes, H.W. **10**-1846, **10**-1848, **10**-1849
Adimurthy, S. **11**-294
Adkins, H. **19**-1074
Adkins, J.D. **19**-1092
Adkins, S. **15**-1937
Adler, A. **15**-1064
Adler, E. **19**-261
Adlhart, C. **18**-891
Adlington, R.M. **17**-270, **18**-160, **18**-183
Adolfsson, H. **15**-615, **15**-1828, **15**-1848, **16**-553, **16**-824, **16**-829, **19**-1034
Adrian, F.J. **5**-229, **5**-297
Adrio, J. **10**-1309, **10**-1364, **12**-271, **15**-1537, **15**-1537, **15**-1540, **16**-794
Adude, R.N. **11**-209
Aebisher, D. **15**-159
Aechtner, T. **15**-2623
Aelterman, W. **19**-1314
Aeungmaitrepirom, W. **3**-141
Afanas'ev, I.B. **9**-61, **15**-65
Afanas'eva, L. **10**-1977
Affanasiev, V.V. **12**-552
Affandi, H. **10**-1083
Affo, W. **13**-465
Afonso, C.A.M. **9**-134, **10**-1220, **10**-1285, **15**-1807, **15**-1842, **16**-801
Agababyan, A.G. **16**-372, **16**-373
Agadzhanyan, Ts.E. **18**-948
Agam, G. **3**-204
Agami, C. **10**-1565, **16**-1120
Agapiou, K. **16**-713
Agarrabeitia, A.R. **18**-607
Agarwal, A. **19**-808
Agarwal, S. **19**-81, **19**-94
Agawa, T. **19**-1291
Agbaria, K. **3**-129
Agdeppa Jr., D.A. **18**-127
Agejas, J. **13**-118
Agenet, N. **15**-2588
Ager, D.J. **10**-1805. **12**-320, **13**-245, **14**-454, **16**-1289, **19**-1443
Aggarwal, V. **16**-498
Aggarwal, V.K. **4**-385, **12**-331, **12**-334, **15**-715, **15**-1002, **15**-1019, **15**-1091, **16**-763, **16**-792, **16**-794, **16**-988, **16**-1286, **16**-1382, **16**-1383, **16**-1386, **16**-1434, **16**-1448, **16**-1450, **16**-1452, **18**-259
Aggen, D.H. **16**-154
Aghapoor, G. **17**-468
Aghapoor, K. **19**-130
Aghapour, G. **10**-1176, **18**-697
Aghvami, M. **10**-873
AgirBas H. **5**-344
Agmon, N. **8**-155
Agnihotri, R.K. **15**-581
Agostinho, M. **15**-1104
Agrahari, A. **16**-1751
Agranat, A. **2**-205, **2**-401, **4**-194
Agranat, I. **11**-465
Aguero, A. **16**-1426
Aguiar, L.C.S. **13**-379, **13**-497
Aguinaldo, G.T. **18**-861
Aguirre, S. **11**-324, **15**-2622
Agwada, V.C. **16**-351
Agwaramgbo, E.L.O. **16**-1290
Ahamed, M. **19**-128
Ahern, M.F. **13**-776
Ahlberg, P. **3**-63, **6**-66, **8**-226, **17**-53, **17**-153, **18**-9
Ahlbrecht, H. **10**-1828, **10**-1842
Ahlquist M. **15**-906
Ahmad, M. **10**-766
Ahmad, S. **12**-326, **16**-1720, **16**-1834, **18**-756
Ahmad, T. **12**-491
Ahmadi, N. **10**-968
Åhman, J. **5**-85, **10**-1739, **13**-663, **18**-450, **18**-580
Ahmberg, C.H. **14**-450, **19**-1576
Ahmed, E.A.A. **10**-360, **18**-439
Ahmed, G. **15**-1933, **15**-2140
Ahmed, M. **16**-278, **16**-329, **18**-871, **19**-1504
Ahmed, M.S.M. **13**-697
Ahmed, Z. **16**-676
Ahn, C. **10**-727, **13**-718, **19**-543
Ahn, H. **16**-563
Ahn, J.H. **10**-1235, **16**-537, **19**-1286
Ahn, K.H. **15**-1035, **15**-974, **15**-1410, **15**-1989, **16**-2089, **19**-778
Ahn, R.W. **19**-1144
Ahn, W.-S. **13**-401
Ahn, Y. **16**-2070, **19**-1151
Ahn, Y.M. **18**-856
Ahola, C.J. **4**-515
Ahonen, M. **16**-685
Ahr, M. **13**-343
Ahramjian, L. **16**-1272
Ahrendt, K.A. **15**-2236
Ahrens, A.F. **10**-365
Ahrens, M.J. **13**-224
Ai, T. **16**-958
Aida, T. **10**-829, **15**-929, **15**-1990
Aidhen, I.S. **16**-2074
Aihara, H. **15**-911
Aihara, J. **2**-6, **2**-113, **2**-171, **2**-380
Aihara, J-i. **2**-29, **2**-343
Aihara, M. **10**-1098
Aikawa, K. **4**-64, **15**-1025, **16**-716
Aikawa, T. **11**-329
Ainslie, R.D. **12**-582
Ainsworth, C. **16**-2155, **19**-1711
Aires-de-Sousa, J. **15**-2051
Aïssa, C. **18**-168, **18**-243
Aitken, E.J. **8**-251
Aitken, R.A. **17**-266, **17**-267, **17**-268
Aït-Mohand, S. **16**-717
Aizman, A. **10**-37
Aizman, A. **10**-95
Aizpurua, J.M. **10**-1208, **16**-351, **16**-831
Ajami, D. **2**-374, **19**-130, **19**-248, **19**-249, **19**-72
Ajamian, A. **15**-866
Ajiki, K. **19**-831
Ajjou, A.N. **19**-145, **19**-146, **19**-571
Akaba, R. **19**-355

Akabori, S. **7**-62, **10**-521, **19**-1465
Akagawa, K. **16**-1085
Akai, S. **18**-274
Akakura, M. **19**-206
Akamanchi, K.G. **10**-1128, **16**-311, **16**-1983, **17**-470
Akana, J.A. **15**-1648
Akanksha **15**-1439
Akao, H. **4**-108
Akasaka, M. **18**-736
Akasaka, T. **19**-810, **19**-1584
Akashi, K. **15**-1799, **19**-80
Akashi, M. **15**-2639
Akazome, M. **19**-1238
Akehi, M. **10**-663
Akelah, A. **16**-1930
Akelah, A. **16**-1930
Åkermark, B. **10**-1580, **13**-423, **13**-427, **14**-274, **15**-341
Akhbari, M. **13**-99
Akhlaghinia, B. **10**-734, **10**-1951
Akhmatdinov, R.T. **5**-53, **10**-559
Akhmedov, N.G. **16**-2107
Akhmetova, N.E. **17**-310
Akhrem, A.A. **15**-565, **18**-560, **18**-592
Akhrem, I. **10**-1977, **14**-160
Akiba, K. **16**-571
Akiba, M. **15**-1712
Akiike, J. **19**-532
Akila, S. **11**-500
Akimoto, Y. **16**-806
Akine, S. **3**-140
Akita, M. **10**-712
Akiyama, K. **5**-337, **10**-1450, **15**-1025
Akiyama, M. **19**-1371
Akiyama, R. **10**-1672, **15**-443, **15**-1845, **16**-912
Akiyama, S. **2**-330, **2**-357, **19**-60
Akiyama, T. **8**-5, **15**-2349, **15**-2601, **16**-390, **16**-400, **16**-907, **16**-912, **16**-1164
Akiyama, Y. **16**-1965
Akiyoshi, K. **10**-1738
Akkerman, O.S. **12**-596, **12**-612, **12**-614, **12**-633, **12**-642
Akritopoulou, I. **16**-1418
Aksenov, A.V. **11**-548
Aksenov, N.A. **11**-548
Aksenov, V.S. **10**-332
Aksenova, I.V. **11**-548
Aksnes, G. **16**-1398, **17**-125
Akula, M.R. **13**-800, **19**-1485
Akutagawa, K. **15**-987
Akutagawa, S. **14**-268, **19**-1015, **19**-1016
Akutsu, K. **19**-1749
Al Jihad, I. **8**-214
Al Neirabeyeh, M. **19**-688
Alabugin, I.V. **5**-386, **15**-1327, **18**-522
Alacid, E. **13**-462
Aladro, F.J. **14**-200, **15**-1851
Alajarin, M. **16**-427
Alam, M.M. **15**-1067, **18**-384
Alam, N. **13**-63
Alam, S. **18**-703
Alamdari, R.F. **10**-1193
Alami, M. **10**-1494, **13**-606, **13**-704, **15**-214, **15**-781
Alarcon, S.H. **2**-479
Alarid-Sargent, M. **16**-2222
Alauddin, M.M. **15**-2185
Alauze, V. **10**-1005, **16**-766
Alavi, S. **3**-165
Al-Awadi, N.A. **17**-139
Albanese, D. **10**-994, **19**-1241
Albaneze-Walker, J. **13**-673
Albanov, A.I. **19**-1766
Albeck, M. **17**-59
Alberico, D. **13**-302
Albert, B.J. **10**-1636
Albert, K. **19**-178
Albert, M. **15**-1098
Alberti, A. **10**-1278
Alberto, E.E. **16**-666
Albertshofer, K. **16**-1081
Albery, W.J. **6**-25, **6**-27, **6**-29, **8**-153, **10**-371
Albini, A. **7**-27, **13**-76, **13**-832, **19**-1526, **19**-756
Albonico, S.M. **15**-1711
Al-Borno, A. **12**-680
Albrech, H. **8**-74
Albrecht, M. **19**-952
Albrecht, P. **11**-320
Albright, J.D. **10**-1772, **19**-155, **19**-159, **19**-165
Albright, T.A. **1**-2
Alcaide, B. **16**-727
Alcántara, A.R. **19**-993
Alcaraz, L. **16**-1447, **17**-215, **17**-217
Alcarazo, M. **5**-372
Alcock, N.W. **4**-64
Alconcel, L.S. **8**-233
Alcudia, F. **4**-370, **4**-375
Alden, L. **16**-2006
Alden, R.A. **2**-423
Alder, R.W. **4**-246, **4**-248, **4**-249, **4**-250, **4**-257, **4**-258, **4**-245, **4**-247, **8**-96, **8**-197, **13**-138, **18**-557, **18**-558
Aldersey-Williams, H. **2**-392
Alderweireldt, F.C. **4**-18
Aldous, G. **5**-96
Aldred, S.E. **10**-777
Aldridge, C.L. **15**-1622
Al-Duri, B. **15**-2126
Alekseeva, L.A. **16**-442
Aleksiuk, O. **3**-129
Alemán, J. **10**-1915
Alemany, L.B. **14**-3
Alemany, P. **2**-340
Alemparte, C. **12**-230
Aleshi, P. **8**-108
Alesi, S. **16**-903
Alewood, P.F. **12**-237
Alex, A. **16**-1460
Alexakis, A. **4**-113, **7**-124, **10**-1359, **10**-1410, **10**-1506, **10**-1522, **10**-1533, **10**-1546, **10**-1600, **10**-1605, **10**-1612, **10**-1624, **10**-1626, **15**-977, **15**-979, **15**-985, **15**-1034, **15**-1134, **15**-1173, **15**-1174, **15**-1181, **15**-1204, **17**-221, **17**-222, **19**-1667
Alexander, C.W. **15**-1163
Alexander, R. **4**-385
Alexander, V.M. **11**-299
Alexanian, E.J. **15**-415
Alfassi, Z.B. **5**-211
Ali Shaikh, T.M. **19**-621
Ali, I.S. **19**-730
Ali, M. **10**-578
Ali, M. **10**-578
Ali, M.B. **15**-2289
Ali, M.H. **13**-186, **16**-198, **19**-66, **19**-779, **19**-828
Ali, M.M. **11**-500
Ali, Md.A. **12**-127
Ali, R. **11**-303
Ali, S.I. **15**-1768
Ali, T. **15**-2325
Alikarami, M. **13**-123
Alinezhad, H. **16**-337
Aliyan, H. **10**-688, **16**-1778
Alizadeh, A. **11**-454
Alkabets, R. **15**-525
Al-Ka'bi, J. **11**-647
Alker, D. **14**-153
Alkorta, I. **2**-383
Alkorta, I. **8**-14
Allaire, F.S. **13**-793
Allan, G. R. **4**-206
Allan, J.F. **12**-108
Allegretti, M. **15**-2092, **16**-1975
Allegretti, P.E. **2**-433
Allegrini, P. **19**-1428
Allemann, C. **16**-1074
Allen Jr., D.S. **19**-386
Allen, A.D. **2**-263, **5**-55, **10**-222, **10**-310, **15**-25, **15**-80, **16**-1677
Allen, C.F.H. **19**-1435
Allen, C.L. **16**-116
Allen, D.J. **12**-659
Allen, F.H. **1**-55, **1**-66, **1**-68, **2**-33, **3**-21, **3**-76, **4**-485, **4**-100
Allen, J.G. **15**-644
Allen, J.V. **15**-1958
Allen, L.C. **1**-30, **3**-3, **4**-34, **4**-256, **4**-310
Allen, L.E. **14**-498, **14**-499
Allen, N.T. **16**-587
Allen, R.G. **15**-56
Allen, R.H. **11**-639, **11**-640
Allen, W.D. **2**-67, **2**-110, **2**-220
Allenmark, S. **18**-721
Allenmark, S.G. **4**-178
Allerhand, A. **3**-64, **16**-1033

Alleston, D.L. **19**-1293
Allin, S.M. **18**-646
Allinger, N.L. **1**-56, **2**-219, **2**-421, **2**-425, **4**-270, **4**-272, **4**-290, **4**-308, **4**-344, **4**-363, **4**-403, **4**-415, **4**-416, **4**-422, **12**-701, **15**-463, **18**-931
Alliot, J. **13**-288
Allred, E.L. **4**-466, **10**-118, **10**-119
Allukian, M. **18**-126
Allwein, S.P. **18**-837
Al-Mallah, K.Y. **18**-431
Almansa, R. **16**-897
Almaşi, D. **15**-1045
Al-Masum, M. **10**-1547, **12**-296, **13**-576
Almeer, S. **11**-135
Almeida, L.M.P.M. **7**-129
Almeida, M. **12**-282
Almeida, W.P. **16**-796
Almela, C. **19**-128
Almena, J. **11**-521
Almog, J. **11**-139
Almond Jr., H.R. **16**-1355
Almond, M.R. **18**-302
Almy, J. **12**-31
Alnajjar, M.S. **12**-660
Alonso, C. **16**-1407
Alonso, D.A. **13**-494, **15**-1045, **15**-2066
Alonso, E. **16**-988
Alonso, F. **10**-1722, **13**-369, **13**-486, **15**-507, **15**-540, **15**-541, **15**-968, **16**-344, **16**-860
Alonso, J. **13**-587
Alonso, R.A. **7**-100, **11**-688, **13**-67, **13**-632
Alonso-Cires, L. **15**-2029, **15**-2036
Alpatova, N.M. **15**-572
Alper, H. **3**-89, **10**-484, **10**-917, **10**-1264, **10**-1998, **10**-2002, **10**-2003, **12**-569, **12**-773, **12**-781, **12**-782, **12**-785, **12**-786, **13**-306, **13**-375, **15**-552, **13**-597, **13**-668, **13**-669, **15**-598, **15**-1502, **15**-1516, **15**-1518, **15**-1579, **15**-1582, **15**-1594, **15**-1598, **15**-1608, **16**-168, **16**-868, **16**-1343, **16**-2247, **17**-226, **19**-325, **19**-706, **19**-1342, **19**-1432
Alpha, S.R. **19**-1739
Alphonse, F.-A. **15**-158
Alphonse, P. **15**-2646
Al-Rashid, Z.F. **15**-2563, **19**-720
Al-Rifai, R. **10**-3
Alsabeh, P. **13**-340
Al-Sader, B.H. **15**-2120
Al-Shalchi, W. **16**-1664
Alssteers, P. **19**-167
Alsters, P.L. **15**-1795, **15**-1883
Alston, P.V. **15**-2190, **15**-2229
Alt, G.H. **10**-1785, **10**-1795
Al-Talib, M. **5**-61, **11**-481
Altamura, A. **19**-293
Altenhoff, G. **13**-605
Alterman, M. **13**-671, **19**-1609, **19**-1612
Altermann, S. **19**-532
Altink, R. **10**-909
Altland, H.W. **13**-109, **13**-110, **13**-270, **13**-297
Altman, L.J. **10**-1850, **14**-43
Altman, R.A. **13**-188
Altmann, J.A. **2**-39
Altona, C. **4**-378
Altundaş, R. **10**-1173, **19**-379
Alumbaugh, R.L. **10**-528
Alunni, S. **11**-497, **17**-105, **17**-57
Aluotto, P.F. **8**-57
Alvarado, L. **15**-1650
Alvarado, S.I. **13**-270, **13**-747
Alvarez, C. **16**-2184
Alvarez, E. **17**-160
Alvarez, F.J. **6**-94
Alvárez, J. **19**-1418
Alvarez, M.T. **10**-1059
Alvarez, P. **15**-205
Alvarez, R. **13**-569
Alvarez, R.M. **11**-498, **16**-2174
Alvarez, S.G. **10**-1059
Alvarez-Manzaneda, E.J. **15**-597, **17**-160, **19**-342, **19**-912
Alvarez-Manzaneda, R. **17**-160
Alves, L.M. **16**-247
Alzérreca, A. **2**-245
Amabilino, D.B. **3**-194, **3**-201
Amantini, D. **10**-690, **10**-1221
Amaratunga, S. **12**-569
Amaratunga, W. **12**-562
Amardeil, R. **13**-590
Amaresh, R.R. **11**-501
Amatore, C. **12**-288, **13**-59, **13**-63, **13**-94, **13**-442, **13**-479, **13**-545
Amatore, M. **13**-450, **15**-1221
Amaya, T. **11**-427
Amberg, W. **15**-1830, **15**-1832, **15**-1843
Ambidge, I.C. **10**-222
Ambroise, L. **15**-1406
Ambrosetti, R. **15**-22
Ambroz, H.B. **5**-69, **13**-28, **13**-29
Ambulgekar, G.V. **13**-385
Amedio Jr., J.C. **12**-685
Amedjkouh, M. **8**-212, **16**-392, **16**-1085
Amemiya, R. **10**-1925, **12**-424
Amemiya, T. **15**-1479
Amer, I. **10**-1998, **15**-1598, **19**-597
Amer, M.I. **11**-562
Ameriks, M.K. **10**-1999
Amice, P. **12**-163
Amick, D.R. **11**-553
Amiel, Y. **14**-331, **15**-1730
Amii, H. **15**-2600
Amii, H. **19**-1146
Amin, A.H. **13**-602
Amin, H.B. **9**-28
Amin, M. **17**-66, **17**-68
Amin, S. **19**-610
Amin, S.R. **16**-1444
Amishiro, N. **15**-1249
Amiya, T. **16**-1709
Amorati, R. **1**-116
Amorelli, B. **16**-1109
Amoroso, F. **13**-503
Amos, D.T. **15**-2321
Amos, R.D. **4**-173, **4**-299
Amosova, S.V. **10**-804, **11**-354
Amouroux, R. **10**-1191, **10**-1200, **16**-2050, **16**-509
Ampleman, G. **11**-56, **19**-895
Amrollah-Madjdabadi, A.A. **10**-106
Amstutz, E.D. **17**-399
Amstutz, R. **5**-201
Amupitan, J.O. **19**-1770
Amurrio, I. **16**-1504
Amy, S. **15**-1083
Amyes, T.L. **5**-12, **5**-20, **8**-70, **10**-68, **10**-93, **10**-94, **5**-101, **10**-558, **10**-564, **16**-2053, **18**-333
An, D.K. **19**-884, **19**-1097
An, G. **19**-676
An, G.-i. **18**-351
An, M. **15**-505
An, T.D. **17**-28
Anand, M. **18**-25
Anand, N. **17**-446
Anand, R.C. **16**-1796
Anand, R.V. **15**-1956
Anani, W.Q. **14**-197
Ananikov, V.P. **15**-318
Anantakrishnan, S.V. **15**-28
Anastasi, N.R. **15**-419
Anastasia, L. **12**-306, **13**-617
Anastasiou, D. **15**-1616
Anastassiou, A.G. **2**-281, **2**-284, **2**-285, **2**-286, **12**-240
Anatol, J. **16**-2182
Anbar, M. **7**-70
Anbazhagan, M. **17**-156
Ancliff, R. **15**-1434
Andappan, M.M.S. **7**-125, **13**-409
Anders, E. **5**-192
Anders, K. **14**-79
Andersch, J. **19**-1771
Andersen, K.K. **4**-30, **4**-48, **4**-49, **4**-221, **16**-2271
Andersen, M.W. **15**-1018
Andersen, N.G. **4**-166
Andersen, N.H. **5**-128, **19**-1179
Andersen, P. **5**-297
Andersen, T.P. **16**-1920
Andersh, B. **11**-241
Anderson III, F.E. **14**-180
Anderson Jr., A.G. **10**-1201, **16**-2000
Anderson, A.G. **11**-348
Anderson, A.M. **18**-144

Anderson, B.R. **4**-496
Anderson, C.D. **18**-640
Anderson, C.E. **18**-368, **18**-743
Anderson, D.J. **15**-2053
Anderson, E.D. **5**-365, **16**-163
Anderson, E.W. **10**-144
Anderson, G.J. **19**-615, **19**-616, **19**-618
Anderson, G.K. **10**-1983, **15**-1494
Anderson, H.J. **11**-72
Anderson, J. E. **4**-361
Anderson, J.C. **16**-410, **16**-412, **18**-450, **18**-741
Anderson, J.E. **4**-381, **4**-325, **4**-337, **4**-388
Anderson, J.M. **14**-380
Anderson, J.R. **15**-147
Anderson, K.R. **7**-84
Anderson, K.W. **11**-435, **13**-98, **13**-188, **13**-189, **13**-237
Anderson, L.L. **15**-327, **15**-367
Anderson, O.P. **16**-2221
Anderson, P.E. **9**-107
Anderson, P.H. **10**-284, **18**-98
Anderson, R. **10**-512, **12**-411, **16**-1297
Anderson, R.J. **15**-1133, **16**-2097
Anderson, R.S. **19**-1218
Anderson, S.R. **16**-1735
Anderson, S.W. **10**-462, **10**-463, **10**-467
Anderson, V.E. **3**-48
Anderson, W.K. **18**-749
Andersson, A.S. **12**-532
Andersson, C. **12**-314, **13**-368
Andersson, C.-M. **15**-274
Andersson, K. **2**-453
Andersson, P.G. **13**-438, **15**-234, **15**-449, **15**-452, **15**-471, **15**-2060, **15**-2066, **17**-223, **19**-470, **19**-928
Andisik, D. **10**-1078, **15**-424
Ando, A. **15**-1468., **19**-495
Ando, F. **18**-426
Ando, H. **10**-1070, **11**-503
Ando, J.-i. **14**-358
Ando, K. **12**-88, **16**-752, **16**-1377, **16**-1393, **16**-1695
Ando, M. **10**-695, **18**-367, **18**-385
Ando, T. **6**-74, **7**-102, **7**-87, **10**-176, **10**-184, **10**-215, **10**-1019, **10**-1934, **16**-2162, **18**-803, **19**-107
Ando, W. **10**-813, **14**-256, **15**-2535, **16**-1867, **18**-223, **18**-226, **19**-810
Ando, Y. **15**-856
Andrade, C.K.Z. **16**-247, **16**-581, **16**-629, **16**-912
Andrade, J.G. **16**-2159
Andrea, T. **16**-1013
Andrea, T. **19**-1745
Andreev, A.A. **10**-1928
Andreev, S.A. **12**-745
Andreev, S.M. **16**-1929
Andrei, D. **10**-1469
Andrejevic, V. **14**-235
Andres, J. **10**-247
Andrés, J. **15**-2242
Andrés, J.M. **16**-857, **16**-2076
Andres, P.C. **16**-614
Andresen, B.M. **15**-522
Andréu, P. **17**-180, **17**-319
Andrews, A.E. **16**-1414
Andrews, B.K. **5**-313
Andrews, C.W. **10**-568
Andrews, G.C. **18**-786
Andrews, G.D. **15**-99
Andrews, L. **5**-214, **5**-290, **5**-363, **14**-184, **19**-349
Andrews, L.J. **11**-271
Andrews, M.A. **17**-335
Andrews, P.C. **16**-909
Andrey, O. **15**-1034
Andrianov, K.A. **15**-739
Andrieux, J. **10**-1079
Andringa, H. **15**-564
Andrioletti, B. **13**-378
Andrisano, R. **10**-279
Andrist, A.H. **15**-136, **15**-2308, **18**-533
Andrukiewicz, R. **15**-1338
Andrus, A. **10**-1961
Andrus, M.B. **13**-529, **16**-774, **16**-776, **19**-455
Andrussow, K. **8**-25
Andrzejewski, D. **17**-254
Andrzejewski, D. **17**-264
Anelli, P.L. **3**-214, **3**-216, **5**-266, **16**-1813
Anet, F.A.L. **1**-94, **3**-111, **4**-215, **4**-273, **4**-332, **4**-336, **4**-342, **4**-348, **4**-360, **4**-400, **4**-410, **10**-169
Anet, R. **4**-273
Ang, K.P. **8**-56
Angel, L.A. **10**-19
Angelaud, R. **16**-1448
Angeletti, E. **10**-1669
Angelini, G. **10**-12, **10**-274, **17**-99
Angelis, Y. **15**-1925
Angelis, Y.S. **19**-226
Angell, E.C. **19**-576
Angell, R.M. **16**-777
Angelo, B. **16**-2155
Angeloni, A.S. **10**-279
Angelov, Kh.M. **15**-61
Angiolini, L. **16**-372
Angioloni, S. **4**-326
Angle, S.R. **18**-256
Angus Jr., R.O. **4**-509
Angus, J.C. **17**-44
Angyal, S.J. **4**-270, **4**-272, **4**-363, **19**-317, **19**-628
Anh, N.T. **1**-51, **4**-140, **4**-142
Anilkumar, G. **12**-257, **15**-1885
Anilkumar, R. **18**-359
Anjaneyulu, S. **10**-894, **16**-768, **16**-980, **18**-328, **18**-699
Ankner, T. **19**-1188
Annaka, K. **13**-590
Annamalai, V. **16**-666
Annby, U. **15**-274
Annese, C. **15**-1924, **19**-227
Annesi, D. **16**-1734
Anniyappan, M. **15**-2316
Annoura, H. **11**-555
Annunziata, R. **4**-30, **5**-145, **11**-646, **15**-1836, **16**-1169, **16**-776
Ano, Y. **10**-1286
Anosike, P. **15**-2224
Ansar, I.A. **19**-183
Ansell, H.V. **11**-53, **11**-76
Ansell, M.F. **15**-209, **16**-1984
Anselme, J. **16**-2216, **18**-248, **18**-788
Anselmi, C. **10**-1888, **15**-126
Ansersh, B. **10**-1478
Anslyn, E.V. **8**-116, **8**-187
Ansmann, A. **15**-2385
Anson, M.S. **13**-395, **13**-396
Antczak, M.I. **15**-421
Antebi, S. **13**-668
Anteunis, M. **16**-1552
Antharjanam, P.K.S. **15**-1363
Anthony, J.E. **2**-354, **15**-2621, **18**-525
Antilla, J.C. **10**-1008, **19**-1149
Antoft-Finch, A. **13**-513
Anton, D.R. **17**-301
Antonchick, A.P. **16**-1223, **18**-643, **18**-748
Antonioletti, R. **15**-1683, **15**-1967
Antoniotti, S. **15**-242, **18**-152
Antonova, N.D. **16**-1567
Antony, A. appendixa-1
Antunes, A.M.M. **15**-2063
Antunes, A.M.M. **15**-2072
Antunes, C.S.A. **18**-55
Antunes, O.A.C. **13**-379, **13**-497, **13**-591, **13**-597
Antúnez, S. **4**-340
Anunziata, J.D. **13**-15
Anuradha, K. **15**-1456
Anuradha, M.V. **16**-1880
Anuradha, V. **11**-128
Anvia, F. **8**-104, **8**-176
Anwer, M.K. **11**-687
Anxionnat, B. **16**-2178
Anzai, J. **19**-665
Anzalone, P.W. **16**-164
Anzovino, M.E. **15**-2412
Aoi, K. **10**-1519
Aoki, K. **10**-1297, **15**-2406
Aoki, M. **16**-866, **19**-677
Aoki, S. **10**-1445, **10**-1431, **12**-686, **13**-655
Aoki, T. **11**-391
Aono, M. **15**-2105
Aonuma, S. **5**-124, **5**-210

Aouad, E. **12**-386
Aoun, R. **19**-1473
Aounallah, N. **19**-1629
Aoyagi, K. **15**-1411
Aoyagi, S. **13**-589
Aoyagi, T. **16**-1816
Aoyagi, Y. **16**-838
Aoyama, H. **16**-1362
Aoyama, M. **15**-1259
Aoyama, N. **16**-396, **16**-623, **16**-770
Aoyama, T. **12**-541, **18**-224, **18**-240
Aoyama, Y. **3**-156
Aparicio, D. **16**-1407, **16**-276
Aparna, P. **11**-128
Apeloig, Y. **2**-86, **2**-449, **5**-276, **10**-190, **10**-191, **10**-262, **13**-33, **15**-1952, **15**-2313
Apfel, R.E. **7**-71, **7**-72
Apler, H. **10**-1631
Apodaca, R. **16**-325
Aponte, G.S. **18**-70
Apparu, M. **15**-183, **17**-211
Appel, R. **1**-12, **10**-402, **10**-1160, **16**-1369, **17**-485
Appella, D.H. **15**-451
Appelman, E.H. **15**-1698
Appelt, H.R. **16**-598
Appendino, G. **4**-123, **16**-1029
Appl, M. **18**-312
Applegath, F. **12**-772
Applequist, D.E. **2**-63, **4**-51, **5**-108, **10**-1301, **14**-62, **15**-143
Applequist, J. **4**-51, **4**-129, **4**-150, **15**-635
Appukkuttan, P. **7**-127, **7**-129, **13**-219, **13**-598
Aprahamian, N.S. **11**-304
Aprile, C. **15**-229
ApSimon, J.W. **4**-139
Aquino, L.B. **11**-461, **11**-462
Arabindoo, B. **19**-86
Arad, D. **2**-88, **2**-449, **10**-190, **10**-191, **13**-33
Arad-Yellin, R. **4**-169, **4**-170, **9**-12
Arai, H. **16**-1054
Arai, K. **10**-975
Arai, M. **10**-1445, **14**-214, **18**-128
Arai, N. **19**-1301
Arai, S. **12**-77, **15**-1912, **15**-1953, **16**-1051, **16**-1277, **16**-1281, **16**-1287, **16**-1372, **16**-1458
Arai, T. **12**-449, **15**-146, **15**-1913, **16**-1220
Araki, H. **18**-263
Araki, K. **3**-131, **10**-325, **10**-1420, **19**-1557
Araki, M. **15**-2194, **16**-2054
Araki, S. **10**-235, **10**-1589, **10**-1630, **15**-987, **16**-1459, **16**-656, **16**-836, **16**-916
Araki, Y. **5**-263, **19**-918
Aramendia, M.A. **13**-544, **13**-643
Aramini, A. **16**-1975
Arapov, O.V. **7**-123
Arase, A. **12**-574, **15**-1282
Arata, K. **8**-18
Aratake, S. **16**-395
Araújo, M.A. **16**-700
Arayama, K. **15**-897
Arbuj, S.S. **12**-116
Arbuzov, B.A. **18**-96
Arbuzov, P.V. **14**-177
Arbuzov, Yu.A. **16**-1567
Arcadi, A. **11**-693, **13**-493, **15**-245, **15**-2633, **16**-146
Arcand, H.R. **18**-736
Arcelli, A. **10**-926
Archer, C.M. **16**-503
Archer, D.A. **17**-245
Archer, S. **18**-934
Arcoria, A. **16**-2273
Ardakani, A. **15**-1942
Ardhapure, S.S. **10**-611
Ardoin, N. **13**-82
Arduengo III, A.J. **5**-412, **12**-372
Arend, M. **16**-386
Arends, I.W.C.E. **15**-1881, **15**-1894, **18**-377, **18**-382, **19**-167, **19**-169, **19**-218
Arens, J.F. **10**-1617, **15**-217, **15**-218
Arentsen, K. **13**-493
Arenz, T. **16**-1252
Aretakis, A.J. **15**-102
Arévalo, M.J. **15**-2193
Argabright, P.A. **17**-289
Argade, N.P. **10**-1372, **15**-152
Argile, A. **9**-21
Argyropoulos, J.N. **16**-1019, **19**-958
Arhart, R. **14**-177
Arias, L.A. **15**-1937
Arifuddin, M. **16**-74
Ariga, M. **15**-2112
Ariger, M.A. **10**-934, **19**-1183
Arigoni, D. **15**-817, **17**-504, **19**-450
Arii, T. **15**-2598
Arimatsu, S. **17**-179
Arime, T. **16**-841
Arimori, S. **4**-112
Arimoto, H. **19**-142
Arimoto, K. **15**-626
Arimura, T. **10**-886, **15**-175
Arinich, A.K. **11**-621
Arisawa, M. **10**-856, **15**-816
Arisawa, M. **10**-1091, **10**-1925, **14**-194, **15**-384, **18**-358
Arison, B.H. **15**-2120
Arjona, O. **15**-303
Arkle, S.R. **16**-2251
Arlt, R.E. **10**-237
Armantrout, J.R. **2**-318, **18**-678
Armesto, D. **18**-607, **18**-917
Armet, O. **5**-269
Armit, J.W. **2**-105
Armour, A.G. **18**-452
Armspach, D. **3**-189
Armstrong III, J.D. **18**-730
Armstrong, A. **10**-650, **15**-1930, **15**-1932
Armstrong, D.A. **1**-107
Armstrong, D.R. **13**-726, **13**-733
Armstrong, III, J.D. **19**-955
Armstrong, K.B. **4**-388
Armstrong, R. **14**-122
Arnason, I. **4**-384
Arnauld, T. **13**-659, **18**-871
Arnaut, L.G. **10**-5, **7**-48
Arndt, D. **19**-10
Arndt, M. **14**-338
Arndtsen, B.A. **16**-911
Arnestad, B. **11**-145
Arnett, E.M. **2**-414, **4**-521, **4**-523, **5**-2, **5**-74, **5**-75, **5**-137, **5**-209, **6**-94, **8**-25, **8**-27, **8**-36, **8**-38, **8**-40, **8**-124, **8**-131, **8**-208, **8**-237, **8**-240, **8**-248, **10**-59, **10**-190, **12**-694, **16**-1041, **16**-1347
Arnold, A.P. **3**-221, **3**-222
Arnold, B.R. **2**-243, **15**-1313
Arnold, C. **10**-1931
Arnold, D.R. **5**-277, **15**-2446, **16**-2205, **16**-2207, **17**-507, **17**-509
Arnold, F.H. **19**-500
Arnold, J. **15**-327, **15**-367
Arnold, J.N. **16**-63, **16**-154
Arnold, J.R.P. **18**-400
Arnold, L.A. **10**-1447, **16**-822
Arnold, R.T. **16**-1567, **17**-123, **17**-491, **17**-493, **18**-589
Arnold, S. **15**-4, **15**-34
Arnoldi, A. **14**-385
Arnould, D. **10**-1825
Arnould, J.C. **13**-794
Aroella, T. **8**-118
Aronica, L.A. **16**-2016, **17**-380
Aronoff, M.S. **15**-666
Arora, A. **10**-1652
Arora, S. **12**-468
Arora, S.K. **19**-494, **19**-854
Arote, N.D. **16**-311, **16**-1983
Arotsky, J. **11**-306
Arouisse, A. **16**-2017
Aroyan, C.E. **16**-818
Arp, F.O. **10**-1472
Arques, A. **16**-427
Arrad, O. **10**-723
Arrayás, R.G. **15**-2114, **15**-2349
Arrieta, A. **15**-2119, **15**-2239, **16**-852, **16**-1773
Arrowood, B.N. **15**-965
Arrowsmith, C.H. **8**-118
Arrowsmith, R.J. **4**-249
Arsenijevic, L. **16**-2059
Arsenijevic, V. **16**-2059
Arseniyadis, S. **10**-1695, **16**-1892, **19**-309

Arshinova, R.P. **4**-400
Arslancan, E. **16**-584
Arsmtrong, A. **15**-1933
Artamanova, N.N. **13**-117
Artamkina, G.A. **10**-1391, **12**-655, **12**-662, **13**-274
Artaud, I. **10**-1710
Arterburn, J.B. **15**-602, **19**-131
Arthur Jr., P. **15**-1624
Artok, L. **13**-493
Arukwe, J. **2**-489
Arulananda, S. **12**-382
Arumugam, N. **5**-408, **11**-575
Arun Kumar, M. **11**-253
Aruna, S. **17**-385
Arunachalam, P.N. **16**-2179
Arunan, E. **3**-41, **3**-77
Arundhathi, R. **10**-937
Arvanaghi, M. **10**-152, **10**-214, **11**-263, **11**-485, **11**-487, **12**-164, **16**-93, **16**-2057, **16**-2160, **19**-631, **19**-1427
Arvela, R.K. **13**-267, **13**-278, **13**-294, **13**-397, **13**-503, **13**-506
Arvidsson, P.I. **8**-226, **16**-495, **19**-928
Arya, P. **13**-668
Aryanasab, F. **15**-1450
Arzoumanian, H. **15**-726
Asady Tamami, M.V. **19**-776
Asai, C. **10**-1585
Asai, S. **10**-1269
Asai, T. **16**-893, **18**-426
Asaka, N. **15**-2112
Asakawa, K. **16**-771
Asakawa, Y. **19**-441
Asami, K. **15**-1341
Asami, M. **16**-1023
Asano, F. **19**-78
Asano, K. **12**-756, **16**-804
Asano, R. **10**-740
Asano, T. **9**-87, **10**-507, **11**-169, **15**-2208, **17**-71, **18**-231
Asanuma, Y. **16**-431
Asao, N. **10**-1625, **15**-1164, **15**-789, **15**-823, **15**-940
Asao, T. **2**-225, **5**-45, **5**-46
Asaoka, M. **15**-1196, **16**-859
Asaumi, T. **15**-2690
Aschberger, J. **10**-1062
Asencio, G. **11**-16
Asensio, A. **5**-239
Asensio, G. **15**-1672, **15**-1673, **15**-2029, **15**-2036, **15**-383, **18**-387, **19**-70, **19**-479, **19**-777
Asfandiarov, N.L. **4**-40
Asfari, Z. **3**-141, **3**-144, **3**-145
Asghari, J. **11**-245
Ashby, E.C. **4**-141, **5**-163, **5**-165, **5**-169, **5**-174, **5**-175, **5**-176, **5**-177, **5**-257, **5**-389, **10**-100, **10**-101, **10**-106, **10**-109, **10**-112, **10**-634, **10**-801, **12**-582, **12**-616, **12**-656, **12**-660, **15**-527, **15**-978, **15**-1217, **16**-5, **16**-512, **16**-513, **16**-514, **16**-515, **16**-516, **16**-654, **16**-1005, **16**-1019, **16**-2143, **17**-181, **19**-923, **19**-958, **19**-998, **19**-999, **19**-1000, **19**-1324, **19**-1370, **19**-1736
Ashby, M.T. **15**-636
Ashe III, A.H. **5**-47
Ashe III, A.J. **10**-205, **10**-208, **10**-210
Ashfeld, B.L. **15**-603
Ashford, S.W. **19**-323
Ashikawa, M. **10**-1091
Ashley, K.R. **19**-312
Ashmawy, M.I.A. **15**-2004
Ashton, P.R. **2**-342, **3**-194, **3**-201, **3**-210
Ashton, R.P. **3**-195
Ashweek, J. **12**-441
Asinger, F. **12**-503, **12**-582, **19**-1769, **19**-1776, **19**-1777
Asirvatham, E. **16**-1198
Askani, R. **15**-2465, **18**-529
Askin, D. **12**-759
Askitoglu, E. **16**-1970
Aslam, M. **10**-1817, **17**-351
Aslan, A. **16**-667, **16**-1215
Asleson, G.L. **13**-472
Aspaas, A.W. **19**-881
Aspari, P. **7**-36
Aspinall, H.C. **10**-618, **16**-632, **16**-912, **16**-1515, **19**-1630
Assadourian, L. **8**-17
Asscher, M. **15**-1727
Assenheim, H.M. **5**-218
Assfeld, X. **15**-2244
Astaf'ev, I.V. **12**-61
Astruc, D. **13**-82, **18**-804
Asveld, E.W.H. **14**-264
Atanas'ev, V.V. **15**-393
Atanesyan, K.A. **15**-1783
Atavin, A.S. **10**-680, **15**-255
Ateeq, H.S. **15**-2677
Ates, A. **10**-575, **15**-349, **15**-356, **16**-1295
Athanasopoulos, J. **16**-1899
Atherton, J.C.C. **19**-1020
Atherton, J.H. **11**-155, **11**-158
Atherton, J.I. **17**-266
Atherton, M. **16**-446
Atherton, M.J. **11**-312
Atienza, C. **15**-2620
Atkins, R.L. **19**-747
Atkinson, J.G. **12**-55, **15**-494, **15**-495
Atkinson, R. **19**-372, **19**-373
Atkinson, R.C. **15**-74
Atkinson, R.F. **17**-242
Atobe, M. **11**-325
Atsumi, K. **16**-1839
Attanasi, O. **17**-431, **19**-1494
Atta-ur-Rahman. **10**-1142
Attinà, M. **11**-101
Atwood, J.L. **3**-65, **3**-106, **3**-110, **3**-124, **3**-147, **3**-162, **3**-166, **3**-170, **3**-172, **3**-175, **3**-176, **3**-183, **3**-185, **3**-186, **3**-222, **4**-169
Au, S.-M. **19**-537
Aubé, J. **18**-323, **18**-324, **18**-325, **18**-331
Aubert, C. **15**-877, **15**-2588, **15**-2612, **15**-2623
Aubrecht, K.B. **8**-218, **12**-277
Aubrey, D.W. **17**-232
Aubry, J.-M. **14**-255
Auclair, K. **14**-97
Audhuy, M. **7**-120
Audic, N. **18**-848
Audrain, H. **15**-2336
Aue, D.H. **8**-236, **8**-241, **12**-243, **19**-1303
Auerbach, R.A. **16**-2123
Aufdermarsh Jr., C.A. **10**-57
Augé, J. **15**-1075, **15**-1234, **5**-2217, **15**-2333, **16**-564
Augstine, A. **15**-1658
August, A.T. **13**-205
August, R. **17**-139
Augustijn, G.J.P. **11**-680
Augustín, J. **16**-1868
Augustine, A. **15**-1729, **15**-1757, **19**-707
Augustine, J.K. **10**-539
Augustine, R.L. **10**-1694, **12**-246, **12**-447, **14**-250, **14**-271, **15**-428, **15**-486, **15**-489, **15**-591, **15**-1869, **15**-1884, **16**-1017, **16**-1037, **18**-379, **19**-11, **19**-16, **19**-42, **19**-64, **19**-301, **19**-331, **19**-434, **19**-448, **19**-547, **19**-614, **19**-668, **19**-843, **19**-844, **19**-1368, **19**-1406
Augustínová, I. **11**-473
Aujard, I. **19**-1667
Aulmich, G. **5**-246
Ault, B.S. **3**-53, **5**-433
Aumiller, J.C. **10**-1302
Aurell, M.J. **15**-2181, **15**-2292, **16**-861, **19**-817
Aurich, H.G. **5**-267, **5**-268
Aurrekoetxea, N. **16**-831
Austad, T. **10**-518
Austel, V. **18**-528
Austin, E. **11**-688, **16**-1066
Autrey, T. **5**-432
Au-Yeung, T.T.-L. **15**-1202, **16**-746
Avakian, S. **13**-45
Avalos, M. **4**-5, **4**-312, **4**-315, **15**-2187, **15**-2193, **15**-2290
Avedissian, H. **10**-1386
Avellan, A.-V. **11**-190
Avendaño, C. **10**-1039, **15**-2334, **19**-1334
Averko-Antonovich, I.G. **10**-1112

Avery, M.A. **16**-331, **19**-1121
Aver'yanov, V.A. **14**-138
Avey, A.A. **19**-1390
Avila, D.V. **15**-1304
Avila, W.B. **13**-724
Avila-Zárraga, J.G. **10**-748
Avilov, D.V. **16**-584
Avison, A.W.D. **16**-1830
Aviyente, V. **15**-2188, **18**-708, **18**-712, **18**-734
Avnir, D. **4**-83
Avola, S. **10**-1309
Avramovitch, B. **10**-257, **10**-280
Aw, C. **10**-1207
Awachie, P.I. **16**-351
Awasthi, A.K. **10**-54, **15**-1858, **19**-392, **19**-521
Awasthi, C. **16**-2248
Awasthi, R. **10**-1068
Awasthi, S. **13**-458
Axe, F.U. **4**-314
Axelrod, E.H. **10**-1165, **10**-1328
Axelrod, J. **14**-225
Axelsson, A.-K. **15**-2223
Axelsson, L. **13**-219
Axelsson, O. **13**-760
Axenrod, T. **16**-1879
Axiotis, G.P. **16**-995
Ay, M. **12**-536
Ayad, T. **4**-155, **13**-494
Ayala, A.M. **19**-1234
Ayala, L. **10**-1503
Ayala, P.Y. **1**-106
Aycard, J. **18**-234
Aycock, B.F. **15**-55
Aydin, R. **18**-679
Aydoga, F. **16**-1592
Ayerbe, N, **19**-1605
Ayers, J.T. **16**-1735
Ayers, P.W. **8**-163
Ayers, T.A. **19**-1067
Ayhan, P. **16**-1031
Aylett, B.J. **4**-26, **12**-1
Ayling, A. **16**-978
Aylward, F. **15**-511
Aylward, J.B. **19**-10, **19**-301
Ayokosok, E. **7**-32
Ayres, R.L. **15**-1640
Ayrey, G. **13**-20, **17**-63
Ayrey, P.M. **16**-1387
Ayuba, S. **10**-1102, **10**-1103
Ayyangar, N.R. **4**-199, **13**-810, **19**-1203
Azadi, R. **10**-734, **13**-401
Azap, C. **16**-1530, **19**-1152
Azar, J.K. **18**-647
Azarm, M. **16**-68
Azevedo, N.R. **16**-581, **16**-629
Azhar, M.A. **10**-971
Azizi, N. **10**-959, **10**-966, **10**-1650, **15**-1450
Azizoglu, A. **17**-391
Aznar, F. **15**-2031, **15**-2500, **15**-2657, **17**-271
Azoulay, S. **10**-974
Azovskaya, V.A. **15**-119
Azrak, R.G. **3**-57
Azuma, N. **5**-291
Azzaro, M. **19**-1236
Azzena, U. **11**-381, **19**-1519

Ba, T. **16**-353
Baader, W.J. **15**-2366
Baag, Md.M. **15**-152
Baarda, D.G. **17**-503
Baarschers, W.H. **16**-2304
Baas, B.-J. **18**-389
Baas, J.M.A. **11**-55
Baba, A. **10**-624, **10**-815, **10**-1070, **10**-1153, **10**-1154, **10**-1592, **10**-1594, **10**-1716, **10**-1726, **12**-327, **15**-1130, **16**-356, **16**-612, **16**-621, **16**-643, **16**-840, **16**-912, **16**-2032, **19**-1085, **19**-1127, **19**-1285, **19**-1295, **19**-1340
Baba, A.R. **19**-1194
Baba, H. **2**-28
Baba, K. **18**-142, **18**-154
Baba, S. **10**-1451, **10**-1463
Baba, T. **16**-1580
Baba, Y. **15**-911
Baban, J.A. **14**-20
Babayan, E.V. **15**-1783
Babayan, V.I. **18**-54
Babić, D. **2**-118
Babiak, K.A. **12**-601
Babiano, R. **4**-5, **4**-312, **4**-315, **15**-2187, **15**-2193, **15**-2290
Babichev, S.S. **15**-2280
Babinski, D. **12**-306
Babitskii, B.D. **15**-2498
Babler, J.H. **10**-1107, **19**-637, **19**-987, **19**-988, **19**-1086, **19**-1193
Baboul, A.G. **14**-51
Babrizi, G. **13**-667
Babston, R.E. **18**-729
Babu, A. **12**-382
Babu, G. **15**-2332
Babu, K.G. **10**-1248
Babu, K.S. **14**-313
Babu, R.S. **10**-984
Babudri, F. **10**-1377, **16**-2015, **16**-2020
Baburao, K. **16**-1978
Bacaloglu, R. **13**-21, **16**-18
Bacci, J.P. **15**-407
Bach, P. **15**-2353
Bach, R.D. **1**-106, **4**-318, **4**-432, **4**-433, **4**-434, **10**-242, **12**-215, **14**-51, **15**-1874, **15**-1937, **15**-2428, **17**-254, **17**-255, **17**-264
Bach, T. **10**-1608, **11**-336, **15**-1487, **16**-722, **16**-1137, **16**-1169
Bacha, J.D. **19**-424
Bachand, C. **19**-639
Bachhuber, H. **15**-515
Bachman, G.B. **14**-470
Bachman, R.E. **18**-180
Bachmann, C. **18**-234
Bachmann, S. **12**-123, **12**-124, **19**-178
Bachmann, W.E. **18**-36, **19**-1627
Bachrach, S.M. **2**-97, **4**-435, **4**-368, **10**-26, **15**-2408, **18**-576
Baciocchi, E. **11**-104, **11**-231, **11**-278, **15**-1780, **17**-33, **17**-36, **17**-54, **17**-105, **17**-116, **17**-300, **17**-371, **19**-822
Baciocchi, W. **17**-392
Back, R.A. **14**-67, **15**-512
Back, T.G. **4**-533, **12**-250, **14**-448, **15**-252, **17**-293, **19**-1567, **19**-45, **19**-1573
Backer, H.J. **17**-497
Backnejad, H. **19**-87
Bäckvall, J.-E. **4**-186, **10**-240, **10**-1385, **10**-1361, **10**-1506, **10**-1507, **11**-339, **15**-234, **15**-276, **15**-329, **15**-875, **15**-1801, **15**-1807, **15**-1848, **15**-1858, **15**-2011, **15**-2023, **15**-2034, **16**-466, **16**-1178, **19**-214, **19**-500, **19**-794, **19**-1133
Bacon, J. **5**-24
Bacon, R.G.R. **13**-263
Badaev, F.Z. **12**-638
Badanyan, Sh.O. **15**-1783, **19**-374
Badaringarayana, V. **13**-236
Baddar, F. G. **12**-86
Badding, V.G. **19**-1369
Bade, T.R. **14**-232, **16**-1274
Bader, R.F.W. **2**-169, **4**-288, **4**-421, **4**-440, **12**-678, **17**-238
Bader, S.J. **15**-2403
Bader, W. **4**-289
Badet, B. **10**-431
Badger, G.M. **2**-99
Badger, R.C. **12**-215
Badía, D. **15**-1045, **15**-1401
Badiger, V.V. **10**-276
Badine, D.M. **16**-1487
Badlani, R.N. **9**-107
Bădoiu, A. **15**-2144
Badone, D. **12**-270, **13**-487
Badri, M. **10**-491
Bae, C. **5**-100
Bae, D. **10**-634
Bae, I. **15**-1524
Bae, J.W. **19**-966, **19**-1722
Bae, S.W. **19**-128
Bae, Y.H. **12**-134
Baechler, R.D. **4**-35, **4**-256
Baek, D.Y. **13**-668
Baek, H.S. **19**-1581, **19**-1660
Baekeberg, O.G. **14**-13
Baele, J. **10**-902
Baenziger, N. **17**-330

Baer, D.R. **18**-161
Baer, H.H. **15**-1052, **16**-376, **16**-1199
Baer, S. **10**-379
Baerends, E.J. **15**-1617
Baes, M. **4**-71, **4**-193
Baeza, J. **16**-1761
Bagal, L.I. **14**-400, **18**-320
Baganz, H. **10**-661
Baggott, J.E. **2**-392
Baghel, S.S. **11**-692
Bagheri, V. **12**-363, **19**-136
Bagherzadeh, M. **11**-134, **12**-739
Baghurst, D.R. **10**-502
Bagley, M.C. **15**-2637, **16**-117, **19**-533
Bagnell, L. **15**-1217, **19**-949
Bagnell, L.J. **19**-1351
Bagno, A. **5**-72, **8**-11, **8**-142, **14**-409, **16**-1682
Bagnol, L. **14**-53
Bagnoli, L. **10**-694
Bagrovskaya, N.A. **11**-674
Bagutskii, V. **18**-87
Bahl, M.K. **8**-251
Bahn, C.A. **10**-271
Bähn, S. **10**-909, **10**-927, **10**-933
Bahr, M.L. **10**-1060
Bahrami, K. **11**-199, **11**-441, **16**-208, **19**-789
Bahramian, B. **13**-591, **13**-602
Bahrmann, H. **10**-1979, **10**-1980, **15**-1494
Bahzad, D. **11**-277
Bai, C. **15**-453, **16**-1512
Bai, D. **16**-1906
Bai, K. **16**-906
Bai, L. **7**-126, **13**-398, **16**-2046
Bai, Y. **19**-32
Baidossi, M. **19**-837
Baigrie, L.M. **16**-1104
Baik, M.-H. **15**-2692
Baik, T.-G. **13**-333, **13**-339, **15**-248, **15**-2381, **16**-714
Baik, W. **12**-116, **16**-906, **19**-1186, **19**-1204, **19**-778
Baiker, A. **19**-128
Bailey, A.D. **16**-137
Bailey, D.M. **19**-1456
Bailey, D.S. **17**-28, **17**-100
Bailey, G.C. **18**-813
Bailey, K.E. **19**-1407
Bailey, M. **15**-1655
Bailey, N.A. **2**-287, **2**-293
Bailey, P.S. **19**-331, **19**-341
Bailey, T.R. **13**-374
Bailey, W.F. **4**-333, **10**-1306, **12**-646, **12**-655, **12**-656, **15**-916, **15**-917, **15**-918, **15**-920, **15**-921, **15**-1326, **15**-1339, **16**-465, **18**-437, **19**-187
Bailey, W.J. **16**-175, **17**-133, **17**-148, **17**-233, **18**-586, **19**-1358
Baillargeon, M.M. **15**-166
Baillargeon, V.P. **10**-1967
Baillie, C. **13**-520, **13**-522
Baine, P. **8**-31
Baines, K.M. **5**-254
Bains, S. **15**-2224, **16**-109, **16**-1986
Baiocchi, F. **12**-772
Bair, K.W. **10**-1824, **17**-254
Baird Jr., W.C. **13**-691
Baird, C.W. **14**-486
Baird, J.C. **5**-218
Baird, J.D. **13**-517
Baird, M.C. **12**-6, **14**-485
Baird, M.S. **4**-485, **16**-2073, **18**-86, **18**-181
Baird, N.C. **2**-206
Baishya, G. **10**-846, **15**-310, **15**-1438, **15**-1696
Baizer, M.M. **10**-1412, **14**-150, **14**-456, **19**-617, **19**-926, **19**-1219, **19**-1666
Baj, S. **15**-158
Bajkó, Z. **13**-683
Bajracharya, G.B. **15**-405
Bajwa, G.S. **18**-771
Bak, D.A. **13**-260, **15**-2392
Bak, R.R. **11**-144
Bakalova, S.M. **15**-2231
Baker III, T.N. **15**-1751
Baker, A.D. **1**-16, **1**-19
Baker, B.E. **13**-433
Baker, B.G. **15**-147
Baker, C. **1**-16
Baker, E.B. **5**-16
Baker, G.R. **16**-2121
Baker, J.M. **14**-87
Baker, J.R. **16**-1726
Baker, J.W. **2**-410, **2**-411, **2**-431, **10**-330
Baker, K.V. **12**-610, **12**-626
Baker, N.J. **11**-29
Baker, R. **10**-1318, **15**-2661, **18**-810
Baker, R.T. **15**-731, **19**-1588
Baker, S.R. **19**-1608
Baker-Glenn, C. **15**-1434
Bakherad, M. **13**-591, **13**-602, **13**-614
Bakke, J.M. **3**-65, **11**-145, **13**-766, **19**-437, **19**-579
Bakker, C.N.M. **11**-310
Baklouti, A. **10**-961
Bakó, P. **16**-1268
Bakoss, H.J. **11**-637
Bakshi, R.K. **18**-466
Bakthadoss, M. **11**-332
Bakulev, V.A. **16**-1521
Bakunin, V.N. **12**-34, **12**-37
Bal, G. **13**-190
Balaban, A.T. **2**-99, **2**-100, **2**-104, **2**-130, **2**-316, **11**-415, **12**-311, **15**-1781, **15**-2259, **18**-683, **18**-685, **18**-807
Balachandran, K.S. **19**-10
Balagopal, L. **15**-1757
Balakumar, R. **19**-1056
Balamraju, Y. **16**-1066
Balamurugan, R. **4**-142
Balan, C. **19**-981
Balan, D. **16**-824, **16**-829
Balanarsaiah, E. **10**-1653
Balandin, A.A. **1**-101, **15**-478
Balanikas, G. **19**-610
Balaraman, K. **14**-341
Balas, L. **13**-82
Balasubramaniam, S. **16**-2074
Balasubramanian, A. **2**-417
Balasubramanian, K. **11**-500, **19**-90
Balasubramanian, K.K. **11**-268, **11**-700, **18**-602
Balasubramanian, N. **15**-2105
Balavoine, G.G.A. **18**-432
Balcells, D. **4**-50
Balch, A.L. **2**-405, **5**-232
Balchunis, R.J. **12**-247, **16**-1691
Balci, M. **2**-274, **15**-2358, **17**-391
Balcom, B.J. **16**-1768
Bałczewski, P. **15**-1296
Balderman, D. **10**-1077
Baldino, C.M. **13**-506
Baldino, S. **17**-316
Baldovino-Pantaleón, O. **13**-150
Baldridge, K.K. **2**-88, **2**-403, **3**-210, **11**-83
Baldwin, A.R. **16**-1991
Baldwin, J.E. **5**-415, **6**-18, **6**-21, **6**-22, **12**-283, **12**-432, **14**-499, **15**-1465, **15**-2234, **15**-2308, **15**-2428, **16**-215, **16**-1259, **16**-1330, **16**-1795, **17**-483, **18**-79, **18**-160, **18**-176, **18**-177, **18**-183, **18**-213, **18**-508, **18**-533, **18**-573
Baldwin, J.E. **18**-579, **18**-584, **18**-594, **18**-597, **18**-604, **18**-606, **18**-619, **18**-666, **18**-780, **19**-58, **19**-1540
Baldwin, J.J. **4**-214
Baldwin, M.A. **17**-249
Baldwin, S.W. **15**-2445, **18**-249, **19**-1444
Baleizão, C. **16**-1516
Balenkova, E.S. **15**-2086, **15**-2088
Balensiefer, T., **16**-1592
Bales, B.C. **19**-440
Balicki, R. **19**-228, **19**-757, **19**-795, **19**-1533, **19**-1534
Balint, A.E. **12**-481
Balkenhol, F. **16**-1936
Balkovec, J.M. **4**-214
Balkus Jr., K.J. **15**-459
Ball, R.G. **15**-6, **13**-774
Ball, Z.T. **10**-1546, **15**-543, **15**-780, **15**-785, **15**-925
Balla-Achs, M. **3**-172
Ballantine, J.A. **15**-271

Ballard, R.E. **1**-16
Ballard, T.E. **15**-1887
Ballester, M. **5**-250, **5**-269, **16**-1271
Ballester, P. **13**-23
Ballesteros, A. **10**-686
Ballestri, M. **10**-1278, **14**-96, **15**-68, **19**-1399
Ballini, R. **10**-870, **10**-1056, **12**-82, **12**-720, **15**-1048, **15**-1051, **16**-91, **16**-94, **16**-212, **16**-298, **16**-827, **16**-1199, **16**-1207, **19**-642, **19**-1515
Ballistreri, F.P. **16**-2273, **19**-770
Ballod, A.P. **12**-209
Ballweg, D.M. **16**-894
Bally, T. **2**-218, **2**-233, **5**-439
Balog, M. **2**-485
Balsells, J. **15**-2562
Balta, B. **18**-708
Baltork, I.M. **16**-80, **19**-247
Baltzly, R. **10**-952
Balu, N. **16**-795
Bal'yan, Kh.V. **18**-718
Balzani, V. **3**-194, **7**-13
Bambridge, K. **16**-880
Bamfield, P. **13**-483
Bamford, C.H. **5**-387, **6**-11, **6**-52, **6**-55, **6**-58, **6**-59, **6**-60, **7**-48, **8**-108, **8**-114, **8**-148, **10**-226, **11**-2, **11**-111, **11**-201, **11**-212, **11**-271, **11**-580, **11**-648, **11**-651, **11**-668, **11**-673, **11**-700, **12**-2, **12**-24, **12**-38, **12**-57, **12**-448, **12**-533, **12**-579, **12**-668, **13**-4, **13**-745, **14**-77, **15**-479, **16**-16, **16**-1613, **16**-1619, **16**-1653, **16**-1665, **16**-1693, **17**-3, **17**-8, **17**-40, **17**-42, **17**-61, **17**-128, **17**-180, **18**-627, **18**-788, **19**-2, **19**-675
Bamford, W.R. **17**-282
Bamkole, T. **17**-150
Bamoniri, A. **10**-664
Ban, H. **15**-1546
Ban, Y. **13**-763
Banaag, A.R. **15**-1089
Banait, N. **10**-346, **15**-219
Banait, N.S. **17**-52
Banchet, A. **16**-534
Banciu, M. **2**-99, **2**-316, **18**-683, **18**-685
Banco-Urgoiti, J. **15**-1558
Bandarage, U.K. **19**-150
Bandera, D. **2**-403
Bandgar, B.P. **10**-803, **10**-848, **10**-1170, **11**-219, **11**-448, **13**-534, **16**-55, **16**-1211, **16**-1707, **16**-1725, **16**-1787, **16**-1790, **16**-2022, **16**-2311, **19**-1422
Bandin, E. **15**-2380
Bandini, M. **10**-1544, **16**-1513
Bando, M. **10**-1724
Bando, T. **18**-787
Bandyapadhyay, A. **17**-370
Bandyopadhyay, A. **17**-401
Bandyopadhyay, A. **19**-1580
Bandyopadhyay, A.K. **10**-1618
Bandyopadhyay, T. **19**-1299
Baneres, J.-L. **18**-157
Banerjee, A. **15**-2344
Banerjee, A.K. **19**-1418
Banerjee, B. **11**-250, **16**-149
Banerjee, D. **13**-362, **16**-2037
Banerjee, J. **15**-1212, **16**-1630
Banerjee, S. **10**-1230, **14**-425, **16**-666, **17**-216, **18**-167, **18**-705
Banerjee, S.K. **10**-620
Banerji, A. **19**-1442, **19**-1601, **19**-1688
Banerji, K.K. **19**-635, **19**-693, **19**-808
Banert, K. **10**-334
Banfi, S. **15**-1959
Banik, B.K. **7**-109, **15**-1386, **16**-254, **16**-569, **16**-2219, **19**-216, **19**-1125, **19**-1126, **19**-1184, **19**-1187, **19**-1629
Banik, I. **16**-254, **19**-1125, **19**-1184, **19**-1629
Banik, N.K. **16**-193
Bank, J. **10**-1016
Bank, S. **10**-100, **10**-135, **10**-954
Bankovskii, Yu.A. **3**-55
Banks, J.-T. **18**-89
Banks, J.T. **14**-82
Banks, J.T. **14**-89
Banks, J.T. **5**-330
Banks, R.L. **18**-807
Banks, R.L. **18**-813
Banks, R.L. **18**-813
Banks, R.L. **18**-815
Bankston, D. **19**-400
Bannister, T.D. **4**-126
Bannister, W. J. **12**-488
Bannwarth, W. **16**-1934
Bansal, G. **17**-372
Bansal, R.K. **16**-1269
Banthorpe, D.V. **3**-86, **11**-30, **11**-611, **11**-614, **17**-93, **17**-117, **17**-120, **17**-249, **18**-96, **18**-99, **18**-306, **18**-317, **18**-788, **18**-791, **18**-792, **18**-793, **18**-794
Banwell, M. **16**-1912
Banwell, M.G. **4**-485, **15**-2488
Banwell, T. **11**-62
Banziu, M. **18**-685
Bao, F. **15**-782
Bao, H. **10**-977
Bao, J. **13**-450
Bao, J. **15**-643
Bao, L.Q. **12**-182
Bao, M. **16**-744
Bao, W. **14**-299, **16**-582, **16**-1051, **16**-2039, **19**-184, **19**-202
Bao, X. **19**-1182
Bao, Z. **16**-546
Bar, G.L.J. **15**-2040
Bar, N. **13**-495
Bar, S. **11**-322
Barabé, F. **10**-1025, **13**-340
Barager III, H.J. **12**-187, **19**-798
Baragwanath, L. **16**-1591
Barahate, N.B. **10**-679
Barak, G. **10**-628
Baram, S.G. **9**-20
Baran, J. **15**-2149
Baran, P.S. **19**-599
Baranne-Lafont, J. **19**-271
Baránski, A. **13**-762
Barany, G. **16**-1929
Barar, D.G. **17**-182
Baratta, W. **13**-503, **17**-269
Barba, G.R. **17**-296
Barbachyn, M.R. **4**-48, **15**-1853
Barbarow, J.E. **18**-504
Barbas III, C.F. **12**-148, **15**-1052, **15**-1056, **15**-1109, **16**-395, **16**-914, **16**-958, **16**-961, **16**-1080, **16**-1081, **16**-1082, **16**-1085, **16**-1324
Barbayianni, E. **16**-1624
Barbe, G. **19**-1481
Barber, J. **10**-1250
Barber, J.J. **12**-634
Barber, M. **4**-523
Barbier, J. **15**-447
Barbier, P. **16**-471
Barbillat, J. **14**-255
Barboni, L. **10**-1056, **16**-827
Barborak, J.C. **18**-9
Barbosa, A.G.H. **11**-123
Barbosa, M.C.N. **14**-379, **14**-383, **14**-384
Barbot, F. **15**-43
Barbour, J.B. **5**-33
Barbour, L.J. **3**-94, **3**-178
Barbry, D. **16**-345, **16**-347, **18**-413, **19**-630, **19**-948
Barbu, E. **10**-1053
Barcan, G.A. **15**-1418
Barchuk, A. **16**-946
Barcina, J.O. **10**-1435, **10**-1488
Barcina, J.O. **11**-498
Barclay, L.R.C. **4**-523, **11**-365, **16**-1668, **18**-78
Barco, A. **15**-2385
Barcóczy, J. **2**-489
Barczynski, P. **2**-101
Bard, A.J. **14**-458
Bard, R.R. **13**-656, **13**-657
Bardales, E. **10**-1236, **17**-219, **17**-400, **19**-873
Barden, M.C. **15**-2140, **19**-1644
Bardenm, T.C. **14**-499
Barder, T.E. **10**-1027, **13**-131, **13**-494, **13**-570, **13**-707
Bareille, L. **16**-575
Baret, P. **4**-252
Baretta, A. **18**-206
Bargar, T. **13**-656

Barge, A. **16**-1872
Barger, T.M. **17**-466
Bargiggia, F. **15**-160
Bargiggia, F.C. **18**-852
Bargon, J. **5**-229, **5**-232, **14**-367
Bargon, R.M. **15**-1998, **15**-2002
Barhdadi, R. **10**-1956
Barić, D. **4**-423, **4**-424
Barid Jr., T.A. **4**-475
Barik, S.K. **11**-302
Barilli, P. **14**-382
Bariwal, J.B. **10**-918
Bark, T. **15**-1357
Barker, J.M. **18**-315
Barker, P.J. **5**-311
Barkhash, V.A. **10**-131, **10**-424
Barkley, R.M. **10**-522
Barlow, M.G. **18**-528
Barlow, S.E. **5**-113, **10**-363
Barltrop, J.A. **7**-1, **11**-699, **16**-2195, **16**-2206
Barluenga, J. **10**-686, **12**-433, **12**-454, **14**-162, **15**-372, **15**-383, **15**-1672, **15**-1673, **15**-2029, **15**-2031, **15**-2036, **15**-2133, **15**-2500, **15**-2526, **15**-2654, **15**-2657, **17**-271, **18**-276
Barma, D.K. **16**-1432
Barman, D.C. **19**-295, **19**-1537
Barnard, C.F.J. **13**-547
Barnard, P.W.C. **10**-548
Barnard, T.M. **13**-397
Barnatt, A. **17**-232
Barnea, E. **16**-1013, **19**-1745
Barner, L., **16**-218
Barnes, C.L. **15**-710, **15**-1093, **19**-972
Barnes, C.S. **19**-47
Barnes, D. **19**-1232
Barnes, D.M. **15**-2249
Barnes, M.W. **19**-741
Barneto, J.L. **4**-312, **4**-315
Barnett, D.S. **16**-751
Barnett, J.W. **11**-100, **16**-1705
Barnette, W.E. **12**-141
Barney, C.L. **16**-339
Barnhart, R.W. **15**-1478, **15**-1484
Barnhart, T.M. **10**-1403
Barnhurst, L.A. **10**-836
Barnier, J.P. **18**-589
Baron D.L. **19**-1567
Baron W. **10**-955
Barón, M. **16**-2185
Baron, R. **19**-936
Baroni, A.C.M. **15**-322, **15**-1676
Baroni, M. **13**-487
Barr, D. **13**-726
Barr, D.P. **5**-307
Barrault, J. **10**-807
Barreiro, E. **10**-1504
Barrelle, M. **15**-183
Barren, J.P. **11**-692
Barrero, A.F. **15**-597, **15**-1330, **19**-342, **19**-912
Barrett, A.G.M. **10**-745, **10**-1043, **11**-136, **11**-417, **11**-438, **16**-777, **16**-1199, **16**-1246, **16**-1298, **16**-1367, **16**-1888, **16**-2235, **17**-270, **17**-338, **18**-871, **19**-124, **19**-600, **19**-1197, **19**-1390, **19**-1391, **19**-1746
Barrett, I.C. **13**-5, **16**-277
Barriault, L. **18**-632
Barrientos-Astigarraga, R.E. **16**-700
Barrio, J.R. **10**-1115
Barrio, P. **15**-2133
Barrish, J.C. **15**-691
Barron B.G. **19**-1363
Barron, L.D. **4**-6. **4**-17, **4**-158
Barros, D. **15**-1942
Barros, I.M.A. **16**-1898
Barrow, M.J. **2**-181
Barry, B.J. **12**-81
Barry, J. **16**-1797, **17**-309
Bart, S.C. **15**-664
Bartell, L.S. **1**-59, **1**-64, **1**-79
Bartels, H.M. **15**-113
Bartelson, K. **15**-2252
Barter, R.M. **19**-98
Barth, G. **4**-22
Barth, J. **10**-1247
Bartholomew, E.R. **10**-1410
Barthuber, A. **16**-1496
Bartik, K. **7**-80
Bartkus, E.A. **13**-846
Bartlett, P.A. **4**-141, **10**-1602, **15**-3, **15**-818, **15**-1710, **16**-5, **18**-627, **18**-691
Bartlett, P.D. **4**-532, **9**-7, **10**-50, **10**-131, **10**-135, **14**-254, **15**-29, **15**-1875, **15**-2309, **15**-2364, **15**-2366, **15**-2417, **15**-2419, **15**-2431, **15**-2461, **16**-507
Bartlett, R.J. **3**-47
Bartlett, R.S. **19**-1218
Bartley, J.P. **10**-1113
Bartmess, J. **8**-162
Bartmess, J.E. **2**-259, **8**-248, **8**-252, **8**-253, **8**-255
Bartnicka, H. **8**-246
Bartók, M. **10**-406, **17**-176, **18**-125
Bartok, W. **19**-839
Bartolacci, M. **15**-1397
Bartoli, G. **10**-616, **10**-972, **10**-1125, **10**-1189, **11**-314, **11**-483, **13**-83, **15**-910, **15**-1065, **15**-1106, **15**-1182, **15**-1238, **15**-1388, **15**-1397, **16**-606, **16**-610, **16**-1229, **16**-1242, **16**-1723, **17**-164, **19**-969, **19**-1254
Barton, D.H.R. **4**-533, **5**-329, **9**-15, **10**-785, **10**-579, **12**-253, **12**-353, **12**-549, **12**-765, **13**-227, **13**-651, **13**-659, **14**-153, **14**-248, **14**-372, **14**-373, **14**-462, **14**-476, **16**-2175, **17**-130, **17**-142, **17**-338, **17**-525, **18**-927, **18**-928, **18**-929, **19**-47, **19**-51, **19**-421, **19**-422, **19**-487, **19**-488, **19**-489, **19**-1237, **19**-1381, **19**-1383, **19**-1384, **19**-1390, **19**-1391, **19**-1393, **19**-1395, **19**-1419, **19**-1522
Barton, H.J. **16**-1980
Barton, J.K. **10**-222
Barton, T.J. **8**-24, **18**-568, **18**-673
Bartoszewicz, A. **10**-633
Bartsch, M. **15**-2022
Bartsch, R.A. **3**-183, **9**-139, **10**-501, **17**-95, **13**-776, **16**-835, **17**-8, **17**-16, **17**-23, **17**-24, **17**-31, **17**-33, **17**-92, **17**-97, **17**-98
Bartuska, V.J. **10**-1185
Baru, A.R. **16**-137
Barua, N.C. **10**-1058, **10**-989, **10**-1171, **16**-1213, **19**-907
Baruah, A. **10**-1058
Baruah, B. **16**-2030, **19**-1669
Baruah, M. **10**-1482, **16**-375, **19**-1256, **19**-1413, **19**-1730
Barun, O. **18**-257
Barvian, N.C. **13**-874
Basak, A. **10**-748
Basak, A.K. **9**-133, **13**-174, **16**-1234
Basavaiah, D. **11**-332, **15**-680, **16**-785, **16**-790, **16**-826, **18**-468, **18**-476, **18**-480, **19**-1021, **19**-1024, **19**-1727
Basch, H. **1**-19, **10**-27, **10**-28, **10**-117, **10**-336, **10**-338
Baseer, M.A. **11**-259
Basetti, M. **15**-205
Basha, A. **12**-540
Bashe, R.W. **10**-1423
Bashore, C. **5**-422
Bashore, C.G. **13**-46
Baskaran, S. **10**-1004, **12**-768, **15**-193, **15**-194, **15**-2109, **16**-1058, **19**-708, **19**-712
Baskin, J.M. **13**-161
Basl, O. **11**-426
Basra, S. **16**-899
Bass, L.S. **15**-1853
Bassarello, C. **4**-123
Basselier, J. **11**-229
Bassendale, A.R. **18**-958
Basset, J.-M. **5**-413, **18**-873, **19**-37, **18**-807, **18**-842, appendixa-26
Bassetti, M. **15**-279, **15**-862
Bassindale, A.R. **1**-48, **15**-292, **16**-1293
Bässler, T. **10**-265
Basso, E. **2**-423
Basso, E.A. **4**-366
Bast, P. **5**-155
Bastiaan, E.W. **2**-67

Bastiansen, O. **2**-265, **3**-56, **4**-270, **4**-329
Bastide, J. **15**-2150, **15**-2253
Bastien, I.J. **5**-16
Bastos, C. **4**-150, **15**-635
Basu, A. **5**-196, **10**-651, **10**-1344
Basu, B. **13**-204, **13**-504, **15**-654
Basu, M.K. **16**-107, **16**-193, **16**-569, **16**-1625, **19**-1187
Basu, P.K. **15**-1343, **15**-1373
Basu, S.N. **19**-92, **19**-94
Batal, D.J. **15**-1965
Bateman, L.C. **10**-43, **10**-46, **10**-347
Bates, C.G. **12**-305
Bates, D.M. **7**-86
Bates, G.S. **19**-1281
Bates, R.B. **5**-105, **15**-580
Bates, T.F. **5**-158
Batey, R.A. **10**-871, **10**-649, **10**-1285, **10**-1892, **13**-225, **16**-761, **16**-762, **16**-1916
Batlaw, R. **12**-640
Batlle, A. **13**-69
Batog, A.E. **15**-1878
Batory, L.A. **18**-262, **18**-263
Batr, R. **19**-59
Batra, H. **15**-1735
Batrak, T.A. **15**-1878
Bats, J.-P. **10**-995
Batsanov, S.S. **1**-25
Batt, F. **19**-128
Batt, L. **5**-312, **6**-55
Battace, A. **13**-409
Battaglia, A. **4**-123
Battiste, M.A. **2**-178, **8**-78, **10**-159, **15**-135, **15**-139, **16**-1291
Battle, G.M. **16**-2231
Batts, B.D. **10**-547
Baucherel, X. **19**-185
Baud, C. **15**-2066
Baudequin, C. **9**-137
Bauder, A. **2**-202, **2**-458
Baudin, J. **19**-818
Baudoin, O. **13**-540
Baudoux, D. **10**-1794
Baudouy, R. **10**-1422
Baudry, D. **18**-216
Baudry, M. **15**-914
Bauduin, C. **19**-766
Bauer, D. **19**-1644
Bauer, L. **18**-313
Bauer, M. **16**-2186
Bauer, P. **16**-471, **16**-507
Bauer, S.H. **2**-64
Bauer, W. **5**-161, **5**-183, **5**-184, **5**-193, **12**-431, **12**-578
Baugh, S.P.D. **10**-760
Baughman, E.H. **8**-131
Baughman, T.W. **10**-1695
Bauld, N.L. **2**-235, **14**-459, **15**-2197, **15**-2198, **18**-623
Baum, A.A. **18**-911
Baum, E.W. **10**-1544, **15**-2692
Baum, J.S. **2**-221, **12**-221
Baum, K. **12**-218, **12**-764
Baum, M.W. **6**-73
Baum, S. **18**-683
Baumann, H. **2**-320, **2**-327
Baumann, M.E. **18**-133
Baumann, W. **15**-647
Baume, E. **13**-477
Baumgarten, H.E. **18**-283, **18**-288, **18**-301
Baumgarten, R.J. **10**-414, **10**-415, **10**-752, **17**-247
Baumgartner, M.T. **13**-354
Bäuml, E. **15**-2095
Baumstark, A.L. **19**-226, **19**-1692
Baumstark, R. **5**-11
Baus, U. **4**-147
Bausch, C.C. **16**-1593, **16**-1594
Bausch, M.J. **5**-259
Bauslaugh, P.G. **15**-2448
Bauta, W.E. **13**-101
Bautista, F.M. **15**-482
Baxendale, I.R. **13**-506
Baxendale, I.R. **15**-157
Baxter III, H.N. **14**-138
Baxter, A.G.W. **18**-181
Baxter, S.L. **14**-440, **19**-1452, **19**-1560
Bay, E. **13**-260, **18**-911, **18**-914
Bayardon, J. **15**-2514
Bayer, E. **10**-890, **10**-1142, **16**-1929
Bayer, R.P. **19**-728
Bayle, J.P. **19**-673
Baylis, A.B. **16**-790
Baylon, C. **10**-1277
Baylouny, R.A. **17**-148, **18**-586
Bayón, J.C. **15**-1614
Bayquen, A.V. **10**-1083
Bays, J.T. **19**-484
Bazán-Tejeda, B. **16**-1150
Bazán-Tejeda, B. **16**-1162
Bazan, G.C. **18**-818
Bazaral, C. **13**-673
Bazarova, I.M. **10**-1664, **12**-201
Bazdi, B. **16**-575
Baze, M.E. **4**-499
Baze, M.E. **15**-2418, **15**-279
Bazureau, J.P. **15**-2125
Beadle, B.M. **10**-124
Beadle, J.R. **13**-776, **13**-823
Beagley, B. **4**-301
Beak, P. **2**-471, **2**-472, **5**-131, **5**-131, **6**-37, **10**-57, **10**-58, **10**-1334, **10**-1335, **10**-1343, **10**-1343, **10**-1345, **10**-1832, **10**-1835, **10**-1843, **12**-429, **12**-433, **12**-538, **12**-539, **12**-540, **12**-659, **13**-728, **15**-1194, **15**-2167, **16**-874, **16**-1572
Beal, M.F. **5**-222
Beale, W.J. **12**-81
Bean, C.J. **16**-1444
Bean, D.E. **2**-371
Bean, F.R. **12**-471
Beard, W.Q. **13**-848, **13**-849
Bearpark, M.J. **15**-2454
Beatle, J.C. **18**-647
Beaton, J.M. **18**-929
Beatty, H.R. **13**-256
Beauchamp, J.L. **5**-76, **5**-87
Beauchamp, P.S. **11**-324, **15**-2622
Beauchamp, T. **5**-266
Beauchemin, A. **15**-2569
Beauchemin, A.M. **15**-1291
Beaudegnies, R. **15**-2338
Beaudoin, S. **16**-1374
Beaudry, C.M. **15**-2271, **18**-500
Beaufort, L. **15**-2501
Beaulieu, C. **16**-2312
Beaumont, S.K. **13**-613
Beauseigneur, A. **14**-17
Beautement, K. **10**-727
Bebb, R.L. **10**-1350, **12**-409
Bebout, D.C. **5**-80
Becattini, B. **14**-17, **15**-1332
Becht, J.-M. **13**-304, **13**-494, **13**-509, **13**-723, **15**-1070
Beck Jr., K.R. **19**-742
Beck, A.K. **16**-2124
Beck, B. **13**-277
Beck, B.R. **4**-466
Beck, E.J. **17**-362
Beck, E.M. **13**-220
Beck, F. **19**-544
Beck, J.P. **15**-2216
Beck, J.R. **13**-88
Beck, K. **18**-849
Beck, S.M. **11**-602
Becke, A.A.A. **3**-1
Beckendorf, S. **10**-1309
Becker, A.R. **12**-750
Becker, D. **15**-2429, **15**-2451, **15**-2459
Becker, D.A. **5**-222
Becker, E.I. **2**-184, **17**-429
Becker, F.F. **16**-193, **16**-2219, **19**-216, **19**-1125, **19**-1126, **19**-1184, **19**-1187
Becker, H.-C. **4**-55
Becker, H.-D. **4**-55, **7**-39
Becker, H. **2**-453, **16**-2045, **19**-22
Becker, H.G.O. **13**-806
Becker, J. **16**-1312
Becker, J.Y. **2**-203
Becker, K.B. **4**-514, **4**-515, **14**-475, **15**-35, **16**-1395, **17**-405
Becker, N. **1**-45, **15**-1878
Becker, R. **19**-1233
Becker, R.H. **18**-418
Becker, S. **10**-1311, **14**-442, **19**-1563
Becker, W.E. **5**-171
Becker, Y. **17**-330
Beckhaus, H. **5**-284
Beckhaus, H.-D. **1**-113, **4**-399, **5**-280

Beckhaus, H. **4**-306, **9**-77
Beckhaus, K. **4**-422
Beckler, J.D. **12**-605
Beckley, R.S. **18**-901
Beckman, E.J. **9**-105
Beckmann, W. **3**-204
Beckwith, A.L.J. **1**-113, **5**-280, **11**-689, **13**-791, **13**-799, **14**-35, **14**-99, **14**-115, **14**-283, **15**-53, **15**-104, **15**-105, **15**-1319, **15**-1350, **16**-9, **16**-106, **16**-1856, **16**-1878, **16**-1894, **16**-1937, **18**-54, **18**-61, **18**-320, **18**-345, **18**-927, **19**-423, **19**-590
Beckwith, R.E.J. **12**-395
Bedekar, A.V. **11**-252, **11**-294, **15**-1784, **15**-2063, **15**-2066
Bedel, O. **15**-1844
Bedenbaugh, A.O. **10**-148, **19**-1092
Bedenbaugh, J.H. **19**-1092
Bedford, A.F. **1**-103
Bedford, C.D. **12**-743
Bedford, R.B. **10**-1366, **10**-1367, **10**-1368, **13**-338, **13**-554
Bednarz, S. **15**-1904
Bedworth, P.V. **16**-485
Beebe Jr., T.P. **15**-485
Beech, W.F. **14**-404
Beels, C.M.D. **17**-345
Beenen, M.A. **16**-945
Beer, P.D. **7**-65
Beeson, T.D. **12**-146
Begley, M.J. **16**-880
Begtrup, M. **16**-2025
Bégué, J.-P. **10**-969, **15**-1897, **16**-896, **16**-936, **19**-833
Bégué, J. **10**-311, **10**-516, **18**-216, **19**-59
Begum, S.A. **14**-414
Behar, V. **5**-343
Behbahani, F.K. **10**-674, **19**-34
Behenna, D.C. **10**-1735
Beheshtiha, Y.S. **19**-1639
Behforouz, M. **16**-273
Behling, J.R. **12**-601
Behnam, S.E. **12**-88
Behnam, S.M. **12**-88
Behnke, M. **15**-1247
Beholz, L.G. **18**-642
Behr, L.C. **18**-945
Behrens, C.H. **10**-525, **10**-527, **10**-697
Behrens, O.K. **19**-1499
Behrman, E.J. **10**-392, **11**-572
Behrouz, S. **10**-1066
Bei, X. **19**-211
Beilen, J.B. **19**-540
Beiner, J.M. **16**-1466
Bejan, E. **18**-432
Bejan, E.V. **14**-239
Bekárek, V. **10**-479
Bekker, R.A. **2**-456
Beland, F. **16**-339
Belanger, D.B. **18**-835
Bélanger, É. **10**-1757
Bélanger, G. **16**-261
Bélanger, J.M.R. **15**-2203
Belarmino, A.T.N. **10**-560
Belderraín, T.R. **12**-375, **15**-2507, **19**-535
Beleggia, R. **16**-1229, **16**-1242
Belelie, J.L. **10**-1516
Belen'kii, G.G. **15**-73
Belen'kii, L.I. **4**-477, **11**-318, **11**-411, **14**-439, **19**-1559, appendixa-31
Beletskaya, I.P. **5**-106, **5**-136, **8**-16, **8**-17, **10**-61, **10**-360, **10**-509, **10**-520, **10**-798, **10**-1333, **10**-1391, **10**-1488, **10**-1556, **10**-1988, **10**-1994, **12**-2, **12**-34, **12**-37, **12**-552, **12**-555, **12**-655, **12**-662, **12**-703, **13**-165, **13**-274, **13**-369, **13**-486, **13**-580, **13**-644, **13**-670, **14**-393, **14**-419, **15**-318, **15**-385, **15**-393, **15**-397, **15**-797, **15**-968, **16**-512, **18**-439, **19**-418
Belevskii, V.N. **5**-221
Belew, J.S. **19**-331
Belfield, A.J. **15**-1091
Belfield, K.D. **18**-597
Belikov, V.M. **4**-139
Belin, B. **10**-910
Belisle, C.M. **19**-1141
Belkin, Yu.V. **16**-1470
Belkin, Yu.V. **2**-94
Belkova, N.V. **3**-5
Bell, A. **15**-2395
Bell, F. **11**-78
Bell, H.C. **14**-371
Bell, H.M. **19**-1327
Bell, J.A. **12**-403
Bell, K. **10**-565
Bell, M. **16**-775, **16**-776, **18**-391
Bell, M.L. **2**-317
Bell, N.A. **5**-163, **5**-257
Bell, R.P. **6**-66, **8**-1, **8**-2, **8**-28, **8**-49, **8**-149, **8**-175, **12**-91, **12**-159, **16**-38, **16**-39
Bell, T.W. **10**-1219, **10**-1373
Bella, M. **13**-635
Bellassoued, M. **10**-1750, **16**-1126, **16**-1300
Bellatti, M. **14**-385
Bellemin-Laponnaz, S. **19**-1039
Beller, M. **10**-909, **10**-927, **10**-933, **10**-1309, **11**-349, **11**-507, **11**-521, **11**-543, **12**-769, **13**-98, **13**-162, **13**-288, **13**-382, **13**-499, **13**-676, **13**-860, **14**-307, **15**-325, **15**-330, **15**-357, **15**-363, **15**-366, **15**-1497, **15**-1830, **15**-1885, **15**-1901, **16**-278, **17**-472, **17**-473, **19**-231, **19**-929, **19**-1037, **19**-1161, **19**-1478
Bellesia, F. **12**-115, **12**-117, **15**-1654, **15**-1732
Belletire, J.L. **4**-214
Belley, M. **15**-295
Bellina, F. **10**-1888, **13**-, **13**-582
Bello, C.S. **10**-1467
Belloli, R. **2**-139, **4**-26
Bellosta, V. **5**-314, **10**-979, **10**-1005, **16**-1559, **16**-2075
Bellucci, G. **15**-12, **15**-14, **15**-22, **15**-37, **15**-1649, **15**-1651, **15**-1657
Bellucci, M.C. **10**-1125, **15**-1065, **17**-164, **19**-969
Bellus, D. **11**-594, **11**-597, **15**-1775, **15**-2384
Belmonte, F.G. **15**-582
Belokon', Y.N. **16**-1284, **16**-1285, **16**-1518
Belotti, D. **16**-1579, **19**-14
Belotti, S. **19**-257
Belousova, L.I. **16**-2114
Belova, N.V. **2**-450
Belpassi, L. **17**-57
Belsner, K. **10**-1237
Belson, D.J. **11**-148
Beltrame, P. **17**-81
Belyaev, V.A. **14**-243
Bemis, A.G. **14**-248
Ben-Mergui, N. **2**-71
Ben-Efraim, D.A. **4**-221
Ben-David, Y. **10**-1967
Ben-Efraim, D.A. **10**-1898
Ben-Zion, M. **10**-29
Ben-Shoshan, B. **15**-145
Ben-Efraim, D.A. **17**-154, **17**-313, **18**-881
Ben-Daniel, R. **19**-167
Ben-David, Y. **19**-658, **19**-1075
Ben Salem, R. **16**-1568, **16**-1569
Benaglia, M. **16**-776, **16**-927, **16**-1081, **16**-1085, **19**-179, **19**-1156
Benaim, J. **10**-1797
Benati, L. **15**-2080, **18**-327, **19**-1258
Bencivenni, G. **19**-1258
Bendale, P.M. **16**-108
Bender, C.J. **3**-103
Bender, M.L. **3**-183, **6**-42, **6**-78, **8**-148, **16**-23, **16**-24, **16**-26, **16**-33, **16**-35, **16**-1614, **16**-1623, **16**-1663, **16**-1689, **16**-1875
Benderly, A. **16**-1039
Bendikov, M. **5**-276
Bendová, L. **16**-1490
Benedetti, E. **8**-31
Benedetti, F. **6**-15
Benet-Buchholz, J. **2**-58, **4**-460
Benezra, C. **10**-1209
Benfey, O.T. **10**-42
Bengtson, A. **10**-781
Benhaim, C. **10**-1506
Beni, Y.A. **16**-64, **19**-256

Benicewicz, B.C. **15**-299, **16**-1780
Benito-López, F. **9**-86
Benjamin, B.M. **18**-16, **18**-40
Benjamin, S.B. **16**-1809
Benjaminov, B.S. **18**-40
Benkeser, R.A. **12**-435, **12**-436, **12**-606, **12**-693, **15**-497, **15**-581, **15**-582, **19**-1474, **19**-1488, **19**-1489, **19**-1490
Benkovic, P.A. **16**-381
Benkovic, S.J. **16**-381
Benn, R. **5**-170
Bennabi, S. **15**-1138
Bennacer, B. **15**-2695
Bennani, Y.L. **15**-1832, **15**-1843
Benner, C.W. **18**-658
Benner, J.P. **16**-1573
Benner, S.A. **4**-261
Bennet, A.J. **15**-12, **16**-1700, **16**-1701
Bennett, C.E. **15**-808
Bennett, G.B. **16**-2006 **18**-691
Bennett, G.D. **16**-561
Bennett, J.M. **11**-109, **11**-271
Bennett, J.N. **15**-2169, **15**-2268
Bennett, M.A. **2**-46, **3**-89, **4**-501
Bennett, R.G. **7**-30
Bennett, R.P. **11**-175, **12**-777
Bennett, S.M. **15**-932
Bennett, W.D. **13**-651
Benning, W.F. **16**-283
Bennouna, L. **3**-141
Bennur, T.H. **19**-1648
Beno, B.R. **15**-2280
Benoit, R.L. **8**-207, **8**-236
Bensari, A. **11**-444
Benson, C.L. **15**-1530
Benson, G.A. **11**-606
Benson, S.W. **1**-96, **15**-60
Benson, W.R. **18**-550
Bent, H.A. **1**-7, **1**-53, **3**-103
Bentley, J.T. **16**-666
Bentley, K.W. **4**-104, **17**-244, **19**-12, **19**-300, **19**-843
Bentley, M.D. **3**-88
Bentley, P.A. **12**-114, **15**-1958, **16**-157
Bentley, T.W. **10**-92, **10**-146, **10**-298, **10**-342, **10**-343, **10**-409, **10**-430, **10**-435, **10**-452, **10**-461, **10**-464, **10**-465, **10**-466, **10**-468, **10**-469, **16**-17, **16**-1612, **16**-1614, **16**-1706
Bento, A.P. **10**-2
Bentrude, W.G. **5**-262, **18**-62
Bentrup, KL.H. **16**-2129
Bentz, E. **10**-1493
Beockman Jr., R.K. **15**-1465
Bera, M. **10**-1654
Beránek, L. **17**-180
Berbdk, H. **19**-1734
Bercaw, J.E. **15**-354, **15**-773, **15**-2644
Bercaw, J.E. **19**-15
Bérces, A. **4**-281
Bérces, T. **7**-48
Bercot, E.A. **16**-2099, **16**-2100
Berdahl, D.R. **15**-2494
Berdnikov, V.M. **14**-351
Berecoechea, J. **16**-2182
Berecz, E. **3**-172
Berg, U. **4**-283, **4**-345, **4**-526, **9**-65, **9**-68, **10**-879
Bergbreiter, D.E. **10**-1404, **10**-1799, **10**-1855, **12**-15, **15**-1774, **16**-2008, **19**-1284
Bergens, S.H. **12**-72, **15**-1478, **19**-1732
Berger, D. **15**-1596
Berger, J.G. **5**-419, **12**-364
Berger, M. **19**-330
Berger, P. **13**-665
Berger, R. **2**-260, **16**-954
Berger, S. **15**-1214, **16**-1351
Bergeron, R. **3**-183, **16**-2295
Bergeron, R.J. **3**-183
Bergersen, H. **11**-42
Bergin, E. **19**-767
Bergin, W.A. **19**-1092
Berglund-Larsson, U. **11**-7
Berglund, P. **10**-956, **15**-1110
Bergman R.G. **15**-367
Bergman, A. **4**-490
Bergman, R. **15**-2207
Bergman, R.G. **5**-302, **10**-270, **10**-272, **11**-417, **15**-327, **15**-382, **15**-967, **15**-1429, **15**-2644, **16**-986, **17**-464, **18**-39, **18**-100, **18**-176, **18**-178, **18**-504, **18**-522, **18**-687, **18**-747, **19**-807, **19**-1259
Bergmann, D. **1**-31
Bergmann, E.D. **2**-99, **2**-193, **2**-229, **10**-1215, **14**-491, **14**-493, **15**-1032
Bergmans, W. **4**-161
Bergquist, K.-E. **15**-1066
Bergson, G. **12**-63, **12**-64
Bergstad, K. **15**-1801
Bergstrom, R.G. **10**-551, **13**-36
Berhal, F. **4**-155
Beringer, F.M. **19**-1416
Berk, S.C. **16**-2009
Berkessel, A. **16**-576, **16**-815
Berkheimer, H.E. **5**-73, **8**-134
Berkoff, C.E. **12**-727
Berkovitch-Yellin, Z. **4**-104, **4**-195
Berkowitz, D.B. **19**-1302
Berkowitz, W.F. **10**-1479, **18**-286
Berks, A.H. **5**-133
Berlan, J. **7**-109, **7**-120, **15**-1114, **16**-102
Berlin, J.M. **18**-844
Berliner, E. **9**-37, **11**-77, **13**-78, **15**-85
Berliner, M.A. **15**-329
Berman, A.M. **13**-215, **13**-216
Berman, J.D. **14**-496
Bermudez, A. **18**-399
Bernabé, M. **10**-1611
Bernabé, P. **16**-1844
Bernad, P.L. **17**-400
Bernadou, F. **10**-1898, **17**-154
Bernard, D. **10**-1313
Bernard, H.W. **5**-365
Bernard, J.-M. **19**-1600
Bernard, M. **16**-1322
Bernardelli, P. **10**-1590
Bernardi, A. **16**-1098
Bernardi, C.R. **13**-575
Bernardi, F. **2**-94, **4**-48, **4**-303, **5**-126, **5**-127, **5**-128, **10**-800, **15**-21, **15**-2298, **15**-2421, **15**-2559, **16**-1470, **18**-906
Bernardi, L. **10**-1568, **10**-1915, **15**-1049, **16**-976
Bernardi, R. **14**-172
Bernardinelli, G. **4**-488, **15**-1034, **15**-2047, **15**-2235
Bernardo, J.E. **19**-899, **19**-1335
Bernasconi, C.F. **5**-129, **5**-218, **6**-9, **6**-25, **6**-34, **6**-42, **6**-43, **6**-46, **6**-58, **6**-59, **6**-62, **6**-65, **6**-66, **8**-108, **8**-115, **9**-16, **10**-255, **11**-117, **12**-100, **13**-4, **13**-16, **15**-42, **15**-189, **15**-192
Bernatchez, M. **16**-2052
Bernáth, G. **16**-36
Bernath, P.F. **5**-430
Berndt, A. **15**-95, **17**-59
Berneis, H.L. **17**-113
Berner, D. **10**-423, **18**-127
Bernhardt, J.C. **14**-427
Bernhardt, S. **13**-95
Bernheim, M. **12**-538
Bernheim, R.A. **5**-365
Berninger, R.W. **11**-655
Bernini, R. **13**-163, **18**-381
Bernsmann, H. **15**-643
Bernstein, E.R. **4**-276
Bernstein, H.I. **18**-13
Bernstein, M.P. **5**-197, **8**-222
Bernstein, R.B. **6**-16, **17**-44
Bernstein, S. **19**-46
Bernstein, W.J. **4**-71, **4**-159
Beronius, P. **10**-99
Berova, N. **4**-118
Berrier, A.L. **10**-152, **10**-204, **17**-454
Berrier, C. **11**-570
Berrigan, P.J. **10**-519
Berry, J.F. **15**-1993
Bersohn, R. **5**-218
Berson, J.A. **4**-221, **9**-95, **15**-2308, **17**-428, **18**-38, **18**-39, **18**-100, **18**-104, **18**-176, **18**-587, **18**-595, **18**-596, **18**-598, **18**-599, **18**-665, **18**-667
Bersuker, I.B. **2**-268
Berteau, P. **17**-180
Bertelli, D.J. **2**-174, **2**-193
Bertelsen, S. **12**-124

Berthelette, C. **16**-1437
Berthelot, J. **11**-229
Berthelot, M. **1**-54, **8**-101, **8**-102, **8**-104, **8**-105, **8**-106, **8**-107
Berther, C. **19**-733
Berthet, J.-C. **16**-1013
Berthier, G. **2**-13
Berthiol, F. **13**-429, **13**-528
Berthod, M. **4**-63
Berthon-Gelloz, G. **15**-784
Berti, F. **17**-158
Berti, G. **10**-600, **10**-637, **15**-37, **15**-126, **16**-1268, **16**-1438
Bertie, J.E. **2**-239
Bertilsson, S.K. **17**-223
Bertini, F. **14**-174, **16**-484
Bertogg, A. **15**-1086
Bertolini, F. **10**-1002, **10**-1891
Bertolini, G. **16**-1125
Bertoux, F. **15**-1497
Bertozzi, C.R. **19**-1259
Bertozzi, F. **15**-2277
Bertram, A.K. **12**-368
Bertran, J. **10**-879
Bertrand, G. **5**-360, **15**-379, **16**-1846
Bertrand, J.A. **18**-123
Bertrand, M.-J. **16**-687
Bertrand, M. **15**-2393, **15**-2422
Bertrand, M.P. **17**-144
Bertrand, N. **16**-1958
Bertrand, S. **15**-1118
Bertrand, W.S. **14**-478
Bertsch, H. **17**-155
Bertsch, R.J. **19**-1282, **19**-1329
Bertus, P. **12**-303, **15**-2673, **16**-886, **16**-1482
Bertz, S.H. **10**-1400, **10**-1404, **10**-1408, **10**-1410, **10**-1428, **10**-1430, **10**-1437, **10**-1438, **10**-1439, **12**-590, **12**-600, **14**-420, **15**-1139, **15**-1144, **15**-1154, **15**-1240, **15**-1245, **15**-1396, **16**-877
Besançon, J. **19**-1647
Besemer, A.C. **19**-185
Besev, M. **15**-1354
Beslin, P. **12**-248
Besnard, C. **18**-266
Besra, R.C. **16**-210
Bessard, Y. **10**-1989
Besseau, F. **8**-102, **8**-105, **8**-106
Bessho, K. **16**-1628
Bessmernykh, A. **13**-665
Besson, L. **15**-1745
Besson, T. **11**-399
Besstmann, H.-J. **10**-1052
Best, D.C. **10**-174
Bestian, H. **16**-2235
Bestmann, H.J. **4**-71, **10**-898, **16**-1311, **16**-1318, **16**-1321, **16**-1341, **16**-1397, **16**-1403, **16**-1404, **16**-1476
Beswick, P.J. **15**-1033
Betancort, J.M. **16**-1324
Betham, M. **10**-1368
Bethell, D. **5**-72, **5**-351, **6**-71, **12**-360, **12**-396, **12**-407, **13**-228, **19**-813
Bethune, D.S. **2**-393
Betkouski, M. **7**-61
Betschart, C. **19**-1683
Bettadaiah, B.K. **10**-876
Bettati, M. **15**-1932
Betteridge, D. **1**-16, **1**-19
Betti, C. **18**-344
Bettigeri, S.V. **13**-534, **16**-2311
Bettinger, H.F. **2**-290, **5**-415
Betts, J. **14**-237
Betts, M.J. **16**-2235
Betz, J. **5**-183
Betzemeier, B. **10**-1457, **19**-170
Beug, M. **11**-11
Beugelmans, R. **13**-354, **13**-632
Beumel Jr., O.F. **10**-1901, **16**-540
Beutner, G.L. **8**-157, **16**-1029, **16**-1158, **16**-1173, **18**-264
Bevan, C.W.L. **16**-1616
Bevan, M.J. **5**-181
Beveridge, D.L. **2**-16
Bevington, J.C. **16**-2183
Bevins, C.L. **12**-59
Bewersdorf, M. **12**-652
Bewick, A. **15**-2004, **15**-2085
Beyer, K. **3**-187
Beylerian, N.M. **19**-100
Beynek, H. **16**-1405
Bez, G. **10**-989, **15**-1933
Bezbarua, M. **10**-989
Bezbozhnaya, T.V. **10**-215, **10**-294, **10**-456
Bezman, S.A. **15**-2410
Bhacca, N.S. **18**-918
Bhaduri, A.P. **11**-228
Bhagwat, M.M. **15**-548
Bhalay, G. **19**-775
Bhalerao, D.S. **16**-311, **17**-470
Bhalerao, U.T. **10**-490, **18**-322, **19**-1623
Bhanage, B.M. **13**-385, **13**-615, **13**-683
Bhanamathi, N. **10**-1003
Bhandari, K. **19**-414, **19**-1469
Bhanu, S. **10**-1902
Bhanumathi, N. **10**-974
Bhanushali, M.J. **13**-683
Bhar, S. **10**-1673, **11**-248, **15**-1129, **16**-52, **19**-657, **19**-939, **19**-1357
Bharadwaj, A.R. **15**-1031, **15**-1455, **15**-1487, **16**-722
Bharadwaj, P.K. **3**-123
Bharatam, P.V. **12**-423
Bharathi, B. **19**-759
Bharathi, E.V. **16**-2292
Bharathi, P. **13**-751, **16**-2087
Bhargava, S.K. **13**-494
Bhat, K.S. **16**-462
Bhat, N.G. **10**-1865, **12**-517, **12**-519, **15**-1258, **18**-468, **18**-476, **18**-484, **18**-487
Bhat, S.V. **16**-795
Bhatia, A.V. **16**-240
Bhatia, B. **14**-119
Bhatia, K.A. **18**-139
Bhatnagar, A.K. **19**-58
Bhatnagar, S.P. **16**-1545
Bhatt, A. **19**-465
Bhatt, M.V. **10**-1180, **17**-325, **18**-681, **19**-610
Bhatt, P. **19**-808
Bhatt, S. **10**-1211
Bhattacharjee, M. **10**-909, **14**-482, **15**-620
Bhattacharjya, G. **16**-1878
Bhattacharya, A.K. **16**-1364
Bhattacharya, S. **13**-388, **13**-813
Bhattacharya, S.N. **12**-499
Bhattacharyya, A. **10**-653
Bhattacharyya, K.X. **15**-1648
Bhattacharyya, S. **16**-320, **16**-331, **16**-335, **16**-1857, **19**-1121
Bhattacharyya, T. **18**-744
Bhatti, A.M. **12**-722
Bhatti, Z.A. **16**-1618
Bhawal, B.M. **10**-1083
Bhayana, B. **13**-494
Bhor, S. **15**-1901, **16**-911
Bhuiyan, Md.M.H. **13**-204, **13**-504, **15**-654
Bhunia, D.C. **10**-1205, **16**-550
Bhupathy, M. **14**-451, **18**-245
Bhusare, S. **19**-837
Bhusare, S.R. **10**-611, **10**-1178, **11**-259
Bhushan, V. **4**-201, **15**-1790, **15**-1811
Bhuvaneswari, N. **11**-700
Biaggio, F.C. **19**-1759
Biale, G. **17**-74, **17**-81
Bialeck-Florjanczyk, E. **15**-1018
Biali, D.A. **2**-452
Biali, S.E. **2**-448, **2**-452, **3**-129, **3**-130, **3**-135, **4**-339, **4**-357, **4**-525, **4**-527
Bian, X. **16**-897
Bian, Y.-J. **16**-573, **19**-1626
Bian, Y. **19**-792
Bianchi, G. **15**-2105, **15**-2118, **15**-2633
Bianchi, M. **10**-1979
Bianchi, R. **2**-296
Bianchi, T.A. **16**-2302
Bianchini, C. **15**-278, **15**-2645
Bianchini, R. **15**-12, **15**-14, **15**-22, **15**-1651, **15**-1657
Bible Jr., R.H. **15**-140
Bible, R. **2**-405
Bickel, A.F. **14**-249
Bickelhaupt, F. **2**-66, **2**-68, **2**-67, **12**-596, **12**-611, **12**-612, **12**-613, **12**-614, **12**-633, **12**-642, **18**-686

Bickelhaupt, F.M. **1**-6, **1**-120, **2**-7, **2**-111, **2**-146, **3**-22, **6**-3, **10**-2, **12**-428, **17**-114, **17**-115
Bickley, J.F. **15**-1414, **15**-1958, **18**-156
Bidd, I. **10**-1109
Bie, H.-Y. **16**-797
Bieber, L.W. **10**-851, **10**-1919, **16**-328, **16**-847, **19**-1212
Bieberbach, A. **2**-285
Biedermann, P.U. **2**-205, **2**-401
Biedermannová, L. **16**-776
Biehl, E.R. **13**-85, **13**-638
Biehl, E.R. **16**-103
Biellmann, J.-F. **10**-1329, **10**-1818, **10**-1840, **12**-409, **17**-281, **17**-390
Bielmann, R. **10**-188
Bielski, B.H.J. **5**-220
Bielski, R. **17**-338
Biemann, K. **16**-2169
Bieniarz, C. **13**-140
Bienz, S. **4**-140, **12**-702
Bierbaum, V.M. **2**-26, **5**-113, **5**-338, **10**-282, **10**-363, **17**-35, **17**-187
Bieri, J.H. **4**-481
Biermann, D. **15**-2259
Bieron, J.F. **11**-625, **17**-461
Bierzynski, I.R. **18**-744
Biethan, U. **18**-677
Bietti, M. **5**-324, **14**-15, **14**-117, **18**-55
Biffin, M.E.C. **10**-1059, **15**-423, **15**-1757
Bifulco, G. **4**-123
Bigam, G. **2**-278
Bigdeli, M.A. **19**-36
Bigeleisen, J. **6**-66
Bigg, D.C.H. **16**-1846
Biggs, J. **10**-526
Bigi, F. **11**-416, **11**-526, **15**-1930, **16**-1202, **19**-466
Bigler, P. **18**-199
Bigley, D.B. **12**-673, **12**-674, **12**-680, **16**-2195, **19**-854
Bihan, D. **16**-1448
Bijanzadeh, H.-R. **4**-312
Bijoy, P. **11**-370
Bijvoet, J.M. **4**-100
Biller, W.T. **16**-394
Billet, M. **16**-354
Billingham, N.C. **14**-495
Billingsley, K.L. **12**-589
Billington, D.C. **10**-1318
Billion, A. **12**-353
Billmers, J.M. **19**-508
Billups, W.E. **2**-87, **2**-221, **2**-392, **4**-487, **4**-512, **6**-46, **14**-173, **14**-176, **18**-180, **18**-397
Biloski, A.J. **19**-736
Binder, J.B. **18**-850
Bindu, K.H. **16**-1717, **16**-2034
Binev, I.G. **9**-23
Binfield, S.A. **15**-2067
Bingel, W.A. **1**-86
Binger, P. **12**-468, **15**-2495
Bingham, R. **12**-337
Bingham, R.C. **5**-295, **10**-66, **10**-296, **14**-120, **18**-114
Bingham, T.E. **18**-308
Bini, L. **15**-1625
Bini, R. **15**-2225
Binkley, R.W. **18**-678
Binnemans, K. **11**-125, **19**-126
Binsch, G. **4**-382, **4**-394, **6**-62
Binshtok, E.V. **16**-1353
Binzet, S. **10**-292
Binzet, S. **4**-535
Biolatto, B. **12**-493, **13**-572
Biondini, D. **19**-273
Biordi, J. **10**-617
Biradar, A.V. **16**-158
Biran, C. **12**-332
Birch, A.J. **12**-725, **15**-433, **15**-446, **15**-565, **15**-573
Birchal, J.M. **11**-632
Bird, C. W. **15**-1497
Bird, C.N. **17**-133, **17**-233
Bird, C.W. **2**-101, **2**-155, **2**-163, **2**-166, **14**-485, **15**-1511, **19**-698
Bird, P.H. **15**-2410
Bird, R. **19**-813
Bird, S.J. **16**-1726
Biresaw, G. **15**-2568
Birikaki, L. **16**-1500
Birladeanu, L. **18**-625
Birlirakis, N. **19**-309
Birman, V.B. **16**-1728
Birmingham, J.M. **12**-592
Birnbaum, J.C. **19**-484
Birney, D.M. **17**-428
Birr, C. **16**-1929
Bisaha, J. **10**-1744, **16**-1194
Bisai, A. **10**-1006, **15**-1016, **16**-667, **16**-1535, **19**-160
Bisaro, F. **10**-1573
Bisarya, S.C. **11**-239
Bischof, P. **2**-199
Biscoe, M.R. **10**-1027, **13**-642, **15**-1944
Bishop III, K.C. **18**-896
Bishop, C.A. **17**-70
Bishop, C.E. **17**-524
Bishop, L.M. **18**-504
Bishop, R. **3**-162
Bishop, S.W. **19**-1550
Biskup, M. **2**-292, **2**-293, **2**-294, **2**-305
Bissell, E.R. **15**-1647
Bissett, J.S. **16**-632, **16**-912
Bissinger, H.J. **4**-492
Bistri, O. **13**-135
Biswas, G. **10**-867
Biswas, S. **10**-1046
Bisztray, K. **7**-126, **7**-127
Bitsi, G. **12**-767
Bittar, M.S. **13**-591
Bitterlich, B. **15**-1885
Bittl, R. **7**-20
Bittner, S. **19**-584
Bjorklund, C. **12**-726
Björkman, E.E. **15**-2023
Bjørsvik, H.-R. **14**-159, **19**-320, **19**-325, **19**-1535
Black, C.J. **12**-182
Black, D.A. **16**-911
Black, G.W. **16**-103
Black, K.A. **18**-638
Black, K.W. **18**-122
Black, P.J. **15**-955
Black, S.J. **11**-135
Black, T.H. **10**-509, **17**-496, **18**-955
Blackburn, E.V. **14**-60, **18**-547
Blackburn, G.M. **16**-1960
Blackburn, P. **16**-1448
Blackburn, T. **13**-513
Blackburne, I.D. **1**-94
Blacker, A.J. **10**-1535, **15**-1909, **15**-1942, **15**-1943
Blacker, J. **16**-1531, **19**-1034
Blackert, J.F. **14**-73
Blacklock, T.J. **11**-257, **16**-1939, **19**-652
Blackman, S.W. **10**-952
Blackmond, D. G. **13**-443, **13**-190, **15**-460, **15**-1957, **16**-1892
Blackstock, S.C. **3**-100, **5**-342
Blackwell, J.M. **12**-329, **19**-1130
Blackwell, L.F. **17**-67, **17**-69
Blackwood, R.K. **10**-517
Bladé-Font, A. **16**-1356, **16**-1904
Blades, K. **15**-1816
Blagoev, B. **10**-1801, **12**-422
Bláha, K. **10**-1785
Blair, L.K. **8**-248, **8**-250, **8**-251
Blaise, E.E. **16**-1004
Blake, A.J. **15**-320, **15**-1366, **16**-410
Blake, J.F. **10**-23, **15**-2291
Blake, M.R. **11**-120
Blake, P.G. **15**-289
Blakey, S.B. **13**-550
Blakskjær, P. **15**-1454
Blanc, G. **19**-1076
Blanch, R. **4**-497
Blanch, R.J. **3**-221, **3**-222
Blanchard, E.P. **15**-2415, **15**-2556, **15**-2559
Blanchard, M. **16**-2169
Blanchette, P.E. **15**-1874
Blanchfield, J.T., **16**-1743
Blanchot-Courtois, V. **10**-1621
Blanchot, M. **15**-409
Blanco-Urgoiti, J. **15**-1549, **15**-1561
Blanco, E.G. **15**-2527
Blanco, L. **12**-163
Blanco, O.M. **18**-862
Blandamer, M.J. **2**-462, **6**-64, **9**-97, **10**-40, **10**-41, **10**-88

Blander, M. **3**-10
Blank, J. **15**-1487, **16**-722
Blank, J.J. **18**-850
Blankert, J.F. **10**-1319
Blanksby, S.J. **1**-95
Blanton, J.R. **19**-909, **19**-1284
Blanzat, J. **4**-251
Blart, E. **11**-300
Blaschke, G. **4**-178, **4**-179, **4**-534
Bläser, D. **2**-87, **3**-71, **4**-488, **11**-491
Blaser, H.-U. **16**-1237
Blaskó, A. **13**-21, **16**-18
Blass, B.E. **10**-1031
Blavins, J.J. **15**-2130
Błażej, S. **13**-95
Blazejewski, J. **13**-651
Blazek, J.M. **18**-144
Blazevic, N. **10**-910
Blechert, S. **15**-1346, **18**-745, **18**-804, **18**-825, **18**-853, **18**-864, **18**-870
Bleeke, J.R. **15**-551
Blettner, C.G. **13**-507
Blewett, M.M. **15**-1981
Blid, J. **18**-782
Bloch, R. **19**-1048
Block, E. **2**-94, **5**-126, **10**-123, **10**-1775, **10**-1817, **12**-425, **13**-856, **14**-438, **16**-1438, **16**-1470, **17**-339, **17**-351, **18**-756, **19**-784, **19**-826, **19**-1558, **19**-1583, **19**-1755, **19**-1765
Blodgett, J.K. **18**-302
Blokzijl, W. **2**-462, **15**-2210
Blom, C.E. **2**-458
Blomberg, C. **5**-169, **12**-612, **12**-632, **12**-633, **16**-471
Blomgren, P.A. **13**-561, **13**-603
Blomquist, A.T. **4**-81, **4**-493, **16**-1548
Bloodworth, A.J. **15**-2358
Bloom, S.H. **17**-279
Bloomfield, J.J. **16**-1483, **16**-2138, **19**-1457, **19**-1700, **19**-1705, **19**-1709, **19**-1710, **19**-1711
Blotny, G. **16**-2300
Blough, B.E. **15**-584
Blouin, M. **10**-626
Blount, J.F. **10**-1526
Blue, E.D. **15**-1382
Blues, E.T. **19**-1318
Bluet, G. **16**-1160, **16**-1162
Bluhm, H.J. **19**-26
Blukis, V. **1**-88
Blum, J. **10**-1073, **11**-364, **11**-676, **13**-360, **14**-491, **14**-493
Blum, L. **19**-1547
Blum, S.A. **12**-275, **19**-807
Blume, E. **16**-1255
Blume, R.C. **16**-1761
Blumenfeld, J. **19**-992
Blunt, J.W. **15**-614
Bly, R.K. **10**-148
Bly, R.S. **10**-148
Blyumberg, E.A. **19**-675
Boar, R.B. **19**-1390, **19**-1391
Boas, U. **10**-1092
Boaz, N.W. **10**-243, **10**-248, **10**-1437, **10**-1536, **15**-1244
Bobbitt, J.M. **19**-186, **19**-187, **19**-328, **19**-665
Bobrowski, K. **7**-37, **7**-38
Bobylev, V.A. **10**-524
Bocharov, B.V. **17**-487
Boche, G. **2**-285, **5**-143, **5**-155, **5**-287, **12**-30, **12**-428, **12**-538, **16**-1246, **18**-540
Bocher, S. **10**-271
Bochkov, A.F. **8**-172
Bocian, W. **15**-1923, **16**-556
Bock, C.W. **2**-30
Bock, H. **1**-16, **11**-178, **16**-238, **19**-263
Bock, M.G. **16**-192
Bockman, T.M. **15**-1620
Bockrath, B. **5**-116
Bockstiegel, B. **10**-1768
Bodansky, M. **16**-1907
Bodanszky, A. **16**-1909
Bodanszky, M. **16**-1909
Bode, J.W. **12**-464, **14**-302, **15**-2112, **15**-2340, **18**-709
Bode, K. **16**-169
Boden, E.P. **16**-1774
Bodepudi, V.R. **15**-120
Bodewitz, H.W.H.J. **12**-633
Bodineau, N. **16**-527
Bodkin, J.A. **15**-2016
Bodmann, K. **16**-1363
Bodnar, B.S. **19**-1076
Bodor, A. **19**-126
Bodot, H. **18**-234
Bodrikov, I.V. **15**-21
Bodwell, G.J. **2**-73, **2**-74, **2**-309
Boechat, N. **19**-1070
Boeckman Jr., R.K. **10**-1740, **15**-134, **15**-137, **15**-269, **15**-1466, **16**-1119, **18**-614, **18**-695, **18**-702
Boeda, F. **18**-265, **18**-821
Boeder, C.-L. **16**-1929
Boehm, P. **19**-1086
Boekelheide, V. **2**-304, **2**-364, **6**-81, **10**-1809, **10**-1814, **17**-186
Boele, J. **8**-94
Boelens, H. **17**-278
Boelens, M. **10**-902
Boelhouwer, C. **10**-1288
Boer, F.P. **5**-64, **5**-75
Boero, M. **18**-347
Boersma, J. **16**-853
Boersma, M.A.M. **18**-603
Boerth, D.W. **8**-75, **8**-77, **8**-81
Boerwinkle, F. **15**-20
Boese, R. **2**-58, **2**-87, **3**-71, **4**-460, **4**-488, **18**-87
Boese, W.T. **19**-56
Boesten, W.H.J. **16**-1844, **19**-1463
Boeters, C. **17**-268
Boettcher, R.J. **18**-912
Boev, V.I. **12**-369
Boezio, A.A. **16**-899
Bofill, J.M. **2**-340, **11**-366
Bogatkov, S.V. **16**-33
Bogatskii, A.V. **10**-501
Bogavac, M. **16**-2059
Bogdal, D. **10**-608, **15**-1904, **19**-648
Bogdanov, G.N. **18**-196
Bogdanov, V.S. **15**-50
Bogdanovic, B. **12**-608, **15**-743
Bogen, S. **15**-1319
Boger, D.L. **15**-155, **15**-1197, **15**-1469, **15**-2295, **15**-2319, **15**-2352
Bøgevig, A. **16**-364, **19**-516
Boggs, R.A. **7**-53
Bogseth, R.C. **10**-558
Boguslavskaya, L.S. **4**-134, **10**-787, **14**-155, **14**-322, **15**-1668, **15**-1681
Bohall, B.R. **12**-384
Bohé, L. **15**-1940
Bohé, L. **19**-800
Bohle, D.S. **4**-228, **15**-375
Bohlmann, F. **7**-10, **14**-352
Böhm, H.P. **12**-612
Böhm, S. **11**-91
Böhm, V.P.W. **10**-1388, **13**-584
Bohme, D.K. **8**-23, **8**-240, **8**-254, **10**-355, **10**-365, **10**-366
Böhme, H. **16**-85
Böhme, M. **10**-1403
Böhmer, V. **3**-125, **3**-128, **3**-129, **3**-144
Bohn, A.A. **2**-54
Bohne, C. **2**-439, **7**-35
Boiadjiev, S.E. **4**-61
Boice, G.N. **16**-998
Boireau, G. **19**-925
Bois-Choussy, M. **13**-354
Boiteau, J.-G. **15**-1278
Boitiaux, J.P. **15**-447
Boivin, J. **12**-353, **16**-1598, **16**-1599
Bojanowska, I. **8**-246
Bojarski, J.T. **16**-1980
Bolan, J.L. **16**-273
Boland, W. **19**-477
Boldeskul, I.E. **16**-1471
Boldi, A.M. **18**-965
Boldt, G.E. **15**-1973
Boldt, P. **10**-1690, **10**-1691, **15**-113
Boleslawski, M.P. **16**-485
Bolesov, I.G. **16**-2073
Bolestova, G.I. **10**-1454, **15**-501, **15**-750, **16**-763
Bolhofer, W.A. **10**-1033
Bolig, A.D. **19**-43

Bolitt, V. **10**-1912, **15**-257
Böll, W.A. **2**-292, **2**-293, **2**-294
Bollinger, J.M. **4**-521, **4**-523, **10**-129
Bolm, C. **4**-161, **13**-218, **16**-393, **13**-135, **13**-218, **15**-1269, **15**-1833, **15**-2250, **15**-2574, **16**-549, **16**-667, **16**-669, **16**-746, **16**-748, **16**-887, **16**-893, **16**-903, **16**-1084, **18**-388, **18**-392, **19**-177, **19**-178, **19**-1014, **19**-1023, **19**-1136
Bolourtchian, M. **19**-236, **19**-1673
Bols, M. **15**-2353, **16**-1982
Bolster, J.M. **4**-499
Bolte, M. **19**-1152
Bolton, G.L. **10**-1822, **10**-1839, **15**-918
Bolton, J.R. **2**-422, **5**-218
Bolton, P.D. **8**-255, **8**-256
Bolton, R. **13**-822, **14**-46, **14**-365, **15**-1
Boltukhina, E.V. **17**-197
Bolusheva, I.Yu. **17**-353
Bolze, C. **12**-772
Bolze, R. **15**-95
Bombek, S. **11**-232
Bomben, K.D. **8**-251
Bombicz, P. **16**-1268
Bombrun, A. **10**-940, **10**-1361
Bommer, P. **4**-211
Bon, E. **16**-1846
Bonacorso, H.G. **9**-129
Bonadies, F. **15**-1967
Bonaga, L.V.R. **15**-1533, **15**-1534, **15**-1549, **15**-1559, **15**-2628
Boñaga, L.V.R. **15**-2686, **15**-1552
Bonačić-Koutecký, V. **7**-1
Bonanni, M. **19**-1222
Bonato, M. **15**-713
Bonaventura, M.M. **4**-382
Bonchev, D. **4**-269
Bond, F.T. **17**-273, **17**-278
Bond, G.C. **15**-147
Bondarenko, T.N. **10**-1994
Bonde, S.E. **10**-1366
Bondlela, M. **10**-1452
Bondock, S. **16**-2211, **16**-2212
Bonesi, S.M. **11**-297
Bonet, J. **18**-195
Bongini, A. **15**-1177
Bonham, R.A. **1**-63, **1**-64
Bonhoeffer, K.F. **19**-1738
Bonifácio, V.D.B. **15**-2063
Bonifant, C.L. **4**-228
Bonilla, R.J. **15**-554
Bonini, B.F. **10**-1568
Bonini, C. **10**-1219, **10**-1222, **10**-1242
Bonini, G. **11**-526
Bonitatebus Jr., P.J. **18**-847
Bonitz, G.H. **16**-385
Bonjoch, J. **15**-1336
Bonk, P.J. **6**-19
Bonnat, M. **19**-1468
Bonneau, R. **5**-416
Bonnekessel, M. **10**-1384
Bonner, O.D. **16**-42
Bonner, W.A. **14**-449, **18**-32, **19**-1575
Bonnet-Delpon, D. **10**-969, **10**-312, **11**-393, **15**-1897, **16**-896, **16**-936, **19**-833
Bonnet, L. **6**-47
Bonnet, V. **13**-350
Bonnett, R. **18**-937
Bonnichon, F. **5**-380
Bonnier, J. **14**-124
Bonnier, J.M. **13**-836
Bonnin, J.P. **11**-479
Bonollo, S. **10**-974
Bonrath, W. **7**-123
Bonthrone, W. **19**-99
Bonvicino, G.E. **13**-863
Bonvin, Y. **19**-600
Bonvino, V. **11**-338
Boogers, J.A.F. **15**-1278
Boojamra, C.G. **14**-325
Booker-Milburn, K.I. **15**-2040
Booker, S.K. **13**-473
Boone, A.W. **6**-71
Boone, J.R. **19**-923, **19**-998, **19**-999, **19**-1000
Boons, G.-J. **10**-613
Boord, C.E. **4**-430
Booth, B.L. **10**-1981, **11**-562
Booth, H. **4**-351, **4**-379, **4**-380, **17**-88
Booth, S. **10**-1935
Booth, S.E. **5**-149
Boothe, T.E. **17**-145
Boovanahalli, S.K. **10**-1183
Boozer, C.E. **10**-224
Bopp, R.J. **10**-126
Borah, A.J. **16**-618
Borah, H.N. **13**-612
Borah, K.J. **16**-1205
Borah, R. **16**-332, **16**-1205
Borate, H.B. **16**-1203
Borau, V. **13**-643
Borbaruah, M. **19**-907
Borch, R.F. **5**-52, **16**-1273, **19**-1173
Borchardt, J.K. **17**-34
Borcic, S. **10**-147
Borcsek, B. **13**-683
Bordeau, M. **12**-332
Borden, G.W. **18**-502
Borden, J.E. **18**-604
Borden, W.T. **1**-2, **2**-259, **4**-491, **4**-542, **4**-543, **5**-128, **5**-251, **5**-299, **5**-300, **5**-302, **5**-353, **5**-429, **10**-55, **14**-31, **18**-575, **18**-578, **18**-678, **19**-744
Bordwell, F.G. **1**-108, **1**-109, **1**-112, **2**-157, **5**-112, **5**-145, **5**-258, **5**-259, **5**-408, **8**-25, **8**-58, **8**-63, **8**-94, **8**-234, **10**-233, **10**-236, **10**-319, **10**-350, **10**-352, **10**-1687, **17**-3, **17**-42, **17**-51, **17**-58, **17**-61, **17**-225, **17**-346, **17**-348, **17**-350, **17**-356, **18**-207
Borecka, B. **3**-181
Boregeaud, R. **15**-169
Borg-Karlson, A.-K. **10**-1053
Borgen, G. **4**-406
Borges dos Santos, R.M. **1**-121
Borhan, B. **15**-1720, **19**-329, **19**-382, **19**-671
Borisenko, A.A. **15**-797
Borkar, S.D. **19**-552
Borkent, J.H. **4**-73
Borkowski, M. **9**-9
Born, D. **4**-458
Born, R. **15**-372
Börner, A. **13**-98, **15**-648, **16**-317, **16**-352, **19**-1150
Bornscheuer, U.T. **4**-188, **16**-1624
Borodin, A. **14**-466
Borodkin, G.I. **11**-1, **15**-657, **18**-6, **18**-11
Borodkin, V.S. **12**-703
Borosky, G.L. **13**-66, **18**-95
Borpuzari, S. **16**-1755
Borredon, E. **10**-605
Borredon, M.E. **10**-842
Bors, D.A. **8**-67
Borthakur, N. **15**-1861
Borths, C.J. **15**-2236
Bortolini, O. **15**-1953, **16**-92
Boruah, A. **10**-1482, **16**-2030, **18**-350, **19**-1256, **19**-1669
Boruah, M. **17**-467, **19**-1239
Boruah, R.C. **13**-612
Boruwa, J. **16**-1213
Børve, K.J. **11**-42, **11**-47
Bos, H. **10**-739
Bos, H.J.T. **15**-217, **15**-218
Bos, W. **10**-1699
Bosanac, S. **2**-114
Bosc, J. **10**-1604
Bosch, A. **18**-932
Bosch, E. **8**-86, **11**-123, **16**-2205, **19**-264
Bosch, I. **16**-1906
Bosch, J. **10**-1906
Bosch, R.J. **4**-362, **5**-362, **10**-1254
Bosco, J.W.J. **16**-1751, **16**-1804
Bosco, M. **10**-972, **10**-616, **10**-1125, **11**-314, **11**-483, **15**-1065, **15**-1106, **15**-1182, **15**-1238, **15**-1388, **16**-610, **16**-1723, **19**-969
Bosco, W. **16**-239
Bose, A.K. **7**-109, **10**-1684, **11**-128, **16**-1900
Bose, D.S. **10**-1087, **16**-299, **16**-1231, **16**-1685, **16**-1788, **17**-443
Bose, G. **10**-582

Bosica, G. **12**-720, **15**-1048, **15**-1051, **16**-94, **16**-212, **16**-827, **16**-1207
Bosman, C. **15**-2008
Bosnich, B. **4**-154, **12**-72, **15**-456, **15**-1478, **15**-1484, **16**-1129, **16**-1557, **18**-743, **19**-1732
Bosret, J. **16**-702
Bossart, M. **14**-432, **18**-57
Bosscher, M.A. **18**-368
Bosser, G. **17**-371
Bosshard, H. **18**-133
Boswell Jr., G.A. **16**-441
Boswell, C.J. **10**-268
Botella, L. **13**-388
Bothe, H. **4**-452
Botoshansky, M. **5**-276
Bott, K. **10**-421
Bott, R.W. **11**-12
Botta, M. **10**-928
Botta, M. **10**-1917
Bottalico, D. **10**-1903
Bottaro, J.C. **12**-743
Böttcher, A. **16**-2045
Botteghi, C. **15**-1607
Botteron D.G. **17**-149
Bottini, A.T. **4**-496, **10**-277, **10**-879, **13**-97
Bottino, A. **4**-167
Bottino, F.A. **19**-1687
Bottle, R.T. appendixa-1
Botto, R.E. **10**-204
Bottoni, A. **5**-128, **15**-2421, **15**-2559, **16**-774
Botuha, C. **16**-1819
Bouab, O. **10**-568
Bouas-Laurent, H. **10**-1940
Bouaziz, Z. **7**-95
Boubaker, T. **10**-399
Boucard, V. **10**-1595
Bouchez, L.C. **16**-2299
Bouchoule, C. **16**-2169
Bouchu, D. **15**-1138
Bouda, H. **10**-842
Boudakian, M.M. **10**-253
Boudin, A. **12**-622
Boudjouk, P. **7**-84, **7**-90, **7**-94, **10**-1296, **15**-174, **15**-625, **16**-834, **16**-2115
Boudreaux, G.J. **17**-352
Bouffard, J. **16**-750
Bougauchi, M. **15**-1913
Bouhlel, E. **16**-833
Bouillon, G. **10**-773
Bouillon, J.-P. **16**-1107
Bouinidane, K. **19**-1773
Bouis, P.A. **5**-96
Bouloc, N. **11**-438
Boumizane, K. **16**-449
Bounds, P.L. **12**-59
Bouquant, J. **16**-1107
Bourcet, E. **19**-128
Bourcier, S. **4**-99
Bourdelande, J.L. **15**-1947
Bourdon, F. **16**-1840
Bourgain, M. **10**-1610
Bourgeois, M. **10**-769
Bourguet, E. **18**-157
Bourhani, Z. **15**-1886
Bourhis, M. **10**-1604
Bourissou, D. **5**-360, **5**-425
Bourn, A.J.R. **4**-336
Bourns, A.N. **6**-74, **17**-63, **17**-238
Bourque, L.E. **12**-385
Bousquet, C. **15**-1983
Boussu, M. **16**-2021
Boustany, K.S. **19**-841
Boutagy, J. **16**-1361
Boutin, R.H. **18**-302
Boutonnet, F. **15**-54
Boutureira, O. **15**-1932
Bouveault, L. **19**-1076
Bouvier, J.-P. **15**-1339
Bouwkamp, M.W. **15**-2379
BouzBouz, S. **18**-866
Bouzide, A. **15**-993
Bovenkamp, J.W. **3**-118
Bovicelli, P. **10**-706, **16**-437, **17**-218
Bovin, Y. **16**-2261
Bovonsombat, P. **11**-303
Bowden, K. **1**-45, **2**-482, **2**-483, **8**-55, **8**-139, **16**-1699
Bowe, C. **8**-162
Bowe, M.D. **5**-148
Bowen, C.T. **10**-92
Bowen, J.P. **3**-15
Bowen, P. **18**-931
Bower, J. **15**-2637
Bower, J.F. **10**-1575, **15**-1486
Bower, T.R. **15**-4, **15**-34
Bowers, A. **19**-66
Bowers, C.W. **3**-107
Bowers, K.W. **15**-575
Bowers, M.T. **8**-241, **8**-236
Bowles, D.M. **18**-525
Bowlus, S.B. **16**-1250
Bowman, A.C. **15**-2379
Bowman, N.S. **18**-188
Bowman, P.S. **8**-96
Bowman, W.R. **10**-1556, **10**-1688, **15**-1373, **16**-1600, **19**-1516
Bowry, V.W. **14**-90, **14**-99
Box, V.G.S. **4**-379
Boxwell, C.J. **15**-558
Boy, J. **1**-69
Boyall, D. **16**-544
Boyd R.H. **8**-129
Boyd, D.R. **18**-682
Boyd, G.V. **15**-39, **15**-991
Boyd, R.H. **8**-39
Boyd, R.J. **1**-32
Boyd, S.D. **10**-1557
Boyd, S.E. **3**-194, **3**-201
Boydston, A.J. **2**-318
Boyer, B. **10**-668, **19**-923, **19**-998
Boyer, J.H. **10**-1088, **12**-84, **12**-741, **12**-742, **12**-747, **13**-809, **18**-291, **19**-741, **19**-755, **18**-203, **18**-593
Boykin, D.W. **13**-525
Boyle, B.A. **18**-931
Boyle, P.H. **4**-160, **4**-162
Boyles, D. **8**-162
Boynton, W.A. **10**-268
Boz, E. **16**-1085
Bozzelli, J.W. **15**-2137
Brabandt, W.V. **16**-2225
Brace, N.O. **10**-1018
Brackenridge, I. **10**-650
Brackman,W. **14**-395
Brada, B. **16**-12
Bradamante, S. **2**-159, **5**-122
Bradbury, D. **11**-699
Braddock, D.C. **10**-745, **10**-1043, **11**-136, **11**-438, **16**-777, **16**-1487, **18**-871, **19**-124
Bradley, J. **14**-48, **14**-368
Bradley, M. **10**-1935, **15**-1829, **19**-775
Bradshaw, J.S. **3**-106, **3**-110, **3**-155, **4**-168, **4**-182, **13**-143, **14**-440, **16**-223, **19**-1452, **19**-1560
Bradshaw, R.W. **10**-1032
Bradsher, C.K. **11**-394, **11**-395, **12**-644
Brady, D.G. **15**-50
Brady, J.D. **11**-22
Brady, W.T. **15**-2390, **15**-2392, **15**-2424, **15**-2426, **16**-2232, **17**-172, **17**-174
Braenden, J.E. **19**-437
Braendlin, H.P. **11**-224
Braga, A.C. **13**-445
Braga, A.L. **10**-813, **12**-300, **12**-304, **14**-361, **15**-217, **15**-290, **15**-943, **15**-1436, **16**-598, **16**-666, **16**-677, **16**-746
Bragin, J. **4**-457
Brahmachari, G. **16**-1865
Brahmachary, E. **15**-2681
Braier, A. **15**-2690
Braillon, B. **16**-238
Braish, T.F. **15**-41
Braisted, A.C. **18**-637
Bram, G. **10**-359, **10**-520, **10**-723, **10**-723, **10**-1106, **10**-1932, **16**-1797, **17**-309
Brammer Jr., L.E. **5**-226
Brammer, C. **15**-2171
Brammer, C.N. **15**-1737
Brammer, L. **1**-55, **1**-68, **2**-33
Branca, J.C. **5**-408
Branca, S.J. **4**-464
Branchadell, V. **15**-2454, **15**-2501
Branchaud, B.P. **17**-210
Branco, L.C. **9**-134, **15**-1807, **15**-1842
Branco, P.S. **15**-2063, **15**-2072, **16**-989
Brand, D.J. **4**-20

Brand, M. **12**-145, **15**-1645
Brand, W.W. **13**-862
Branda, N.R. **4**-75
Branda, R.F. **16**-247
Brandänge, S. **11**-339, **19**-1317
Brandberg, M. **16**-392
Brandenberger, S.G. **19**-402
Brandes, B.D. **15**-1981
Brandes, E. **18**-715
Brandes, E.B. **18**-704
Brandi, A. **17**-452, **19**-752
Brandl, M. **6**-83, **19**-59
Brandsma, L. **10**-245, **10**-1698, **10**-1839, **12**-418, **12**-506, **15**-217, **15**-218, **15**-564, **15**-577, **16**-2010
Brandt, P. **12**-441, **15**-452, **19**-928
Brandvold, T.A. **15**-2039
Branneby, C. **10**-956
Brannen Jr., W.T. **10**-319
Brannock, K.C. **15**-2395
Brant, J.B. **19**-694
Branton, G.R. **18**-609
Brard, L. **15**-2027
Bräse, S. **10**-780, **10**-1561, **16**-680
Braslavsky, S.E. **7**-1, **7**-13
Bratcher, M.S. **2**-401
Braten, M.N. **2**-345
Bratovanov, S. **16**-606
Bratsch, S.G. **1**-32
Braude, E.A. **8**-25, **8**-47
Brauman, J.I. **5**-113, **5**-130, **8**-17, **8**-112, **8**-250, **8**-251, **10**-367, **10**-379, **10**-443, **10**-355, **10**-364, **10**-374, **10**-1958, **12**-697, **19**-439
Braun, A. **15**-1753
Braun, A.M. **14**-179
Braun, H. **16**-1443
Braun, J.B. **13**-586
Braun, M. **10**-1525, **10**-1528, **15**-1994, **16**-1058, **16**-1076
Braun, M.P. **12**-269
Brauner, J. **10**-1627
Braunstein, D.M. **19**-1226
Braunton, A. **12**-123, **12**-124
Bräutigam, S. **19**-995
Braverman, S. **15**-2204
Bravo-Zhivotovskii, D. **5**-276
Bravo-Altamirano, K. **15**-421
Bravo-Borja, S. **19**-1506
Bravo, A. **14**-159
Bravo, J.A. **3**-210
Bravo, J.L. **4**-312, **15**-2187, **15**-2193
Bray, C.D. **10**-979, **16**-256
Bray, T. **7**-106
Bray, T.M. **5**-273
Brayer, J.-L. **13**-814, **13**-815
Brazier, C.R. **5**-430
Brazis, N.J. **18**-889
Brazzillo, J. **18**-203
Breau, L. **16**-1400
Breault, G.A. **15**-2273
Breaux, E.J. **7**-28
Brebion, F. **10**-1537
Breccia, A. **7**-109
Brechbiel, M. **14**-103, **16**-1568, **18**-795, **18**-799
Brechbühler, H. **10**-751
Brechot, P. **15**-1917
Brecht-Forster, A. **14**-17
Bredikhin, A.A. **19**-800
Breen, P.J. **4**-276
Bregadze, V.I. **13**-270, **13**-747
Brégeon, D. **9**-137
Breger, I.K. **17**-96
Bregman, J. **2**-321
Breinbauer, R. **13**-599, **18**-856
Breindl, C. **15**-325, **15**-357
Breit, B. **15**-1601, **15**-1613
Breitmaier, E. **12**-564, **15**-2246
Bremer, M. **1**-57
Bremeyer, N. **15**-443, **15**-1081, **15**-2523
Bremner, D.H. **15**-1690
Brenek, S.J. **15**-522
Breneman, C. **4**-288
Breneman, C.M. **2**-44, **10**-1402, **12**-590
Brener, L. **18**-675
Brenn, J. **3**-129
Brennan, J. **16**-1402
Brennan, P.E. **15**-2140
Brennen, C.E. **7**-70, **7**-73
Brenner, E. **13**-210, **13**-213
Brenner, S. **15**-580
Breslow, R. **2**-173, **2**-222, **2**-223, **2**-228, **2**-234, **2**-251, **2**-255, **2**-256, **2**-257, **2**-258, **2**-259, **2**-260, **2**-261, **2**-262, **3**-183, **8**-82, **9**-96, **11**-56, **15**-1934, **15**-1944, **15**-2210, **18**-162, **18**-538, **18**-610, **19**-57, **19**-59, **19**-589, **19**-1296
Bresson, A. **15**-1706
Brestensky, D.M. **16**-1121
Breton, G.W. **15**-166
Brett, A.M. **2**-30
Brettar, J. **15**-760
Breuckmann, R. **15**-2442
Breuer, E. **5**-268, **12**-544, **16**-2289, **18**-314
Breuer, S.W. **14**-435
Breuer, Th. **8**-94
Breugst, M. **10**-393, **10**-400
Breuker, K. **1**-94
Breuzard, J. **15**-892
Brewer, R.G. **1**-98
Brewster, J.H. **4**-24, **4**-104, **4**-129, **4**-134, **18**-416
Briand, S. **12**-699, **16**-507
Bribes, J.L. **5**-80, **10**-218
Brice, J.L. **10**-1030, **15**-419
Brichford, N.L. **16**-556
Brickman, M. **11**-46
Bricout, H. **10**-951
Bridge, A. **16**-2231
Bridge, A.W. **19**-1113
Bridgwood, K.L. **16**-1938
Bridon, D. **14**-462, **19**-422
Bridson, J.N. **2**-73, **2**-74, **2**-309, **10**-1881, **12**-161
Brieger, G. **15**-506, **15**-2169, **15**-2268, **17**-182
Briegleb, G. **12**-86
Briehl, H. **4**-497
Brielmann, H.L. **15**-400
Brienne, M. **4**-189
Brienne, M.J. **4**-99
Brier, P.N. **4**-287
Briggs, E.M. **10**-1049
Briggs, J.P. **8**-241
Briggs, W.S. **17**-131
Brilkina, T.G. **12**-456, **12**-461
Brill, T.B. **16**-1364
Brill, W.F. **10**-307
Brillon, D. **10**-1685
Brimble, M.A. **10**-1336, **15**-1818, **18**-828
Brinchi, L. **10**-438, **10**-725, **19**-273
Brinck, T. **18**-379
Brindell, G.D. **18**-66
Bringer-Meyer, S. **19**-995
Bringmann, G. **13**-469, **19**-1522
Brinich, J.M. **10**-129
Brinker, U.H. **5**-393, **17**-391
Brinkman, G.A. **11**-310
Brinkman, H.R. **19**-1192
Brinkmann,Y. **15**-2144
Brinksma, J. **15**-1795
Briody, R.G. **10**-78, **10**-79
Brion, J.-D. **13**-606, **13**-704, **15**-214, **15**-781
Brisbois, R.G. **12**-223, **13**-586
Brittain, H.G. **4**-118
Brittain, J. **10**-839
Brittain, J.M. **11**-230
Britten, A.Z. **10**-1789
Britton Jr., G.H. **17**-19
Britton, T.C. **12**-224
Brix, B. **12**-578
Brixius, D.W. **19**-421
Brizzolara, A. **10**-1791
Broaddus, C.D. **12**-57
Broadhurst, A.T. **12**-40
Broadwater, S.J. **16**-792
Brocchetta, M. **16**-1813
Bröcher, D.J. **15**-2690
Brochu, C. **15**-2571
Brochu, M.P. **12**-123
Brock, C.P. **2**-407
Brockmann Jr., H. **4**-148
Brocks, J.J. **1**-113, **5**-280
Brocksom, T.J. **12**-251
Brockway, N.M. **5**-371
Brod, A.O. **10**-755
Brod, L.H. **10**-565
Brodie, B.B. **14**-225
Brodsky, B.H. **19**-457, **19**-509
Broeckaert, L. **7**-86
Broekhof, N.L.J.M. **16**-1376

Brogan, J.B. **15**-2577
Broger, E.A. **15**-636
Broggini, G. **15**-2103
Brohm, D. **18**-856
Brois, S.J. **4**-37
Brokaw, M.L. **8**-66
Brokhovetsky, D.B. **11**-318
Broline, B.M. **18**-604
Bromilow, J. **9**-47, **9**-55
Bromley, D. **11**-235
Bromley, K. **16**-1699
Brönstrup, M. **12**-637
Brook, A.G. **18**-958. **18**-959
Brook, M.A. **4**-134, **14**-227, **16**-1775, **18**-734
Brook, P.R. **15**-2425
Brookes, P. **13**-487
Brookes, P.C. **17**-220
Brookhart, M. **10**-144, **10**-169, **15**-1481, **15**-2065, **15**-2498, **15**-2499, **15**-2581, **19**-38, **19**-43, **19**-1289
Brooks R. **12**-384
Brooks, C.A. **15**-601
Brooks, M.A. **18**-63
Brophy, J.E. **18**-568
Broster, F.A. **14**-435
Brotzel, F. **10**-396, **10**-397, **10**-401
Broutin, P.-E. **11**-293
Brouwer, C. **10**-1928, **15**-339
Brouwer, D.M. **8**-30, **11**-5, **18**-7, **18**-8, **18**-29
Brovetto, M.C. **15**-1693
Browej, E.I. **16**-1417, **16**-1419
Brower, H.E. **17**-71
Brower, K.R. **14**-152, **17**-71
Brown II, J. **4**-403
Brown, A.R. **13**-462
Brown, B.L. **4**-407
Brown, C.A. **16**-2144, **19**-1006
Brown, D. **10**-849
Brown, D.E. **4**-301
Brown, D.H. **13**-521
Brown, D.J. **15**-433
Brown, D.S. **15**-1548, **19**-120
Brown, E. **16**-1822
Brown, E.C. **18**-676
Brown, E.S. **15**-1623, **15**-1625
Brown, E.V. **19**-1767
Brown, F.K. **15**-2283
Brown, G.R. **19**-1274
Brown, G.W. **10**-1049
Brown, H.C. **4**-199, **5**-96, **8**-25, **8**-47, **8**-195, **8**-206, **9**-4, **9**-6, **9**-8, **9**-9, **9**-20, **9**-33, **10**-141, **10**-170, **10**-190, **10**-192, **10**-211, **10**-337, **10**-1228, **10**-1827, **10**-1858, **10**-1859, **10**-1860, **10**-1862, **10**-1863, **10**-1864, **10**-1865, **10**-1866, **10**-1867, **10**-1868, **10**-1869, **10**-1870, **10**-1874, **10**-1878, **10**-1881, **11**-22, **11**-25, **11**-55, **11**-85, **11**-86, **11**-93, **11**-95, **11**-315, **11**-378, **11**-379, **11**-689, **12**-451, **12**-458, **12**-465, **12**-466, **12**-470, **12**-477, **12**-512, **12**-513, **12**-513, **12**-514, **12**-515, **12**-517, **12**-519, **12**-544, **12**-545, **12**-548, **12**-585, **14**-16, **14**-433, **14**-434, **14**-436, **14**-437, **15**-117, **15**-118, **15**-183, **15**-262, **15**-263, **15**-517, **15**-520, **15**-608, **15**-671, **15**-676, **15**-677, **15**-678, **15**-679, **15**-680, **15**-681, **15**-682, **15**-683, **15**-684, **15**-685, **15**-686, **15**-689, **15**-694, **15**-695, **15**-696, **15**-700, **15**-703, **15**-704, **15**-708, **15**-709, **15**-710, **15**-712, **15**-714, **15**-718, **15**-719, **15**-720, **15**-723, **15**-724, **15**-725, **15**-727, **15**-728, **15**-1255, **15**-1256, **15**-1257, **15**-1258, **15**-1262, **15**-1282, **15**-1767, **16**-462, **16**-536, **16**-736, **16**-752, **16**-753, **16**-1039, **16**-1040, **16**-1063, **17**-91, **17**-94, **17**-104, **17**-113, **17**-325, **18**-68, **18**-105, **18**-106, **18**-107, **18**-278, **18**-280, **18**-451, **18**-452, **18**-453, **18**-454, **18**-455, **18**-456, **18**-457, **18**-458, **18**-459, **18**-463, **18**-464, **18**-466, **18**-469, **18**-470, **18**-471, **18**-473, **18**-474, **18**-475, **18**-480, **18**-482, **18**-484, **18**-486, **18**-487, **19**-844, **19**-846, **19**-847, **19**-851, **19**-854, **19**-855, **19**-856, **19**-857, **19**-858, **19**-862, **19**-867, **19**-921, **19**-965, **19**-997, **19**-1007, **19**-1046, **19**-1058, **19**-1068
Brown, H.C. **19**-1080, **19**-1093, **19**-1099, **19**-1162, **19**-1177, **19**-1279, **19**-1280, **19**-1327, **19**-1359, **19**-1470, **19**-1510, **19**-1615
Brown, J. **2**-257, **3**-181
Brown, J.M. **2**-327, **4**-64, **5**-372, **12**-287, **12**-610, **12**-626, **13**-448, **13**-547, **15**-455, **15**-472, **15**-735
Brown, L.R. **18**-295
Brown, M.J. **15**-2386, **16**-2216
Brown, M.K. **10**-1450
Brown, M.S. **19**-1070
Brown, P. **19**-440
Brown, P.B. **15**-2464
Brown, R F.C. **18**-554
Brown, R. **17**-397
Brown, R.A. **15**-651, **16**-97
Brown, R.D. **2**-210, **13**-51
Brown, R.E. **15**-1566
Brown, R.F.C. **5**-309, **5**-413, **18**-553
Brown, R.K. **18**-771, **19**-1370
Brown, R.S. **8**-240, **15**-6, **16**-1701, **15**-12, **15**-22, **15**-1650, **16**-1700, **16**-1701
Brown, S.H. **14**-324
Brown, S.M. **15**-1864
Brown, S.N. **19**-207
Brown, S.P. **12**-123
Brown, T.H. **11**-552
Brown, T.L. **5**-155, **5**-156
Brown, W.G. **19**-904
Brown. H.C. **18**-468
Brownawell, M. **18**-800
Brownawell, M.L. **11**-618m **18**-798
Brownbridge, P. **12**-320, **15**-2080, **18**-32
Browne, A.R. **2**-192, **4**-463
Browne, D.M. **15**-2100
Browne, W.R. **15**-1795
Browning, R.G. **12**-376, **13**-236
Brownlee, R.T.C. **9**-47, **9**-51, **9**-55
Brownlie, G. **18**-113
Brownstein, S. **4**-523, **11**-477, **15**-1786
Broxterman, Q.B. **16**-895, **19**-1463
Broxton, T.J. **16**-1675, **19**-1552, **19**-1556
Bruce, D.W. **10**-1366, **10**-1367, **10**-1368
Bruce, M.I. **2**-185, **3**-89
Bruce, M.I. appendixa-30
Bruch, M.D. **15**-2177
Bruck, A. **3**-46
Bruck, D. **5**-52, **11**-17
Bruckenstein, S. **8**-9, **8**-46
Bruckmann, A. **16**-960, **16**-1084
Brückner, C. **19**-186
Brückner, R. **18**-784
Brückner, S. **4**-39
Bruckner, V. **9**-13
Brugger, W. **16**-2168
Brugman, A. **15**-44
Bruice, P.Y. **12**-92
Bruice, T.C. **4**-261, **10**-391, **16**-27, **16**-1676, **16**-1956, **16**-1957, **16**-1958
Bruin, J.W. **12**-614
Brummond, K.M. **15**-877, **15**-918, **15**-1564, **15**-1565, **15**-1570
Brun, P. **12**-67, **15**-1039, **15**-2091, **15**-2548
Brundle, C.R. **1**-16, **1**-18, **1**-19
Bruneau, C. **10**-1535, **15**-278, **15**-281, **15**-453, **16**-430, **16**-1084, **18**-835, **19**-1473
Bruneh, J.-M. **16**-1496
Brunel, J.M. **4**-63, **15**-450, **15**-621, **19**-1021
Brunel, Y. **15**-2010, **16**-1329
Brunelle, D.J. **10**-1414, **10**-1443, **10**-1424, **10**-1505
Brunelle, P. **10**-137
Brunelle, W.H. **19**-351
Bruner, H.S. **16**-174
Brunet, J.-J. **10**-491, **15**-1503, **15**-1507
Brunet, J. **10**-1955, **11**-698, **13**-677

Bruni, R. **19**-842
Brunner, H. **4**-150, **4**-153, **4**-154, **15**-635, **19**-1233, **15**-1582
Brunner, M. **16**-2045
Bruno, F. **14**-460
Brunow, G. **16**-1270
Brüntrup, G. **16**-1043, **17**-418, **17**-422
Brunvoll, J. **2**-132, **2**-300
Brus, L.E. **11**-602
Brusova, G.P. **18**-259
Brussee, J. **4**-95
Brutcher Jr., F.V. **15**-1819
Bruyere, D. **15**-863
Bruylants, A. **16**-82
Bruylants, P. **10**-1563
Bruza, K.J. **15**-1465, **15**-1466
Bruzinski, P.R. **15**-2512
Bryan, C.J. **11**-304
Bryan, V.J. **16**-2034
Bryant, G.L. **13**-144
Bryany, J.A. **3**-126
Bryce-Smith, D. **10**-1397, **11**-374, **12**-436, **13**-736, **14**-479, **18**-528, **19**-1318
Bryce, M.R. **13**-39, **15**-2262
Bryce, M.R. **15**-2302
Brycki, B. **10**-417
Brycki, B.E. **10**-94
Brycki, B.E. **10**-1
Bryker, W.J. **13**-803
Brylikowska-Piotrowicz, J. **10**-1049
Bryson, T.A. **10**-1823, **16**-385
Brzaszcz, M. **19**-678
Brzezinski, L.J. **16**-813
Bu, J. **11**-402
Bu, Y.-P. **16**-1140
Buback, M. **13**-400
Bubenitschek, P. **17**-18
Bublitz, D.E. **2**-185, **11**-67, **12**-592, **19**-1454
Bubnov, Y.N. **16**-2083, **18**-584
Bubnov, Yu.N. **16**-736, **16**-2084
Bucciarelli, M. **4**-39
Buch, C. **15**-330
Buch, F. **15**-760
Büch, H.M. **15**-2495
Buchan, C. **10**-2002
Buchanan, D.N. **15**-2310
Buchanan, G.L. **4**-512, **12**-675, **12**-700
Buchanan, G.W. **2**-271, **3**-118, **4**-349
Buchanan, J.G.S. **19**-1415
Buchardt, O. **4**-71, **4**-158, **4**-159
Buchbauer, G. **16**-176
Bucher, B. **16**-2290
Bucher, G. **5**-217
Buchholz, B. **10**-1646
Buchholz, S. **12**-30
Büchi, G. **15**-361, **15**-2453, **15**-2454, **18**-438
Büchi, G.H. **10**-711
Büchi, H. **10**-751
Buchneva, L.M. **9**-34
Buchwald, S.L. **3**-120, **10**-1027, **10**-1309, **10**-1496, **10**-1739, **11**-179, **11**-542, **12**-589, **13**-98, **13**-129, **13**-130, **13**-131, **13**-132, **13**-186, **13**-187, **13**-188, **13**-189, **13**-190, **13**-191, **13**-193, **13**-200, **13**-205, **13**-206, **13**-210, **13**-234, **13**-236, **13**-237, **13**-240, **13**-265, **13**-268, **13**-365, **13**-494, **13**-530, **13**-570, **13**-640, **13**-642, **13**-646, **13**-663, **13**-680, **13**-707, **15**-451, **15**-630, **15**-632, **15**-842, **15**-1001, **15**-1536, **15**-1559, **15**-1581, **15**-1603, **15**-1631, **16**-1366, **16**-1410, **19**-1119, **19**-1155, **19**-1451
Buck, H.M. **7**-17, **10**-165, **10**-1319
Buck, J.S. **16**-1581
Buck, P. **13**-4, **17**-313
Buckingham, A.D. **4**-128
Buckingham, J. **4**-99, **16**-274
Buckle, M.J.C. **12**-4
Buckle, R. **10**-685
Buckles, R.E. **15**-1665, **19**-815
Buckley, B.R. **15**-1909, **15**-1942, **15**-1943
Buckley, P.D. **17**-69
Buckmelter, A.J. **14**-95, **15**-919
Buckner, J.K. **10**-81
Bucsi, I. **11**-123
Buda, A.B. **2**-78, **4**-525
Buda, V. **10**-1053
Buddhsukh, D. **17**-412
Budelman, N.S. **15**-909
Budzelaar, P.H.M. **16**-853
Buehler, C.A. **11**-224, **11**-438, **11**-568
Buehler, E. **10**-799
Buehler, N.E. **18**-912
Buendia, J. **10**-1362
Bueno, A.B. **13**-118
Buess, C.M. **2**-151
Bug, T. **10**-375, **10**-438
Bugaenko, L.T. **5**-221
Bugl, M. **18**-814
Bühl, H. **4**-493
Bühl, M. **2**-395, **4**-140, **15**-2507
Buhler, J.D. **16**-508
Bühler, R.E. **14**-139
Bui, T. **16**-1084, **16**-1173
Buijsman, R.C. **18**-848
Buiry, P.J. **13**-436
Buist, G.J. **16**-2251, **19**-316
Bujok, R. **10**-1101
Bulat, H. **13**-493
Bulbule, V.J. **16**-1203
Bulger, P.G. **18**-820
Bull, H.G. **10**-551
Bull, J.A. **15**-2550
Bull, S.D. **4**-112, **19**-1500, **19**-1603
Bullen, J.V. **11**-107
Bullock, R.M. **15**-502
Bullock, V.R. **4**-321
Bulman Page, P.C. **15**-1909
Bulten, E.J. **15**-550
Bultinck, P. **2**-389
Bulut, A. **16**-667, **16**-1215
Bumagin, N.A. **10**-1488, **10**-1988, **12**-555, **13**-497, **13**-553, **13**-557, **13**-580, **13**-670, **12**-168, **13**-855
Bunce, N.J. **5**-218, **14**-115, **14**-480
Bunce, R.A. **10**-1671
Buncel, E. **5**-105, **5**-110, **5**-117, **5**-137, **5**-152, **5**-207, **5**-208, **5**-408, **8**-17, **8**-72, **8**-73, **8**-146, **18**-788, **18**-943, **10**-378, **10**-382, **10**-384, **10**-385, **10**-388, **10**-389, **10**-392, **10**-439, **10**-480, **10**-482, **10**-712, **10**-1520, **10**-1763, **12**-411, **12**-443, **12**-669, **13**-4, **13**-6, **13**-9, **13**-10, **13**-34, **16**-17, **16**-1058, **16**-2276, **18**-941, **18**-943, **18**-947, **18**-949
Buncel, I.M. **11**-580
Bunch, B. **10**-222
Bundel', Yu.G. **10**-1163
Bundhoo, D. **16**-12
Bunina-Krivorukova, L.I. **18**-718
Bunlaksananusorn, T. **15**-387, **15**-953
Bunnelle, W.H. **16**-443
Bunnett, J.F. **6**-40, **6**-41, **6**-59, **6**-65, **8**-3, **8**-140, **8**-143, part **2**-2, **10**-73, **11**-234, **11**-683, **11**-684, **13**-64, **13**-255, **13**-631, **13**-645, **11**-650, **11**-653, **11**-684, **12**-719, **13**-4, **13**-13, **13**-17, **13**-45, **13**-47, **13**-56, **13**-60, **13**-77, **13**-93, **13**-154, **13**-221, **13**-638, **13**-656, **13**-657, **13**-657, **13**-843, **13**-866, **16**-1957, **16**-1961, **17**-3, **17**-61, **17**-77, **17**-90, **17**-95, **19**-1354, **19**-1552
Buntain, G.A. **18**-371, **18**-373
Bunting, J.W. **8**-51, **17**-56
Bunton, C.A. **6**-95, **10**-453, **10**-560, **13**-21, **16**-18, **19**-301, **19**-316
Bunton, L.A. **10**-438
Buñuel, E. **5**-321, **10**-1463
Bunyan, P.J. **19**-1718
Bunz, U.H.F. **2**-341
Bünzli, J. **2**-323
Buono, G. **15**-640, **15**-2674, **19**-1021
Buonora, P. **15**-2316
Buonora, P.T. **16**-1034
Bur, S. **16**-379
Bur, S.K. **15**-2182, **19**-1753
Buranaprasertsuk, P. **13**-126, **13**-152
Burawoy, A. **3**-44
Burch, R.R. **15**-474

Burden, F.R. **2**-210
Burdett, J.K. **1**-2
Burdisso, M. **15**-2127
Burditt, A.M. **6**-44, **16**-2194
Burdon, J. **19**-1441
Bureau, C. **3**-130
Burfield, D.R. **14**-245
Burford, S.C. **15**-982
Burg, D.A. **15**-2167
Burgard, A. **18**-285
Burger, E.C. **18**-724
Burger, G. **4**-179
Burger, T.F. **17**-256
Burger, U. **15**-2303, **18**-512, **18**-688
Burgess, E.M. **16**-30
Burgess, J. **6**-64, **10**-41
Burgess, K. **15**-195, **15**-196, **15**-448, **15**-692, **15**-731, **15**-732, **15**-1883
Burgos, C.H. **13**-131, **16**-756
Burgoyne, W. **19**-1283
Burgstahler, A.W. **15**-817, **19**-1082
Burguete, M.I. **16**-667
Burham, R.L. **15**-1665
Burk, M. J. **10**-602, **15**-636, **15**-644, **19**-1120
Burk, M.T. **16**-708
Burk, P.L. **15**-2409
Burk, S. **19**-1014
Burka, L.T. **18**-70
Burkart, M. **10**-756
Burke, C.P. **15**-1935
Burke, J.J. **8**-40, **8**-131
Burke, J.P. **10**-1537
Burke, L.A. **2**-57
Burke, S.D. **12**-365, **15**-2470, **18**-930
Burkert, U. **1**-56
Burkert, U. **4**-422, **4**-516
Burkett, H. **11**-649
Burkhardt, E.R. **12**-629
Burkoth, T.L. **2**-275, **2**-278
Burkus, T. **16**-2154
Burlak, N. **2**-362
Burland, M.C. **15**-2692
Burlingame, A.L. **12**-101
Burlingame, T.G. **4**-264
Burmakov, A.I. **16**-442
Burn, D. **12**-315
Burnell, D.J. **15**-2247
Burns, C.L. **10**-1390
Burns, M.J. **13**-494
Burns, S.E. **10**-1671
Burns, S.J. **17**-193
Burns, T.P. **12**-628
Burrell, R.C. **18**-79
Burri, P. **13**-30, **13**-836
Burrous, M.L. **15**-581
Burrows, E.P. **19**-727
Bürstinghaus, R. **15**-1192
Burt, R.A. **10**-588
Burton, A. **16**-460
Burton, A.J. **19**-600
Burton, D.J. **5**-370, **14**-347, **16**-2000
Burton, J.W. **15**-452
Burton, K.A. **5**-313
Burton, N.A. **2**-474
Burton, P.E. **18**-53
Burtscher, D. **18**-850
Burwell Jr., R.L. **15**-481, **15**-484
Bury, A. **10**-408
Busch, P. **17**-521, **17**-522, **17**-524
Buschmann, E. **10**-1711
Buschmann, J. **4**-392, **18**-674
Buschmann, N. **18**-853
Buse, C.T. **12**-330
Bushby, R.J. **12**-74
Bushweller, C.H. **4**-270, **4**-328, **4**-338, **4**-343, **4**-344, **4**-363, **4**-364
Buskens, P. **16**-960
Buss, E. **15**-1701
Buss, V. **5**-87, **15**-665
Bussell, G.E. **6**-40
Bussolari, J. **16**-1380
Bussolari, J.C. **13**-492
Bustamante, J.M. **15**-1851
Buston, J.E.H. **18**-429, **18**-430
Busujima, T. **16**-1172, **16**-1134
But Scammells, P.J. **9**-117
But, T.Y.S. **10**-727, **10**-730
Butchko, M.A. **5**-379
Buteiko, Zh.F. **10**-1399
Butenschön, H. **15**-2402, **15**-2588
Butin, K.P. **5**-106, **8**-16, **8**-17, **12**-43
Butler, A.B. **11**-113
Butler, A.R. **11**-282, **13**-772, **13**-772, **16**-1855, **16**-1956, **19**-727
Butler, C.R. **13**-452, **13**-706
Butler, D.N. **15**-94, **15**-533
Butler, K.E. **2**-339
Butler, R. **11**-306
Butler, R.N. **5**-54, **13**-744, **13**-780, **13**-829, **14**-229, **14**-272, **14**-278, **15**-184, **19**-741
Butova, E.D. **14**-163
Butskus, P.F. **15**-2175, **17**-108
Butsugan, Y. **10**-1589, **16**-656, **16**-836, **16**-1459
Buttenberg, W.P. **17**-318
Button, M.A.C. **18**-646
Buynak, J.D. **16**-736
Buys, H.R. **4**-329, **4**-378
Buzard, D.H. **13**-244
Buzás, A. **16**-2191
Buzas, A.K. **18**-277
Buzbee, L.R. **13**-111
Buzby, J.H. **19**-729
Buzek, P. **10**-221
Bydlinski, G.A.S. **15**-2566
Byeon, S.-H. **19**-778
Byers, G.W. **17**-527
Bykhovskaya, M.Sh. **15**-46
Bykowski, D. **15**-2477
Byrne, C.J. **9**-30
Byrne, J.J. **16**-1539
Byrne, K. **4**-108
Byrne, M.P. **3**-107
Byrne, N.E. **16**-2204
Byström, S.E. **14**-274, **15**-2023, **17**-388
Bytschkov, I. **15**-366
Byun, E. **16**-350
Bzowej, E.I. **16**-1411

Cabaleiro, M.C. **17**-55
Caballero, A. **12**-375
Caballero, G.M. **10**-571
Cabaret, D. **16**-530
Cabello, J.A. **15**-593
Cabiddu, S. **1**-110
Cablewski, T. **11**-188
Cabral, S. **16**-336
Cabrera, A. **10**-1330, **15**-598
Cabrera, C.R. **15**-688
Cabrera, G. **17**-192
Cabrera, S. **15**-2114
Cabri, W. **13**-367, **13**-426, **13**-439, **19**-1352, **19**-1659
Cacace, F. **10**-275, **11**-101
Caccamese, S. **4**-167
Cacchi, S. **10**-1990, **13**-163, **13**-238, **13**-608, **13**-667, **15**-245, **15**-907, **16**-2104, **19**-1115, **19**-1352
Cacciapaglia, R. **10**-362
Caddick, S. **7**-109, **7**-116, **13**-493
Caden, C.E. **10**-974
Cadierno, V. **15**-2683
Cadilhac, C. **13**-794
Cadiot, P. **14**-329
Cadogan, J.I.G. **10**-1159, **10**-1160, **13**-833, **14**-395, **15**-16, **15**-1474, **16**-1311, **16**-1361, **16**-1381, **17**-339, **19**-1400, **19**-1404, **19**-1528, **19**-1551, **19**-1718
Cadot, C. **15**-673
Cady, G.H. **3**-172
Cafferata, L.F.R. **10**-300
Caggiano, L. **12**-139
Caglioti, L. **19**-1494
Cahard, D. **12**-141
Cahiez, G. **10**-1313, **10**-1362, **10**-1366, **10**-1384, **10**-1386, **10**-1416, **10**-1446, **10**-1483, **10**-1494, **12**-324, **13**-336, **13**-343, **13**-345, **15**-984, **15**-985, **16**-605, **16**-2035
Cahingt, B. **11**-258
Cahn, R.S. **4**-101
Cai, C. **12**-123, **13**-284, **13**-291, **16**-312
Cai, D. **15**-466
Cai, G. **19**-115
Cai, H.-Q. **16**-545
Cai, J. **13**-595
Cai, J. **4**-371, **4**-388, **16**-800

Cai, M.-Z. **10**-1380, **10**-1995, **13**-675
Cai, P. **18**-136
Cai, Q. **10**-1029, **13**-125, **13**-205
Cai, X.-h. **19**-33
Cai, X. **5**-308
Caijo, F. **18**-821
Caille, J.-C. **13**-665
Caillot, F. **13**-505
Cain, C.M. **12**-109
Cain, E.N. **14**-60
Cain, G.A. **19**-1337
Cain, M.E. **10**-818
Caine, D. **10**-1694, **10**-1760, **12**-246, **12**-447, **15**-534, **16**-1037, **17**-415
Cainelli, G. **15**-2241, **16**-484, **16**-500, **16**-1021, **19**-10, **19**-65, **19**-89, **19**-253, **19**-374, **19**-377, **19**-401, **19**-436, **19**-670
Caira, M.R. **3**-178
Cairncross, A. **15**-2415
Cairns, T.L. **15**-2437, **15**-2490, **15**-2549, **16**-185
Cais, M. **3**-89, **15**-1643, **16**-2003
Cajthami, C.E. **8**-220
Cal, P.M.S.D. **19**-687
Calabrese, J.C. **12**-372, **15**-731
Calder, G.V. **8**-24, **13**-51
Calder, I.C. **2**-300, **2**-354, **2**-359
Calderbank, K.E. **2**-156
Calderon N. **18**-807, **18**-809, **18**-812, **18**-881, **18**-894
Calderón, O. **16**-1249
Calderwood, D.J. **16**-2069
Caldin, E.F. **6**-69
Caldwell, D.J. **4**-128
Caldwell, G. **8**-249, **10**-286, **10**-447
Caldwell, J.J. **15**-2096
Caldwell, R.A. **5**-303, **6**-86, **7**-52, **8**-78, **15**-2462, **16**-191
Caldwell, S.T. **19**-1156
Calet, S. **17**-226
Calhorda, M.J. **3**-52, **3**-62
Caliando, B.J. **15**-2059
Calimano, E. **13**-315
Çalimsiz, S. **16**-1756
Callaghan, O. **15**-1362
Callahan, J.H. **2**-393
Callens, E. **19**-600
Callier, A.-C. **15**-413
Callis, N.M. **15**-450
Calmes, M. **11**-491
Calò, V. **9**-132, **10**-1611, **13**-382, **13**-500
Calter, M.A. **16**-1073, **16**-2196
Calvert, J.G. **7**-29, **7**-42, **7**-69, **19**-1662
Calvert, R.L. **2**-156
Calvin, M. **4**-71, **4**-159
Calvo, R.L. **15**-2664
Calzada, J.G. **10**-1881
Camaioni, D.M. **11**-574, **19**-100, **19**-484
Camarena, R. **16**-2184
Cambie, R.C. **12**-169, **14**-473, **15**-1682, **15**-1715, **15**-1733, **15**-1734, **15**-1759, **15**-1764, **15**-1822
Cambron R.T. **18**-62
Cameron A.G. **18**-729
Cameron D.K. **15**-16
Cameron G.S. **12**-65
Cameron K.S. **4**-395
Cameron, T.S. **5**-151, **19**-129
Cami-Kobeci, G. **10**-923
Caminati, W. **3**-17, **3**-35
Caminiti, R. **15**-1895
Cammers-Goodwin, A. **4**-278
Camp, D. **10**-726
Campagne, J.-M. **10**-1595, **13**-378, **15**-333, **16**-1150, **16**-1160, **16**-1162, **16**-1763, **18**-890
Campaigne, E. **16**-2, **16**-183, **16**-186
Campaña, A.G. **5**-321
Campana, C.F. **1**-13
Campbell Jr., J.B. **14**-436, **10**-1865, **15**-723, **15**-725
Campbell, A. **18**-10
Campbell, A.D. **15**-417
Campbell, A.L. **10**-1258, **12**-601
Campbell, E. **15**-1548, **16**-1695
Campbell, E.J. **10**-1627, **19**-952, **19**-957
Campbell, G. **16**-1666
Campbell, J.R. **10**-1226
Campbell, M.L. **8**-44
Campbell, M.M. **15**-1690
Campbell, M.S. **2**-81
Campbell, P. **11**-56
Campbell, T.W. **16**-2188, **16**-2189
Campelo, J.M. **15**-188, **15**-482, **15**-593
Campi, E. **15**-1607
Campi, E.M. **15**-1616, **15**-1821
Campillo, N. **8**-14
Campion, A. **2**-243
Campo, M.A. **13**-428, **15**-959, **15**-2618
Campos, K. **5**-226
Campos, K.R. **6**-37, **15**-466, **15**-2249, **18**-766
Campos, P.J. **12**-509, **15**-1672, **15**-1673, **15**-2655, **18**-617, **19**-1679
Camps, F. **10**-619, **10**-1944, **15**-1671
Camps, P. **4**-511
Canales, E. **15**-2252, **15**-2402, **16**-756
Canali, L. **15**-1972
Canary, J.W. **2**-262
Candeias, N.R. **19**-687
Candiani, I. **13**-367, **13**-426, **13**-439
Candler, J. **13**-46
Candlin, J.P. **19**-843
Candran, N. **15**-877
Candy, J.-P. **5**-413, **19**-37
Cane, D. **10**-1679
Cane, D.E. **16**-1374
Canepa, C. **15**-1874
Canet, J,-L. **19**-1702
Cañibano, V. **11**-269
Canivet, P. **8**-26
Canle, L.M. **8**-87
Cann, P.F. **17**-49
Cannella, R. **16**-1532
Cannizzaro, C.E. **3**-72, **15**-270
Cannizzo, L.F. **16**-1409
Cannon, J.F. **15**-370, **15**-1747
Cano, A.C. **16**-2184
Canonne, P. **16**-510, **16**-994, **16**-2052
Cantacuzène, J. **16**-257
Cantagalli, G. **15**-1238
Cantello, B.C.C. **19**-423
Cantin, K. **10**-1757
Cantlin, R.J. **12**-99
Cantow, H. **4**-302
Cantrell Jr., W.R. **13**-101
Cantrill, S.J. **3**-195, **3**-196
Cantu, A.A. **13**-835
Canturk, B. **13**-570
Cao, B. **15**-452
Cao, C. **15**-309, **15**-367
Cao, G. **16**-1512
Cao, H. **13**-453
Cao, J. **13**-386
Cao, P. **15**-811
Cao, S. **11**-264
Cao, X. **13**-211
Cao, Y.-Q. **10**-647, **10**-1933
Cao, Y. **5**-398, **13**-397
Capacci, A.G. **15**-452, **16**-599
Capan, E. **16**-1496
Capdevielle, P. **11**-573, **19**-271
Capitò, E. **10**-1568
Capitosti, G.J. **5**-377
Capitta, F. **17**-316
Capka, M. **19**-889
Caplar, V. **15**-635
Caple, R. **15**-2205
Capobianco, A.M. **17**-96
Capon, B. **2**-447, **2**-458, **10**-113, **10**-451, **12**-93, **16**-29, **16**-34
Caporusso, A.M. **15**-378
Capozzi, F. **15**-1738
Capozzi, G. **15**-21, **15**-1738, **19**-769, **19**-826
Cappelli, F.P. **6**-93
Capperucci, A. **10**-691, **15**-1141
Capponi, M. **2**-445, **2**-468, **15**-211
Capraro, D. **15**-1653
Caprentier, J.-F. **13**-695
Capretta, A. **16**-1748
Capretto, D.A. **10**-1011, **12**-242
Capriati, V. **13**-731
Caputo, J.A. **19**-395

Caputo, R. **10**-1220, **17**-205
Caputo, T.D. **16**-820
Capwell, R.J. **4**-391
Caramella, P. **15**-81, **15**-2121
Caramori, G.F. **2**-70, **2**-389
Carballares, S. **16**-1295
Carballeira, J.D. **16**-799
Carbone, G. **6**-37
Carboni, B. **12**-547
Carda, M. **16**-1039
Cardamone, R. **12**-270
Cardellina, J.H.I. **18**-213
Cárdenas, D.J. **5**-321, **10**-1463, **15**-853
Cárdenas, J.C. **13**-401
Cardenas, R. **10**-247
Cardi, N. **19**-1399
Cardillo, G. **15**-1177, **15**-1415, **15**-1710, **19**-10, **19**-65, **19**-89, **19**-253, **19**-374, **19**-436, **19**-670
Cardillo, M.J. **2**-64
Cardin, D.J. **18**-896
Cardinale, G. **19**-50, **19**-337
Cardomone, R. **13**-487
Cardona, F. **17**-452, **19**-745, **19**-1222
Cardona, R. **15**-2314
Cardoso, S.P. **11**-123
Carducci, M. **15**-2049
Carenzi, D. **13**-236
Caress, E.A. **17**-94
Carey, F.A. **4**-134, **17**-344, **19**-1330
Carey, J.G. **13**-798
Cargill, R.L. **15**-2452
Cargioli, J.D. **8**-30
Carhart, R.E. **4**-131
Cariou, K. **15**-877
Carless, H.A.J. **7**-48, **15**-1864, **16**-2205, **16**-2205, **16**-2206
Carlier, P.R. **4**-200, **5**-98, **5**-204, **8**-227
Carlone, A. **10**-972, **11**-314, **15**-1106
Carloni, S. **19**-466
Carlqvist, P. **18**-379
Carlsen, P. **10**-795
Carlsen, P.H.J. **11**-279, **14**-483, **19**-579
Carlsmith, L.A. **13**-40
Carlson, B.A. **18**-459
Carlson, R. **15**-526, **15**-2223, **16**-262, **16**-263, **19**-1768
Carlson, R.M. **17**-364
Carlson, S.C. **10**-1555, **19**-1514
Carman, R.M. **10**-1113
Carmeli, M. **10**-1057, **19**-754
Carmichael, G. **17**-504
Carmichael, I. **3**-48
Carmody, M.J. **2**-191, **15**-2442
Carnahan Jr., J.C. **5**-68, **17**-336
Carnahan, E. **7**-44
Carneiro, J.W. de M. **10**-221
Carneiro, J.W. **10**-219
Carnell, A. J. **4**-206, **15**-1931
Carninji, J.J. **15**-864
Caro, B. **19**-923, **19**-998
Caron H. **16**-510
Caron M. **10**-527, **15**-1689
Caron, S. **13**-634
Caronna, T. **14**-385
Caroon, J.M. **16**-1817
Carpenter, B.K. **2**-242, **6**-34, **14**-31, **15**-2641, **18**-537
Carpenter, G.B. **5**-200, **10**-361, **16**-742
Carpenter, T.C. **10**-1262
Carpentiere, J.-F. **13**-696
Carpita, A. **13**-489, **13**-582
Carr, G. **18**-385
Carr, M.D. **12**-81
Carr, R. **19**-1148
Carr, R.V.C. **15**-2179
Carrasco, M.C. **19**-1418
Carrasco, N. **8**-90
Carrea, G. **19**-738, **19**-801
Carrée, F. **10**-974
Carreira, E.M. **15**-426, **10**-934, **15**-629, **15**-1170, **15**-1269, **15**-2112, **16**-543, **16**-544, **16**-924, **16**-978, **19**-1048, **19**-1183, **19**-1513
Carreira, L.A. **4**-398
Carreño, M.C. **11**-269, **15**-163, **19**-1482
Carrera, D.E. **16**-358
Carrera, I. **15**-1693
Carretero, J.C. **10**-518, **10**-1309, **10**-1364, **12**-271, **15**-1157, **15**-1273, **15**-1537, **15**-1540, **15**-2114, **15**-2349, **16**-794
Carreyre, H. **11**-570
Carrick, P.G. **5**-430
Carrié, D. **15**-2524
Carrié, R. **12**-547
Carrigan, D. **16**-1778
Carril, M. **13**-218
Carrillo, J.R. **7**-129
Carrillo, L. **15**-1045, **15**-1401
Carringan, M.D. **10**-576
Carrington, A. **2**-422, **15**-575
Carrión, A.E. **18**-124
Carriuolo, J. **16**-1957
Carroll, A.R. **19**-1686
Carroll, F.A. **6**-1
Carroll, F.I. **11**-516, **15**-584
Carroll, L. **10**-1179
Carroll, M.A. **13**-201, **13**-392, **13**-501
Carroll, M.F. **18**-722
Carroll, P.J. **10**-1537, **15**-2246, **16**-666
Carroll, T.X. **2**-58, **8**-186, **11**-42
Carrupt, P. **15**-2448
Carruthers, N.I. **13**-517
Carruthers, W. **4**-515, **10**-1661, **15**-991, **15**-2105, **15**-2169, **15**-2371, **18**-923
Cársky, P. **8**-185
Carson, A.S. **4**-243
Carson, K.G. **16**-340
Carson, M.W. **15**-1326
Carson, R.J. **11**-329
Carswell, E.L. **16**-1155
Cartaya-Marin, C.P. **16**-1570
Carter, C. **16**-1066
Carter, C. **10**-1702
Carter, D.S. **12**-367, **13**-737
Carter, E.A. **18**-91
Carter, G.E. **10**-465, **10**-468, **10**-469
Carter, K.R. **13**-363
Carter, P. **10**-136
Carter, P.L. **16**-2237
Carter, R.E. **6**-81
Carter, R.L. **4**-193
Carter, T.L. **15**-4, **15**-34
Carter, W.L. **18**-178
Carter, W.P.L. **19**-372, **19**-373
Carter. L.G. **10**-1843
Cartledge, F.K. **12**-1
Caruso, A.J. **13**-144
Caruso, T.C. **3**-107, **10**-1756
Carvalho, E. **12**-743
Casaarini, D. **4**-436
Casadei, M.A. **12**-789
Casadevall, A. **10**-93
Casadevall, E. **10**-93
Casado, A.L. **12**-291
Casado, F. **13**-71
Casado, J. **12**-737
Casagrande, B. **16**-1237
Casagrande, F. **18**-202
Casanova Jr, J. **14**-459
Casanova, J. **4**-400, **4**-457, **17**-275, **17**-453, **19**-427
Casares, A. **15**-1247
Casares, J.A. **10**-1463
Casarini, D. **4**-57, **4**-62, **4**-90
Casarini, D. **4**-327
Casarrubios, L. **15**-1549, **15**-1558, **15**-1561, **15**-2065
Casas, J. **16**-394, **19**-371
Casati, S. **16**-1795
Caselli, A. **16**-718
Casely, I.J. **15**-355
Cásensky, B. **19**-888
Caserio, M.C. **10**-655, **15**-2082
Casewit, C.J. **4**-413
Casey, C.P. **7**-53, **10**-1505, **12**-69, **14**-420
Casey, M. **10**-1560
Casi, G. **10**-940
Casimir, M.D. **13**-205
Casini, G. **11**-338
Casiraghi, G. **11**-386, **11**-389, **11**-519, **16**-1029
Caskey, D.C. **8**-85
Casnati, G. **11**-386, **11**-389, **11**-519, **11**-526
Cason, J. **10**-1129, **16**-997, **16**-2029

Caspar, M.L. **18**-53
Cassar, L. **10**-1983, **13**-664, **18**-898
Cassidy, J. **15**-692
Cassimatis, D. **11**-479
Cassimjee, K.E. **10**-956
Casson, A. **4**-249
Cast, J. **18**-443
Castagnetti, E. **11**-43
Castagnoli, G. **10**-691
Castagnolo, D. **10**-1917
Castaldi, G. **18**-202, **19**-934
Castañer, J. **5**-269
Castanet, A.-S. **11**-293, **13**-618, **13**-729
Castanet, Y. **13**-695, **13**-696, **15**-1497, **15**-1574
Castaño, A.M. **10**-1548
Castedo, L. **15**-851, **15**-2627, **15**-2667, **15**-2685, **18**-862, **18**-869
Castejon, H. **4**-333
Castellano, G. **19**-479
Castellano, R.K. **3**-78
Castellino, S. **16**-461, **16**-774
Castellnou, D. **16**-682
Castelluzzo, F. **16**-776
Castillo, M. **19**-1629
Castillón, S. **10**-1532, **18**-305
Castle, G.H. **10**-613
Castle, L. **14**-227
Castle, S.L. **15**-1284, **15**-1289
Castonguay, R. **16**-1364
Castro, A. **12**-734, **12**-737
Castro, A.M.M. **10**-1946, **15**-1451, **15**-2355, **18**-690
Castro, B. **10**-946, **12**-619
Castro, B.R. **10**-1159
Castro, C. **2**-214, **2**-277, **2**-345, **2**-373
Castro, C.E. **13**-580, **16**-2010
Castro, E.A. **2**-433
Castro, I.G. **15**-366
Casu, A. **19**-822
Casy, G. **15**-644
Catak, S. **18**-605
Catalán, J. **8**-138, **8**-144, **8**-245
Catalane, D.B. **10**-1049
Cate, L.A. **16**-2302
Catelani, G. **15**-126
Catellani, M. **13**-236, **13**-530
Catino, A.J. **15**-2057, **19**-567
Cativiela, C. **15**-2248
Catto, B.A. **18**-422
Cattoën, X. **5**-360
Catton, X. **5**-425
Caubere, P. **10**-1311, **13**-677, **13**-479, **13**-637, **14**-442, **19**-10, **19**-1563
Caubet, A. **2**-488
Cauble, D.F. **16**-713, **16**-741, **16**-749
Cauci, S. **16**-1821
Caughlan, C.N. **16**-1354
Caulier, T. **7**-86
Caulton, K.G. **15**-2069, **15**-2645
Caumul, P. **16**-798
Cava, M.P. **2**-233, **17**-517
Cavaleiro, J.A.S. **7**-129
Cavalli, A. **15**-1084, **15**-1106
Cavallo, L. **15**-1987, **15**-1988, **18**-891
Cavazza, M. **4**-66, **4**-159, **17**-122
Cavazzini, M. **19**-170, **19**-1752
Cavdar, H. **10**-598
Cave G.W.V. **9**-84
Cavé, A. **10**-1110
Cave, G.W.V. **9**-143
Cavicchioni, G. **10**-533
Cawley, J.J. **10**-557
Cawse, J.N. **10**-1958
Cayen, C. **12**-337
Cayón, E. **13**-69
Cazat, J.T. **18**-873, appendixa-26
Cazaux, M. **12**-312
Cazeau, P. **12**-332
Cazes, B. **15**-1745
Cazes, J. **13**-821
Cazianis, C.T. **18**-201
Ceasar, G.P. **2**-253
Ceccacci, F. **4**-53
Cecchetto, A. **19**-167, **19**-1040
Ceccon, A. **17**-81
Cee, V.J. **4**-143, **4**-145, **16**-1074
Cefalo, D.R. **18**-843
Cekovic, Z. **14**-229, **14**-233, **14**-234, **14**-235, **19**-6
Celani, P. **18**-906
Celebi-Olcum, N. **15**-2188
Celentano, G. **16**-927, **16**-1085
Celewicz, L. **18**-517
Cella, J.A. **10**-1587
Cella, R. **7**-70, **13**-577, **14**-362, **16**-240
Cenini, S. **12**-786, **19**-1719
Ceppi, E. **1**-47
Cercone, S. **16**-1439
Cerè, V. **16**-976
Cerero, S. de la M. **11**-498
Cerezo, A.d.F. **10**-1488
Cerfontain, H. **8**-35, **8**-36, **11**-196, **11**-201, **11**-202, **11**-203, **11**-204, **11**-205, **11**-206, **11**-208, **11**-668, **11**-669, **11**-673, **13**-864
Cerichelli, G. **11**-693, **13**-493, **16**-146
Cerioni, G. **3**-130
Cermola, F. **15**-2115
Cerny, M. **19**-850, **19**-1004, **19**-1491
Cerreti, A. **10**-691, **14**-86
Cerritelli, S. **12**-82
Ceruti, M. **16**-1338
Cerveau, G. **12**-622
Cerveny, L. **19**-927
Cervera, M. **13**-71
Cervinka, O. **10**-1785
César, V. **19**-1039
Cesati III, R.R. **15**-900
Cessac, J. **2**-235
Cessna, A.J. **18**-24
Cesta, M.C. **16**-1975
Çetinkaya, B. **13**-595, **18**-896
Çetinkaya, E. **13**-595
Ceulemans, A. **2**-268
Cha, H.T. **14**-398
Cha, J.K. **11**-64
Cha, J.S. **19**-964, **19**-1080, **19**-1090, **19**-1091, **19**-1093, **19**-1095, **19**-1098, **19**-1178
Cha, K.L. **12**-391
Cha, Y. **5**-356
Chaabouni, R. **12**-226
Chabaud, B. **10**-816, **19**-453, **19**-454
Chablay, E. **19**-1076
Chaboche, C. **10**-1416, **13**-343
Chadha, A. **19**-1157
Chadha, M. S. **18**-146
Chadha, P. **4**-316
Chadwick, D. **11**-438
Chadwick, D.J. **3**-65
Chadwick, S.T. **13**-727, **13**-729
Chadwick, S.T. **13**-734
Chae, J. **10**-1207
Chafetz, H. **12**-312
Chahboun, R. **15**-597, **17**-160, **19**-342, **19**-912
Chahen, L. **14**-363
Chahma, M. **14**-81, **18**-606
Chai, C.L.L. **15**-1824
Chai, L. **19**-224
Chai, Q. **16**-776
Chai, Y. **18**-731
Chai, Z. **16**-751
Chaiez, G. **12**-524
Chaigne, F. **15**-2164
Chaiken, I.N. **16**-1936
Chaikin, S.W. **19**-904
Chaikovskii, V.K. **11**-292
Chaisupakitsin, M. **11**-535
Chaki, N.K. **18**-220
Chaki, S. **15**-846
Chakrabarti, D. **15**-1309
Chakrabartty, S.K. **12**-705
Chakraborti, A.K. **10**-748, **10**-964, **10**-965, **15**-1441, **16**-122, **16**-210, **16**-295, **16**-1633, **16**-1723, **19**-396
Chakraborty, A. **16**-1711, **16**-1714, **16**-1863
Chakraborty, D. **19**-127, **19**-680
Chakraborty, R. **15**-188, **19**-910
Chakraborty, U.R. **18**-897
Chakrapani, H. **15**-853, **15**-855
Chakrapani, L. **16**-1087
Chakravarti, R. **11**-223
Chaładaj, W. **16**-624
Chalais, S. **18**-192
Chalfont, G.R. **14**-369

Challis, B.C. **10**-1020, **11**-159, **11**-160, **12**-733, **12**-736, **12**-738, **13**-772, **13**-781, **16**-365, **16**-1693, **16**-1977, **18**-939, **19**-727, **19**-1472
Challis, J.A. **10**-1020, **12**-733, **16**-365, **16**-1977, **19**-1472
Challis, J.C. **16**-1693
Challis, M.S. **16**-1855
Chaloner, P.A. **15**-455, **15**-1000
Chamberlain, N.C. **19**-1390
Chamberland, S. **16**-13
Chamberlin, A.R. **17**-278, **17**-279
Chamberlin, R.M. **15**-602
Chambers-Asman, D.M. **12**-388
Chambers, E.J. **4**-358
Chambers, M.R.I. **13**-295
Chambers, R.A. **10**-1256
Chambers, R.D. **11**-312, **12**-143, **13**-80, **15**-71, **15**-253, **16**-446
Chambers, V.C. **10**-333
Chambers, W.T. **10**-204
Chambron, J.-C. **3**-191, **3**-211
Chameil, H. **13**-565
Chamness, J.T. **18**-791
Chamorro, E. **15**-1671
Chamot, E. **2**-192
Champagne, P. **19**-630
Champeau, R.M. **19**-338
Chan, A.S.C. **15**-1629, **13**-516, **13**-661, **15**-643, **15**-1202, **15**-1204, **15**-1218, **15**-1600, **15**-1997, **16**-746, **16**-658, **16**-664, **16**-670, **16**-893, **18**-155, **19**-1024
Chan, B. **15**-555
Chan, C. **16**-1726
Chan, D.M.T. **10**-1026
Chan, E.D. **18**-302
Chan, H.-L. **19**-468
Chan, H. **4**-515
Chan, H.O. **13**-661
Chan, K.-Y. **15**-2068
Chan, K.S. **13**-249
Chan, M.C.W. **19**-492
Chan, P.-M. **19**-723
Chan, P.W.H. **10**-821, **13**-126, **13**-152
Chan, R.P.K. **19**-1115
Chan, T.-L. **4**-84
Chan, T.-H. **10**-1295, **16**-2034
Chan, T. **2**-270, **2**-378, **16**-1289, **18**-425
Chan, T.C. **16**-577
Chan, T.H. **10**-535, **10**-829, **10**-841, **12**-500, **15**-1899, **15**-1964, **16**-561, **16**-577, **16**-583, **16**-588, **16**-644, **16**-918, **16**-919, **16**-1775, **19**-512
Chan, T.Y. **15**-2273
Chan, W.-K. **15**-1891, **15**-1933
Chan, W.H. **11**-95, **16**-1924
Chan, W.L. **15**-1218, **16**-670
Chan. A.S.C. **15**-456
Chanan, H. **10**-1323
Chance, J.M. **2**-78
Chand, D.K. **19**-793
Chand, P.K. **16**-768, **16**-1635
Chanda, A. **9**-90
Chanda, B.M. **15**-2063
Chandake, S.I. **16**-1809
Chandler, M. **8**-162
Chandler, W.D. **8**-43, **19**-117
Chandra, A. K. **3**-37
Chandra, K.L. **11**-341, **16**-153
Chandra, P.P. **4**-475
Chandra, S. **1**-82
Chandraiah, L. **19**-1228
Chandrasakar, R. **13**-858
Chandrasekaran, S. **11**-319, **15**-193, **15**-194, **15**-1997, **16**-1828, **16**-1851, **19**-553, **19**-565, **19**-708, **19**-712, **19**-920
Chandrasekhar, J. **5**-131, **10**-20, **10**-24, **16**-7, **18**-2
Chandrasekhar, M. **10**-1008, **19**-160
Chandrasekhar, S. **9**-91, **10**-703, **10**-866, **10**-1003, **10**-1189, **13**-390, **15**-430, **15**-464, **16**-77, **16**-329, **16**-764, **16**-802, **16**-819, **16**-1241, **16**-1472, **16**-1723, **18**-316, **18**-346, **18**-359, **19**-1100, **19**-1228, **19**-1504
Chandrasekharan, J. **15**-689, **19**-997
Chandrashekar, G. **15**-430, **15**-464
Chandrashekar, S.P. **16**-666
Chandrashekar, V. **19**-1021, **19**-1024
Chaney, M.O. **12**-227
Chang, C.-W. **16**-1515
Chang, C.-L. **18**-153
Chang, C.J. **8**-71
Chang, C.T. **13**-481
Chang, D.-H. **15**-970
Chang, D. **19**-540, **19**-541, **19**-542
Chang, D.W.L. **7**-58
Chang, F.-R. **16**-1778
Chang, F.C. **16**-2281
Chang, G. **10**-1160
Chang, H.-M. **13**-413, **13**-456
Chang, H.-T. **15**-2020
Chang, H.-M. **16**-729
Chang, H.W. **2**-173, **2**-223, **2**-261
Chang, J. **11**-95
Chang, J.W.W. **13**-126, **13**-152
Chang, K. **12**-751
Chang, K.Y. **16**-2108
Chang, L.-B. **15**-1364
Chang, L.W. **11**-114
Chang, M.H. **10**-1593
Chang, S.-Y. **15**-1310
Chang, S. **10**-1546, **13**-208, **15**-1248, **15**-1493, **15**-1523, **15**-1524, **17**-439, **18**-888, **18**-889
Chang, T. **3**-220
Chang, T.C.T. **10**-1738
Chang, V.H. **15**-1288
Chang, V.S. **19**-375, **19**-389
Chang, W.-T.T. **13**-320
Chang, W.-X. **16**-631
Chang, Y. **15**-444, **16**-1206
Chanon, F. **5**-333
Chanon, M. **5**-333, **10**-101, **10**-474, **13**-57, **16**-527
Chanson, E. **16**-2116
Chantarasriwong, O. **10**-1162
Chanthavong, F. **13**-506
Chantigny, Y.A. **13**-341
Chanumathi, N. **10**-967
Chanysheva, I.R. **10**-294
Chao, B. **17**-369
Chao, C.S. **13**-481
Chao, D.-Y. **15**-1633
Chao, I. **10**-291, **16**-513, **16**-1005
Chao, W. **18**-838
Chao, Y.L. **10**-1250
Chaouchi, M. **13**-119
Chaouk, H. **15**-1616
Chapaneri, K. **16**-117
Chapdelaine, M.J. **15**-1165
Chapleur, Y. **15**-1320
Chaplinski, V. **5**-341
Chapman, B.R. **18**-579
Chapman, C.J. **11**-438, **15**-1072
Chapman, D. **15**-1247
Chapman, K.T. **10**-1744, **16**-1194, **19**-234, **19**-1048
Chapman, N.B. **8**-149, **8**-164, **9**-16, **9**-19, **9**-20, **9**-38, **9**-58, **9**-61, **10**-372, **10**-526
Chapman, O.L. **2**-238, **4**-332, **4**-498, **4**-500, **5**-418, **13**-51, **16**-2205, **18**-236, **18**-502
Chapman, R.D. **12**-743
Chapman, R.G. **3**-182
Chapuis, C. **10**-1744
Chaquin, P. **11**-229, **15**-2295
Chardon, C. **15**-2645
Charette, A.B. **13**-250, **15**-2550, **15**-2560, **15**-2563, **15**-2566, **15**-2569, **15**-2571, **16**-227, **16**-228, **16**-361, **16**-899, **16**-1812, **19**-1481
Charkraborti, A.K. **10**-974
Charles, N.R. **15**-2677
Charleson, D.A. **19**-507
Charlton, J.L. **7**-58, **15**-2185
Charman, H.B. **12**-17
Charmant, J.P.H. **12**-374, **13**-441
Charonnat, J.A. **15**-1155
Charpentier-Morize, M. **10**-311, **10**-312, **10**-516, **11**-393, **18**-216
Charpiot, B. **13**-651
Charrada, B. **10**-961
Charrier, N. **15**-1301
Charruault, L. **15**-1008
Charton, B. **14**-126

Charton, M. **4**-441, **5**-69, **9**-31, **9**-32, **9**-38, **9**-39, **9**-41, **9**-47, **9**-51, **9**-56, **9**-64, **9**-68, **9**-70, **9**-71, **9**-78, **9**-80, **10**-298, **13**-29, **14**-126, **15**-129, **15**-663, **17**-92
Charushin, V.N. **13**-722
Chary, Ch.J. **15**-1696
Chary, K.P. **19**-1199, **19**-1248, **19**-1250, **19**-1529, **19**-1622
Chase, E. **15**-1361
Chase, P.A. **19**-1123
Chass, D.A. **17**-412
Chassaing, C. **16**-1885
Chassaing, G. **5**-145
Chassin, C. **19**-1323
Chastrette, M. **10**-474, **10**-1200, **16**-509, **16**-995
Chataigner, I. **16**-1488
Chatani, N. **10**-1267, **12**-571, **10**-1286, **10**-2004 **11**-329, **11**-424, **11**-490, **13**-451, **13**-563, **15**-793, **15**-813, **15**-873, **15**-874, **15**-960, **15**-1590, **15**-2690, **16**-2092, **16**-2093, **19**-1492, **19**-1497
Chatgilialoglu, C. **10**-1278, **14**-32, **14**-33, **14**-96, **15**-68, **15**-790, **15**-1311, **17**-144, **19**-1399
Chattaraj, P.K. **8**-170, **8**-182, **10**-38, **15**-2298
Chattaway, F.D. **14**-13
Chatterjee, A. **19**-1648, **19**-1652
Chatterjee, A.K. **16**-1631, **18**-858
Chatterjee, B.G. **10**-1684
Chatterjee, S.K. **19**-1469
Chatterton, C. **10**-1530
Chattopadhyay, A. **16**-846
Chattopadhyay, B. **18**-703, **18**-744
Chattopadhyay, K. **10**-1719, **10**-1732, **13**-497, **19**-1312
Chattopadhyay, S. **19**-1688, **19**-1681
Chattopadhyaya, J.B. **18**-357
Chatwichien, J. **15**-329
Chau, N.T.T. **13**-729
Chauder, B. **10**-1349, **13**-725
Chaudhari, K.H. **17**-470
Chaudhari, R.V. **15**-1499, **19**-1181
Chaudhari, S.S. **10**-1128
Chaudhary, K. **16**-660
Chaudhary, S.S. **10**-1010
Chaudhuri, M.K. **16**-631, **15**-1398
Chaudhuri, P. **3**-120, **14**-353
Chaudhuri, S.K. **10**-1673, **11**-248, **19**-657
Chaudret, B. **10**-1532
Chauhan, K. **18**-679
Chauhan, K.K. **15**-2325
Chauhan, P.M.S. **11**-228
Chauhan, S. **17**-372
Chauhan, S. **19**-898
Chauhan, S.M.S. **13**-115, **15**-1900, **19**-103
Chaulagain, M.R. **16**-706
Chauncy, B. **13**-827
Chauret, D.C. **10**-1622
Chauvin, R. **2**-344
Chauvin, Y. **18**-804
Chavan, S.P. **10**-586, **15**-2212, **16**-1785, **16**-1809, **19**-683
Chavan, V.B. **18**-220
Chavant, P.Y. **16**-948, **16**-978, **16**-1539
Chavarot, M. **16**-1539
Chavasiri, W. **10**-852, **10**-1162, **10**-1168, **13**-126, **13**-152, **14**-217, **16**-1987
Chavez, D.E. **15**-2354
Chawla, H.P.S. **15**-462
Chawla, R. **14**-190
Chayangkoon, P. **4**-91
Chaykovsky, M. **16**-1327, **16**-1442
Chaysripongkul, S. **16**-1987
Che, B.-H. **10**-1933
Che, C.-M. **15**-1809, **15**-1891, **15**-1933, **15**-2068, **15**-2509, **19**-492, **19**-536, **19**-537, **19**-723
Che, D. **4**-166
Che, D.C. **6**-47
Che, J. **15**-622
Chebolu, V. **14**-138
Cheboub-Benchaba, K. **15**-2186
Chechik, V.O. **10**-524
Check, C.E. **15**-2417
Chee, S. **13**-126
Cheedrala, R.K. **10**-1723
Cheekoori, S. **16**-1748
Cheeseman, J.R. **4**-16, **4**-119, **4**-288
Cheikh, R.B. **12**-226
Chekhuta, V.G. **9**-48
Chekulaeva, I.A. **15**-363
Chelius, E.C. **5**-57, **15**-140
Chelius, E.C. **5**-57
Chelucci, G. **17**-316
Chemat, F. **16**-102, **16**-1683
Chemla, F. **5**-146, **16**-368, **16**-1819, **19**-518
Chemler, S.R. **15**-415
Chen, A. **5**-109, **8**-69, **15**-1512
Chen, B.-L. **7**-55
Chen, B. **18**-751, **19**-511, **19**-1614
Chen, C. **13**-13
Chen, C.-T. **3**-210, **8**-184, **16**-1754
Chen, C.-y. **13**-120, **13**-285, **19**-1142
Chen, C. **10**-660, **10**-1468, **11**-77, **13**-210, **13**-288, **13**-332, **13**-548, **16**-544, **16**-545, **16**-670, **16**-691, **16**-832, **19**-991
Chen, C.H.-T. **13**-515
Chen, D.-J. **16**-71
Chen, D. **15**-2061, **16**-649, **16**-814
Chen, D.X. **19**-623
Chen, F.-X. **15**-1079, **16**-1512, **16**-1515
Chen, F.-E. **16**-313, **16**-79, **18**-878, **19**-1605
Chen, F. **13**-698, **15**-1720, **19**-238, **19**-383
Chen, F.M.F. **18**-769
Chen, G.-F. **5**-347
Chen, G. **5**-273, **13**-595, **13**-661
Chen, H.-Y. **13**-495
Chen, H. **10**-1522, **10**-1885, **13**-559, **14**-195, **15**-453, **15**-643, **15**-877, **15**-1565, **15**-1862, **19**-1014
Chen, H.G. **16**-2173
Chen, H.Y. **18**-812
Chen, I.-H. **15**-2328
Chen, J.-P. **16**-637
Chen, J.-S. **19**-956
Chen, J. **3**-3, **4**-278, **10**-1693, **11**-694, **13**-585, **13**-697, **15**-597, **15**-1522, **15**-1576, **16**-743, **16**-944, **19**-174, **19**-686, **19**-1516
Chen, J.C. **15**-685
Chen, J.S. **15**-994
Chen, K.-H. **4**-403
Chen, K. **4**-416, **15**-1803, **16**-823
Chen, K.S. **5**-295, **14**-59, **18**-81
Chen, K.X. **15**-1976
Chen, L.-H. **16**-955
Chen, L.-C. **19**-503
Chen, L. **4**-183, **13**-222, **15**-825, **15**-1224, **16**-269
Chen, M.-J. **10**-1309
Chen, M.-F. **16**-78
Chen, M. **10**-1904, **10**-2000, **13**-648, **14**-343, **15**-1520, **15**-2648
Chen, M.C. **16**-1614, **16**-1663
Chen, M.H. **10**-681 **19**-1058
Chen, M.S. **19**-473
Chen, P. **10**-893, **15**-1318, **18**-891
Chen, Q.-Y. **16**-395
Chen, R. **16**-376, **16**-1718, **19**-1252
Chen, R.H.K. **16**-1307
Chen, R.S. **2**-300
Chen, S.-L. **2**-309
Chen, S.-N. **10**-1733
Chen, S.-Y. **13**-453
Chen, S.-L. **16**-1159
Chen, S.-F. **16**-1895
Chen, S. **15**-643, **16**-1085, **16**-1974
Chen, S.M. **15**-1600
Chen, T. **5**-226
Chen, T.-H. **3**-8
Chen, T. **5**-376, **13**-166, **19**-808, **19**-981
Chen, W. **10**-1530, **13**-520, **13**-630, **15**-452, **15**-1610
Chen, W.M. **18**-135
Chen, X.-F. **15**-1427
Chen, X.-H. **16**-1084
Chen, X.-M. **16**-664

Chen, X. **8**-112, **8**-231, **9**-128, **10**-367, **10**-1309, **10**-1887, **11**-237, **14**-261, **15**-1046, **15**-2136, **16**-1084, **16**-1208, **19**-1021
Chen, Y.-J. **16**-1140, **19**-332
Chen, Y.K. **15**-1402
Chen, Y.-H. **18**-641
Chen, Y.-C. **10**-701, **13**-386, **16**-408
Chen, Y.-J. **16**-915, **19**-724, **19**-780
Chen, Y.-Y. **3**-128
Chen, Y.-X. **19**-1627
Chen, Y.-W. **15**-646
Chen, Y. **2**-407, **11**-362, **13**-285, **13**-587, **15**-1227, **15**-1447, **15**-1908, **15**-2516, **16**-324, **16**-1434, **16**-1731, **16**-1732, **19**-1182
Chen, Z.-B. **16**-794, **16**-797
Chen, Z.-C. **10**-725, **10**-900, **10**-1550, **10**-1894, **11**-185, **11**-243, **11**-528, **13**-156, **13**-351, **13**-419, **13**-574, **16**-71, **16**-1230, **16**-1333, **16**-1884, **19**-204, **19**-464
Chen, Z.-N. **4**-198
Chen, Z.-R. **18**-841
Chen, Z. **2**-390, **2**-395, **2**-396, **16**-544
Chen. M.-F. **16**-68
Chênevert, R. **11**-56, **19**-895
Cheng, C.-c. **8**-122
Cheng, C.-H. **13**-266, **13**-413, **13**-456, **13**-481, **13**-621, **15**-283, **15**-802, **15**-927, **15**-1013, **15**-1069, **15**-1216, **15**-2597, **15**-2605, **15**-2613, **16**-686, **16**-729
Cheng, C. **16**-249
Cheng, D.-P. **16**-71
Cheng, D. **12**-531, **15**-1010
Cheng, G. **13**-106
Cheng, H.-S. **16**-614
Cheng, H.-Y. **17**-234
Cheng, H.N. **15**-997
Cheng, J. **13**-698, **15**-503
Cheng, J.-P. **1**-108, **5**-259, **14**-75, **15**-607, **15**-1055, **16**-786, **16**-794, **16**-800, **16**-1084
Cheng, J.-Y. **18**-706
Cheng, J. **10**-233, **12**-98, **13**-592, **13**-630, **14**-415, **16**-944, **19**-686
Cheng, K.-m. **10**-233
Cheng, K.-F. **16**-1122
Cheng, K.-W. **19**-492
Cheng, K. **11**-428, **16**-2024, **16**-2026
Cheng, L. **10**-301, **10**-1207
Cheng, M.-J. **15**-1013
Cheng, P. **8**-121
Cheng, S. **16**-743
Cheng, T. **16**-1085
Cheng, W.-C. **19**-723
Cheng, X. **19**-1014
Cheng, Y.-H. **1**-115
Cheng, Y. **18**-121
Cheng, Y.M. **12**-398
Chenier, J.H.B. **14**-60, **14**-241
Chenier, P.J. **10**-164
Chens, H. **15**-1830
Cheon, C.H. **10**-593
Cheong, H.-L. **15**-1222
Cheong, P.h.-Y. **15**-2699
Cheong, P.H.-Y. **16**-395, **16**-1074
Cheramie, J. **16**-1066
Cherednichenko, L.V. **12**-744
Cherepanov, I.A. **10**-1163
Chérest, M. **4**-142
Cherkasova, E.M. **16**-33
Cherkinski, M. **15**-2204
Chermprapai, A. **10**-1255
Chern, C. **10**-771, **19**-89
Chern, M.-S. **11**-403
Cherng, C.-D. **15**-1310
Chernick, E.T. **13**-224, **17**-317
Chernov, A.N. **15**-279
Cherry, W. **7**-21, **7**-23
Chervin, I.I. **4**-40, **4**-43
Chervin, I.T. **11**-177
Cheskis, B.A. **19**-71
Chesney, A. **15**-1393
Chesnokov, A.A. **16**-1457
Chesnokova, A.E. **16**-2186
Chettiar, S.N. **16**-1853
Chettle, S.J. **19**-1081
Cheung, H.K.Y. **14**-115
Cheung, K.-K. **15**-899, **15**-1926
Cheung, Y. **14**-216
Chevallier, F. **10**-1405, **19**-872
Chevli, D.M. **10**-126
Chevrier, B. **11**-439, **11**-480
Chhabra, B.R. **19**-449, **19**-451
Chhatriwalla, A. **16**-561
Chhattise, P.K. **11**-238
Chhibber, M. **19**-72
Chi, D.Y. **10**-442, **10**-532, **10**-1183, **11**-682, **13**-307, **15**-1989, **19**-254
Chi, K.W. **13**-795
Chi, Y. **15**-1033, **15**-1056, **15**-1107, **16**-317, **16**-1085
Chia, L.H.L. **4**-304
Chiacchiera, S.M. **13**-15
Chiacchio, U. **16**-51
Chiampanichayakul, S. **19**-267
Chianelli, D. **13**-113 **13**-142
Chiang, C. **19**-341, **19**-359
Chiang, C.C. **2**-286, **2**-302
Chiang, G.C.H. **13**-222
Chiang, S. **15**-709
Chiang, Y. **2**-435, **2**-438, **2**-440, **2**-441, **8**-64, **10**-567, **10**-588, **11**-113, **12**-83, **12**-93, **12**-96, **12**-97, **15**-26, **15**-80, **15**-211
Chiao, W. **17**-29
Chiappe, C. **9**-120, **10**-442, **11**-244, **15**-12, **15**-14, **15**-22, **15**-1641, **15**-1649, **15**-1651, **15**-1653, **15**-2225
Chiara, J.L. **19**-1659
Chiarelli, R. **5**-271
Chiarini, M. **11**-693, **13**-493, **16**-146
Chiarotto, I. **16**-430
Chiba, K. **10**-744, **10**-1013, **11**-325, **15**-1130, **15**-1634, **19**-1353
Chiba, N. **15**-1196
Chiba, T. **10**-1641, **16**-1541
Chichilla, R. **16**-1897
Chickos, J.S. **4**-483
Chidambaram, N. **15**-193, **19**-565
Chidara, S. **16**-620
Chidrala, R.K. **16**-239
Chiechi, R.C. **2**-317
Chieffi, A. **10**-1739, **13**-663, **15**-2454
Chien, C.-T. **16**-1421, **16**-1422
Chien, Y.-Y. **12**-483
Chiesa, A. **11**-534
Chiev, K.P. **16**-901
Chihal, D.M. **18**-918
Chihara, T. **10**-656, **16**-235
Chikamatsu, H. **2**-76
Chikami, Y. **15**-173
Childs, R.F. **2**-383, **2**-385, **2**-386, **5**-50, **7**-48, **18**-574
Chilingaren, A. **18**-187
Chill, S.T. **16**-304
Chimishkyan, A.L. **16**-1967
Chimni, S. **16**-568
Chimni, S.S. **16**-567, **16**-1081, **16**-1085
Chin, C.-P. **10**-471
Chin, C.S. **2**-459
Chin, J. **16**-20
Chinchilla, R. **13**-582
Ching-Yun, C. **16**-43
Ching, C.B. **11**-402
Ching, W. **16**-1519
Chini, M. **10**-683, **10**-837, **10**-997, **10**-1219
Chinn, L.J. **19**-11, **19**-434, **19**-668
Chiocconi, A.A. **10**-897
Chiou, B.L. **18**-472
Chirik, P.J. **15**-664, **15**-2379
Chirinko Jr., J.M. **10**-1802
Chirskaya, M.V. **15**-1702
Chisholm, J.D. **15**-1226, **16**-1764
Chisholm, M.H. **19**-1689, **19**-1697
Chistyakov, A. **14**-160
Chittattu, G. **14**-447, **19**-1572
Chitwood, J.L. **16**-2237
Chiu, P. **12**-264, **16**-1122, **19**-1366
Chiu, R.-T. **15**-1340
Chiu, S.-H. **3**-195, **3**-197, **3**-199
Chiurdoglu, G. **3**-190, **3**-202, **4**-270, **4**-363, **5**-79
Chiusoli, G.P. **10**-1983

Chivers, T. **5**-109, **8**-69, **12**-615
Chiyo, T. **16**-590
Chizhov, B.A. **19**-71
Chizhova, N.V. **16**-234
Chloupek, F.J. **16**-35
Chmielewski, M. **15**-1923
Chmurny, G.N. **4**-228
Chmurzynski, L. **8**-88
Chng, S.-S. **16**-614
Cho, B.P. **13**-169
Cho, B.R. **17**-97, **17**-98, **17**-447
Cho, B.T. **16**-333, **19**-884, **19**-1007, **19**-1020, **19**-1059
Cho, C.-C. **16**-1421
Cho, C.-G. **11**-168, **12**-305, **16**-1854
Cho, C.-W. **16**-2089, **16**-929
Cho, C.H. **10**-1939
Cho, C.S. **10**-1574, **13**-323, **13**-668, **16**-2244, **19**-14
Cho, D.H. **11**-446, **15**-1295, **16**-1861, **19**-1445, **19**-1453
Cho, H.-N. **18**-818
Cho, H.Y. **16**-1560
Cho, I.H. **19**-104
Cho, I.S. **10**-1072
Cho, J.H. **10**-888, **18**-856
Cho, M.H. **11**-652
Cho, M.S. **10**-1224, **16**-548
Cho, M.Y. **19**-1313
Cho, S.-D. **19**-543
Cho, S. **17**-170
Cho, S.H. **10**-606, **10**-718, **15**-1524
Cho, W.K. **16**-1511
Cho, Y.J. **19**-1308, **19**-1722
Cho, Y.S. **10**-1593, **10**-1265, **19**-1185, **19**-1213, **19**-1496
Chobanian, H.R. **13**-290
Chobe, P. **18**-433
Chodkiewicz, W. **14**-329, **14**-345
Chodowska-Palicka, J. **11**-657
Choe, J. **19**-363, **19**-365
Choghamarani, A.G. **12**-739
Choguill, H.S. **11**-681
Choi, D.S. **11**-331, **15**-1556
Choi, E.B. **17**-528
Choi, H. **11**-682, **15**-1208, **19**-778
Choi, H.K.J. **5**-385
Choi, H.Y. **19**-254
Choi, I.S. **16**-1511
Choi, J.-K. **10**-1235
Choi, J.-W. **13**-150
Choi, J.-H. **11**-321, **19**-321, **19**-530
Choi, J. **15**-524, **16**-334, **16**-1639, **19**-1200, **19**-1286
Choi, J.W. **19**-1536
Choi, K.H. **16**-2108, **19**-1531, **19**-1591
Choi, K.I. **19**-1185, **19**-1213, **19**-1530, **19**-1531, **19**-1591
Choi, M. **15**-1558
Choi, M.K.W.C. **19**-153
Choi, N. **18**-553
Choi, S. **18**-183
Choi, S.-Y. **5**-326, **5**-328, **5**-330
Choi, S.-C. **13**-339, **13**-692, **10**-1458
Choi, S.-Y. **14**-85
Choi, S.-B. **15**-625
Choi, S. **15**-1989, **16**-1193, **16**-1197, **18**-184, **19**-778
Choi, S.U. **11**-379
Choi, S.Y. **14**-41
Choi, T.-L. **18**-858, **18**-865, **18**-872
Choi, W.-K. **13**-201
Choi, W.-W. **19**-468
Choi, W. **16**-1069
Choi, Y. **10**-718, **19**-438, **19**-531, **19**-892
Choi, Y.J. **16**-2298
Choi, Y.K. **15**-1559, **19**-1151
Choi, Y.M. **19**-1068, **19**-1162
Chong, A.O. **15**-2012, **15**-2032
Chong, J.A. **4**-517, **10**-52
Chong, J.M. **10**-527, **10**-1123, **10**-1338, **10**-1516, **10**-1622, **10**-1623, **15**-1267, **15**-1268, **15**-1274, **16**-468
Chong, S.-S. **14**-84
Chong, Y. **16**-800
Chong, Y.H. **15**-1489
Choo, D.J. **10**-986
Choo, H. **16**-800
Choo, J. **4**-365
Choony, N. **15**-992
Chopade, P.R. **19**-945
Choppin, S. **13**-619, **13**-739
Choquesillo-Lazarte, D. **16**-575
Chorbadjiev, S. **10**-858
Chordia, M.D. **15**-2260
Chorev, M. **3**-213
Chotana, G.A. **12**-588
Chotii, K.Yu. **9**-48
Chou, F.E. **2**-469
Chou, J. **10**-670
Chou, M.-Y. **12**-483
Chou, M.-C. **16**-1895
Chou, P.K. **5**-142
Chou, S.-S.P. **15**-2317
Chou, S. **10**-1355, **10**-1356
Chou, S.P. **12**-523
Chou, T.-C. **16**-309
Chou, T. **10**-534, **12**-602, **15**-2279
Chou, W.-C. **16**-1895
Chou, W. **15**-537
Choucair, B. **16**-916
Choudary, B.M. **10**-779, **11**-686, **13**-205, **13**-509, **15**-1806, **16**-357, **16**-620, **19**-212, **19**-759
Choudhary, D. **12**-119
Choudhary, M.I. **10**-890, **10**-1142
Choudhary, V.R. **11**-438, **13**-394, **15**-2047
Choudhury, J. **11**-333
Choudhury, L.H. **12**-127, **19**-562
Chouhan, G. **16**-200
Chounan, Y. **10**-249
Chouraqui, G. **15**-2612
Chouthaiwale, P.V. **15**-2061
Chow, A. **4**-323, **5**-162, **5**-194
Chow, H.-F. **13**-604
Chow, J. **12**-232, **15**-2059
Chow, L. **18**-161
Chow, Y. **16**-35
Chow, Y.L. **11**-181, **14**-211, **14**-212, **15**-1744
Chowdappa, N. **10**-539
Chowdari, N.S. **10**-779, **15**-1806, **16**-914, **16**-961
Chowdhury, C. **16**-2041
Chowdhury, S. **9**-126, **14**-467
Choy, G.S.-C. **10**-232
Choy, W. **4**-152, **16**-1097
Chrétien, J.-M. **11**-258
Chrétien, J.R. **15**-98
Chris H. **15**-452
Chrisman, W. **19**-1038
Christen, D. **4**-488
Christensen, C. **16**-1213
Christensen, J.B. **10**-1092
Christensen, J.J. **3**-106, **3**-110, **3**-113, **4**-168
Christenson, B. **15**-1169, **15**-1241
Christiaens, L. **10**-824
Christian, B. **10**-512
Christianson, D.W. **4**-475
Christl, M. **2**-90, **10**-409, **15**-2122, **18**-688
Christmann, K.-F. **16**-1349, **16**-1391
Christmann, M. **16**-1160
Christoffers, J. **10**-1662, **15**-1068, **19**-497, **19**-498
Christol, H. **10**-816, **15**-1495
Christophy, E. **7**-50
Christy, J.P. **15**-2692, **15**-2696
Christy, M.E. **4**-214
Christy, M.E.L. **13**-700
Chrobok, A. **18**-397
Chrzanowska, M. **16**-889
Chu, C.-M. **13**-841, **15**-1440, **15**-1444, **15**-1445
Chu, C. **12**-590
Chu, C.C.C. **10**-1798
Chu, F. **10**-758, **16**-180
Chu, G. **5**-389
Chu, J.H. **19**-724
Chu, K. **18**-490
Chu, K.C. **12**-31
Chu, M. **16**-533
Chu, S.-Y. **15**-1013
Chu, S. **15**-2301, **18**-513
Chu, W.K.C. **8**-66
Chu, Y.-H. **18**-706
Chu, Y. **19**-1158
Chu, Y.C. **10**-396
Chua, P. **16**-227, **16**-1812
Chua, P.S. **15**-456
Chuah, G. **19**-953
Chuang, C. **15**-106

Chuang, L. **14**-112
Chuang, T.-H. **10**-895
Chuaqui, C. **10**-392
Chuchani, G. **11**-39, **11**-372, **17**-137, **17**-151, **17**-151
Chuche, J. **15**-247
Chudek, J.A. **16**-237
Chughtai, M.J. **15**-417
Chuit, C. **12**-524, **12**-622, **15**-984, **15**-1134
Chukovskaya, E.C. **15**-1773
Chukovskaya, E.Ts. **10**-1300
Chung, B.Y. **10**-1072, **10**-1593, **16**-641, **19**-1213, **19**-1633
Chung, C.-M. **15**-1295
Chung, D.S. **10**-22
Chung, D.W. **13**-594
Chung, E.-A. **16**-2089
Chung, F. **11**-689
Chung, J.-K. **19**-1190
Chung, K.-G. **13**-551
Chung, K.H. **17**-432
Chung, M. **15**-2005
Chung, R.P. **16**-1675
Chung, S. **11**-689, **15**-527, **19**-104, **19**-1324, **19**-1325, **19**-1739
Chung, S.K. **15**-1183
Chung, S.Y. **9**-21, **10**-320
Chung, Y.K. **15**-1550, **15**-1529, **15**-1535, **15**-1551, **15**-1556, **15**-1558, **15**-2254
Chupak, L.S. **13**-341
Chupakhin, O.N. **13**-231, **13**-722
Chupp, J.P. **16**-245
Chuprakov, S. **15**-880, **16**-808
Church, D.F. **14**-110, **19**-340, **19**-343
Churchill, M.R. **3**-89, **15**-2521, **18**-884
Churchill, R.M. **15**-2664
Chuvatkin, N.N. **10**-787, **14**-155
Chuzel, O. **16**-760
Chvalovský, V. **19**-889
Chwang, A.K. **5**-91
Chwang, W.K. **10**-589
Chylinska, J.B. **19**-352
Ci, Z. **16**-744
Ciabattoni, J. **2**-227, **15**-1948
Ciaccio, J.A. **10**-1219, **10**-1937
Ciamician, G. **15**-2453
Ciappenelli, D.J. **12**-414
Ciattini. P.G. **19**-1352
Ciavarri, J.P. **16**-594
Cibulka, R. **19**-800
Cicchi, S. **17**-452, **19**-298, **19**-752, **19**-1222
Ciccolini, R.P. **15**-376
Cid, J.M. **10**-884
Cieplak, A.S. **15**-121, **15**-122
Cieplak, P. **4**-370
Ciganek, E. **15**-2175, **15**-2543, **16**-1000, **17**-260, **18**-505, **18**-680
Cilento, G. **14**-252, **15**-2362, **15**-2364
Ciminale, F. **15**-1238
Cimiraglia, R. **11**-169
Cindric, B. **15**-1921
Cingolani, G.M. **11**-338
Cinquini, M. **4**-30, **4**-48, **5**-145, **10**-321, **12**-192, **15**-1836, **16**-776, **16**-1169
Cintas, P. **4**-3, **4**-5, **4**-312, **4**-315, **7**-122, **15**-2187, **15**-2290, **16**-558
Cintrat, J.-C. **12**-281
Cioffi, C.L. **13**-567
Cioffi, N. **13**-382
Ciofini, I. **13**-545
Ciorba, V. **2**-99, **2**-316
Ciro, S.M. **5**-29
Cisneros, A. **19**-307
Cistone, F. **15**-673, **19**-1283, **19**-1505
Citterio, A. **11**-182, **11**-539, **13**-652, **13**-652, **14**-385, **14**-389, **14**-405
Ciuffarin, E. **8**-65, **16**-2268, **16**-2274, **16**-2275
Ciuffreda, P. **16**-1795
Ciufolini, M.A. **2**-392, **15**-1138, **16**-2204, **16**-2210, **16**-2261
Cívicos, J.F. **13**-494
Cividino, P. **15**-1078
Cizmeciyan, D. **8**-230
Clabo Jr., D.A. **2**-67
Claesson, A. **10**-1610, **19**-1306
Claisen, L. **16**-1177, **18**-701
Clapham, B. **12**-279
Clar, E. **2**-131, **2**-152
Claramunt, R.M. **2**-479
Clardy, J. **12**-712
Clardy, J.C. **15**-1853
Claremon, D.A. **17**-465
Claridge, T.D.W. **13**-448
Clark J.H. **9**-84
Clark J.M. **9**-116
Clark Jr., B.C. **2**-385, **10**-142, **10**-144
Clark, A.J. **15**-1316, **15**-1329, **15**-1374, **16**-2231
Clark, B.C. **18**-105
Clark, B.M. **16**-1400
Clark, C.G. **13**-239
Clark, C.T. **14**-225, **15**-798, **16**-2061
Clark, D.H. **12**-266
Clark, D.L. **15**-537
Clark, D.R. **16**-450
Clark, D.T. **10**-194, **10**-219
Clark, G.M. **16**-45, **18**-210
Clark, G.R. **2**-226
Clark, G.W. **4**-456
Clark, I.D. **12**-40
Clark, J.D. **10**-681, **18**-602, **18**-704
Clark, J.H. **10**-721, **13**-167, **13**-263, **13**-264, **18**-385, **19**-602
Clark, J.S. **12**-387
Clark, K.B. **1**-107
Clark, L.W. **12**-668
Clark, M. **4**-414
Clark, M.T. **11**-632
Clark, N.A. **4**-209
Clark, R.F. **16**-440
Clark, R.G. **1**-4
Clark, R.J. **5**-386
Clark, T. **1**-2, **2**-14, **2**-17, **2**-21, **2**-219, **5**-347, **14**-91, **14**-101, **19**-193
Clark, T.J. **2**-430
Clark, T.P. **15**-1613
Clark. P. **16**-324
Clarke, E. D. **8**-113
Clarke, E.M. **2**-442
Clarke, G.M. **18**-39
Clarke, J.K.A. **15**-479
Clarke, M. **18**-400
Clarke, M.J. **12**-673
Clarke, M.L. **10**-1535, **15**-1017, **15**-1515
Clarke, M.T. **5**-158, **5**-205
Clarke, P.A. **16**-1726
Clarke, T.C. **10**-272
Clarkson, D. **2**-4, **2**-7
Clary, D.C. **10**-365
Clary, D.W. **11**-213
Clasby, M. C. **17**-196
Clase, J.A. **10**-613
Classon, B. **10**-1150
Claus, P. **11**-552
Clausen, K. **16**-217, **16**-224
Clausen, T.P. **10**-195
Clausius, K. **18**-772
Claver, C. **10**-1522, **10**-1532, **15**-1614, **18**-305
Claverie, C.K. **16**-1562
Clavier, H. **15**-1181, **18**-821, **18**-848
Clawson, L. **10**-120, **16**-1410
Clay, D. **16**-362
Clay, J.M. **15**-675
Clayden, J. **11**-335, **13**-303, **13**-353, **17**-306
Clayman, L. **10**-449
Clayton Jr., T.W. **15**-741
Clayton, J.W. **10**-223
Clayton, T.L. **15**-1127
Cleary, D.G. **10**-820, **10**-1640
Cleary, P.A. **12**-385
Cleator, E. **15**-1414
Clegg, W. **13**-733
Cleland, W.W. **16**-1695
Clemens, A.H. **10**-233, **11**-110
Clemens, I. **10**-1935
Clement, A. **15**-1947, **18**-231
Clément, G. **19**-1401
Clément, J. **10**-1965
Clemente, F.R. **15**-2290, **15**-2355, **16**-1074
Clemente, F.R. **4**-315
Clementi, S. **11**-278, **17**-36

Clennan, E.L. **7**-32, **14**-261, **15**-159, **15**-1924, **15**-2356, **15**-2364
Clerici, A. **14**-111, **16**-9, **16**-121, **16**-1532, **19**-100, **19**-947, **19**-1641
Cléry, P. **12**-324
Clifford, A.A. **13**-430, **14**-351, **15**-2220
Clift, S.M. **16**-1410, **16**-1427
Clikeman, R.R. **4**-362
Cline Jr., R.E. **7**-75
Clippinger, E. **10**-63, **10**-187
Clive, D.L.J. **14**-447, **16**-1608, **19**-1572
Cloke, G.N. **13**-493
Cloonan, M.O. **15**-1373
Clos, N. **4**-150, **15**-635
Closs, G.L. **2**-221, **4**-485, **5**-229, **5**-351, **5**-409, **10**-1395, **15**-2530, **15**-2539, **18**-419
Closson, A. **15**-1807
Closson, W.D. **17**-336, **19**-1265
Clot, E. **18**-892
Clough, J.M. **10**-727
Clough, R.L. **4**-531
Clouthier, C.M. **18**-389
Clowes, G.A. **11**-419
Clunie, J.C. **16**-39
Clutterbuck, L.A. **16**-1531
Coates, G.E. **2**-190, **5**-152
Coates, G.W. **10**-1632, **10**-1633
Coates, R.M. **15**-1166, **18**-107, **18**-113, **18**-541
Coble, H.D. **16**-174
Cobley, C.J. **16**-424
Coche, L. **19**-926
Cochran, B.M. **15**-415
Cochran, J.C. **11**-509
Cocivera, M. **16**-291
Cockerill, A.F. **10**-424, **10**-551, **16**-288, **16**-1345, **17**-3, **17**-8, **17**-40, **17**-42, **17**-61, **17**-88, **17**-105, **17**-107, **17**-178, **17**-246, **17**-392, **19**-97, **19**-812
Cockroft, S.L. **3**-85
Cocks, A.T. i. **17**-128
Coe, D.E. **15**-2085
Coe, D.M. **16**-776
Coe, G.R. **12**-599
Coe, J.C. **13**-46
Coelho, F. **16**-796
Coenen, J.W.E. **6**-42
Coetzee, J.F. **6**-94, **8**-129
Coffey, D.S. **12**-430
Coffey, P.E. **15**-1962
Coffi-Nketsia, S. **10**-761
Coffman, N.B. **8**-83
Cofré, P. **19**-485
Cogen, J.M. **5**-343
Coggins, P. **12**-104
Cogolli, P. **13**-145
Cohen, G.M. **15**-2419
Cohen, J.F. **10**-1740
Cohen, L.A. **19**-1069
Cohen, M. **19**-93
Cohen, M.D. **9**-12
Cohen, M.H. **18**-753
Cohen, N. **1**-96
Cohen, R.J. **10**-849
Cohen, S. **3**-129, **14**-94
Cohen, S.G. **7**-36, **7**-37, **14**-496, **19**-1663
Cohen, T. **10**-225, **10**-1310, **11**-654, **11**-655, **12**-408, **12**-412, **13**-475, **13**-788, **13**-837, **14**-451, **14**-453, **14**-454, **14**-455, **15**-1010, **15**-1187, **15**-2229, **16**-1478, **16**-1839, **16**-2070, **17**-190, **18**-245
Cohen, Y. **2**-363, **10**-488
Cohen, Z. **19**-435
Cohn, G. **12**-487
Cohn, M. **16**-40
Cohrs, C. **2**-90
Coisne, J.M. **12**-444
Coke, J.L. **10**-175, **17**-19, **17**-22, **17**-24, **17**-25
Colacino, E. **13**-611, **19**-760
Colacot, T.J. **13**-526, **13**-641
Colagioia, S. **16**-1975
Colapret, J.A. **16**-1252
Colard, N. **15**-2009
Colaux-Castillo, C. **15**-1849
Colb, A.L. **13**-301
Colborn, R.E. **15**-2641, **15**-2642
Colbry, N.L. **16**-322
Colby, D.A. **3**-139
Colclough, T. **12**-490
Coldham, I. **6**-37, **12**-441, **13**-187, **15**-913, **15**-2105, **18**-429, **18**-430
Cole-Hamilton, D.J. **19**-1473
Cole, C.M. **15**-580
Cole, L.L. **10**-448, **10**-1127
Cole, S.M. **15**-319
Cole, T.E. **12**-545, **15**-678, **15**-679, **15**-681, **18**-455, **18**-484
Coleman III, D.T. **19**-1736
Coleman, M.G. **12**-373
Coleman, M.J. **17**-345
Coleman, R.A. **15**-727, **18**-470, **18**-471
Colens, A. **16**-1990
Coleridge, B.M. **10**-1467
Coliboeuf, M. **16**-896
Colins, C.C. **6**-51
Coll, J. **10**-619
Collazo, L.R. **10**-1253
Collet, A. **3**-147, **4**-10, **4**-160, **4**-189
Colley, A.M. **13**-144
Collier, T.L. **4**-139
Collin, J. **10**-974, **10**-1071, **10**-2007, **11**-445, **16**-1131, **16**-2113, **19**-950
Collings, B.A. **6**-16
Collington, E.W. **10**-1847
Collins Jr., M.J. **13**-397
Collins, C. **18**-41
Collins, C.J. **6**-43
Collins, C.H. **15**-33, **17**-146
Collins, C.J. **10**-419, **15**-138, **18**-1, **18**-16, **18**-22, **18**-40, **18**-125, **18**-186, **18**-188, **19**-1166, **19**-1484
Collins, G.R. **14**-289
Collins, J.A. **18**-40
Collins, J.C. **19**-80
Collins, J.J. **18**-654
Collins, J.R. **4**-228
Collins, S. **16**-2086
Collins, S.K. **4**-85, **14**-359
Collison, C. **15**-1082
Colllins, C.J. **19**-1483
Collman, J.C. **18**-893
Collman, J.P. **3**-89, **10**-1318, **10**-1402, **10**-1955, **10**-1957, **10**-1958, **10**-1959, **10**-1983, **10**-1985, **10**-1986, **13**-425, **14**-485, **15**-433, **15**-1597, **15**-1599, **15**-2642, **19**-439
Collum, D.B. **5**-191, **5**-197, **5**-204, **6**-37, **8**-216, **8**-218, **8**-219, **8**-220, **8**-221, **8**-222, **8**-223, **8**-224, **10**-896, **10**-1702, **10**-1747, **10**-1748, **10**-1769, **11**-603, **11**-604, **12**-277, **12**-348, **12**-421, **13**-46, **13**-727, **13**-729, **13**-734, **16**-882, **16**-1022, **16**-1180, **16**-1974, **17**-306
Collumeau, A. **8**-25
Colobert, F. **11**-293, **13**-618, **13**-619, **16**-927
Colombo, L. **16**-1125
Colonna, S. **4**-30, **4**-49, **5**-145, **10**-321, **12**-192, **15**-1959, **19**-738, **19**-777, **19**-801
Colquhoun, H.M. **10**-1974, **12**-67
Coltart, D.M. **16**-788, **16**-1185
Colter, A.K. **5**-92
Coluccini, C. **4**-57
Colussi, A. J. **7**-77
Colussi, A.J. **7**-78
Colvin, E.W. **12**-320, **12**-538, **16**-1289, **16**-1294
Comasseto, J.V. **12**-300, **12**-301, **10**-813, **15**-1151, **16**-700, **19**-1405
Combellas, C. **13**-63, **13**-94
Comelles, J. **15**-1070
Comely, A.C. **15**-1560
Comes-Franchini, M. **10**-1568
Comfort, D.R. **16**-381
Comins, D.L. **11**-72, **12**-342, **13**-738, **10**-1701, **15**-601, **16**-2071
Comisarow, M. **16**-1672
Comisarow, M.B. **10**-179
Comisso, G. **15**-635

Commerçon-Bourgain, M. **15**-1134
Commeyras, A. **5**-80, **10**-218, **16**-105, **10**-1610, **18**-108
Compagnon, P.L. **16**-98, **16**-177
Compain, P. **15**-208
Company, M.D. **15**-1319
Compton, R.G. **6**-11, **19**-936
Comte, V. **19**-981
Concellón, C. **10**-1236, **16**-1431
Concellón, J.M. **10**-1236, **15**-2527, **15**-2572, **16**-496, **16**-1431, **17**-167, **17**-171, **17**-219, **17**-400, **17**-402, **19**-873
Concepcion, A.B. **12**-390, **19**-948
Condo, A. **16**-1022
Condon-Gueugnot, S. **15**-879, **15**-2484
Condon, F.E. **8**-238, **11**-24
Condon, S. **15**-1235
Condroski, K.R. **15**-1880
Confalone, P.N. **15**-2105
Conggui, Y. **10**-609
Conia, J.M. **10**-571, **12**-163, **15**-991, **15**-2552, **15**-2575, **16**-2055, **18**-160, **18**-217, **18**-589, **18**-720
Coniglio, S. **16**-1975
Conlan, D.A. **18**-622
Conley, R.A. **15**-581
Conley, R.T. **17**-454, **17**-457, **18**-282, **18**-363
Conlon, E.H. **16**-83
Conlon, L.E. **10**-680
Connolly, D.J. **13**-436
Connolly, J.P. **15**-1412
Connolly, J.W. **3**-167
Connon, S.J. **16**-789, **16**-805, **16**-1441, **16**-1591, **18**-870
Connor, D.S. **10**-1307
Connor, J.A. **13**-276, **13**-282
Connor, J.K. **10**-426
Connor, T.M. **1**-35
Connors, K.A. **6**-49, **6**-58, **6**-59, **9**-16
Conrad, J.C. **18**-811
Conrad, K.M. **19**-955
Conroy, H. **18**-696
Consani, K.A. **9**-103
Considine, W.J. **12**-620
Consiglio, G. **4**-153, **10**-1538, **10**-1588, **15**-1611
Consolandi, E. **16**-1169
Consoli, G.M.L. **3**-133, **4**-69
Consorti, C.S. **9**-122, **13**-379, **13**-447
Constabel, F. **16**-2259
Constantino, M.G. **2**-389
Constantinou-Kokotou, V. **16**-1624, **16**-1725
Conte, V. **15**-1653
Contento, M. **19**-377
Conticello, V.P. **15**-2027
Continetti, R.E. **8**-233
Contreras, R. **10**-36, **10**-37, **10**-95, **11**-436, **15**-2181, **15**-2282, **15**-2292, **15**-2298
Convers, E. **16**-1765
Cook Jr., J.A. **10**-178, **10**-179
Cook, A.G. **10**-1785, **10**-1795, **12**-84, **14**-277, **15**-2394, **16**-87, **16**-259, **16**-968, **19**-42, **19**-1128
Cook, F.L. **3**-107
Cook, G.K. **17**-335
Cook, G.R. **11**-355, **15**-1315, **16**-911
Cook, J.L. **3**-46
Cook, J.M. **10**-1465, **11**-406
Cook, M.J. **4**-346
Cook, R.S. **11**-87
Cooke Jr., M.P. **10**-1954, **10**-1961, **15**-1188, **16**-1011, **16**-2018, **17**-19, **19**-1512
Cooke, D.W. **15**-436
Cooke, F. **16**-1296
Cooke, G. **19**-1156
Cooke, G.A. **16**-1668
Cooke, T.W. **17**-96
Cookson, P.G. **10**-769
Cookson, R.C. **2**-236, **15**-1511, **18**-601
Cookson, R.F. **8**-8
Cooksy, A. L. **5**-326
Cooksy, A.L. **14**-99
Cooley, J.H. **10**-1257, **10**-1260
Cooley, N.A. **12**-287
Coombes, R.G. **11**-202
Coon, C.L. **19**-747
Cooney, B.T. **2**-415
Cooney, J.J.A. **13**-353
Cooney, J.V. **16**-1645
Cooney, M.J. **2**-387
Cooper, A. **18**-792
Cooper, A.I. **9**-108
Cooper, A.J.L. **16**-2266
Cooper, C.F. **13**-778
Cooper, C.N. **18**-22, **18**-102
Cooper, D.L. **2**-14, **2**-133, **15**-2129, **15**-2130
Cooper, J. **14**-59
Cooper, J.S. **10**-449
Cooper, K.A. **10**-347, **17**-37, **17**-124, **17**-127
Cooper, M.A. **2**-142
Cooper, N.J. **18**-630
Cooper, P.J. **15**-90, **15**-689
Cooper, R.A. **5**-228, **5**-231, **10**-1395
Coote, M.L. **1**-118
Coote, S.C. **19**-1754
Coote, S.J. **16**-256, **16**-497
Cope, A.C. **4**-77, **4**-232, **4**-478, **10**-16, **14**-55, **17**-244, **17**-249, **17**-250, **17**-251, **17**-259, **17**-260, **18**-50, **18**-53, **18**-629, **18**-723, **18**-933
Cope, S. **10**-1408, **10**-1410, **15**-1154
Copéret, C. **18**-873, **18**-892
Copley, S.D. **18**-694
Coppens, P. **4**-452
Coppola, G.M. **4**-138, **4**-502, **10**-572, **10**-246, **15**-107, **15**-469, **15**-2389, **16**-2213, **17**-386, **18**-179
Coppolino, A. **16**-1113
Copret, C. **18**-873, appendixa-26
Coquerel, Y. **18**-851
Coratti, A. **18**-381
Corbally, R.P. **4**-243
Corbin, R.A. **19**-980
Corbin, V.L. **15**-1133
Cordes, D.B. **15**-529
Cordes, E.H. **10**-551, **10**-556, **16**-84
Córdoba, R. **16**-1504
Córdova, A. **19**-516, **15**-1402, **15**-2078, **16**-392, **16**-394, **16**-1084, **16**-1795, **19**-1020
Corey, E.J. **10**-243, **10**-248, **10**-580, **10**-771, **10**-1174, **10**-1212, **10**-1319, **10**-1322, **10**-1353, **10**-1437, **10**-1442, **10**-1679, **10**-1759, **10**-1805, **10**-1809, **10**-1811, **10**-1813, **10**-1819, **10**-1820, **10**-1984, **12**-323, **14**-459, **15**-513, **15**-1145, **15**-1167, **15**-1197, **15**-1244, **15**-1280, **15**-1458, **15**-1711, **15**-1741, **15**-1802, **15**-1820, **15**-1835, **15**-1883, **15**-1912, **15**-1976, **15**-1981, **15**-2089, **15**-2196, **15**-2243, **15**-2249, **15**-2250, **15**-2252, **15**-2391, **15**-2402, **16**-192, **16**-205, **16**-483, **16**-1070, **16**-1095, **16**-1102, **16**-1193, **16**-1197, **16**-1251, **16**-1307, **16**-1327, **16**-1339, **16**-1374, **16**-1375, **16**-1389, **16**-1442, **16**-1443, **16**-1497, **16**-1514, **16**-1534, **16**-1577, **16**-2151, **16**-2152, **16**-2199, **17**-241, **17**-242, **17**-328, **17**-340, **17**-341, **17**-343, **17**-344, **17**-425, **18**-111, **18**-482, **18**-735, **19**-81, **19**-427, **19**-566, **19**-587, **19**-732, **19**-753, **19**-1345
Corkey, B.K. **15**-870, **15**-1006
Corley, E. **16**-998
Corley, R.C. **5**-320
Corma, A. **15**-242, **15**-203, **15**-227, **16**-1516, **19**-128, **19**-951
Cormanich, R.A. **4**-291
Cormier, R.A. **19**-1436
Corminboeuf, C. **2**-110, **2**-172, **10**-1522
Cornejo, J.J. **19**-275
Cornelisse, J. **13**-62, **19**-1210
Cornell, C.N. **19**-700, **19**-701
Cornforth, J.W. **4**-143

Cornforth, R.H. **4**-143
Cornils, B. **10**-1979, **13**-425, **15**-1497
Cornwell, M.J. **13**-140
Corral, J. **19**-479
Correa, A. **13**-135, **13**-218, **16**-872
Correa, M. **13**-493
Correa, W. **19**-972, **19**-1158, **19**-1234
Correi, V.R. **19**-1405
Correia, C.F. **1**-104
Correia, C.R.D. **13**-437, **15**-2383
Correia, J.S. **10**-1129
Correia, R. **10**-727, **13**-718
Corrette, C.P. **15**-772, **15**-1004
Corriu, R. **11**-437
Corriu, R.J.P. **4**-27, **12**-622, **19**-1083
Corsaro, A. **16**-51, **16**-204
Corset, J. **5**-145, **15**-1042
Corsi, M. **17**-452, **19**-298
Corson, F.P. **10**-277
Cortés-Guzmán, F. **4**-289
Cortés, D.A. **2**-259
Cortez, G.A. **18**-845
Cortez, G.S. **16**-1190
Coryn, M. **16**-1552
Cosa, J.J. **11**-633
Cosgrove Jr., W.R. **3**-167
Cosmo, R. **4**-531
Cossar, J. **8**-61, **8**-64, **12**-706, **12**-710
Cossé-Barbi, A. **4**-307
Cossey, K.N. **16**-1815
Cossío, F.P. **10**-1208, **15**-2119, **15**-2123, **15**-2239, **15**-2304, **16**-852
Cossu, S. **15**-1381
Cossy, J. **5**-314, **10**-979, **10**-1005, **12**-255, **13**-662, **15**-668, **15**-673, **15**-993, **15**-2191, **15**-2448, **16**-9, **16**-666, **16**-766, **16**-1559, **16**-1579, **16**-1919, **16**-2075, **16**-2178, **18**-349, **18**-833, **18**-866, **19**-14, **19**-257
Costa Cabral, B.J. **1**-121
Costa, A. **13**-23, **16**-1794, **18**-336
Costa, A.L. **16**-774
Costa, A.M. **15**-303, **16**-666
Costa, I. **15**-185
Costa, I.M. **16**-266
Costa, M. **12**-770
Costa, P.R.R. **16**-1171
Costain, C.C. **1**-76
Costas, M. **15**-1803
Costello, A.M. **16**-1978
Costentin, C. **5**-319, **13**-57
Coster, M.J. **19**-1487
Costero, A.M. **13**-50
Costisella, B. **16**-1045
Costopanagiotis, A. **16**-1684
Cosyns, J. **15**-447
Cota, D.J. **16**-2170
Côté, A. **16**-361, **16**-899
Cotelle, P. **18**-413
Cott, P. **15**-2070
Cottard, F. **5**-316
Cotterrell, G. **15**-1133
Cottier, L. **10**-1161
Cotton, F.A. **1**-10, **3**-90, **4**-390
Cotton, H.K. **16**-466
Cottrell, C.E. **2**-266, **5**-178, **18**-658
Cottrell, F.D. **4**-457
Couderet, G. **19**-1605
Coudert, G. **10**-949
Coughlan, N. **15**-1655
Coulson, C.A. **2**-4, **2**-7, **2**-8, **2**-28, **2**-35, **2**-127
Coulson, J. **11**-628
Coulston, K.J. **18**-553
Coulter, J.M. **19**-1509
Coumbarides, G. **12**-109
Councler, C. **12**-485, **12**-486
Courgeon, T. **12**-547
Couri, M.R.C. **18**-928
Court, J. **14**-124, **19**-1030
Court, J.J. **16**-2080
Courtieu, J. **19**-673
Courtneidge, J.L. **5**-315, **5**-339, **13**-745
Courtney, J.L. **19**-10
Courtois, G. **12**-33
Cousins, K.R. **18**-746
Cousins, R.P.C. **12**-109
Cousseau, J. **15**-173
Coussemant, F. **16**-319, **16**-1547, **16**-1550, **16**-1552
Couteliera O. **18**-884
Couto, A. **8**-138, **8**-144
Coutts, I.G.C. **12**-388, **18**-302
Couture, A. **16**-1379
Couture, P. **5**-414
Couture, Y. **15**-1740
Couturier, D. **18**-413
Couturier, M. **15**-522
Couty, F. **10**-1565, **16**-702, **16**-1460
Couve-Bonnaire, S. **13**-695, **13**-696
Couvillon, T.M. **18**-85
Covell, D.J. **19**-472
Coverdale, A.K. **10**-455
Covey, W.D. **11**-29
Cowan, D. **12**-605
Cowan, D.O. **7**-7
Cowan, P.J. **16**-2118
Cowdrey, W.A. **10**-6, **16**-1667
Cowell, G.W. **17**-496
Cowen, K.A. **16**-339
Cowley, A.R. **5**-372
Cox, D. **5**-21
Cox, D.P. **15**-2534, **18**-127
Cox, E.D. **11**-406
Cox, G.R. **15**-1133
Cox, G.S. **7**-43
Cox, J.D. **1**-99, **1**-100, **1**-105
Cox, J.L. **14**-279
Cox, J.M. **18**-837
Cox, K. **17**-217
Cox, R.A. **8**-129, **8**-132, **8**-142, **16**-1104, **18**-788, **18**-941, **18**-946, **18**-949
Cox. P.J. **10**-1743
Coxon, J.M. **7**-1, **8**-78, **15**-124, **15**-135, **15**-139
Coyle, J.D. **7**-1, **7**-15, **7**-45, **7**-48, **15**-2445, **16**-2205
Coyle, J.J. **5**-409
Coyne, É.J. **16**-1325
Cozens, F.L. **5**-12
Cozzi P.G. **16**-673
Cozzi, F. **4**-48, **5**-145, **15**-1836, **16**-776, **16**-1169
Cozzi, P.G. **16**-549, **16**-844, **16**-845, **16**-849, **16**-903, **16**-1169, **16**-1513
Crabb, T.A. **4**-367
Crabbé, P. **10**-1504
Crabbé, P. **4**-277
Crabtree, R.H. **2**-45, **14**-324, **14**-325, **15**-490, **17**-301, **18**-892, **19**-952
Craft, J. **2**-405
Cragg, G.M.L. **10**-1862, **15**-671, **15**-682, **18**-451, **19**-851, **19**-858, **19**-870, **19**-964
Craig, D. **15**-2169, **15**-2274, **16**-1292, **16**-1295, **17**-196
Craig, D.P. **4**-8
Craig, J.C. **18**-204, **19**-655, **19**-1112, **19**-1115
Craig, N.C. **15**-515
Craig, R.A. **4**-430
Craig, S.L. **10**-444, **15**-166
Cram, D.G. **17**-103
Cram, D.J. **2**-66, **2**-237, **3**-106, **3**-122, **3**-126, **3**-148, **3**-161, **3**-180, **4**-140, **4**-168, **5**-105, **5**-144, **5**-145, **8**-16, **8**-54, **8**-69, **8**-81, **10**-9, **10**-140, **10**-166, **10**-168, **10**-169, **10**-174, **12**-28, **12**-29, **12**-30, **12**-31, **12**-63, **12**-716, **15**-463, **16**-2271, **17**-85, **17**-103, **17**-262, **18**-12, **18**-31, **18**-94, **18**-284, **19**-1412, **19**-1706, **19**-1707
Cram, J.M. **2**-66, **3**-106, **10**-9, **12**-29
Cramer III, R.D. **4**-414
Cramer, C.J. **4**-145, **4**-380, **5**-442, **10**-356, **13**-53, **18**-678
Cramer, J. **19**-421
Cramer, N. **15**-2159
Cramer, P. **15**-216
Cramer, R. **12**-68
Crameri, Y. **15**-636
Cramp, S.M. **16**-1367
Crampton, M.R. **3**-55, **8**-50, **13**-9, **13**-10, **13**-21, **16**-1531
Crandall, J.K. **10**-1984, **15**-1965, **15**-1966, **17**-211
Crane, L.J. **4**-154, **4**-176

Crane, Z. **15**-1932, **15**-1936
Crans, D.C. **4**-216
Cravero, R.M. **2**-460
Cravotto, G. **7**-122, **16**-1872
Craw, J.S. **18**-704
Crawford, J.T. **11**-368
Crawford, K.R. **13**-241
Crawford, M. **16**-1267
Crawford, R.J. **10**-135
Crawford, T.D. **2**-280, **5**-98
Crawley, M.L. **10**-1519
Creary, X. **5**-58, **5**-361, **5**-379, **10**-45, **10**-161, **10**-312, **10**-313, **10**-315, **10**-322, **10**-467, **13**-154, **13**-657
Credi, A. **3**-194
Creed, D. **15**-2462
Creedon, S.M. **17**-480
Creese, M.W. **17**-131
Cregar, P.L. **10**-1804
Cregge, R.J. **10**-1699
Cremeens, M.E. **13**-46
Cremer, D. **2**-232, **4**-411, **4**-418, **4**-436
Crespo, R. **2**-204, **10**-1989
Crévisy, C. **16**-645, **18**-265, **19**-128
Crich, D. **10**-913, **15**-1337, **15**-1380, **17**-296, **18**-60, **18**-62, **19**-152, **19**-421, **19**-563, **19**-1393
Crick, D.C. **10**-881
Cridland, A. **17**-215
Cridland, A.P. **17**-217
Criegee, R. **15**-1791, **15**-2465, **18**-402, **18**-506, **18**-507, **18**-529, **19**-314, **19**-315, **19**-347, **19**-354
Crimmin, M.J. **18**-810
Crimmin, M.R. **15**-355, **19**-1746
Crimmins, M.T. **15**-2451, **16**-660, **16**-1196
Crimmins, T.F. **10**-1690
Cripe, T.A. **5**-408
Cripe, T.H. **5**-259
Crisp, G.T. **12**-261, **13**-439
Crispino, G.A. **15**-1793, **15**-1832, **15**-1843
Crist, D.R. **11**-275
Cristau, H-.J. **10**-816, **13**-293, **13**-647
Cristol, S.J. **10**-76, **14**-471, **15**-2452, **17**-12, **17**-17, **18**-66
Croatt, M.P. **15**-1543
Crocker, M.J. **7**-73
Croft, A.P. **3**-183, **17**-33
Croizy, J.F. **15**-834
Crombie, L. **16**-1302
Cromer, F. **2**-405
Cron S. **19**-1493
Cronin, M.F. **6**-51
Crookes, M.J. **12**-204
Crooks III, W.J. **19**-1341
Crooks, J.E. **8**-108
Crosby, D. **19**-1516
Crosby, J. **4**-137
Crosignani, S. **10**-1175, **16**-1752, **16**-1753, **16**-1897
Cross, L.E. **16**-325
Cross, M.J. **15**-254
Cross, R.J. **2**-406
Cross, R.M. **17**-236
Cross, R.T. **19**-423
Crossland, I. **16**-521
Crossland, R.K. **10**-412
Crotti, C. **12**-786
Crotti, P. **10**-683, **10**-837, **10**-996, **10**-997, **10**-1219, **10**-1647, **10**-1891
Crotti, S. **10**-1002
Crouch, R.D. **13**-576
Crounse, N.N. **11**-506
Crouse, B. **16**-936
Crouse, G.D. **15**-2179
Crousse, B. **10**-969, **16**-896
Crowe, D.F. **17**-424
Crowe, W.E. **18**-808
Crowley, H.K. **17**-480
Crowley, J.I. **16**-1930, **16**-1936, **16**-2140
Crowley, P.B. **16**-1325
Cruces, J. **10**-918
Crudden, C.M. **15**-1512, **15**-1810
Cruickshank, D.W.J. **2**-134
Cruickshank, F.R. **10**-3
Crum, L.A. **7**-73, **7**-79
Crumbliss, A.L. **12**-650
Crumine, D.S. **18**-921
Crump, R.A.N.C. **4**-82
Crumrine, D.S. **16**-1042
Cruse, R.W. **14**-223
Cruz-Almanza, R. **18**-241
Cruz, G. **15**-688
Cruz, R. **4**-346
Cruz, R.P.A. **11**-461, **11**-462
Cruz, S.G. **16**-1410
Cryberg, R.L. **5**-444
Csajági, C. **13**-683
Csákÿ, A.G. **16**-1504
Cserr, R. **12**-481
Csizmadia, I.G. **2**-94, **4**-48, **5**-126, **10**-800, **15**-21, **16**-1470, **18**-235
Csjernyik, G. **19**-214
Csuhai, E. **19**-487, **19**-488, **19**-489
Csuk, R. **15**-535, **19**-1626
Cubbage, J.W. **17**-287
Cubero, E. **3**-81, **3**-82, **3**-85
Cuerva, J.M. **5**-321, **15**-1330, **16**-575, **19**-342
Cuervo, H. **16**-496
Cueto, O. **12**-459
Cuevas, G. **4**-372, **4**-377
Cui, C. **11**-594
Cui, D.-M. **11**-432, **11**-453, **11**-468, **15**-1201, **15**-307, **15**-852
Cui, J.-L. **16**-408
Cui, L. **12**-381
Cui, M. **15**-1976
Cui, P. **16**-132
Cui, S.-C. **11**-128
Cui, W. **16**-1822, **19**-1640
Cui, X. **10**-797, **10**-1067, **10**-1270, **13**-496, **15**-448, **15**-2326, **16**-1082
Cui, Y.-T. **10**-599
Cui, Y. **15**-2069, **19**-163, **19**-238
Culkin, D.A. **13**-359, **13**-658
Cullen, E. **13**-846
Cullen, W.R. **2**-266
Cullis, P.M. **4**-32, **18**-400
Culmann, J. **12**-49
Cummings, D.L. **3**-73
Cummings, T.F. **16**-380
Cummins, J.M. **12**-404
Cun, L.-F. **16**-1084
Cun, L. **15**-619
Cundall, R.B. **15**-2449
Cundari, T.R. **8**-236
Cunha, R.L.O.R. **13**-577
Cunico, R.F. **12**-78, **16**-493
Cunningham Jr., A.F. **4**-464
Cunningham, I.D. **16**-2251
Cunsolo, F. **3**-133, **4**-69, **4**-167
Cuny, G.D. **15**-1603
Cuong, N.K. **19**-271
Cupone, G. **10**-1189
Cuppen, T.J.H.M. **18**-549
Curci, R. **15**-1888, **15**-1924, **15**-2369, **19**-10, **19**-227, **19**-293, **19**-478, **19**-490, **19**-496, **19**-739, **19**-810
Curillon, C. **10**-1342
Curini, M. **12**-757, **15**-1482, **15**-1716, **15**-1758, **19**-1698
Curl, R.F. **2**-392
Curnow, O.J. **18**-850
Curphey, T.J. **10**-410, **10**-1798, **15**-1947, **16**-220, **16**-1781
Curran, D.P. **10**-106, **10**-727, **10**-729, **10**-1024, **10**-1278, **12**-123, **12**-272, **12**-273, **13**-435, **14**-2, **14**-50, **15**-66, **15**-79, **15**-1287, **15**-1293, **15**-1339, **15**-1342, **15**-1351, **16**-2290, **18**-821, **19**-1319, **19**-1661
Curran, E.L. **10**-126
Currie Jr., J.O. **16**-200, **18**-426
Currie, G.S. **15**-1481
Currier, H. **16**-817
Curriev Jr., Y.O. **10**-1805
Curry, M.J. **10**-678
Curti, R. **16**-1975
Curtin, D.Y. **4**-189, **4**-194
Curtis, M.D. **15**-1194
Curtis, R.F. **14**-348
Curtis, V.A. **10**-414, **10**-415, **10**-752
Curtiss, L.A. **1**-55, **3**-10
Cusack, K.P. **16**-2303
Cushnyr, B. **19**-465
Cussans, N.J. **10**-579
Cutting, G.A. **16**-396

Cuvigny, T. **16**-2282, **17**-451, **19**-506
Cuyegkeng, M.A. **4**-529
Cuzens, J.R. **19**-1166
Cvetanović, R.J. **5**-354, **15**-2446, **15**-2457, **19**-344
Cwik, A. **13**-591
Cybulski, M. **19**-1534
Cygon, P. **5**-308
Cynkowski, T. **2**-388
Cyr, C.R. **12**-69
Cyr, D.R. **10**-1623
Cyr, J.S. **16**-1066
Cyrański, M.K. **2**-74, **2**-98, **2**-123, **2**-153, **2**-207
Cyvin, B.N. **2**-132, **2**-300
Cyvin, S.J. **2**-131, **2**-132, **2**-300
Cywin, C.L. **16**-1095
Czaja, R.F. **15**-55, **15**-127
Czaplik, W.M. **10**-1495
Czarnik, A.W. **16**-1810, **16**-1936
Czech, B.P. **10**-501
Czekay, G. **19**-59
Czekelius, C. **15**-629
Czemerys, L. **15**-1887
Czernecki, S. **19**-82
Czira, G. **17**-213
Czopp, M. **16**-990
Czuba, L.J. **12**-341
Czugler, M. **3**-163

da C. Rodrigues, R. **16**-1898
da Conceição Silva, A. **13**-497
da Costa, A.P. **19**-793
da Costa, J.C.S. **19**-1070
da Costa, R.C. **19**-1212
da Ponte, M.N. **15**-1807
da Rocha, S.R.P. **9**-104
da Silva, C.M.F. **13**-591
da Silva, F. de C. **15**-2520
da Silva, F.C. **16**-850
da silva, F.M. **15**-1037
da Silva, G. **15**-2137
da Silva, M.F. **10**-1919, **19**-1212
da Silva, R.A. **16**-328
da Silva, V.T. **13**-591
Da, C.-s. **16**-670
Daasbjerg, K. **8**-79, **10**-102
Daasvatn, K. **3**-111
Dabbagh, G. **10**-1400, **10**-1430, **12**-590, **16**-877
Dabdoub, M.J. **15**-322, **15**-1676, **16**-701
Dabdoub, V.B. **15**-1676, **16**-701
Dabin, G. **10**-724
Dabiri, M. **19**-88
Dabkowska, I. **8**-97
Dabora, S.L. **15**-436
D'Accolti, L. **15**-1924, **19**-227, **19**-293, **19**-478, **19**-490, **19**-496
D'Achille, R. **10**-1242
Dadali, V.A. **16**-2301
Dadjour, D.F. **12**-40
Dadush, E. **12**-296, **13**-576
Dafaye, J. **17**-337
Dafforn, G.A. **10**-299
Dagani, D. **15**-2480
Dagonneau, M. **16**-517
D'Agostino, J. **7**-58
Dahan, A. **15**-1553
Dahiya, R. **19**-110, **19**-201
Dahl, M. **10**-1701
Dahlen, A. **10**-1189, **15**-504, **15**-964, **19**-942, **19**-1677
Dahlgren, L. **6**-81
Dahlman, O. **19**-1317
Dahmen, A. **18**-532
Dahmen, S. **10**-780, **10**-1561, **16**-670
Dahn, H. **10**-550, **18**-127
Dai, C. **13**-459
Dai, G. **15**-959, **15**-2626
Dai, H.-F. **16**-313, **18**-878
Dai, L.-X. **10**-699, **10**-700, **10**-1243, **10**-1657, **16**-880, **16**-1386, **16**-1597
Dai, L. **15**-693, **16**-1034, **19**-1073
Dai, M. **13**-585, **15**-1522, **15**-2255
Dai, P. **19**-1403
Dai, R. **16**-1879
Dai, W.-M. **13**-495, **16**-1314
Dai, X. **10**-1730, **15**-2669
Dai, Y. **16**-776
Dai, Z. **10**-976
Daibuzono, K. **15**-1334
Daïch, L. **13**-611
Daignault, R.A. **19**-1454
Daikai, K. **15**-1403
Dailey, B.P. **1**-60, **2**-253
Dailey, W.P. **4**-449, **4**-452, **5**-394
Daim L.-X. **16**-1481
Dainty, R.F. **11**-585
Dais, P. **9**-52
Dakamin, M.G. **11**-605
Dakarapu, R. **11**-462
Dake, G.R. **15**-420, **18**-135
Dake, S.A. **18**-395
Dakhil, O.O. **13**-537
Dakin, L.A. **10**-583
Dakka, G. **10**-1130
Dakka, J. **10**-723
Dakternieks, D. **12**-643
Dalcanale, E. **19**-673
Dale, J. A. **4**-107
Dale, J. **1**-9, **3**-111, **3**-112, **4**-270, **4**-363, **4**-406, **16**-530
Dale, J.A. **4**-107
Dale, J.W. **15**-2637
Dale, S.H. **13**-733
D'Alessandro, F. **16**-1975
Dalessandro, J. **19**-1283
Dalipi, S. **15**-21
Dalko, P.I. **15**-673
Dalla Croce, P. **10**-1041
Dall'Acqua, F. **9**-111, **12**-784
Dallas, A.S. **13**-187
Dallavalle, S. **19**-801
Dallemer, F. **16**-2113
Dalley, N.K. **4**-168, **4**-182
D'Alliessi, D.G. **15**-2250
Dallinger, D. **7**-129, **9**-98
Dalman, G.W. **13**-97
Dalmolen, J. **16**-895
Dalpozzo, R. **10**-1189, **15**-910, **15**-1238, **16**-1723
Dalton, A.M. **12**-379
Dalton, D.M. **19**-1047
Dalton, D.R. **15**-1687
Dalton, J.C. **7**-27, **7**-48, **15**-2445
Dalvi, P.V. **15**-2201
Daly, A.M. **15**-1983
Dalzell, H.C. **14**-421
Dam, J.H. **10**-1044
Damavandi, J.A. **19**-29
Damayanthi, Y. **19**-1256
Dämbkes, G. **16**-1588
D'Ambrosi, A. **15**-1971
Dambruoso, P. **4**-123
Damin, B. **15**-1691
Damm, L. **12**-35
Damm, W. **5**-255, **14**-72, **14**-109, **15**-67
Dammel, R. **16**-238
Damodar, K. **15**-1662
Damodharan, L. **3**-6
Damrauer, R. **5**-113, **8**-85
Dams, R. **19**-1687, **19**-1689, **19**-1699
Danca, D.M. **15**-1367
Dance, I. **3**-221
Dance, I.G. **3**-162
Dancer, R.J. **16**-465
Danda, H. **16**-1070
Danda, Y. **13**-713
Dandapani, S. **10**-727, **10**-729
Danehy, J.P. **19**-1621
Danen, W.C. **5**-293, **14**-63, **14**-118, **15**-1744
Daney, M. **10**-1940
Danforth, R.H. **13**-109
Dang, H.-S. **15**-792, **15**-1470
Dangat, V.T. **11**-274
d'Angelo, J. **10**-670, **10**-1754, **10**-1771, **12**-106, **15**-1101, **15**-1108, **15**-1406, **15**-2444, **16**-1171
D'Angelo, N.D. **13**-473
Danheiser, R.L. **10**-1299, **12**-223, **12**-379, **12**-553, **13**-175, **15**-376, **15**-2255, **15**-2321
Danhui, Y. **16**-861
Daniel, C. **15**-491
Daniel, K.L. **12**-387
Daniel, T. **11**-240, **11**-242, **11**-442, **13**-592
Danielmeier, K. **14**-456
Danikiewicz, W. **13**-757
Danilova, N.A. **14**-428
Danilova, T.I. **16**-680
Danishefsky, S. **15**-145, **15**-2186, **15**-2322

Danishefsky, S.J. **15**-2255, **16**-1838, **19**-735
Danjo, H. **15**-800, **15**-1206
Danjo, T. **13**-452
Dan'kov, Yu.V. **15**-10
Danks, T.N. **15**-655, **16**-253
D'Anna, F. **8**-84
Dannenberg, J.J. **5**-239, **10**-222, **14**-10, **18**-83
D'Annibale, A. **14**-86, **15**-1351, **15**-2008, **15**-2090, **15**-2092
D'anniballe, G. **16**-1975
Danovich, D. **5**-276
Dantale, S.W. **16**-1785, **19**-683
Dao, L.H. **10**-317
Daoust, K.J. **4**-409
Daplozzo, R. **19**-969
Dapurkar, S.E. **19**-1054
Darba, P. **4**-535, **10**-292
Darby, A.C. **11**-306
Darby, N. **2**-275
Darcel, C. **19**-766
Darcy, M.G. **19**-729
Dardis, R.E. **16**-385
Dardoize, F. **10**-1801
Dargel, T.K. **15**-2558
Darling, S.D. **17**-393
Darmency, V. **14**-17, **14**-18, **14**-21
Darowska, M. **8**-97
Darrin, M. **19**-595
Darses, S. **10**-1893, **12**-346, **13**-381, **13**-571, **13**-814, **13**-815, **13**-816, **15**-1279, **15**-1280, **16**-760, appendixa-27
Darsigny, V. **16**-261
Dart, E.C. **8**-15
Darvas, F. **13**-683
Darville, K. **19**-911
Das, A. **10**-835, **17**-216, **17**-378, **18**-167
Das, A.R. **19**-916
Das, B. **10**-840, **11**-286, **15**-609, **15**-1212, **15**-1662, **16**-294, **16**-302, **16**-1629, **16**-1630, **16**-1636, **16**-1744, **16**-1750, **16**-1808, **17**-444
Das, B.C. **15**-1265
Das, G. **16**-1053
Das, J. **10**-1068, **15**-1071, **15**-1820, **19**-708
Das, J.P. **14**-311, **14**-468
Das, K.K. **16**-1879
Das, K. **10**-702
Das, P. **13**-504, **15**-654, **16**-1371, **15**-1265, **15**-1391, **16**-1100, **16**-1851, **17**-472, **17**-473, **19**-653, **19**-1478
Das, U. **10**-969
Dasent, W.E. **15**-84
Dasgupta, S.K. **13**-418
Daskapan, T. **15**-917
Dastagiri, D. **16**-2292
Dastbaravardeh, N. **13**-133
Datar, R. **16**-891
Datta Gupta, A. **19**-469
Datta, A.P. **11**-486
Datta, D. **9**-74
Datta, I. **12**-220
Datta, M. **16**-203
Datta, S. **18**-581
DattaGupta, A. **15**-2512
Daub, G.H. **16**-1186
Dauban, P. **15**-2068
Dauben Jr., H.J. **2**-107, **2**-173, **14**-202, **14**-205, **19**-429
Dauben, W.G. **4**-464, **5**-343, **7**-43, **15**-1026, **15**-2452, **16**-130, **16**-1335, **17**-274, **18**-498, **18**-499, **18**-520, **18**-521, **18**-569, **18**-571, **18**-915
Daubignard, J. **16**-645
Daugulis, O. **13**-478
d'Augustin, M. **15**-1181, **15**-1173
Daunis, J. **11**-491
Dauphin, G. **15**-1706
D'Auria, M. **15**-1683, **19**-81, **19**-712
Daus, K.A. **15**-166
Dauvergne, J. **15**-1555
Davankov, V.A. **4**-178, **10**-882
Dave, B. **13**-183
Dave, H.R. **16**-1881
Dave, P.R. **16**-1879
Dave, V. **15**-2473, **18**-251
Davenport, D. **4**-294
Daverio, P. **19**-1028
Daves Jr., G.D. **13**-409, **13**-411
Davey, P.N. **15**-1002, **15**-1019
Daviaud, G. **15**-1156
Davico, G.E. **2**-26
David, D.E. **5**-286
David, O. **16**-1460
Davidov, P. **19**-346
Davidovich, Yu.A. **10**-553, **16**-1929
Davids, K.L. **4**-407
Davidson, D. **16**-1978
Davidson, E.R. **5**-128, **5**-299, **5**-302, **5**-353
Davidson, E.W. **15**-580
Davidson, F. **12**-372
Davidson, M. **16**-1547, **16**-1550, **16**-1552
Davidson, M.H. **15**-246
Davidson, R.B. **4**-168, **4**-310, **4**-439
Davidson, R.S. **14**-77, **15**-2463
Davidsson, Ö. **3**-63, **8**-225, **16**-495, **16**-1024
Davie, C.P. **12**-379
Davies, A.G. **4**-371, **4**-388, **5**-219, **5**-336, **5**-339, **10**-712, **10**-769, **11**-81, **12**-460, **13**-745, **14**-20, **14**-266, **15**-1003
Davies, D.G. **12**-715
Davies, D.I. **14**-2, **14**-13, **14**-24, **14**-125, **14**-127, **15**-1329, **15**-1710, **19**-419
Davies, D.T. **15**-2102
Davies, H.M.L. **12**-221, **12**-370, **12**-373, **12**-384, **12**-386, **12**-394, **12**-395, **15**-2502, **15**-2510, **15**-2512, **15**-2513, **15**-2521, **15**-2522, **15**-2664, **15**-2666, **15**-2669, **16**-1456
Davies, I.W. **9**-112, **13**-416, **15**-380, **15**-793, **19**-1135, **19**-1142
Davies, J.A. **10**-1983, **15**-1494, **15**-1597
Davies, J.E. **3**-106, **3**-110, **3**-124, **3**-147, **3**-162, **3**-166, **3**-170, **3**-172, **3**-175, **3**-176, **3**-183, **3**-185, **3**-186
Davies, J.E.D. **3**-222, **4**-169
Davies, J.W. **18**-371
Davies, K.M. **4**-228
Davies, M. **15**-271
Davies, M.W. **15**-2650
Davies, P.W. **15**-926, **18**-883
Davies, R.V. **16**-2069
Davies, S.G. **2**-47, **19**-1500, **19**-1603
Davies, T.E. **19**-459
Davies, T.M. **10**-301
Davis Jr., J.C. **3**-45
Davis Jr., J.H. **16**-1117
Davis, A.B. **13**-21
Davis, B. **15**-1932
Davis, B.A. **16**-346
Davis, B.G. **16**-849
Davis, B.H. **17**-163
Davis, B.R. **19**-1407
Davis, C.B. **16**-1979
Davis, D.D. **12**-7, **12**-12
Davis, F.A. **4**-29, **12**-136, **12**-145, **12**-463, **16**-883, **19**-508, **19**-510, **19**-511, **19**-519, **19**-713
Davis, G.T. **16**-1957, **16**-1961
Davis, H.A. **19**-1370
Davis, J.H. **18**-687
Davis, N.R. **13**-191, **18**-330
Davis, P. **4**-204
Davis, P.D. **10**-1969
Davis, R.E. **16**-325
Davis, R.F. **18**-675
Davis, R.L. **15**-1083, **18**-952
Davis, S. **14**-166
Davis, S.A. **10**-1368
Davis, T.A. **19**-945
Davis, T.P. **16**-218
Davis, W.M. **18**-894
Davister, M. **11**-358
Davoli, P. **10**-1260, **16**-2246
Davoust, D. **17**-320
Davy, H. **16**-231
Dawes, H.M. **3**-32
Dawes, K. **7**-48
Dawson, B.T. **12**-630, **16**-2011
Dawson, I.M. **11**-581. **11**-589
Dawson, L.R. **8**-258
Dawson, M.I. **10**-1354

Day, A. **3**-222
Day, A.C. **16**-272, **16**-2195
Day, A.I. **3**-221
Day, B.W. **11**-456
Day, J.C. **14**-209
Day, L.S. **18**-176
Day, M.W. **18**-895
Dayagi, S. **16**-240, **19**-274
D'yakonov, V.A. **15**-889
Daynard, T.S. **19**-1701
Dayton, D.C. **5**-286
D'az-Ortiz, A. **7**-129
De-xiang, W. **15**-2298
de Mayo, P. **18**-94
de Alaniz, J.R. **15**-1485
de Almeida, M.V. **18**-928
De Angelis, F. **10**-928, **10**-954, **17**-57
de Armas, J. **15**-891, **15**-900
de Azeredo, J.B. **14**-361
De Bakker, C. **16**-2045
De Bernardinis, S. **19**-1352
De Bo, G. **15**-784
De Boer, C.D. **18**-665
de Boer, H.J.R. **2**-68, **12**-642
de Boer, J.W. **15**-1795
de Boer, T.J. **13**-79, **17**-497, **19**-1728
De Borggraeve, W. **7**-129
de Bruin, T.J.M. **15**-1540, **15**-1573
De Castro, K.A. **16**-350
De Cock, C. **15**-2388, **15**-2432
de Diego, C. **19**-1334
de Dios, A. **10**-1314
de Echagüen, C.O. **15**-2293
de Fays, L. **8**-205, **15**-2187
De Felippis, J. **4**-490
de Filippis, A. **13**-662
de Franca, K.W.R. **13**-311
de Frutos, Ó. **13**-376, **15**-2620
de Gelder, R. **11**-409
de Groot, A. **17**-298
de Gunst, G.P. **13**-62
de Haan, J.W. **10**-165, **18**-603
de Heer, M.I. **1**-110
de Jeso, B. **2**-477
de Jesús, E. **13**-698
De Jesús, M. **19**-972, **19**-1158, **19**-1234
de Jong, G.Th. **17**-114
de Jonge, A.P. **16**-1762
de Jonge, C.R.J.I. **19**-10
de Julien de Zélicourt, Y. **2**-323
De Kimpe, N. **10**-309, **10**-902, **10**-1244, **10**-1300, **12**-110, **15**-2043, **15**-2470, **16**-1280, **16**-1416, **16**-2225, **18**-258, **19**-35, **19**-1314
de Klein, W.J. **15**-1473
de Koning, A.J. **11**-696
de Koning, C.D. **18**-866
de la Cruz, P. **7**-118
de la Cruz, W. **19**-972
de la Hoz, A. **7**-118, **7**-129, **15**-2203
de la Mare, P.B.D. **2**-410, **9**-27, **11**-6, **11**-68, **11**-123, **11**-224, **11**-230, **11**-271, **15**-1, **15**-69, **15**-74, **15**-1637, **17**-84
de la Pradilla, R.F. **10**-1314, **18**-757
de la Vega, F. **11**-260
de la Zerda, J. **10**-628
de Lange, B. **7**-65, **16**-895
de Leon, S. **11**-324, **15**-2622
de Lera, A.R. **13**-569
de Ligny, C.L. **9**-57
de Lima, P.G. **13**-597
De Lombart, S. **16**-702
de los Santos, J.M. **16**-276, **16**-1407
De Luca, L. **12**-760, **16**-1901, **16**-2291
De Lucchi, O. **15**-2180, **17**-502, **18**-912, **19**-428, **19**-1755
De Lue, N.R. **12**-512, **12**-513, **12**-514
de M. Carneiro, J.W. **5**-81, **11**-123
de Manderola, O.B. **16**-2185
De Maria, P. **10**-279, **12**-82
de Mattos, M.C.S. **15**-1704
de Mayo, P. **5**-132, **5**-413, **7**-50, **7**-58, **14**-252, **15**-1319, **15**-2362, **18**-1, **18**-2, **18**-54, **18**-104, **18**-176, **18**-203, **18**-290, **18**-311, **18**-361, **18**-403, **18**-499, **18**-610, **18**-665, **18**-794, **18**-908, **18**-915, **18**-919, **18**-922, **18**-958
De Meese, J. **16**-1456
de Meijere, A. **4**-460, **5**-90, **5**-335, **5**-341, **10**-1729, **12**-285, **12**-780, **13**-400, **13**-439, **15**-2652, **15**-2697, **18**-87, **18**-562, **18**-608, **18**-625, **18**-667
De Meio, G.V. **13**-271
de Mendoza, J. **19**-1168
de Mendoza, P. **13**-445
de Meyer-van Duyse, A. **9**-47
De Micheli, C. **15**-2105, **15**-2118
De Mico, A. **15**-1683
De Nino, A. **16**-92
de Nooy, A.E.J. **19**-185
de O. Jardim, A.H. **16**-850
de Oliveira-Neto, J. **16**-1384
de Oliveira, P.S.M. **19**-1070
de Oliveira,K.T. **2**-389
de Parrodi, C.A. **10**-1231, **16**-681
de Petris, G. **11**-101
De Proft, F. **14**-113
De Roma, A. **15**-1170
De Rose, V.T. **15**-1883
de Rossi, R.H. **11**-595, **11**-633, **13**-16, **13**-57
de Rosso, C.R.S. **19**-355
de Ryck, P.H. **12**-535
de S. Santos, E. **16**-850
de Sá, A.C.P.F. **10**-851
de Sanabia, J.A. **18**-124
de Savignac, A. **10**-1060
De Shazo, M. **11**-44
De Sio, V. **16**-776
de Souza-Barboza, J.C. **12**-638, **15**-1213
de Souza-Barboza, J.D. **16**-472
de Souza, A.L.F. **13**-379, **13**-497
de Souza, R.F. **9**-122
de Souza, R.O.M.A. **13**-591
De Tar, D.F. **6**-13, **9**-66
de V.F. Neder, A. **11**-461
de Vincente, J. **16**-1434
de Vires, J.G. **15**-1278
de Visser, S.P. **14**-94
De Vleeschouwer, F. **14**-113
De Vos, D.E. **19**-126
de Vos, M.J. **16**-702
de Vries, A.H.M. **15**-1278, **16**-822
de Vries, E.F.J. **4**-95
de Vries, J.G. **13**-148, **15**-643, **16**-424, **16**-746, **19**-217
de Wildeman, S. **19**-993
de Wit, P. **11**-196
de Wolf, W.E. **2**-67, **18**-686
de Wolf, W.H. **2**-68
De, A. **16**-81
De, P. **10**-658, **11**-242
De, R.L. **13**-509
De, S.K. **10**-974, **16**-62, **16**-124, **16**-201, **16**-1517, **16**-1538, **16**-1723, **18**-337, **18**-338
Deacon, G.B. **12**-290, **12**-689, **15**-1821
Deady, L.W. **10**-879, **10**-921, **10**-1259, **6**-1620
Deak, H.L. **18**-621
Dean, C.L. **15**-21
Dean, F.H. **15**-1670
Dean, M.A. **16**-668
DeAngelis, A. **15**-2504
Deardorff, D.R. **10**-762
Deardorff, J.D. **19**-1297
Deaton-Rewoliwski, M.V. **19**-1604
Deb, A.C. **18**-705
Deb, K.K. **3**-45
Debailleul, B. **16**-1138
Debenham, S.D. **10**-1536
DeBergh, J.R. **15**-1860
Deberly, A. **19**-925
Debleds, O. **18**-890
DeBoef, B. **15**-759, **15**-2692
DeBoer, A. **15**-55, **15**-127
DeBoer, C.D. **15**-2449
DeBoos, G.A. **11**-135
DeBruin, K.E. **15**-190
DeBruyn, D.J. **16**-161
Debû, F. **18**-234
DeBuyck, L. **12**-115
Dechoux, L. **12**-103, **17**-212
Decken, A. **19**-1588
Declerck, V. **13**-397, **16**-955
Declercq, J. **16**-1280
Declerzq, J.-P. **18**-157

Decock-Le Révérend, B. **18**-671
Decodts, G. **17**-309
DeCorso, A.R. **15**-1695
Decorzant, R. **10**-1760
Decouzon, M. **8**-97, **19**-1236
Dedeoglu, E. **11**-99
Dedov, A.G. **14**-221, **15**-549
Deeth, R.J. **13**-448
Deetz, M.J. **4**-322
Defay, N. **4**-71
Defieber, C. **10**-934, **15**-1269
DeFrees, D.J. **6**-79, **8**-252, **10**-198, **10**-199, **10**-213
Degani, I. **16**-1338
Degani, Y. **16**-240, **19**-274
Degen, H.-G. **15**-1912, **15**-1916
Degenhardt, C.R. **10**-87
Deger, H.M. **2**-364
Degering, E.F. **19**-1240
Degl'Innocenti, A. **10**-691, **15**-1141, **16**-1198
Deglise, X. **12**-761
Degnan, A.P. **15**-2351
Degorre, F. **10**-388
DeHaan, F.P. **11**-29, **11**-95
Dehaen, W. **7**-126, **7**-127, **7**-129, **13**-598, **15**-2203
Dehestani, A. **19**-440
Dehghani, A. **12**-342
Dehmlow, E.V. **10**-484, **10**-489, **10**-497, **12**-685, **15**-2378, **15**-2489
Dehmlow, S.S. **10**-484
Dehn, R.L. **17**-424
Dehnicke, K. **15**-1757
DeHoff, B. **10**-1418
Dehury, S.K. **16**-631
Deiter, S.A. **18**-823
Deiters, A. **15**-2614
Dejaegher, Y. **16**-2225
Dejroongruang, K. **2**-387
Dekerckheer, C. **7**-80
Dekeukeleire, S. **16**-2225
Dekker, J. **16**-853
Dekkers, H.P.J.M. **4**-224
DeKock, R.L. **8**-83
Del Bene, J.E. **3**-47
Del Cierva, C.O. **15**-863
Del Re, G. **2**-13
del Río, R.E. **19**-800
Del Valle, L. **10**-1508
Del Verme, F. **10**-694
del Villar, A. **10**-1507
Del Zotto, A. **13**-503
DeLaat, A.M. **3**-53
Delacroix, A. **15**-361
Delacroix, T. **16**-2035
Delahunty, C. **9**-66
Delair, P. **19**-1641
Delaney, E. **16**-1942
Delas, C. **15**-2382
DeLaTorre, K. **16**-560
Delaumeny, M. **10**-1610
Delavarenne, S.Y. **12**-506
Deleuze, M. S. **3**-206
Delfly, M. **11**-587
Delgado, A. **12**-712, **18**-869
Delgado, F. **16**-2184
Delgado, M. **18**-841
Delgass, W.N. **6**-42
Delguzzo, L. **10**-121
D'Elia, V. **16**-1975
Delker, G.L. **11**-29
Dell, S. **10**-749
Della Sala, G.D. **15**-232
Della, E.W. **4**-454, **5**-84, **5**-86, **10**-53, **14**-476
Dellaria Jr., F.F. **16**-1837
Dellaria Jr., J.F. **13**-820, **14**-396, **19**-1550
Dell'Erba, C. **8**-183, **17**-60
Delmas, M. **10**-842, **16**-1384
Delmon, B. **17**-180
Delogu, G. **11**-381
DeLong, G.T. **5**-205
deLong, M. **15**-2679
Delorme, D. **10**-632
Delpont, N. **15**-2517
DeLuca, L. **7**-46, **12**-766, **16**-1811, **16**-2064, **19**-649
DeLucca, J.P. **12**-399
DeLucchi, O. **15**-1381
Delude, C. **10**-670
Delville, M.M.E. **10**-917
DelZotto, A. **17**-269
Demange, L. **15**-147
DeMarco, A.M. **18**-329
DeMaria, P. **8**-183
DeMario, D.R. **14**-346
DeMatteo, M.P. **5**-317
Demay, S. **15**-717
Dembech, P. **12**-45
Dembinski, R. **10**-727
Dembinski, R. **16**-218
Dembofsky, B.T. **4**-112
Demchuk, D.V. **4**-373
Demchuk, O.M. **18**-832
DeMello, N.C. **15**-1880
DeMember, J.R. **5**-80, **10**-200, **10**-218, **12**-357, **18**-108
Demerseman, B. **10**-1535
Demerseman, P. **11**-587, **13**-108
Demicheli, G. **16**-1202
DeMico, A. **19**-199, **19**-1747
Demir, A.S. **11**-422, **13**-552, **14**-280, **15**-1098, **16**-1031, **16**-1590, **19**-523, **19**-527
DeMira, M. **18**-400
Demirtas, I. **8**-87
Demizu, Y. **19**-142
Demko, Z.P. **15**-2022
Demonceau, A. **10**-659, **15**-1776, **15**-2142, **15**-2501
Demoute, J.-P. **13**-814, **13**-815
Dempsey, B. **8**-25, **8**-175
Demuth, M. **15**-2445, **18**-916, **18**-919, **18**-922
Demuynck, M. **16**-186
Dem'yanov, N.Ya. **4**-486
den Hartog, T. **15**-1185
den Hertog, H.J. **13**-54
Denekamp, C. **10**-34, **15**-2429
Denes, A.S. **16**-1551
DeNet, R.W. **10**-1668
Deng, C.-L. **10**-1732, **13**-502
Deng, G.-H. **14**-342
Deng, G.-J. **15**-643, **16**-664
Deng, G. **11**-663, **19**-1430
Deng, H. **16**-672, **16**-1515
Deng, J. **15**-619
Deng, L. **11**-314, **15**-1052, **15**-1059, **15**-1402, **15**-1447, **15**-1921, **15**-1978, **15**-2252, **15**-2669, **16**-398, **16**-1219, **16**-1731, **16**-1732
Deng, L.X. **15**-1294
Deng, M.-Z. **10**-1885, **12**-293, **12**-294, **13**-524, **13**-559
Deng, M. **16**-898
Deng, Q. **15**-2000
Deng, W. **13**-236
Deng, X.-M. **16**-1461, **16**-1963, **18**-148
Deng, Y. **10**-1469, **15**-751, **16**-59, **16**-134, **18**-348
Deniau, E. **16**-1379
DeNino, A. **10**-1189, **15**-910, **16**-1723
Denis, G.I. **17**-108
Denis, J. **2**-468, **5**-39
Denis, J.M. **15**-2552, **16**-238
Denis, J.N. **12**-758, **17**-205, **19**-1598
Denis, P. **15**-834
Denis, R.C. **15**-54
Denisenko, S.N. **4**-40
Denisov, E.T. **14**-37
Denmark, S.E. **8**-157, **10**-766, **10**-1491, **10**-1729, **10**-1746, **13**-320, **13**-452, **13**-517, **13**-698, **13**-700, **13**-706
Denmark, S.E. **13**-708, **13**-709, **13**-714, **13**-717, **15**-868, **15**-957, **15**-1249, **15**-1924, **15**-1926, **15**-1933, **15**-2557, **16**-463, **16**-557, **16**-597, **16**-648, **16**-708, **16**-774, **16**-776, **16**-889, **16**-970, **16**-1029, **16**-1067, **16**-1084, **16**-1091, **16**-1129, **16**-1145, **16**-1154, **16**-1158, **16**-1173, **16**-2254, **18**-732, **19**-1141
Denney, D.B. **12**-461, **14**-285
Denney, D.Z. **12**-461, **14**-285
Dennis, N. **4**-375, **15**-2319, **15**-2352
Denniston, A.D. **5**-128
Denny, R.W. **14**-258, **14**-250, **15**-2356
Deno, N.C. **5**-34, **5**-35, **5**-38, **5**-43, **5**-48, **5**-49, **5**-63, **5**-73, **5**-75, **8**-29, **8**-42, **8**-134, **9**-47, **9**-50, **10**-827, **12**-158, **12**-312, **14**-80,

Deno, N.C. (*Continued*) **14**-168, **14**-170, **14**-171, **14**-173, **18**-397, **18**-924, **19**-442, **19**-638
Denson, D.D. **17**-524
Dent III, W.H. **15**-1876
Denzel, T. **16**-1404
Deobald, A.M. **14**-361
Deora, N. **5**-98
DePalma, V.M. **5**-137
Depew, M.C. **5**-334
Depew, R.E. **3**-219
Depezay, J. **16**-1102
Depezay, J.C. **10**-1771
DePomar, J.C.J. **12**-593
Deprèle, S. **15**-389, **15**-390
Depriest, R.N. **10**-634
DeProft, F. **13**-52
DePue, J.S. **10**-896
DePuy, C.H. **2**-26, **5**-113, **10**-282, **12**-222, **15**-132, **15**-136, **17**-9, **17**-70, **17**-103, **17**-146, **17**-147, **17**-187, **17**-231, **17**-237, **17**-259, **18**-539, **18**-542
Derane, D. **10**-1728
Derdour, A. **16**-1946
Derenberg, M. **12**-715
Derendyaev, B.G. **18**-35
Derevitskaya, V.A. **16**-1779
Derfer, J.M. **4**-430
Dérien, S. **15**-1506
Derikvand, F. **16**-54
Dermer, O.C. **10**-525, **10**-698, **10**-901, **10**-998, **14**-147, **15**-2043, **17**-363, **18**-615
Dernell, W. **16**-2070
Derock, M. **10**-853
Derome, A.E. **19**-1540
Derrien, N. **19**-1023
Dershem, S.M. **14**-106
DeRussy, D.T. **18**-658
des Abbayes, H. **10**-1965, **10**-1987
Desai, B. **15**-655
Desai, D.G. **17**-435, **19**-938, **19**-944
Desai, L. **19**-525
Desai, L.V. **13**-136
Desai, M.C. **18**-475
Desai, N.B. **16**-1317
Desai, U.V. **11**-252, **16**-1209
Desai, V.R. **18**-68
Desbène, P. **11**-229
Deschamps, J. **4**-228
Deschamps, N.M. **15**-1543, **15**-1544
Deselnicu, M.I. **10**-1390
Deshayes, H. **19**-1392
Deshayes, K. **3**-181
Deshayes, S. **10**-499
Deshmukh, A.R.A.S. **10**-1083
Deshmukh, R.R. **11**-331, **16**-1203
Deshmukh, R.Y. **16**-158
DeShong, P. **10**-727, **10**-1284, **13**-515, **13**-699, **13**-716, **13**-718, **15**-2105
Deshpande, A.K. **5**-389, **19**-1324
Deshpande, R.M. **19**-1181
Deshpande, S.S. **15**-2210
Deshpande, V.H. **10**-679, **16**-1203
Deshpande, V.M. **19**-930
DeSimone, J. **10**-443
Desimoni, G. **11**-314, **15**-991, **15**-1100, **15**-2319, **15**-2385, **18**-713
Desio, P.J. **16**-685
Desiraju, G.R. **3**-76, **8**-13
Deskus, J. **10**-893, **16**-2049
Deslongchamps, P. **4**-376, **10**-569, **10**-1685, **15**-2169, **16**-32
Desmaële, D. **10**-902, **15**-1108, **15**-1406, **16**-1171
Desmaris, L. **10**-1161
DesMarteau, D.D. **11**-311
Desmond, K.M. **14**-207
Desmond, R. **19**-647
Desmurs, J.-R. **10**-979, **10**-1005, **11**-218, **18**-833
DeSouza, M.V.N. **19**-1070
Despres, L. **16**-1926
Desrosiers, J.-N. **16**-899
Dess, D.B. **19**-190
Dessanti, F. **19**-1519
Dessau, R.M. **15**-1642
Dessole, G. **10**-1568
Dessy, R.E. **5**-109, **8**-69, **12**-599
DeStephano, J.P. **16**-509
Destro, R. **2**-288, **2**-305, **2**-313, **2**-350, **13**-11
Desvard, O.E. **10**-300
Desyroy, V. **16**-1138
DeTar, D.F. **4**-535, **9**-73, **9**-60, **10**-292, **14**-48, **14**-368
Detomaso, A. **19**-293, **19**-739
Detoni, S. **3**-11
Detre, G. **17**-424
Detsina, A.N. **11**-92
D'Ettole, A. **16**-2020
Dettwiler, J.E. **16**-2079
Detz, R.J. **10**-917
Deubel, D.V. **15**-1882, **19**-225
Deuchert, K. **19**-4
Deudon, S. **13**-239
Deussen, R. **15**-1606
Deutsch, C. **15**-1794
Deutsch, J. **16**-1865
Deutsch, P.P. **5**-232
Dev, S. **15**-462, **16**-194, **19**-334, **19**-443
Dev, V. **4**-496
Devaprabhakara, D. **14**-436, **15**-546, **15**-548
Devasagayaraj, A. **10**-1470
DeVasher, R.B. **13**-526
Devi, G. **16**-922
Deville, C.G. **15**-2121
Devin, P. **15**-1368
DeVincentis, D. **10**-538
Devine, P. **19**-1014
Devine, P.N. **13**-273, **19**-993
Devine, S.K.J. **12**-380
Devlin, F.J. **4**-115 **4**-119
Devos, A. **10**-1150, **16**-1990
Devynck, J. **12**-356
Dewald, R.R. **19**-933
Dewar, M.J.S. **1**-2, **2**-5, **2**-9, **2**-13, **2**-18, **2**-20, **2**-39, **2**-127, **2**-208, **2**-209, **2**-410, **2**-423, **2**-428, **3**-88, **3**-93, **6**-86, **10**-236, **11**-18, **15**-168, **15**-2283, **15**-2303, **18**-512, **18**-667, **18**-707, **18**-794
Dewhurst, B.B. **12**-701
DeWitt, S.H. **16**-1936
Dewkar, G.K. **19**-730
DeWolfe, R.H. **10**-226, **10**-227, **10**-305, **10**-551, **10**-677, **10**-1599, **12**-57, **16**-143, **16**-1694, **18**-627
Dey, K. **13**-685
Dey, R. **10**-1732
Dey, S. **19**-620, **19**-691
Dey, S.S. **10**-881
Deyà. P.M. **13**-23
Deycard, S. **5**-296
Deyerl, H.-J. **8**-233
DeYoung, D.J. **1**-13
Deyrup, A.J. **5**-63, **5**-75, **8**-128
Deyrup, C.L. **10**-159
Deyrup, J.A. **7**-61, **16**-1288
Dezyani, S. **19**-88
Dhanoa, D. **10**-192
Dhanoa, D.S. **16**-2007
Dhar, D.N. **15**-72
Dhar, M.L. **17**-109, **17**-110, **17**-124
Dhas, N.A. **15**-2204
Dhavale, D.D. **16**-1084
Dhawan, S.N. **7**-52
Dhillon, R.S. **15**-671, **15**-729, **18**-473
Dhimitruka, I. **16**-1766
Dhokte, U.P. **15**-710
D'hooghe, M. **10**-1244, **15**-2043, **16**-2225
Dhoro, F. **15**-1095
Di Antonio, G. **19**-1254
Di Bari, L. **4**-121
Di Blasio, B. **8**-31
Di Deo, M. **10**-1125
Di Furia, F. **19**-810
Di Giuseppe, S. **15**-2633, **16**-146
di Maio, G. **2**-300
Di Silvestro, G.D. **4**-39
Di Tommaso, D. **16**-774
Di Valentin, C. **15**-2119
Di Vona, M.L. **10**-408, **19**-1440
Diab, Y. **19**-1236
Diamanti, J. **12**-337
Dias, A.K.B. **11**-461
Dias, E.L. **15**-2581
Dias, H.V.R. **12**-372, **12**-376
Dias, J.R. **2**-23 **2**-128, **2**-131, **19**-1443
Dias, S. **10**-873

Díaz-Ortiz, A. **7**-118, **15**-2203
Díaz-Requejo, M.M. **12**-375, **15**-2507, **15**-2517, **19**-535
Diaz, A. **10**-171
Diaz, A.F. **10**-72
Díaz, M.J. **10**-806
Díaz, M.R. **10**-1236, **15**-2527
Dichenna, P.H. **15**-2068
Dick, A.R. **19**-463
Dick, K. **3**-159
Dick, K.F. **19**-75
Dickason, W.C. **10**-86, **10**-88, **15**-720, **18**-457
Dicken, C.M. **15**-2105
Dickens, M.J. **10**-504
Dickenson, G. **9**-131
Dicker, I.B. **16**-1132
Dickerman, S.C. **13**-821
Dickerson, T.J. **15**-1973
Dickhaut, J. **14**-72
Dickinson, C.L. **15**-74
Dickinson, M.G. **11**-339
Dickstein, J.I. **10**-302, **15**-80, **15**-1307
Dickstein, J.S. **16**-898
DiCosimo, R. **14**-291
Didelot, M. **13**-794
Didenko, Y.T. **7**-74, **7**-76
Dideriksen, B.B. **15**-1981
Didillon, B. **5**-413, **19**-37
Didiuk, M.T. **17**-191
Diederich, F. **2**-337, **2**-393, **3**-78, **3**-117, **3**-157, **3**-159, **3**-217, **10**-1729, **13**-440, **13**-543, **13**-582, **14**-328, **16**-1586
Dieffenbacher, A. **15**-2423
Diego-Castro, M.J. **15**-2206
Diéguez, M. **10**-1522
Diehl, W. **16**-300
Diehm, M. **4**-76
Diels, G. **13**-196
Diesen, J.S. **15**-471
Dieter, R.K. **10**-550, **10**-1335, **10**-1343, **10**-1829, **15**-359, **15**-1163, **16**-891, **16**-1002
Dietrich-Buchecker, C.O. **3**-210, **3**-217, **3**-218, **19**-1715
Dietrich, B. **3**-124, **4**-251, **4**-253
Dietrich, C.O. **12**-226
Dietsche, T.J. **2**-48, **2**-49, **10**-1524
Dietz Jr., A.G. **13**-788
Dietz, F. **2**-272
Dietze, P. **10**-376
Dietze, P.E. **10**-75, **10**-295
Dietzel, P. **13**-725
Diev, V.V. **15**-2116
Dieva, S.A. **19**-800
Díez-Barra, E. **7**-118
Díez-González, S. **19**-981
Díez, B.R. **10**-1435
DiFate, V.G. **10**-211
Differding, E. **12**-142
DiGiuseppe, S. **15**-245
Dignam, C.F. **2**-108
Diguez, M. **15**-452
Dijksman, A. **19**-167, **19**-218
Dijkstra, G. **10**-719
DiLabio, G.A. **2**-26, **2**-413
Dill, K. **18**-83
Dillard, D.E. **10**-126
Dilley, G.J. **4**-126
Dilling, W.L. **15**-2371, **15**-2447, **19**-894
Dillinger, S. **12**-303
Dillon, R.L. **8**-48, **10**-30
Dilworth, B.M. **19**-1757
DiMagno, S.G. **9**-92
Dimas, L. **16**-1003
Dimbacher, T. **8**-94
DiMichele, L. **16**-998
Dimitrov, V. **16**-606
Dimock, S.H. **10**-1448, **15**-1140
Dimonie, M. **18**-807
Dimroth, K. **10**-461, **10**-476, **10**-477, **10**-478, **19**-284
Dinadayalane, T.C. **2**-401, **2**-402
Dinan, F.J. **11**-625, **17**-461
Dinér, P. **8**-225, **15**-1409
Diner, U.E. **19**-1370
Ding, F. **8**-7
Ding, H. **16**-893, appendixa-28
Ding, J. **15**-1721, **16**-743, **16**-944, **19**-686
Ding, K. **10**-977, **10**-1529, **13**-244, **13**-279, **15**-2323, **15**-2330, **19**-1014
Ding, L.-S. **10**-701, **16**-408
Ding, L. **16**-631
Ding, M.-X. **19**-180
Ding, Q. **13**-321
Ding, R.-B. **16**-53
Ding, R. **15**-1066, **16**-915, **18**-817
Ding, X. **15**-2076
Ding, Y. **5**-301
Ding, Z.-d. **10**-1476, **19**-1024
Ding, Z. **12**-478, **13**-620
Dingerdissen, U. **16**-317, **16**-352
Dingle, T.W. **2**-308
Dinh, D.C. **10**-1749
Dinjus, E. **16**-879
Dinner, A. **18**-204
Dinnocenzo, J.P. **1**-107, **18**-622
Dinoi, A. **15**-1924, **19**-293, **19**-490
Diogo, H. P. **2**-362
DiPietro, J. **15**-1475
DiProfio, P. **10**-438
Dirk, S.M. **19**-731
Dirkx, I.P. **13**-79
Discordia, R.P. **4**-200, **16**-1947
Distaso, M. **16**-1951
Distler, H. **10**-860
Ditrich, K. **10**-1522, **13**-104, **16**-1064
Dittmer, D.C. **4**-200, **15**-21, **17**-369
Dittmer, D.L. **16**-584
DiValentin, C. **15**-2119, **19**-123
Dive, G. **11**-356
Diver, S.T. **15**-848, **15**-2669, **18**-888, **18**-889, **18**-890
Diversi, P. **4**-67, **18**-882
Diwakar, M.M. **19**-1181
Dix, D.T. **5**-178
Dix, I. **17**-18
Dixneuf, P.H. **15**-393, **15**-278, **15**-281, **16**-430, **18**-835, **19**-1473
Dixon, D.A. **4**-242, **8**-240
Dixon, D.J. **10**-1655
Dixon, J.A. **13**-735
Dixon, J.E. **10**-391
Dixon, J.M. **4**-380
Dixon, N.J. **10**-1613
Diyabalanage, H.V.K. **12**-376
Djakovitch, L. **13**-590
Djerassi, C. **4**-22, **4**-131, **17**-131, **19**-67, **19**-143
Dlugy, C. **19**-992
Dmitrenko, O. **4**-432, **4**-433, **4**-434
Dmitrienko, G.I. **2**-57
Dmitriev, D.E. **4**-373, **16**-135
Dmitrieva, L.G. **12**-744
Dneprovskii, A.N. **14**-80
Dneprovskii, A.S. **6**-32, **14**-148, **14**-177
do Amaral, A.T. **16**-1671
do Amaral, L. **16**-281, **16**-288
Do, H.-Q. **13**-478
Do, Y.-K. **15**-1589
Do, Y. **18**-889
Doad, G.J.S. **16**-1338
Dobashi, S. **15**-2357
Dobbs, A.P. **16**-1566
Dobi, P. **10**-461, **10**-475
Döbler, C. **15**-1901, **19**-231
Dobler, M. **2**-296
Dobrovolny, M. **2**-229
Dobson, H.K. **18**-645
Doca, N. **16**-2191
Dockendorff, C. **15**-589
Dockery, K.P. **18**-62
Doctorovich, F. **5**-389, **12**-561, **13**-687, **16**-864
Doda, K. **10**-741, **16**-1596
Dodd, R.H. **15**-2068
Dodda, R. **16**-1084
Dodderel, D. **4**-342
Dodonov, V.A. **12**-461
Dodsworth, D.J. **16**-1897
Doecke, C.W. **4**-463, **10**-165
Doehring, A. **16**-1429
Doering, W. von E. **2**-175, **2**-182, **10**-15, **12**-222, **12**-366, **12**-397, **15**-2432, **15**-2442, **15**-2541, **18**-200, **18**-403, **18**-579, **18**-625, **18**-658, **18**-670, **18**-677, **19**-156
Dogadina, A.V. **15**-1413, **16**-1364
Dogan, O. **10**-905, **16**-667, **16**-1215
Doherty, A.M. **19**-62
Doherty, M.M. **10**-145

Doherty, R.M. **3**-19, **10**-460, **10**-463, **10**-474, **10**-479
Dohi, T. **19**-198
Dohle, W. **10**-1384
Dohmaru, T. **19**-1474
Dohner, B.R. **17**-30
Döhnert, D. **5**-299
Doi, H. **15**-1211, **15**-1395
Doi, J.T. **19**-827
Doi, M. **19**-1574
Doi, T. **16**-1850
Dolak, T.M. **10**-1823
Dolan, S. **16**-1295
Dolata, D.P. **15**-2207
Dolbier Jr., W.R. **4**-65, **5**-326, **12**-179, **14**-87, **15**-1304, **15**-2374, **15**-2429, **16**-717, **16**-830, **18**-493, **18**-517, **18**-544
Dolbier, D.W. **15**-2429
Dolbier, W.B. **18**-600
Dolby-Glover, L. **13**-261
Dolby, L.J. **19**-1390
Doldouras, G.A. **19**-1501
Dolenc, D. **5**-323, **12**-130, **15**-1697
Dolenko, A. **18**-949
Doleschall, G. **16**-1769, **19**-425
Dolhem, E. **10**-1956
Dolhem, E. **10**-1963
Doll, K.M. **9**-110
Dollat, J. **10**-1504
Dolle, R.E. **11**-489, **15**-2140
Doller, D. **19**-489
Dolling, U.H. **12**-759
Dollinger, H. **10**-1828
Dolliver, D.D. **4**-230
Dolman, S.J. **16**-428, **18**-829
Dolphin, J.M. **16**-1264
Domain, R. **8**-236
Domalski, E.S. **1**-99
Domalski, M.S. **15**-886
Dombrovskii, A.V. **13**-819
Dombrowski, G.W. **1**-107
Domen, K. **5**-70
Domine, M.E. **19**-951
Domingo, L.R. **15**-2173, **15**-2181, **15**-2242, **15**-2282, **15**-2292, **15**-2317
Dominguez-Fernandez, B. **15**-1930, **15**-1933
Dominguez, C. **13**-473
Domínguez, E. **15**-1157, **15**-2099, **16**-351
Domínguez, G. **15**-1549, **15**-1558, **15**-1561, **15**-1563, **15**-2683
Dominguez, R.M. **17**-137, **17**-151
Dommisse, R. **13**-204
Dommisse, R.A. **13**-190
Donahue, N.M. **6**-10
Donald, D.S. **18**-39
Donaruma, L.G. **18**-361
Donati, D. **16**-1765, **16**-2224
Donelson, J.L. **10**-974
Dong, C. **15**-1579, **19**-171
Dong, D.-X. **13**-434
Dong, D. **16**-202
Dong, D.C. **10**-481
Dong, G. **10**-1571, **15**-1522, **16**-758
Dong, G.R. **15**-149
Dong, L. **15**-1272
Dong, M. **14**-212
Dong, Q. **10**-991
Dong, T.-W. **15**-531, **15**-610, **16**-592
Dong, X.-Q. **16**-413
Dong, X. **19**-1017
Dong, Y.-W. **15**-1057
Dong, Y.-Z. **19**-1674
Dong, Z.-B. **10**-1463
Dong, Z.-M. **19**-383
Dong, Z.-R. **19**-956
Dönges, R. **2**-200
Donnelly, D.M.X. **12**-549
Donnelly, S.J. **19**-1427
Donnoli, M.I. **4**-115
Donohoe, G. **16**-172
Donohoe, T.J. **15**-417, **15**-566, **15**-568, **15**-1816, **18**-820, **19**-936
Donohue, J.A. **16**-1698
Donovan, D.J. **5**-22, **5**-94, **10**-214
Donovan, P.M. **1**-74
Donovan, T.A. **10**-1292
Donovan, W.H. **5**-209
Donow, F. **4**-179
Donzel, A. **16**-1956
Dooleweerdt, K. **13**-234
Doomes, E. **17**-348
Doowa, N. **11**-303
Döpp, D. **18**-921
Dorange, I. **15**-875
Dordick, J.S. **19**-223
Dore, D.D. **16**-666
Doré, M. **15**-329, **16**-261
Dorff, P. **16**-1380
Dorfman, E. **18**-403
Dorfman, L.M. **5**-116
Dorigo, A.E. **4**-307
Doris, E. **10**-1952, **12**-103, **13**-659, **15**-600, **17**-212, **19**-872
Dormer, P.G. **9**-112, **13**-120, **13**-573, **13**-673
Dorn, C.R. **11**-398
Dorn, H.C. **2**-405
Dorofeenko, G.N. **16**-252
Dorofeev, A.S. **16**-135, **19**-1666
Doron'kin, V.N. **13**-761
Dörr, F.A. **14**-362
Dörr, M. **18**-912
Dorrell, F.J. **12**-21
Dorsch, H. **4**-505
Dorta, R. **15**-1269, **19**-417
Dorton, D. **10**-1408
Dorwin, E. **13**-21
Dory, Y.L. **15**-2172
dos Santes, L.M.F. **13**-387
dos Santos, C. **19**-355
dos Santos, R.M.B. **1**-104
Dostal, J.M. **17**-55
Dostrovsky, I. **18**-5
Dosunmu, M.I. **16**-29
Dötz, K.H. **15**-2656
Dou, H.-N. **19**-83
Dou, H.J. **13**-822, **13**-830
Douberly, G.E. **5**-10
Doubleday Jr., C. **5**-299, **10**-1443
Doucet, H. **10**-1882, **13**-382, **13**-409, **13**-429, **13**-486, **13**-528, **13**-590, **13**-607, **14**-363, **16**-647, **16**-1910
Doucet, R.J. **19**-129
Douek, M. **2**-258
Douelle, F. **15**-1088
Dougharty, K.W. **15**-4, **15**-34
Dougherty, D.A. **3**-81, **11**-20
Dougherty. R.C. **1**-2
Douglas E. **16**-1497
Douglas, A.W. **18**-770
Douglas, C.J. **10**-1051, **18**-861
Douglas, D.E. **6**-44, **16**-2194
Douglas, J. **11**-249
Douglas, J.E. **16**-1666
Douglas, K.T. **16**-1674, **16**-1973
Douglas, T.A. **6**-29
Douglass, D.C. **10**-144
Douglass, J.E. **11**-638
Douglass, M.R. **15**-2027
Doumaux Jr., A.R. **14**-271, **19**-577
Dounay, A.B. **13**-435
Dourado, J. **16**-989
Douraghi-Zadeh, K. **16**-2187
Doussot, J. **10**-1075, **12**-354
Dow, R.L. **19**-136
Dowd, P. **10**-1947, **15**-1325, **18**-183, **18**-184
Dowd, S.R. **10**-1796
Dowd, W. **10**-461
Dowdy, E.D. **15**-807, **16**-1942
Doweyko, A.M. **12**-194
Dowle, M.D. **15**-1710
Dowling, J.P. **12**-87, **12**-446
Downey, C.W. **16**-551, **16**-1092, **16**-1195
Downie, I.M. **19**-1292
Downing, J.W. **4**-518, **4**-519
Downing, S. **16**-109
Doyarenko, M.N. **4**-486
Doye, S. **15**-328, **15**-350, **15**-366
Doyle, A.G. **10**-1218, **10**-1105
Doyle, D.L. **12**-259
Doyle, M.J. **18**-896
Doyle, M.P. **10**-784, **10**-1254, **11**-267, **12**-360, **12**-363, **12**-367, **12**-387, **12**-390, **12**-393, **13**-803, **13**-820, **14**-232, **14**-396, **15**-741, **15**-1600, **15**-2057, **15**-2250, **15**-2475, **15**-2477, **15**-2497, **15**-2505, **15**-2516, **15**-2521, **15**-2529, **15**-2580, **16**-161, **18**-252, **19**-96, **19**-136, **19**-567, **19**-570, **19**-641, **19**-1288, **19**-1427, **19**-1550

Doyle, T.D. **18**-550
Doyon, J.B. **4**-475
Drabicky, M.J. **10**-548
Drabowicz, J. **4**-48, **10**-865, **19**-773, **19**-799, **19**-803, **19**-1583
Draffehn, J. **9**-43
Dräger, G. **16**-422
Drâghici, C. **15**-2420
Drago, R.S. **3**-22, **8**-236, **10**-434
Dragutn, V. **18**-807
Drahowzal, F.A. **11**-344
Drake, C.A. **4**-537
Drake, J. **12**-99
Drake, R.A. **18**-491
Dralants, A. **2**-271
Dransfeld, A. **2**-116, **18**-618
Draper, J.D. **10**-674
Draper, T.L. **13**-374
Drapo, J.R. **19**-1631
Drauz, K.-H. **15**-1958, **15**-1962
Drauz, K. **10**-1089, **15**-648, **19**-1063
Drechsler, K. **15**-2378
Drees, M. **19**-458
Dreher, E. **13**-789
Dreher, S.D. **13**-573
Dreiding, A.S. **4**-41, **12**-32, **15**-2423
Drent, E. **15**-1497
Drenth, W. **6**-49, **16**-1887
Dresely, S. **16**-462
Dreßel, B. **2**-179
Drew, G.M. **4**-353
Drewello, T. **19**-59
Drewer, R.J. **7**-49
Drewes, R. **18**-597
Drewes, S.E. **16**-790, **16**-791
Drexler, H.-J. **15**-647, **15**-648
Driessen, P.B.J. **10**-165
Driver, T.G. **15**-771
Drobnica, L. **16**-1868
Dronov, V.I. **16**-377
Drowns, M. **10**-1031
Drozd, J.C. **19**-390
Drozd, V.N. **10**-1556, **13**-865
Drozdova, T.I. **15**-1739
Drtina, G.J. **10**-1219
Drucker, G.E. **2**-157
Druelinger, M.L **1**-63
Druet, L.M. **16**-1703
Druey, J. **18**-423
Druliner, J.D. **15**-1625
Drummond, C.J. **9**-119
Drumright, R.E. **4**-442
Drury III, W.J. **12**-175, **15**-2386, **16**-2226
Dryuk, V.G. **15**-1869
D'Souza, C.J.E. **4**-324
D'Souza, M.J. **10**-167
D'Souza, V.T. **15**-2005
Du Bois, J. **12**-231, **12**-232, **12**-233, **15**-403, **15**-2059, **15**-2068, **19**-457
du Mesnil, F.-X. **15**-833, **15**-2266
du Vigneaud, V. **19**-1499
Du, C.F. **13**-342
Du, D.-M. **19**-971, **19**-1021, **19**-1261
Du, H. **15**-2041, **15**-2323, **15**-2562, **15**-2564
Du, J. **12**-114, **15**-2412, **16**-157
Du, L.-H. **13**-397
Du, W. **15**-155
Du, X. **13**-713, **15**-1253, **16**-744
Duan, C.-y. **3**-138
Duan, H.-F. **16**-742, **16**-746, **16**-943, **16**-1560, **19**-1014
Duan, H. **16**-324, **19**-234
Duan, J. **12**-179
Duan, W.-S. **4**-419
Duan, W.-L. **15**-1269, **15**-1427
Duan, W. **15**-1106
Duan, X.-h. **10**-1520
Duan, X.-H. **11**-225
Duan, X.-F. **19**-1640, **19**-1683
Dubac, J. **7**-120, **10**-1152, **11**-218, **11**-438, **16**-2142, **19**-1300
Dubbaka, S.R. **13**-331, **16**-2299
Dubé, D. **10**-1050
Dube, H. **16**-470
Dubé, P. **15**-522
Dubey, A. **10**-1134, **19**-158
Duboc, C. **10**-372
DuBois, J. **19**-509
Dubois, J.E. **2**-435, **4**-307, **9**-21, **9**-74, **9**-21, **10**-1441, **10**-1443, **10**-1864, **12**-95, **12**-694, **14**-460, **15**-14, **15**-69, **15**-98, **16**-507, **16**-2017, **16**-2021, **16**-2157, **17**-162
Dubois, L.H. **12**-636
Duboudin, J.G. **15**-888
Dubree, N.J.P. **13**-737
Dubreuil, J.F. **15**-2125
Dubrova, L.N. **11**-612
Dubuis, R. **15**-462
Duce, P.P. **10**-41
Ducep, J.-B. **15**-2335
Ducep, J. **10**-1840, **12**-409
Ducep, J.B. **10**-1329, **10**-1818
Duchêne, A. **10**-1883, **12**-281, **12**-307
Duchin, L. **16**-1645
Duckett, S.B. **15**-493, **15**-1621
Duclos Jr., R.I. **13**-827
Ducom, J. **5**-173
Ducoux, J.-P. **10**-1601
Ducray, R. **11**-136
Dudás, J. **19**-1206
Duddeck, H. **4**-479
Duddu, R. **16**-1879
Dudfield, P. **10**-1745
Dudinskaya, A.A. **15**-2176
Dudley, G.B. **10**-711, **10**-714, **15**-1142, **16**-480, **18**-272
Dudman, C.C. **19**-1114
Dueno, E.E. **10**-758, **16**-180
Duesler, E. **15**-2420
Duesler, E.N. **4**-194
Duetz, W. **19**-539
Duetz, W.A. **19**-540
Düfert, A. **15**-1928
Duff, J.L. **10**-109
Duff, K. **16**-954
Duffey, D. **18**-948
Duffin, H.C. **19**-608
Duffley, R.P. **14**-421
Duffy, L.A. **19**-1065
Duffy, R. **12**-360
Dufková, L. **16**-776, **16**-778
Dufour, S. **12**-441
Dufresne,Y. **10**-632
Dugave, C. **15**-147
Duggan, M.E. **16**-173
Duggan, P.J. **18**-61
Duguay, B. **6**-47
Duhaime, R.M. **12**-73
Duhamel, L. **10**-1340, **17**-320
Duhamel, P. **16**-257, **16**-258
Duhl-Emswiler, B.A. **16**-1384
Duijvestijn, M.J. **5**-233
Duisberg, C. **11**-397
Dujardin, R. **12**-597
Duke, A.J. **15**-2425, **17**-427, **17**-499, **17**-502, **17**-510, **17**-516
Duke, C.V.A. **13**-167, **13**-263
Dull, D.L. **4**-107
Dumas, F. **15**-1108, **16**-1126
Dumeunier, R. **16**-1723
Dumont, W. **15**-1192, **18**-134, **18**-245
Dumpis,Yu.Ya. **19**-1267
Dumsha, T.C. **16**-1698
Duñach, E. **15**-1506, **16**-879, **18**-152, **19**-1364, **19**-1480
Duncan, A.P. **15**-1204
Duncan, F.J. **5**-354
Duncan, J.A. **18**-647, **18**-744
Duncan, J.H. **5**-196
Duncan, M.A. **5**-10
Duncan, M.P. **19**-821
Duncan, P. **14**-48, **14**-368
Duncan, S.C. **12**-378
Duncan, S.M. **7**-106
Dunet, G. **16**-665
Dunetz, J.R. **12**-553, **15**-2255
Dunford, H.B. **2**-439
Dunford, J.A. **12**-525
Dunham, K.K. **16**-560
Dunham. L.L. **19**-890
Dunitz, J.D. **2**-296, **2**-311, **3**-51, **4**-330, **4**-400, **4**-473, **4**-474, **5**-201
Dunkelblum, E. **15**-683, **15**-686
Dunkin, I.R. **5**-212
Dunlap, M.S. **19**-1651
Dunlap, R.P. **19**-1739
Dunlop, A.K. **3**-168
Dunn, A.D. **15**-2118, **16**-181, **16**-426, **16**-1306
Dunn, G.E. **12**-668

Dunn, J. A. **5**-414
Dunn, K. **12**-643
Dunne, E.C. **16**-1325
Dunne, K. **5**-62, **18**-797
Dünnebacke, D. **5**-249
Dunnigan, D.A. **10**-1668
Dünnwald, T. **16**-1590
Dunoguès, J. **12**-452, **15**-1246, **16**-763
Dunsmore, C.J. **19**-1148
Duong, H.A. **15**-2636
Duong, T. **19**-590
Dupau, P. **7**-130
Duplais, C. **10**-1366
Duplessis, M. **10**-1025, **13**-340
Dupont, J. **9**-122, **13**-308, **13**-379, **13**-447
Dupont, R. **10**-1537
Dupré, D. **15**-1235
DuPriest, M.T. **10**-1841
Dupuis, C. **19**-1600
Dupuis, D. **10**-1744
Dupuy, C. **15**-1213
Dupuy, W.E. **10**-216
Duraisamy, M. **5**-382
Durán, J. **15**-2667
Duran, M. **2**-9, **2**-170, **10**-879
Durandetta, J.L. **10**-1851
Durandetti, M. **10**-1485, **13**-311, **13**-355, **16**-709, **16**-715
Durbut, P. **15**-1917
Durden, D.A. **16**-346
Durham, D.L. **14**-254
Duroure, L. **13**-611
Durr, H. **2**-55, **5**-436, **7**-49
Durr, R. **15**-1381
Durst, H.D. **3**-106, **10**-493
Durst, T. **4**-229, **5**-105, **5**-117, **5**-126, **5**-152, **5**-207, **5**-208, **8**-17, **10**-1520, **10**-1763, **12**-190, **12**-411, **12**-443, **13**-178, **16**-1058, **16**-1251, **16**-1441, **16**-1445, **16**-2149, **19**-614
Duschek, A. **19**-188
Dushenko, G.A. **18**-574
Dusich, C.L. **12**-175
Dusold, L.R. **17**-264
Dussault, P. **19**-697
Dussault, P.H. **19**-339, **19**-1403
Dussin, G. **10**-1470
Dustman, C.K. **5**-105
Duthaler, R.O. **16**-663
Dutler, H. **18**-113
Dutler, R. **10**-296
Dutly, A. **11**-99
Dutra, G.A. **10**-1417
Dutron-Woitrin, F. **19**-1772
Dütsch, H.R. **14**-110
Dutta, J. **15**-544
Dutta, M.P. **19**-1669
Dutta, P. **10**-1293, **16**-1627, **16**-1943
Dutta, S. **11**-242, **11**-302
Dutta, V.P. **15**-1687
Duursma, A. **15**-1208, **15**-1278
Duval, D. **15**-39
Dux III, F. **19**-1283
Dux, F.J. **10**-827
Duygu, A.N. **16**-1031
Dvorak, C.A. **13**-517
Dvorák, D. **15**-958, **16**-2222
Dvořáková, H. **19**-800
Dvoretzky, I. **12**-405, **19**-402
Dvorko, G.F. **10**-40, **10**-437
Dvornikova, E. **11**-280
Dworkin, A. **2**-38
D'yachenko, A.I. **5**-399
Dyadyusha, G.G. **15**-93
D'yakonov, I.A. **2**-230
Dyall, L.K. **5**-436
Dyatkin, B.L. **15**-73
Dybala-Defratyka, A. **10**-4, **10**-1930
Dyckman, A.J. **15**-811
Dye, J.L. **15**-572, **19**-1607
Dyker, G. **13**-329
Dykstra, R.R. **5**-190
Dyson, P.J. **9**-120, **15**-553, **15**-558
Dyumaev, K.M. **8**-234
Dzhemilev, U.M. **15**-738, **15**-740, **15**-889
Dzielenziak, A. **19**-245
Dzierba, C.D. **16**-1540
Dzyuba, S.V. **9**-139

Eaborn, C. **11**-12, **11**-33, **11**-88, **11**-89, **12**-45, **12**-499, **13**-685
Eachus, S.W. **2**-286
Eaddy, J.F. **16**-1891
Eagon, S. **19**-973
Earl, G.W. **10**-301
Earl, H.A. **10**-408
Earle, M.J. **9**-120
Earle, R.B. **13**-7
Early, T.R. **13**-189, **13**-392, **13**-501
Easdon, J.C. **15**-4, **15**-34
Eash, K.J. **18**-139
Eason, R.G. **2**-77
East, S.P. **4**-246
Eastgate, M.D. **16**-1173
Eastham, G.R. **19**-1473
Eastham, J.F. **18**-1, **18**-125, **18**-186, **18**-197
Easton, C.J. **3**-196, **15**-105
Eastwood, F.W. **18**-553, **18**-554
Easwar, S. **16**-1084
Eaton, D.F. **7**-43
Eaton, B.E. **15**-2587
Eaton, D.L. **15**-2621
Eaton, J.T. **16**-104, **16**-1886
Eaton, P.E. **4**-462, **4**-464, **4**-541, **7**-68, **10**-54, **13**-732, **15**-2448, **18**-67, **18**-562, **18**-897, **18**-898, **19**-750
Eatough, D.J. **3**-106
Ebata, K. **4**-524, **4**-539
Ebbesen, T.W. **18**-234
Ebeling, G. **13**-379
Eberhard, J.K. **11**-474
Eberhard, M.R. **13**-386
Eberhardt, G.G. **15**-756
Eberhardt, W.H. **16**-30
Eberius, K.W. **2**-252
Eberle, M.K. **16**-1106
Eberlein, T.H. **10**-1049
Eberlin, M.N. **11**-75, **12**-292, **16**-1412, **18**-692
Ebersberger, J. **11**-360
Eberson, L. **6**-30, **8**-194, **11**-104, **14**-456, **19**-4
Ebert, C. **17**-158
Ebert, G.W. **10**-1292, **12**-626
Ebitani, K. **15**-1890, **15**-1953
Ebner, M. **16**-1941
Ebrahim, S. **15**-1959
Ebrahimi, S. **10**-843, **10**-981
Ebrahimian, G.-R. **16**-143, **16**-148, **16**-155
Ebrahimzadeh, F. **10**-1169
Eby, P. **15**-162
Eby, P.S. **19**-1701
Echavarren, A.M. **10**-1548, **12**-261, **13**-376, **13**-445, **13**-541, **13**-613, **15**-812, **15**-853, **15**-2269, **15**-2375, **15**-2517, **15**-2620, **16**-1562, **19**-1168
Echegoyen, L. **5**-222
Echevarren, E.M. **10**-1434
Eckart, M.D. **18**-40
Eckelt, R. **16**-1865
Ecker, J.R. **15**-1978
Ecker, R. appendixa-22
Eckert-Maksić, M. **2**-88, **2**-383, **8**-93, **11**-82
Eckert, C.A. **15**-651
Eckert, M. **19**-231
Eckes, H. **15**-2232
Eckes, L. **5**-68
Eckhardt, W. **1**-47
Eda, T. **16**-1316
Eda, Y. **12**-686
Edelstein, J. **4**-83
Eder, U. **16**-1120
Edgar, M. **4**-326
Edge, D.J. **18**-72
Edgecombe, K.E. **1**-32
Edgington, D.N. **10**-429
Edman, C. **16**-290
Edmison, M.T. **14**-147
Edmonds, P. **7**-71
Edmondson, P.B. **1**-103
Edward, J.T. **8**-136, **8**-179, **16**-97, **19**-1450
Edwards Jr., W.R. **11**-466, **16**-2054
Edwards, A. **8**-162
Edwards, A.G. **10**-461, **10**-475
Edwards, A.J. **16**-1330
Edwards, B.E. **16**-183, **16**-186
Edwards, G.L. **15**-1821
Edwards, J.D. **12**-363
Edwards, J.O. **10**-369, **15**-1888, **15**-1924, **15**-1948, **19**-10

Edwards, J.P. **15**-2557, **16**-970
Edwards, K. **15**-1814
Edwards, M.L. **10**-925
Edwards, O.E. **10**-283
Edwards, S.D. **18**-836
Edwards, W.D. **18**-678
Eeckhaut, A. **19**-1314
Eeshwaraiah, B. **15**-1456
Effenberger, F. **10**-712, **10**-1089, **11**-14, **11**-50, **11**-214, **11**-380, **11**-458, **11**-474, **11**-584, **13**-88, **13**-840
Effio, A. **16**-291, **18**-73
Efimova, I.V. **12**-552, **15**-393
Efraty, A. **2**-252
Efremov, Yu.Ya. **19**-800
Efros, L.S. **2**-136
Egami, H. **19**-800
Egberink, R.J.M. **9**-86
Egberts, J.B.F.N. **15**-2210
Eggensperger, H. **10**-1137
Egger, K.W. **17**-128, **17**-495
Eggerding, D. **2**-381
Eggers, M.D. **10**-322
Eggestad, J. **3**-112
Egi, M. **11**-472, **16**-2091, **18**-274
Egli, H. **19**-450
Egli, M. **4**-169
Egli, R.A. **19**-1165
Egorochkin, A.N. **3**-42, **9**-20
Eguchi, S. **10**-1358
Ehler, D.F. **19**-1489
Ehmann, W.J. **15**-496
Eholzer, U. **17**-481
Ehrenberg, M. **1**-70
Ehrenkaufer, R.E. **16**-350, **19**-1196
Ehrenson, S. **9**-37, **9**-47, **9**-51, **9**-54
Ehrentraut, A. **13**-499
Ehrlich, P. **16**-1310
Eibler, E. **15**-2225
Eichberger, M. **15**-325
Eichelmann, H. **10**-864
Eichenauer, H. **4**-147
Eicher, T. **2**-229, **16**-455
Eichhorn, I. **16**-120, **16**-893
Eickemeyer, D.B. **13**-869
Eidam, H.S. **15**-1206
Eidam, P. **15**-1206
Eidenschink, R. **15**-2166
Éidus, Ya.T. **10**-1975
Eierdanz, H. **15**-95
Eigen, M. **8**-109
Eigenmann, E.W. **17**-123
Eigenmann, H.K. **14**-73
Eilbracht, P. **15**-1606
Eilers, F. **10**-1608
Einhorn, C. **10**-504, **10**-1219, **15**-187 **16**-861
Einhorn, J. **10**-504, **13**-108, **15**-187, **16**-861, **16**-1011
Einstein, F.W.B. **2**-266
Eisch, J.J. **11**-224, **15**-737, **15**-737, **15**-745, **15**-888, **15**-2642, **15**-2644, **16**-244, **16**-485, **18**-433, **18**-448
Eisele, D. **18**-864
Eisen, M.S. **16**-1013, **19**-1745
Eisenberg, R. **5**-232
Eisenbraun, E.J. **19**-551
Eisenhardt, W. **16**-2206
Eisenschmid, T.C. **5**-232
Eisenstein, O. **1**-51, **4**-142, **15**-2645, **18**-892, **19**-1001
Eisenthal, R. **19**-446, **19**-606
Eisler, S. **17**-317
Eisner, A. **16**-1993
Eissenstat, M.A. **10**-1760
Eiter, K. **17**-305
Ejiri, E. **2**-332, **2**-333, **2**-335, **2**-359
Ek, F. **13**-760, **13**-812
Eklov, B.M. **19**-881
Eklund, L. **15**-2223
Eklund, R. **18**-379
Ekoue-Kovi, K. **14**-294, **16**-2022
Eksterowicz, J.E. **14**-72
Ekström, J. **16**-553
Ekwurieb, N.N. **19**-1112
El-Alaoui, M. **2**-435
El-Saidi, M. **5**-424
El-Sayed, M.A. **7**-26
El-Fekky, T.A. **10**-1981
El-Din, A.M.N. **11**-173
El-Hiti, G.A. **11**-277
El-Bouz, M. **15**-1190, **15**-1192
El-Ghanam, A. **15**-1520
El-Quisairi, A.K. **15**-1660
El-Bassiouny, F.A. **16**-1188
El-Newaihy, M.F. **16**-1188
El-Din, G.N. **16**-1335
El-Shazly, M. **16**-324, **16**-360
El-Hiti, G.A. **16**-589
El-Telbany, F. **19**-1471
El-Mowafy, A.M. **19**-1506
El Ali, B. **12**-786, **15**-1520, **15**-1582
El Bialy, S.A.A. **15**-1347
El Gharbi, R. **16**-1384
El Kaim, L. **16**-378, **16**-1845, **16**-2260, **19**-1246
El Khadem, H. **16**-280
Elad, D. **15**-1471
Elam, C. **8**-162
Elam, E.U. **16**-2202
Elbl, K. **3**-33
Eldin, S. **5**-121, **12**-60
Eldred, S.E. **16**-1842
Elemes, Y. **14**-260, **14**-262
Eleveld, M.B. **12**-109
Elgemeie, G.H. **15**-1863
Elgendy, S. **12**-344
Elguero, J. **2**-383, **2**-471, **2**-479, **8**-14, **8**-245, **19**-1334
Elhamifar, D. **16**-118
Elian, M. **15**-2420
Eliel, E.L. **1**-94, **3**-213, **4**-1, **4**-18, **4**-101, **4**-102, **4**-116, **4**-117, **4**-118, **4**-128, **4**-139, **4**-140, **4**-141, **4**-144, **4**-155, **4**-160, **4**-162, **4**-259, **4**-262, **4**-268, **4**-270, **4**-272, **4**-283, **4**-328, **4**-350, **4**-356, **4**-363, **4**-364, **4**-367, **4**-369, **4**-370, **4**-372, **4**-374, **4**-375, **4**-389, **4**-394, **4**-444, **6**-46, **9**-14, **10**-120, **13**-831, **14**-40, **16**-5, **19**-1002, **19**-1369, **19**-1454
Eliev, S. **19**-1001
Elings, J.A. **18**-385
Elinson, M.N. **12**-711, **16**-135, **19**-1666
Eliseenkov, E.V. **6**-32, **14**-148
Eliseenkova, R.M. **19**-800
Eliseev, O.L. **10**-1994
Elix, J.A. **2**-300, **18**-401
Elizarov, A.M. **3**-199
Elkik, E. **16**-1271
Ell, A.H. **19**-214
Ellenberger, D.H. **10**-1467
Ellenberger, S.R. **15**-1853
Ellensohn, R.M. **16**-700
Ellerd, M.G. **16**-1766, **19**-699, **19**-1117, **19**-1382, **19**-1627
Ellern, D.A. **2**-404
Ellervik, U. **11**-291
Ellestad, K.E. **15**-918
Elliott, G.I. **13**-649, **13**-650
Elliott, R.C. **13**-820
Elliott, S.P. **15**-2419, **15**-2431
Ellis, D.D. **4**-258
Ellis, D.J. **15**-553, **15**-558
Ellis, G.P. **13**-275
Ellis, J.E. **16**-1113
Ellis, R.J. **16**-1293
Ellis, W.W. **16**-1557
Ellison, F.O. **1**-3
Ellison, G.B. **1**-29, **1**-95, **2**-26, **5**-139, **5**-284, **5**-286, **10**-522, **17**-126
Ellison, J.J. **5**-183
Ellman, J.A. **11**-417, **15**-967, **15**-2250, **16**-306, **16**-928, **16**-934, **16**-935, **16**-943, **16**-945, **16**-1222, **16**-1936, **19**-807
Ellmer, U. **19**-993
Ellsworth, B.A. **18**-368
Ellsworth, E.L. **10**-1428, **10**-1448, **12**-600, **15**-742, **15**-1140, **15**-1162
Ellzey Jr., M.L. **2**-143
Elmasmodi, A. **18**-413
Elmore, S.W. **18**-631
Elmorsy, S.S. **10**-1085
Elofson, R.M. **13**-774, **13**-826, **13**-835
Elphimoff-Felkin, I. **19**-1342
Elpiner, I. E. **7**-81
Elschenbroich, C. **5**-152
Elsenbaumer, R.L. **16**-530

Elsevier, C.J. **10**-1422, **10**-1436
Elsinger, F. **10**-1246
Elsom, L.F. **14**-412, **14**-414
Elson, I.H. **14**-59
Elvidge, J.A. **11**-116, **16**-419
Elving, P.J. **8**-9, **8**-46
Elwahy, A.H.M. **3**-152
Elworthy, T.R. **10**-1421, **15**-1460
El'yanov, B. **15**-998
Ema, T. **19**-993
Emami, R. **12**-79
Emblidge, R.W. **5**-57
Emch, J.D. **16**-1414
Emeigh, J. **10**-863
Emeric, G. **18**-349
Emerson, G.F. **2**-254
Emerson, M.T. **3**-12
Emmanuvel, L. **11**-288, **19**-621
Emme, I. **16**-794
Emmerich, D.J. **12**-304, **15**-290
Emmerson, D.P.G. **15**-1932, **16**-849
Emmons, W.D. **15**-1870, **16**-1360, **18**-394
Emrani, J. **18**-729
Emrich, D.E. **15**-990
Emrich, R. **4**-458
Emrullahoglu, M. **13**-552
Emsley, J. **3**-13, **3**-32, **3**-49, **16**-450, **16**-1998
Enami, H. **12**-575
Enayat, E.I. **16**-1188
Encarnación, L.A.A. **15**-2366
Encina, M.V. **7**-51
Enders, D. **4**-147, **10**-780, **10**-1678, **10**-1767, **10**-1768, **10**-1833, **12**-138, **13**-385, **15**-1098, **15**-1463, **15**-1485, **15**-1910, **16**-75, **16**-888, **16**-1102, **16**-1591, **16**-1592, **18**-739, **19**-1269, **19**-1653
Endo, K. **2**-325, **15**-946, **15**-948, **16**-101
Endo, M. **10**-1325, **11**-249, **15**-1805
Endo, R. **4**-220
Endo, T. **5**-88
Endo, Y. **3**-15, **4**-285
Engberts, J.B.F.N. **2**-462, **9**-97, **10**-476, **14**-445, **15**-2210, **15**-2211, **15**-2214, **15**-2219, **19**-1243, **19**-1570
Engdahl, C. **18**-9
Engel, D.A. **18**-272
Engel, J. **4**-280
Engel, P.S. **5**-306, **5**-313, **5**-330, **7**-33, **14**-3, **14**-82, **14**-89, **14**-166, **17**-508
Engeldinger, E. **3**-189
Engelking, P.C. **5**-139, **5**-284, **5**-430
Engels, B. **15**-2122, **16**-12
Engenito Jr., J.S. **11**-188
Engesser, K.-H. **19**-542
England, D.C. **15**-1624
England, M.D. **18**-437
England, W.P. **18**-657
Engler, E.M. **10**-297
Engles, T. **13**-101
English Jr., J. **17**-414
English, R.B. **3**-210
Engman, L. **15**-1354, **15**-1335, **17**-388
Engman, M. **15**-471
Engqvist, M. **16**-1084
Enholm, E.J. **15**-1120, **19**-985
Enikolopiyan, N.S. **10**-525
Eno, S. **15**-1206
Enoki, Y. **10**-934
Enomoto, K. **8**-113, **16**-214
Enomoto, T. **16**-759
Enquist, P.-A. **13**-382
Enright, G.D. **5**-373
Enriquez-Rios, V. **10**-912
Enthaler, S. **19**-929, **19**-1037, **19**-1161
Entreken, E.E. **19**-1071
Entwistle, I.D. **15**-506, **19**-1086, **19**-1193, **19**-1214
Epa, W.R. **19**-521
Ephritikhine, M. **16**-1013, **19**-1699
Epifano, F. **12**-757, **15**-1482, **15**-1716, **15**-1758, **19**-1698
Epiotis, N.D. **5**-128, **15**-2299
Epple, G. **11**-458
Epple, R. **7**-130
Eppley, R.L. **13**-735
Epshtein, L.M. **3**-18, **8**-234
Epstein, L.M. **3**-5
Epstein, O.L. **10**-1570
Epstein, W.W. **19**-614
Equey, O. **10**-1626, **15**-1359, **17**-222
Erashko, V.I. **10**-514
Ercolani, G. **18**-55
Ercoli, M. **19**-1428
Erdélyi, M. **8**-89, **13**-601
Erdik, E. **10**-1360, **12**-536, **12**-583, **16**-474
Erdman, J. **10**-512
Erdmenger, T. **7**-114
Erfort, U. **15**-1474
Erhan, S.Z. **9**-110
Erhardt, J.M. **10**-1643
Erickson, A.S. **10**-1554
Erickson, B.W. **10**-580, **16**-1929, **16**-2152
Erickson, G.W. **10**-1768
Erickson, J.A. **15**-2448
Erickson, M.S. **2**-401
Erickson, W.F. **15**-886
Erickson, W.R. **13**-870
Ericsson, C. **15**-1335
Erikson, C.M. **8**-57
Eriksson, J. **10**-1930, **16**-491, **19**-1034
Eriksson, L.A. **2**-451
Eriksson, M. **10**-1404, **10**-1438
Eriksson, S.O. **16**-1697
Erivanskaya, L.A. **19**-1351
Eriyama, Y. **1**-13
Erker, G. **16**-265, **16**-1352
Erker, T. **13**-285
Erkkilä, A. **16**-1020
Erlandsson, P. **4**-180
Erman, M.B. **16**-310, **16**-2172
Erman, W.F. **18**-98
Ermer, O. **2**-241, **2**-324, **4**-525
Ermolaev, V.L. **7**-30
Ermolat'ev, D.S. **10**-918
Ernst, B. **10**-1150
Ernst, T.D. **11**-176
Erra-Balsells, R. **11**-297
Erre, G. **19**-929, **19**-1161
Ershadi, A. **11**-287
Ershov, B.A. **18**-145
Ershov, V.V. **2**-467, **2**-469, **18**-196
Ertas, E. **16**-218
Ertas, M. **16**-1059
Ervin, K.M. **10**-19
Érzyutova, E.I. **14**-316
Esashi, Y. **19**-1347, **19**-1348
Escale, R. **2**-481
Eschenmoser, A. **4**-37, **10**-18, **10**-751, **10**-1246, **12**-35, **15**-817, **16**-382, **16**-384, **17**-417, **17**-424, **17**-426, **18**-726
Eschner, M. **10**-461
Escolano, C. **15**-1336
Escorihuela, J. **16**-667
Escribano, A. **19**-1482
Esfandiari, S. **19**-1390
Esfandyari, M. **16**-338, **16**-1872
Eshdat, L. **4**-209
Eshghi, H. **11**-586, **16**-1749, **18**-353
Eskandari, M.M. **10**-1234
Esmaeili, A.A. **11**-287
Espenson, J.H. **10**-667, **19**-520, **19**-522, **19**-695, **19**-721
Espín, M. **13**-71
Espinet, P. **10**-1463, **12**-291, **13**-613
Espino, C. G. **12**-232, **12**-233, **15**-2059
Esponet, P. **13**-541
Esquivias, J. **13**-653, **15**-2349
Ess, D.H. **5**-389, **15**-2119, **15**-2135, **15**-2188
Estevam, I.H.S. **16**-328
Esteve Jr., R.M. **12**-678
Esteves, P.M. **11**-123, **11**-241
Estévez, R.E. **16**-575
Esumi, S.-i. **15**-2220
Eswarakrishnan, V. **12**-425, **17**-351
Etemad-Moghadam, G. **15**-1114
Etemadi, S. **19**-111
Etlis, V.S. **15**-2152
Eto, M. **15**-995
Etter, J.B. **16**-841

Etter, M.C. **3**-27, **3**-39, **4**-194
Etxebarria, J. **15**-1401
Eudy, N.H. **19**-1005
Eulaerts, O. **7**-79, **7**-84
Eulenberger, A. **15**-2489
Euler, K. **18**-689
Euranto, E.K. **16**-1653, **16**-1662, **16**-1678
Eustace, S.J. **12**-87, **12**-446
Eustathopoulos, H. **13**-836
Evain, E.J. **10**-1257, **10**-1260
Evano, G. **10**-1565
Evans Jr., E.A. **4**-262
Evans Jr., S.A. **10**-645, **10**-926
Evans, A.C. **2**-339
Evans, B.J. **19**-827
Evans, C.A. **5**-221
Evans, D.A. **4**-143, **4**-145, **10**-1742, **10**-1744, **12**-224, **12**-484, **15**-599, **15**-731, **15**-733, **15**-1022, **15**-1054, **15**-1103, **15**-1827, **15**-2249, **16**-730, **16**-1046, **16**-1058, **16**-1074, **16**-1092, **16**-1194, **16**-1195, **16**-2312, **18**-786, **19**-1048
Evans, D.F. **5**-172
Evans, E.A. **11**-116, **16**-2061
Evans, F.E. **4**-402
Evans, G.L. **16**-185
Evans, J.C. **5**-16
Evans, M.A. **15**-2387
Evans, M.B. **10**-818
Evans, P. **15**-1555
Evans, P.A. **10**-622, **10**-916, **10**-1543, **10**-1544, **15**-868, **15**-2668, **15**-2692, **18**-326, **19**-54
Evans, R.D. **15**-1669, **19**-710
Evans, R.J. **19**-410
Evans, S.A. **4**-375
Evans, S.V. **4**-146
Evans, W.D. **14**-150
Evans, W.G. **3**-61
Evans, W.J. **2**-282, **16**-587
Evans, W.L. **5**-73, **8**-134
Evanseck, J.D. **10**-23
Everett, J.R. **4**-351
Everly, C.R. **14**-58
Evers, M. **10**-823, **10**-824
Everson, D.A. **13**-358
Evstigneeva, R.P. **19**-1777
Evtushenko, N.Yu. **10**-437
Ewing, D.F. **9**-19
Ewing, M. **16**-1686
Exner, J.H. **12**-437
Exner, O. **1**-37, **1**-38, **1**-45, **2**-62, **8**-185, **8**-186, **9**-16, **9**-20, **9**-40, **11**-91, **18**-313
Eyer, M. **16**-1199
Eyet, N. **5**-338, **17**-35
Eymann, W. **10**-265
Eynde, J.J.V. **10**-628
Eyring, H. **4**-128
Ezikiel, G. **16**-627
Ezoe, A. **16**-1560
Ezquerra, J. **19**-1482

Fabbrini, M. **19**-172
Faber, D. **18**-87
Faber, K. **4**-205, **10**-727, **16**-1795
Fabian, J. **7**-5
Fabian, M.A. **4**-388
Fabian, W.M.F. **2**-482, **19**-217
Fabiano, E. **10**-924
Fabienke, E. **16**-2287
Fabre, A. **14**-326
Fabre, C. **12**-729
Fabre, O. **7**-86
Fabre, P. **12**-356
Fabrizi, G. **13**-163, **13**-238, **13**-608, **15**-245, **15**-906, **15**-907, **16**-2104, **18**-381
Faburada, A.L. **10**-512
Facchetti, A. **10**-1682
Facchetti, S. **16**-746
Facelli, J.C. **2**-243
Fache, F. **10**-941, **12**-173, **16**-1889, **19**-128, **19**-467
Fadaei, Z. **16**-1735
Fadel, A. **19**-1702
Fadel, R. **15**-614
Fadini, L. **13**-401, **15**-1402, **15**-1426, **19**-214
Fagan, M.W. **1**-94
Fagerli, A.K. **2**-489
Fagnoni, M. **13**-832
Fagnou, K. **13**-549, **15**-905
Fahey, R.C. **6**-90, **15**-3, **15**-13, **15**-19
Fahrenholtz, S.R. **14**-49, **17**-94
Faibish, N.C. **6**-37
Faid-Allah, H. **16**-426
Faigl, F. **4**-160, **17**-213
Fain, D. **12**-699
Fainberg, A.H. **10**-63, **10**-450, **10**-461
Fainzil'berg, A.A. **10**-514
Fair, J.D. **16**-465
Fairchild, D.E. **8**-108
Fairlamb, I.J.S. **13**-2, **13**-493, **13**-494
Fairlie, D.P. **15**-1478, **19**-1732
Fairweather, N. **14**-50
Faita, G. **11**-314, **15**-991, **18**-713
Fajgar, R. **19**-350, **19**-368
Fakultatea, K. **16**-852
Falahati, A.R. **10**-1167
Falbe, J. **10**-1979, **10**-1980, **15**-1494, **15**-1580, **15**-1597, **15**-1606
Falciola, C.A. **10**-1410, **10**-1533
Falck, J.R. **15**-257, **16**-1432, **16**-1447, **10**-1452, **10**-1882, **16**-1241, **19**-543
Falgayrac, G. **15**-1235
Falk, F. **17**-155
Falkehag, I. **19**-261
Fall, A. **19**-181
Fall, M.J. **15**-2512
Fall, Y. **13**-429, **19**-181
Fallah-Bagher-Shaidaei, H. **2**-172
Fallah, A. **15**-399
Faller, J.W. **10**-916, **10**-1541, **15**-458, **15**-2250
Fallis, A.E. **14**-359
Fallis, A.G. **4**-85, **15**-1513, **15**-1314, **15**-2007, **15**-2243, **15**-2268, **16**-2148
Falomir, E. **16**-1039
Faltin, C. **16**-789
Falvey, D.E. **5**-441, **5**-442
Familoni, O.B. **10**-1348
Fan, B.-M. **19**-1014
Fan, C.-A. **13**-179, **16**-270, **18**-155, **18**-158, **19**-83, **19**-1649
Fan, D.-p. **10**-893
Fan, D. **16**-2049
Fan, H. **15**-2478
Fan, J. **16**-1082, **16**-1084
Fan, Q.-H. **15**-452, **15**-643, **16**-664
Fan, R.-H. **10**-598, **10**-700, **10**-1003, **10**-1243, **10**-1659
Fan, R. **15**-2058, **16**-341, **16**-2213
Fan, W.-Q. **11**-70
Fan, X. **13**-680, **16**-663, **16**-2256
Fan, Y. **16**-1145, **16**-2254
Fañanas, F.J. **12**-433
Fancelli, D. **13**-652
Fandrick, D.R. **10**-1749, **13**-348, **16**-599
Fandrick, K.R. **16**-599
Fang, C. **14**-299
Fang, D. **10**-1141
Fang, G. **16**-988
Fang, J.-M. **14**-305, **16**-309
Fang, K. **19**-1674
Fang, L. **15**-1228
Fang, M.M. **7**-74
Fang, S. **16**-2023
Fang, T. **19**-971
Fang, W.-H. **15**-2556
Fang, W.-k. **18**-325
Fang, X. **10**-991, **16**-765, **19**-150
Fang, Y.-r. **10**-1930
Fang, Y. **10**-1788
Fang, Z. **13**-517, **19**-115, **19**-128
Fanta, P.E. **13**-468, **16**-2294
Fantin, G. **15**-1953, **19**-223, **19**-842
Fantoni, A.C. **3**-35
Fara, D.C. **10**-228
Faraci, G. **11**-262
Farah, B.S. **16**-433
Farah, J.P.S. **10**-560
Farah, M.M. **15**-1943
Farcasiu, D. **5**-14, **6**-24, **10**-45, **11**-13, **18**-52
Fardost, A. **12**-282
Farhadi, S. **11**-659, **14**-464
Faria, A.R. **15**-2383
Farid, S. **1**-107, **15**-2462
Farina, M. **4**-1

Farina, V. **12**-261, **12**-267, **12**-276, **12**-287
Farkas, L.V. **10**-1049
Farkas, M.E. **11**-463
Farkas, Ö. **10**-33
Farley, E.N. **2**-358
Farlow, R.A. **18**-229
Farmer, P.J. **5**-266
Farneth, W. **7**-21, **7**-23
Farnham, W.B. **10**-203, **18**-901
Farnoux, C.C. **16**-418
Farnsworth, M.V. **15**-254, **15**-2682
Farnum, D.G. **5**-93, **10**-195, **10**-201
Farnum, W.B. **10**-204
Farooq, O. **14**-188, **12**-356, **17**-173, **18**-118
Farooq, S. **10**-18
Farooqi, J.A. **11**-647
Farquhar, D. **2**-348
Farrall, M.J. **16**-1445
Farrant, G.C. **15**-2678
Farrar, A.C. **12**-460
Farrar, W.V. **16**-239
Farrington, E.J. **13**-547
Farrington, G. **7**-48
Farrokhi, A. **19**-81, **19**-835
Farrugia, L. **16**-778
Farthing, C.N. **16**-1330
Fasihi, J. **10**-923, **16**-1721
Fassberg, J. **10**-255
Fässler, R. **16**-543, **16**-978
Fastabend, U. **15**-2378
Fataftah, Z.A. **4**-533
Fathi, R. **13**-512, **13**-599, **13**-697
Fatiadi, A.J. **3**-102, **10**-1663, **10**-1929, **15**-72, **15**-1792, **16**-1733, **19**-10, **19**-301
Fatiadi, K. **17**-430
Fatland, A.W. **15**-2587
Fato, M. **18**-906
Fattahi, A. **2**-31, **2**-217, **4**-434, **8**-147
Fattal, E. **18**-91
Fattuoni, C. **1**-110
Faul, M.M. **10**-887
Faulconer, J.M. **12**-740
Faulks, S.J. **12**-689
Faunce, J.A. **16**-1077
Fauré-Tromeur, M. **17**-239
Fausett, B.W. **16**-2096
Faust, R. **2**-24
Fausto, R. **4**-309
Fava, A. **2**-94, **16**-1470, **16**-2268
Favaloro Jr., F.G. **16**-1766, **19**-699, **19**-1117, **19**-1382, **19**-1627
Favero, L. **10**-996, **10**-997, **10**-1647
Favi, G. **15**-2380
Favorskii, A. **18**-187
Favreau, D. **19**-1459
Fazakerley, V. **5**-172
Fazal, A.N. **10**-1544
Fazeli, A. **16**-305, **15**-316, **15**-959
Fberov, Z. **12**-690
Feast, W.J. **18**-807
Feaster, J.E. **19**-1120
Featherman, S.I. **1**-94
Fechter, M.H. **16**-1501
Fedder, J.E. **16**-1981
Fedé, J.-M. **5**-397, **12**-361, **18**-619
Fedenok, L.G. **14**-351
Feder-Kubis, J. **9**-137
Fedor, L.R. **16**-27, **17**-50
Fedorov, A.Yu. **13**-214
Fedorovich, A.D. **18**-560, **18**-592
Fedoruk, N.A. **19**-1390
Fedorynski, M. **10**-1666
Fedrick, J.L. **13**-75
Feducovich, S.K. **16**-135, **19**-1666
Feeder, N. **2**-82, **4**-475
Feely, W. **17**-186
Feenstra, R.W. **7**-128
Fehlner, J.R. **14**-179
Fehlner, T.P. **15**-672
Fehr, C. **16**-2019
Feig, G. **14**-285
Feigel, M. **10**-65
Feigl, F. **11**-675
Feigon, J.F. **11**-29
Feiler, L.A. **15**-2391, **15**-2426, **15**-2435
Feit, B. **5**-142
Feit, I.N. **17**-87, **17**-96
Feiten, H.-J. **19**-539, **19**-540, **19**-542
Feitler, D. **16**-1911
Fel'dblyum, V.Sh. **15**-826
Felder, M. **19**-1136
Felder, P. **5**-345
Feldman, D. **10**-486
Feldman, J. **18**-894
Feldman, K.S. **15**-2138, **19**-1754
Feldmann, R. **15**-2678
Feldus, S. **8**-191
Felix Köhler, F. **2**-107
Felix, D. **12**-35, **17**-424, **17**-426, **18**-726
Felix, D. **4**-37
Felix, L. A. **12**-495, **12**-297
Felker, P.M. **3**-77
Felkin, H. **4**-142, **10**-1588, **15**-899, **19**-1224
Fell, B. **12**-503, **12**-582, **15**-1605
Fellenberger, K. **10**-1617, **18**-545, **18**-776
Fellous, R. **9**-75
Fellows, C.A. **13**-681
Fellows, I. **13**-473
Felpin, F.-X. **10**-866, **13**-494, **13**-498, **16**-687
Felt, G.R. **10**-86, **10**-88
Felton, S.M. **16**-1958
Femoni, C. **4**-90, **16**-976
Feng, A. **15**-1515
Feng, C.-G. **16**-945
Feng, J.-J. **15**-1427
Feng, J.-C. *Sy*. **16**-57
Feng, J.-C. **19**-1073
Feng, J.-X. **19**-1640
Feng, J. **14**-370
Feng, L.-C. **16**-1048, **16**-1156
Feng, L. **18**-527
Feng, M.S. **6**-78
Feng, R.H.C. **14**-55
Feng, S.-Q. **10**-932
Feng, X. **4**-155, **10**-39, **15**-1024, **15**-2326, **16**-649, **16**-663, **16**-1084, **16**-1496, **16**-1497, **16**-1502, **16**-1503, **16**-1512, **16**-1515, **16**-1529
Feng, Y.-S. **13**-148
Feng, Y.-Y. **16**-1233
Feng, Y.-S. **16**-820
Feng, Y. **1**-117, **13**-148, **13**-205, **19**-1020, **19**-1032
Fenichel, L. **15**-1098
Fennie, M.W. **16**-898, **16**-899
Fenoglio, D.J. **4**-307
Fenselau, A.H. **19**-165
Fensterbank, L. **15**-877, **15**-1368
Fentiman Jr., A.F. **10**-153
Fentiman, A. **11**-615
Fenton, G. **19**-1500, **19**-1603
Fenton, S.W. **14**-55
Fenwick, A. **16**-2235
Fenwick, D.R. **10**-1655
Fenwick, J. **18**-233
Fenzl, W. **15**-1255
Feoktistov, L.G. **19**-926
Ferappi, M. **11**-338
Ferber, P.H. **10**-147, **10**-183
Fereidoonnezhad, M. **13**-386
Ferguson, C.P. **1**-94
Ferguson, D.C. **19**-908
Ferguson, G. **2**-65, **3**-144, **19**-571
Ferguson, J.W. **18**-36
Ferguson, L.N. **19**-407
Ferguson, R. **18**-932
Ferguson, R.R. **14**-325
Fergusson, S.B. **10**-2003
Feringa, B.L. **4**-213, **7**-65, **10**-1370, **10**-1447, **15**-414, **15**-643, **15**-1181, **15**-1185, **15**-1208, **15**-1269, **15**-1278, **15**-1795, **16**-466, **16**-746, **16**-822, **16**-849, **19**-470
Ferland, J.M. **19**-1450
Fernamberg, K. **5**-378
Fernandes, A.C. **19**-981, **19**-1589
Fernandes, E. **18**-679
Fernandes, M.A. **18**-866
Fernandes, R. **19**-981
Fernandes, R.A. **16**-912, **16**-951, **19**-77
Fernandes, S.A. **18**-692
Fernández-Fano, R. **16**-496
Fernandez-Picot, I. **14**-462
Fernández-Mateos, A. **10**-146
Fernández-Ibáñez, M.Á. **10**-1946
Fernández-Rodríguez, M.A. **13**-147

Fernández-Pérez, H. **15**-1929
Fernández-Rivas, C. **15**-812
Fernández-Ibáñez, M.A. **16**-849
Fernandez, E. **18**-305
Fernández, I. **10**-287, **10**-329
Fernández, M. **10**-1658, **19**-993
Fernández, R. **5**-372, **19**-292
Fernández, S. **19**-307
Fernandez, X. **16**-225
Fernelius, W.C. **4**-101
Fernholt, L. **3**-56, **4**-295, **4**-329
Fernndez, I. **13**-14
Feroci, M. **12**-783, **12**-789, **16**-430
Ferraboschi, P. **15**-535
Ferraccioli, R. **13**-236
Ferrand, Y. **15**-2525
Ferrara, D.M. **11**-95
Ferrara, M. **16**-988
Ferraris, D. **16**-890, **16**-2228
Ferraz, H.M. **18**-218
Ferraz, H.M.C. **15**-275, **19**-568, **19**-582
Ferreira, F. **16**-1819
Ferreira, J.T.B. **10**-813, **16**-701, **19**-1405
Ferreira, L.M. **15**-185
Ferreira, V.F. **15**-2520, **16**-850
Ferreiro, M.J. **4**-110
Ferrence, G.M. **16**-666
Ferrer, M. **19**-371
Ferreri, C. **10**-1220, **10**-1278, **14**-32, **15**-68, **15**-1311
Ferrero, L. **19**-1236
Ferrier, B.M. **18**-677
Ferrieri, R.A. **14**-66
Ferrini, P.G. **17**-504
Ferris, A.F. **17**-456, **19**-1169
Ferris, D.C. **8**-236
Ferris, J.P. **12**-677, **16**-1542
Fersht, A.R. **16**-34
Fersner, A. **8**-209
Fessard, T.C. **19**-1513
Fessenden, R. **16**-2029
Fessenden, R.W. **2**-109, **5**-294
Fessner, W. **5**-89, **15**-2442, **19**-62
Fettes, A. **16**-1093
Fettinger, J.C. **5**-99, **15**-2067
Fettouhi, M. **15**-1520
Fetzer, U. **17**-481
Feuer, B.I. **12**-239
Feuer, H. **10**-603
Feuer, H. **7**-57, **10**-662, **10**-1016, **10**-1055, **10**-1552, **11**-123, **12**-213, **12**-214, **12**-747, **13**-9, **13**-79, **13**-809, **15**-1052, **16**-90, **16**-376, **16**-1199, **17**-119, **19**-741, **19**-755, **19**-1218, **19**-1226, **19**-1515
Feuerstein, M. **13**-382, **13**-607, **14**-363, **16**-1910
Feutrill, G.I. **10**-825
Fevig, T.L. **15**-1287
Fey, P. **10**-1768
Fey, T. **19**-177, **19**-178
Feyen, P. **18**-19
Feytmants-de Medicis, E. **16**-82
Fiandanese, V. **10**-1377, **10**-1903, **16**-2015, **16**-2020
Fiaschi, R. **16**-436, **17**-192
Fiaud, J. **10**-1508
Fibiger, R. **10**-1078, **15**-424
Fichter, K.C. **15**-737
Ficini, J. **15**-2444
Fiddy, S. **11**-579
Fidler, J. **4**-130
Fiedler, P. **1**-45
Fiege, M. **16**-2212
Field, L. **16**-189, **18**-356
Field, L.D. **12**-50, **12**-356, **18**-281
Fieldhouse, R. **16**-1448
Fielding, M.R. **15**-191
Fields, D.B. **15**-1647
Fields, E.K. **13**-39
Fields, J.D. **15**-1872, **18**-955, **19**-737
Fields, K.W. **16**-2105
Fields, S.C. **12**-492
Fields, T.R. **18**-569
Fierke, C.A. **4**-475
Fierz, H.E. **11**-36
Fieser, L.F. **10**-597, **15**-1657, **17**-310, **19**-65, **19**-888, **19**-1302, **19**-1408
Fieser, M. **10**-597, **15**-1657, **17**-310, **19**-65, **19**-888, **19**-1408, part**2**-6
Fife, T.H. **10**-561, **10**-562, **10**-563, **10**-565, **10**-567, **10**-591
Fife, W.K. **10**-498, **16**-1821
Fifolt, M. **10**-1689
Fifolt, M.J. **10**-1555
Figadère, B. **10**-1110, **12**-324, **13**-317, **16**-605
Figeys, H.P. **2**-99, **2**-271, **12**-444
Figge, L. **15**-2442
Figlus, M. **19**-1156
Figueira, S. **10**-25
Figueras, F. **13**-591
Figuly, G.D. **12**-425
Fihri, A. **13**-590
Fiksdahl, A. **10**-795
Filho, E.P.S. **15**-659, **16**-816
Filimonov, V.D. **11**-292, **13**-795, **13**-795
Filipescu, N. **18**-550
Filipp, N. **18**-654
Filippi, J.-J. **16**-225
Filippini, G. **2**-181
Filippini, L. **11**-539
Filippova, T.Yu. **14**-221
Filler, R. **1**-112, **8**-178, **10**-1099, **12**-111
Filley, J. **10**-522
Fillion, E. **11**-329, **15**-1170
Fillion, H. **7**-95
Fillipi, G. **13**-830
Filmore, K.L. **11**-689
Filon, H. **16**-2036
Filzen, G.F. **18**-60
Finch, A.F. **10**-526
Findeis, M.A. **4**-156
Findik, H. **11**-422
Findlay, P. **15**-219
Finet, J.-P. **13**-214
Finet, J. **12**-549, **13**-226, **13**-227, **13**-651, **14**-372, **14**-373
Finger, A. **10**-519
Fingerhut, B. **15**-332
Fini, A. **7**-109
Fink, D.M. **10**-978, **10**-1299
Fink, M.J. **1**-13
Fink, W.H. **6**-71
Finkbeiner, H.L. **16**-1303
Finke, J. **16**-1043
Finke, R. **10**-1318
Finke, R.G. **3**-89, **10**-1402, **10**-1958, **10**-1983, **13**-425, **14**-485, **15**-433, **15**-449, **15**-1597, **15**-1599, **15**-2642, **18**-893
Finkelhor, R.S. **16**-1476
Finkelstein, M. **19**-575
Finkenbine, J.R. **10**-841
Finlay, J. **10**-595
Finlayson, A.J. **10**-223
Finlayson, W.L. **10**-921, **16**-1620
Finley, K.T. **15**-40, **19**-1704
Finn, J. **4**-218, **4**-219, **19**-508
Finn, M.G. **15**-1830, **15**-1874, **15**-1970, **15**-1974, **15**-1976
Finnegan, D.F. **18**-859
Finnegan, R.A. **11**-593
Finocchiaro, P. **3**-175, **19**-1687
Finston, H.L. **8**-1
Finzi, C. **13**-652
Fiorani, T. **13**-652
Fioravanti, S. **15**-2044, **15**-2049, **15**-2050
Fiorentino, M. **19**-293
Fiori, J.W. **12**-231
Fiori, K.W. **15**-2059
Fiorini, D. **12**-720, **15**-1048, **15**-1051, **16**-94, **16**-298, **16**-827
Fioshin, M.Ya. **14**-460
Firestone, R.A. **2**-2, **9**-89, **10**-508, **15**-2120, **15**-2208, **18**-696
Firmansjah, L. **13**-376
Firnberg, D. **14**-179
Firouzabadi, H. **10**-734, **10**-835, **10**-873, **10**-1151, **10**-1169, **10**-1176, **10**-1177, **10**-1951, **11**-140, **11**-296, **13**-386, **13**-401, **16**-197, **16**-1759, **17**-161, **17**-468, **19**-81, **19**-111, **19**-296, **19**-740, **19**-834
Firouzbakht, M.L. **14**-66
Firth, W.C. **14**-471
Fisch, A. **12**-444
Fischer Jr., W.F. **10**-1423, **15**-1156
Fischer, A. **8**-37, **11**-58, **11**-62, **15**-2452, **18**-34

Fischer, C. **10**-1472, **13**-676, **16**-924
Fischer, E. **15**-7
Fischer, G. **2**-130, **15**-515
Fischer, H. **5**-106, **5**-218, **8**-17, **14**-110, **15**-1303, **15**-2134, **18**-56, **19**-178
Fischer, H.P. **17**-455, **17**-459
Fischer, J. **19**-1487
Fischer, J.W. **4**-463
Fischer, K. **15**-829, **16**-1468
Fischer, N.S. **16**-1469
Fischer, P.B. **11**-108
Fischer, P.M. **13**-511
Fischer, R. **15**-838
Fischer, S. **16**-720
Fischer, S.F. **7**-24
Fischer, W. **17**-410
Fishbein, J.C. **13**-859
Fishbein, R. **12**-158, **14**-80, **14**-173
Fishel, D.L. **16**-282, **19**-403
Fisher, A.J. **2**-405
Fisher, A.M. **5**-133
Fisher, A.S. **15**-206
Fisher, F.J. **16**-1041
Fisher, J. **4**-20
Fisher, K. **15**-662
Fisher, K.D. **15**-1565
Fisher, L.E. **16**-1817
Fisher, R.D. **6**-89, **10**-69, **10**-344, **10**-461
Fisher, R.P. **18**-478, **18**-483
Fisher, T.H. **14**-106
Fishlock, L.P. **18**-820
Fishman, J. **14**-441, **19**-1562
Fisk, J.S. **15**-996
Fitch, R.W. **19**-1189
Fitjer, L. **4**-335, **4**-339, **4**-382
Fitzgerald, P. **18**-404
Fitzgerald, R. **1**-44, **10**-277
Fitzjarrald, V.P. **10**-735
Fitzmaurice, N.J. **15**-1607
Fitzpatrick, J.D. **2**-236, **2**-254
Fitzroy, M.D. **15**-1821
Fizet, C. **16**-297
Fjita, R. **10**-1537
Flack, K. **18**-871
Flack, S.S. **10**-760
Flaherty, A. **18**-741
Flamarique, A.C.R. **10**-1946
Flamm-ter Meer. **4**-306
Flammang, R. **4**-507
Flanders, V.L. **10**-1021
Flaniken, J.M. **19**-1484
Flann, C.J. **18**-702
Flaschenriem, C. **16**-2196
Fleischer, F. **4**-458
Fleischer, R. **5**-194
Fleischhauer, J. **15**-2184
Fleming, E.M. **16**-789, **16**-1441
Fleming, F.F. **10**-1778, **10**-1780, **10**-1948, **12**-576, **15**-1040, **15**-1179, **17**-168, **17**-169, **17**-185
Fleming, I. **6**-2, **10**-712, **10**-1501, **12**-4, **12**-452, **13**-439, **15**-1246, **15**-2297, **15**-2301, **16**-763, **18**-513, **18**-691
Fleming, J.J. **2**-309
Fleming, M.J. **17**-214
Fleming, M.P. **10**-1579, **14**-471, **19**-1682, **19**-1687, **19**-1691
Fleming, N.B. **11**-516
Fleming, S.A. **18**-625
Fleming, T. **19**-1148
Flemming, S. **15**-652, **15**-1128
Fletcher, B. **14**-148
Fletcher, R.S. **9**-6
Fletcher, S.P. **10**-1370
Fletschinger, M. **8**-94
Flippen-Anderson, J.L. **4**-228
Flippin, L.A. **10**-1602, **13**-737, **19**-335
Fliszár, S. **19**-344, **19**-352
Flitsch, W. **2**-481, **16**-1402
Flo, C. **5**-53, **10**-551
Flogaus, R. **16**-2013
Flood, R.W. **15**-1958
Flood, S.H. **11**-26, **11**-27, **11**-28, **11**-357
Flood, T.C. **12**-7, **17**-331
Flores, F.R. **13**-447
Flórez, J. **15**-2526
Florio, S. **10**-1345, **13**-731, **16**-498
Floris, B. **15**-279
Floss, H.G. **4**-22
Flosser, D.A. **10**-1145
Flowers II, R.A. **12**-704, **15**-1363, **16**-1025, **19**-941, **19**-945, **19**-1132, **19**-1677
Floyd, D. **15**-1145
Floyd, D.M. **10**-1429
Floyd, R.J. **13**-491
Flügge, J. **16**-1270
Flury, P. **10**-188
Flygare, J.A. **16**-1298
Flynn Jr., J. **10**-276
Flynn, B.L. **15**-2652
Flynn, D.L. **10**-731, **16**-1688, **16**-2192
Flynn, K.E. **4**-491
Flynn, R. **13**-638
Flynt, M.S. **16**-273
Fo Kron, T.E. **3**-149
Foà, M. **13**-664
Fobare, W.F. **11**-267
Fobker, R. **12**-654
Foces-Foces, C. **2**-479
Fochi, M. **10**-1568
Fochi, R. **16**-1338
Fodor, G. **9**-13, **10**-1262, **11**-401, **11**-405
Fogagnolo, M. **15**-1953, **19**-223
Fogassy, E. **4**-160
Fogg, D.E. **18**-811
Foglia, T.A. **10**-722
Föhlisch, B. **16**-2013
Fok, C.C.M. **17**-199
Fokin, A.A. **14**-4, **14**-163
Fokin, V.V. **7**-130, **9**-90, **10**-840, **15**-2013, **15**-2136
Foldi, V.S. **16**-2188
Folest, J.C. **10**-1956
Foley, K.M. **19**-1488
Follet, M. **15**-713
Folli, U. **2**-62
Folliard, J.T. **16**-89
Folting, K. **15**-2645
Fomina, L. **14**-354
Fomine, S. **14**-354
Fonck, G. **19**-35
Fong, C.W. **12**-502
Fong, G.D. **19**-369
Fonguerna, S.J. **16**-1448
Fonken, G.J. **18**-521
Fono, A. **15**-285
Fonseca, M.T.H. **15**-1080, **16**-1429
Font-Sanchis, E. **14**-239
Fontaine, E. **19**-1234
Fontaine, G. **12**-248
Fontana, A. **8**-183, **12**-82
Fontana, F. **11**-262, **14**-140, **14**-378, **14**-379, **14**-383, **14**-384, **19**-167, **19**-320, **19**-489, **19**-578, **19**-1040
Fontana, G. **4**-123
Fontana, R. **14**-159
Fontenas, C. **18**-432
Foos, J.S. **2**-56
Foot, J. **19**-110
Foot, J.S. **19**-662
Foote, C.S. **14**-253, **14**-256, **14**-258, **14**-263, **14**-266, **15**-994, **15**-2363, **15**-2365
Forbes, C.C. **4**-322
Forbes, D.C. **16**-1117, **16**-1444
Forbes, E.J. **11**-650
Forbes, I.T. **11**-216
Forcato, M. **19**-299
Forch, B.E. **2**-365
Ford, A. **19**-1019
Ford, F. **5**-414
Ford, G.D. **16**-1448
Ford, G.P. **9**-39
Ford, J.G. **15**-1554
Ford, R.A. **4**-344, **14**-245
Ford, W.T. **10**-354, **12**-30, **12**-30, **16**-1322, **17**-72, **17**-79
Foreman, M.I. **3**-99
Foresti, E. **4**-62, **15**-230, **18**-73
Forgione, P. **15**-1513
Forlani, L. **16**-243
Forman, M.A. **18**-203
Formosinho, S.J. **5**-408, **7**-48, **8**-117, **10**-5
Fornarini, S. **10**-275
Forni, A. **4**-39, **16**-2246
Foroughifar, N. **19**-1617
Forrest, J. **13**-474
Forrest, T.P. **18**-769
Forrester, A.R. **5**-237, **5**-364

Forrester, J.L. **15**-1665
Fors, B.P. **13**-191, **13**-234, **13**-290, **13**-494
Forsén, S. **2**-432, **2**-467
Forslund, R.E. **15**-2057, **19**-567
Förster, H. **4**-280, **4**-530
Förster, S. **10**-1089
Forsyth, D.A. **4**-36, **10**-180, **10**-200, **11**-16
Forsyth, M. **9**-140
Forsyth, S.A. **9**-140
Forsythe, G.D. **15**-580
Fort Jr., R.C. **5**-83, **5**-251, **5**-293, **10**-14, **10**-49, **12**-9
Fort, Y. **10**-1311, **10**-1702, **13**-210, **13**-213, **13**-479, **13**-739, **13**-740, **14**-442, **19**-1563
Forte, L. **18**-744
Forth, M.A. **19**-1216
Fortier, S. **3**-118
Fortunak, J.M. **19**-1008
Foscolos, G. **16**-510
Foscolos, G.B. **16**-994
Fosheé, D.O. **9**-78
Foss, R.P. **7**-25
Fossel, E.T. **18**-677
Fossey, J.S. **16**-1510
Foster, G. **19**-407
Foster, G.P. **16**-2267
Foster, R. **3**-86, **3**-99, **3**-101, **13**-9, **16**-237
Foster, R.F. **5**-113, **12**-697
Foster, T.F. **15**-436
Fotakopoulou, I. **16**-1624
Foti, C.J. **15**-1872
Foubelo, F. **12**-433, **15**-324, **16**-884
Foubister, A.J. **19**-1274
Foulon, J.P. **15**-1134
Fountain, K.R. **6**-18
Fouquet, E. **10**-1460, **16**-1598
Fouquet, G. **10**-1393
Fournier, F. **15**-1572
Fournier, J. **16**-430
Fournier, Jr., A. **18**-933
Fournier, L. **16**-188
Fournier, P. **10**-1441
Fournioux, X. **10**-1506
Fowler, C.B. **16**-1002
Fowler, F.W. **15**-1766, **16**-533, **18**-741
Fowler, P. W. **2**-89, **2**-98, **2**-265, **2**-371
Fox, B.G. **19**-234
Fox, B.L. **18**-371
Fox, D.L. **10**-849
Fox, D.N.A. **16**-1135, **16**-1137
Fox, J.M. **10**-1739, **15**-151, **15**-895, **15**-896, **15**-2504, **15**-2508
Fox, M.A. **15**-1399, **15**-2314
Foxman, B.M. **15**-2252
Fréchet, J.M.J. **16**-1085
Fraaije, M.W. **18**-389
Fraancoeur, S. **15**-2569
Frabboni, B. **18**-906
Frach, R. **17**-478
Fradera, X. **2**-170
Fraenkel, G. **4**-323, **5**-162, **5**-178, **5**-194, **5**-196, **6**-62, **16**-435
Fraenkel, R. **19**-368
Fraga-Dubreuil, J. **9**-99
Fraile, A.G. **11**-498, **16**-2174
Fraile, J.M. **15**-2524, **16**-682
Fraisse, P.L. **10**-1546
Français, A. **15**-1844
Francalanci, F. **19**-1352
France, M.B. **15**-1017, **15**-1840
France, S. **12**-125, **12**-175, **15**-2386, **16**-2229, **16**-2230, **17**-322
Francesch, C. **16**-1271
Franciò, G. **19**-1014
Francis, A.W. **15**-9, **11**-359
Franck, E.U. **9**-99
Franck, G. **10**-1513
Franck, X. **13**-317
Francl, M.M. **10**-122
Franco, D. **19**-1480
Franco, F. **15**-1103
François Diederich, F. **2**-391
Frank-Gerrit Klärner, F-G. **2**-267
Frank, D.L. **10**-184
Frank, H. **5**-227
Frank, R.M. **1**-46
Franke, F.P. **14**-58
Franke, J. **3**-106
Franke, W. **5**-68, **17**-253
Frankel, J.J. **19**-1347
Frankel, M.B. **10**-1016
Franken, E. **4**-522
Frankevitch, E.L. **8**-83
Franklin, N.C. **17**-88
Frantz, D.E. **15**-698, **16**-543, **16**-544, **16**-978
Franz, A.K. **15**-771
Franz, L.H. **2**-183
Franz, R. **5**-433
Franz, R.A. **12**-772
Franzén, J. **15**-1439, **15**-1954
Franzén, R. **13**-393, **13**-503, **13**-507, **13**-564
Franzén, R.G. **16**-456
Franzen, V. **19**-629
Franzus, B. **10**-1160
Fraser-Reid, B. **10**-568
Fraser, A.R. **15**-2410
Fraser, J.R. **3**-181
Fraser, L.R. **15**-309
Fraser, M.E. **3**-118
Fraser, R.R. **4**-216, **10**-1763, **12**-113
Frater, G. **18**-233, **18**-759
Frauenrath, H. **16**-1252
Fravel Jr., H.G. **18**-569
Fray, G.I. **2**-264
Frazén, J. **15**-875
Frazier Jr., R.H. **19**-825
Frazier, H.W. **16**-1278
Frazier, K.A. **19**-1444
Freccero, M. **15**-1874, **15**-1876, **15**-1879, **15**-2119, **19**-483
Fréchet, J.M.J. **12**-562, **13**-229, **16**-1445, **16**-1935
Fréchette, M. **8**-207
Fredenhagen, H. **19**-1738
Fredereiksen, M.U. **2**-211
Frederick, M.O. **10**-1051
Fredriksen, S.B. **3**-112
Freed, K.F. **7**-22
Freed, S.L. **15**-1613
Freedman, H.H. **5**-40, **5**-79, **19**-636
Freeman, F. **10**-1663, **15**-1, **15**-1797, **19**-693, **19**-694
Freeman, N.J. **3**-32
Freeman, P.K. **2**-389, **15**-58
Freeman, R. **14**-367
Freeman, R.C. **16**-371
Freeman, W.R. **14**-167
Freenor, F.J. **10**-1201
Freerksen, R.W. **19**-1402
Freiberg, D.A. **16**-143, **16**-1778
Freidlin, V.I. **16**-1553
Freidlina, R.Kh. **10**-1300, **15**-1773, **18**-54, **18**-69, **18**-80, **18**-84
Freiesleben, W. **12**-67, **14**-281, **15**-828, **19**-698, **19**-699
Freifelder, M. **15**-428, **19**-1170
Freilich, S.C. **16**-2209
Freire, A. **8**-87
Freitas, M.P. **4**-291
Frejd, T. **10**-1453, **13**-760, **13**-812, **15**-2277
Frelek, J. **4**-120
Fremaux, B. **16**-1550
French, A.N. **19**-532
French, M.A. **3**-58
French, R. **10**-670
Frenette, R. **10**-626
Frenkel, A.D. **18**-939
Frenking, G. **1**-120, **10**-287, **10**-329, **10**-1403, **13**-14, **15**-1882, **15**-2242, **19**-1699
Frennesson, D.B. **10**-883
Frensdorff, H.K. **3**-106
Frenz, B.A. **4**-390
Frère, S. **11**-399
Frese, E. **16**-1465
Freskos, J. **10**-1334
Fressigné, C. **5**-187, **8**-215
Fretwell, P. **15**-917
Fretz, E.R. **18**-107
Freudenberger, J.H. **19**-1641, **19**-1642
Frey, D. **10**-1190
Frey, E.J. **15**-747
Frey, H. **10**-1052
Frey, H.M. **4**-431, **5**-362, **5**-410, **12**-400, **15**-2440, **15**-2474, **15**-2531, **18**-176, **18**-609

Frey, J. **2**-455, **12**-82
Frey, L.F. **13**-285
Frey, P. A. **3**-26
Freyer, M.W. **10**-1916
Fricke, H. **15**-2545
Frid, M. **10**-1495
Friderichsen, A. V. **5**-286
Fridkin, M. **16**-1929
Fridman, A.L. **10**-1834, **16**-2164, **19**-1272
Fried, A. **19**-44
Fried, H.E. **2**-157
Fried, J.H. **15**-75
Friederang, A. **15**-1765
Friedl, T. **10**-1698
Friedline, R. **14**-81
Friedman, L. **5**-417, **5**-419, **10**-1931, **12**-364, **15**-2261, **19**-403
Friedman, M.D. **19**-889
Friedman, N. **5**-35
Friedrich, A. **18**-590
Friedrich, E.C. **10**-332, **15**-2555, **15**-2568
Friedrich, H.B. **19**-243
Friedrich, K. **10**-1929, **15**-1623, **16**-1493, **17**-154, **17**-430, **17**-461
Friedstad, G.K. **16**-973
Friege, H. **15**-2289
Friel, D.K. **16**-672
Friend, C.L. **15**-320
Friend, C.M. **14**-449, **19**-16, **19**-1575
Friesen, D. **4**-295
Friesner, R. **15**-1934
Friestad, G.K. **16**-890, **16**-893, **16**-1602, **16**-1610, appendix a-28
Frigerio, M. **19**-190, **19**-191
Friguelli, F. **10**-690
Frim, R. **4**-74
Frimer, A.A. **14**-250, **14**-251, **14**-263, **15**-2361, **15**-2364
Frings, M. **3**-129
Fringuelli, F. **2**-165, **10**-690, **10**-974, **10**-987, **10**-1236, **10**-1221, **15**-1817, **15**-1968, **15**-2174, **15**-2186, **15**-2211, **19**-1249
Frisch, A.C. **10**-1309
Frisch, H.L. **3**-209
Frisch, M.J. **4**-119
Friscourt, F. **18**-391
Frisell, C. **12**-461
Frison, J.-C. **18**-388, **18**-392
Frisque-Hesbain, A. **10**-1150, **16**-1990
Fristad, W.E. **14**-463, **15**-1857, **15**-2039, **19**-421
Fristrup, P. **14**-496, **15**-1981
Fritch, P.C. **10**-250
Fritsch, P. **17**-318
Fritz-Langhals, E. **5**-266
Fritz, H. **3**-204, **4**-306, **8**-94, **16**-297
Fritzberg, A.R. **18**-214
Fritzen, E. **10**-1356
Fritzsche, G. **18**-668
Friz, E.M. **15**-529
Frizzo, C.P. **9**-129
Fröch, S. **16**-1064
Frochi, M. **10**-744
Froehner, S. **10**-560
Froemsdorf, D.H. **17**-96, **17**-146
Frøhaug, Az. **19**-579
Fröhlich, H. **11**-684
Fröhlich, R. **2**-179, **16**-1352
Frohn, M. **15**-1925, **15**-1936
Frohning, C. D. **15**-1497
Frolov, A.N. **14**-400
Froment, F. **5**-145, **15**-1042
Fromm, A. **11**-658
Frommeld, H.D. **16**-1101, **19**-1539
Fronczek, F.R. **19**-924
Frontera, A. **12**-410, **13**-23
Frontier, A.J. **15**-1096, **15**-1082
Frost II, K.A. **4**-496, **10**-277
Frost, C.G. **11**-197, **11**-215, **11**-438, **15**-1072, **15**-2325, **16**-2094
Frost, H.N. **13**-189, **16**-1686
Frost, R.M. **10**-1366, **10**-1367, **10**-1368
Froudakis, G. **15**-1311
Frøyen, P. **16**-1398, **16**-1399
Fruchart, J.-S. **12**-106
Fruchey, O.S. **10**-240
Fructos, M.R. **15**-2517
Fruit Jr., R.E. **5**-48, **19**-638
Fruit, C. **12**-245
Frullanti, B. **19**-466
Fry Jr., F.S. **2**-472
Fry, A. **6**-45, **10**-238, **15**-18, **17**-3, **17**-7, **17**-62, **17**-134, **18**-186, **18**-191, **18**-404
Fry, A.J. **10**-203, **11**-700, **14**-456, **16**-2180, **17**-375, **18**-126, **19**-429, **19**-1219, **19**-1666
Fry, D.F. **16**-1002
Fry, J.L. **10**-66, **10**-296, **10**-296, **10**-297, **18**-23, **18**-26, **18**-45, **18**-48, **19**-876, **19**-1714
Fry, M.A. **19**-421
Frye, L.L. **16**-2303
Fryhle, C.B. **10**-824
Fryszkowska, A. **15**-662
Fryzuk, M.D. **4**-154
Fu, C.C. **19**-1112
Fu, F. **16**-1151
Fu, G.C. **10**-1472, **10**-1473, **10**-1498, **10**-1730, **10**-1889, **12**-308, **12**-383, **13**-376, **13**-533, **10**-1470, **10**-1472, **10**-1474, **12**-268, **12**-278, **13**-371, **13**-459, **13**-517, **13**-532, **13**-538, **13**-548, **13**-653, **13**-710, **13**-721, **14**-22, **15**-599, **15**-724, **15**-731, **15**-1369, **15**-1488, **15**-2339, **15**-2342, **15**-2672, **16**-370, **16**-809, **16**-1595, **16**-2058, **16**-2128, **16**-2227, **18**-227, **18**-808, **18**-874, **19**-213, **19**-1382, **19**-1385
Fu, H.-y. **19**-1014
Fu, H. **13**-205, **14**-298, **16**-79, **16**-1364
Fu, I.-P. **16**-1515
Fu, J. **16**-557, **16**-776
Fu, M.Y. **15**-154
Fu, N. **16**-2216
Fu, P. **16**-899
Fu, P.P. **19**-12
Fu, S.S. **15**-47
Fu, X. **5**-396, **12**-298, **13**-148
Fu, X.Y. **15**-491
Fu, Y. **10**-1475, **13**-421, **14**-84, **14**-88, **15**-643, **15**-643, **15**-1346, **16**-2047
Fu, Z. **12**-286, **13**-436
Fuchibe, K. **15**-2349, **15**-2601, **16**-400
Fuchigami, T. **11**-325, **14**-164, **14**-457
Fuchikami, T. **10**-1926, **19**-1172, **19**-1475
Fuchs, B. **4**-393
Fuchs, H. **4**-47
Fuchs, P.L. **10**-1921, **15**-41, **16**-76, **16**-206, **16**-226, **17**-202
Fuchs, R. **10**-448, **10**-1127, **19**-395
Fuchs, S. **15**-810
Fudesaka, M. **19**-148, **19**-151
Fueno, T. **4**-12, **15**-108, **15**-1730
Fuentealba, P. **11**-436, **15**-2298
Fuentes, A. **19**-1736
Fuentes, B. **10**-1463
Fuentes, N. **16**-575
Fuerst, D.E. **16**-1497
Fuest, M. **10**-1376
Fuhlendorff, R. **10**-103
Fuhrman, G. **10**-1350
Fuji, K. **3**-135, **10**-824, **10**-1535, **10**-1724
Fuji, Z. **2**-132
Fujieda, Y. **17**-243
Fujihara, H. **10**-495, **16**-900, **16**-933
Fujihara, T. **15**-1480, **16**-2044
Fujii, A. **16**-388, **16**-1518
Fujii, K. **16**-1336, **16**-1372, **19**-1448, **19**-1477
Fujii, N. **10**-249, **15**-410, **15**-962
Fujii, S. **15**-2576
Fujii, T. **5**-216, **10**-943, **10**-1281, **14**-213, **16**-769
Fujiki, D. **4**-203
Fujikura, R. **16**-1816
Fujimori, C. **19**-1758, **19**-1760
Fujimori, I. **10**-708
Fujimori, M. **10**-1373, **12**-289
Fujimoto, E. **3**-57

Fujimoto, E.K. **10**-372, **10**-456
Fujimoto, H. **15**-1297, **15**-2234, **15**-2301, **18**-659
Fujimoto, K. **11**-576, **16**-733, **16**-2214, **18**-778
Fujimoto, S. **12**-575
Fujimoto, T. **3**-156, **10**-1431, **13**-655, **15**-2607, **19**-1671
Fujimura, Y. **15**-1504
Fujinami, T. **19**-895
Fujino, T. **15**-57
Fujio, M. **8**-240, **10**-73, **10**-182, **10**-183, **10**-289, **10**-290, **10**-327, **10**-434, **10**-471, **10**-472, **10**-473, **11**-169, **16**-1959
Fujioka T. **13**-465
Fujioka, H. **10**-573, **15**-1720, **19**-198
Fujioka, S. **15**-1042, **15**-1052
Fujioka, T. **15**-1360
Fujisaki, S. **10**-822, **12**-118, **12**-755, **12**-756
Fujisawa, H. **16**-389
Fujisawa, M. **16**-2022
Fujisawa, T. **10**-1588, **15**-1738, **15**-2513, **16**-967, **16**-2020, **19**-1053, **19**-1094
Fujisawa, Y. **15**-2528
Fujishima, A. **16**-1301
Fujishima, H. **15**-1264
Fujita, A. **15**-623
Fujita, E. **4**-139, **10**-824, **16**-192
Fujita, H. **10**-903, **15**-358
Fujita, K.-i. **10**-943, **11**-347, **13**-750, **19**-667
Fujita, K. **10**-934, **10**-1047, **10**-1585, **10**-1715, **13**-503, **15**-590, **15**-1358, **15**-1542, **16**-1165
Fujita, M. **3**-203, **3**-207, **5**-120, **7**-87, **7**-102, **12**-729, **10**-758, **12**-507, **15**-57
Fujita, S. **2**-332, **2**-333, **2**-335, **2**-359, **4**-266, **4**-267, part**2**-1, **19**-1758
Fujita, T. **8**-184, **9**-78, **10**-850, **10**-1522, **13**-496, **16**-1793, **17**-377
Fujita, Y. **19**-629
Fujitsuka, H. **15**-2405
Fujitsuka, M. **5**-308
Fujiwara, F.Y. **3**-58
Fujiwara, I. **10**-822
Fujiwara, K. **16**-1227
Fujiwara, M. **10**-84, **10**-1070, **11**-503, **12**-327, **15**-1500, **15**-2695
Fujiwara, N. **15**-938, **18**-274
Fujiwara, S.-i. **14**-26, **16**-431
Fujiwara, T. **10**-1282, **15**-922, **16**-448, **16**-1420
Fujiwara, Y. **3**-84, **10**-740, **10**-1238, **11**-522, **11**-534, **12**-634, **13**-43, **13**-367, **13**-554, **15**-1446, **19**-499, **19**-1632, **19**-1680
Fujiyama, R. **10**-220, **10**-327
Fukamachi, S. **10**-744
Fukata, G. **11**-634
Fukazawa, Y. **4**-279, **13**-871, **16**-2143
Fuks, R. **10**-1794, **15**-2150, **15**-2253, **15**-2443, **15**-2530, **16**-179
Fukuda, E.K. **16**-1673
Fukuda, K. **10**-815, **19**-627
Fukuda, M. **11**-325
Fukuda, T. **13**-741, **15**-2513, **16**-806, **16**-2252
Fukudome, Y. **15**-2042
Fukuhara, H. **16**-931
Fukuhara, J. **10**-1102
Fukuhara, T. **10**-1144, **10**-1217, **10**-1978, **13**-790, **13**-805, **15**-1646
Fukui, K. **15**-2301, **18**-511, **18**-513, **18**-659
Fukui, S. **19**-1758, **19**-1760
Fukuma, T. **16**-593, **16**-784
Fukumoto, K. **9**-128, **15**-821, **19**-643
Fukumoto, T. **12**-752, **18**-944
Fukumoto, Y. **10**-2004, **15**-2690
Fukunaga, J.Y. **15**-2419
Fukunaga, K. **17**-373
Fukunaga, T. **2**-125
Fukuoka, K. **13**-549
Fukushima, D. **19**-841
Fukushima, K.-i. **19**-198
Fukushima, M. **16**-1146
Fukushima, S. **15**-1720
Fukuta, Y. **15**-1588
Fukutani, Y. **15**-2570
Fukuto, J.M. **12**-12, **12**-22
Fukuyama, T. **11**-490, **13**-597, **15**-1372, **15**-1486, **16**-806, **19**-1101
Fukuyama, Y. **10**-1206
Fukuyo, E. **10**-715
Fukuzawa, S.-i. **15**-2220, **19**-943
Fukuzawa, S. **4**-480, **15**-933, **15**-1858, **15**-2250, **18**-255, **19**-895
Fukuzumi, K. **18**-810
Fukuzumi, S. **12**-25, **16**-1486
Fukuzumi, T. **10**-782, **19**-800
Fulford, S.Y. **16**-794
Fuller, C.E. **10**-1434
Fuller, D.J. **8**-222, **14**-42, **14**-77
Fuller, G. **15**-1644
Fuller, J.C. **19**-911, **19**-1141
Fuller, S.E. **14**-172
Fullerton, T.J. **2**-48, **2**-49, **10**-1524
Fülöp, F. **2**-486, **2**-487, **18**-258
Fulton, J.R. **16**-1434
Fulton, R.P. **19**-1397
Fumagalli, T. **13**-463, **16**-1319
Funabashi, Y. **16**-611
Funabiki, K. **15**-1671
Funabiki, T. **14**-224, **15**-1625
Funaki, T. **2**-75
Funakoshi, S. **16**-1181, **16**-2131
Funami, H. **15**-2116
Funaro, J.M. **16**-2303
Funato, M. **10**-1275
Funatsu, M. **15**-814
Funayama, A. **10**-1596
Funderburk, L.H. **6**-69
Fünfschilling, P.C. **15**-136
Fung, A.P. **10**-672
Fung, A.P. **18**-354
Funhoff, D.J.H. **2**-337
Funk, B. **5**-342
Funk, R.L. **10**-1822, **10**-1839, **15**-918, **17**-174
Funk, T.W. **18**-844
Furber, M. **15**-982
Furet, N. **12**-255, **15**-668
Furin, G.G. **11**-352, **18**-943
Furlong, J.J.P. **2**-433
Furmanova, N.G. **2**-466
Furness, K. **18**-323, **18**-324
Furst, A. **19**-1723
Furst, G.T. **16**-878
Fürstner, A. **10**-1383, **10**-1384, **11**-443, **13**-361, **13**-488, **14**-422, **15**-542, **15**-853, **15**-869, **15**-926, **15**-993, **16**-830, **18**-168, **18**-243, **18**-835, **18**-849, **18**-876, **18**-883, **19**-1626, **19**-1694, **19**-1695, **19**-1696
Furuhashi, K. **10**-1274
Furuhata, T. **10**-813
Furukawa, I. **13**-198, **19**-1077
Furukawa, J. **4**-12, **15**-2406, **15**-2549, **16**-685
Furukawa, N. **10**-495, **13**-87, **13**-111, **17**-141, **18**-287, **19**-1596
Furukawa, S. **15**-590
Furukawa, T. **15**-1053
Furumai, S. **19**-1584
Furuno, H. **15**-1403, **16**-636
Furusaki, A. **13**-11
Furusawa, O. **13**-840
Furusho, Y. **3**-192
Furuta, A. **19**-981, **19**-1037
Furuta, H. **11**-169
Furuta, K. **10**-1741, **14**-231, **14**-236, **16**-1094, **16**-1098, **16**-1490
Furuya, T. **12**-527, **13**-801, **19**-475
Furuya, Y. **18**-344
Furuyama, S. **15**-60
Furxhi, E. **15**-1314
Fusco, C. **15**-1924, **19**-227, **19**-293, **19**-478, **19**-490, **19**-496
Fusco, R. **18**-761
Fushimi, M. **15**-2402
Fuso, F. **10**-188
Fuson, R.C. **2**-454, **12**-90, **15**-1237, **19**-1079, **19**-1106

Futatsugi, K. **15**-2252
Fwu, S.-L. **15**-941
Fyfe, C.A. **11**-17, **13**-9, **13**-96

Gaasbeek, C.J. **5**-31
Gabbi, C. **19**-804
Gabe, E.J. **4**-523
Gabhe, S.Y. **13**-104
Gable, C.M. **3**-168
Gable, K.P. **15**-1790, **15**-1835, **15**-2641
Gabriel, A.O. **16**-1489
Gabriel, C. **7**-112
Gabriel, S. **7**-112
Gabriel, T. **15**-844
Gabriele, B. **12**-770, **15**-243, **15**-316
Gabrielsen, B. **10**-91
Gacon, A. **19**-1246
Gadallah, F.F. **13**-826, **13**-835
Gadamasetti, G. **10**-1785
Gadamasetti, K.G. **15**-2493
Gadberry, J.F. **15**-5
Gade, L.H. **19**-1039
Gademann, K. **15**-2354
Gadgil, V.R. **18**-679
Gadhwal, S. **16**-375, **19**-1413
Gadras, A. **13**-647
Gadre, S.R. **3**-41, **15**-100
Gadru, K. **10**-112
Gadzikwa, T.L. **13**-586
Gaemi, E. **11**-134
Gaenzler, F.C. **17**-379
Gaffney, A. **17**-78
Gaffney, A.H. **17**-33
Gaffney, P. R. J. **4**-361
Gagare, P.D. **16**-324
Gage, J.R. **10**-919
Gager, O. **10**-1362
Gaggero, N. **19**-777, **19**-801
Gagné, M.R. **15**-442, **15**-824, **15**-2025, **15**-2027, **16**-1786
Gagnier, R.P. **10**-1306
Gagnier, S.V. **15**-1526
Gagnon, A. **10**-1025, **13**-340
Gagnon, J.L. **19**-310
Gagosian, R.B. **18**-211, **18**-246
Gagosz, F. **18**-277
Gai, Y. **17**-290
Gaikwad, D.D. **18**-395
Gailbreath, B.D. **10**-26
Gais, H.-J. **4**-187, **10**-864
Gais, H. **5**-150
Gaisberger, R.P. **16**-1501
Gajare, A.S. **10**-679, **12**-263, **13**-189
Gajda, A. **16**-955
Gajda, T. **16**-955
Gajewski, J.J. **2**-257, **15**-2283, **15**-2287, **16**-556, **18**-70, **18**-506, **18**-560, **18**-604, **18**-624, **18**-626, **18**-634, **18**-658, **18**-660, **18**-671, **18**-713, **18**-714, **18**-715, **18**-729
Gakh, A.A. **10**-340
Gal, C. **14**-154, **14**-156, **11**-405
Gal, J.-F. **8**-97
Gal, J. **1**-54, **3**-20, **8**-22
Gal, V.M.S. **8**-117
Galabi, S. **16**-2310
Galabov, B. **4**-319, **11**-35, **11**-226, **16**-1955
Galán, A. **19**-1168
Galan, B.R. **18**-890
Galbács, G. **13**-385
Galbiati, F. **15**-2609
Gale, L.H. **4**-341, **12**-534
Galema, S.A. **7**-111
Galembeck, S.E. **2**-70, **2**-389
Galemmo, Jr., R.A. **16**-1953
Galian, R.E. **19**-961
Galili, N. **15**-2513
Galindo, F. **16**-2203
Galindo, J. **16**-2019
Gall, J.S. **10**-80, **10**-353
Gall, M. **10**-1756, **10**-1759, **12**-341, **16**-2123
Gallagher, D.W. **19**-335
Gallagher, G.J. appendixa-1
Gallagher, M.E. **2**-354
Gallagher, M.J. **4**-45, **12**-609
Gallagher, S.P. **18**-281
Gallagher, S.S. **18**-508
Gallagher, T. **12**-374, **13**-441, **15**-380
Gallagher, W.P. **12**-266, **13**-629
Galland, B. **15**-12
Galland, J.-C. **15**-1008, **18**-833
Gallardo, I. **13**-8, **13**-69, **13**-71, **13**-173
Galle, D. **16**-1058
Galle, J.E. **15**-2644
Gallego, A.M. **12**-291
Gallego, C.H. **16**-1410
Gallen, M.J. **19**-193
Galletti, P. **15**-2241, **16**-1021, **19**-1044
Galli, C. **4**-399, **5**-252, **6**-15, **10**-281, **10**-737, **11**-307, **13**-65, **13**-68, **13**-645, **14**-391, **14**-394, **19**-172
Galli, R. **14**-172
Galliford, C.V. **16**-1192
Gallivan Jr., R.M. **15**-703
Gallivan, J.P. **11**-20
Gallo, E.A. **3**-74
Gallo, R. **9**-65, **9**-68
Gallou, F. **16**-1507
Gallucci, J.C. **12**-363, **15**-106
Gallucci, R.R. **12**-149
Gallulo, V. **16**-1003
Galonic, D. **10**-1645
Galpin, J.D. **18**-642
Galton, S.A. **19**-1416
Gálvez, J. **17**-486
Gamasa, M.P. **19**-1736
Gamba, A. **18**-713
Gambarotti, C. **19**-1535
Gambaryan, N.P. **16**-43
Gamber, G.G. **15**-1544, **15**-2676
Gambill, C.R. **16**-2293
Gamboni, R. **19**-504
Gamelas, C.A. **19**-793
Gamez, P. **19**-169
Gamsey, S. **13**-184
Gamsey, S. **16**-560
Gan, C. **13**-388, **16**-1208
Gan, J. **15**-2058
Gan, K.-H. **10**-930
Gan, Y. **15**-1932
Ganapathy, S. **18**-62
Ganboa, I. **16**-308
Gancher, E. **19**-330
Gandhi, S. **10**-1241
Gandler, J.R. **13**-13, **17**-3, **17**-55
Gandolfi, R. **15**-1874, **15**-1876, **15**-1879, **15**-1924, **15**-2105, **15**-2118, **15**-2119, **15**-2127, **19**-223, **19**-483
Gandon, V. **15**-912, **15**-2588, **15**-2623, **16**-886, **16**-1482
Gandour, R.D. **15**-1993
Gandour, R.W. **2**-388, **15**-2121
Ganellin, C.R. **4**-77
Ganem, B. **10**-528, **10**-638, **10**-759, **15**-431, **15**-527, **16**-1974, **17**-285, **19**-161, **19**-736, **19**-1163
Ganesan, K. **16**-1040, **16**-172
Ganesh, K.N. **19**-573
Ganesh, M. **15**-1408
Ganesh, Y.S.S. **11**-396, **19**-1205
Ganganna, B. **10**-1205
Ganguli, S. **10**-388
Ganguly, B. **16**-7
Ganguly, N.C. **11**-242, **11**-302, **16**-203, **18**-339
Ganguly, S. **15**-85
Ganguly, S.N. **11**-128, **16**-1900
Ganin, E. **19**-597
Ganis, P. **2**-311
Gano, J. **4**-500
Gansäuer, A. **14**-18, **16**-575, **19**-1644
Ganter, C. **18**-119
Gantzel, P. **3**-210
Gantzel, P.K. **2**-299
Ganushchak, N.I. **13**-818
Ganzer, D. **13**-125
Ganzer, G.A. **4**-518
Gao, B. **19**-529
Gao, C.-Y. **13**-211
Gao, C.-L. **19**-68
Gao, D. **15**-2197
Gao, F. **15**-2114, **16**-376, **16**-898
Gao, G. **15**-782, **19**-163, **19**-1055
Gao, H. **15**-444, **16**-1206, **19**-1118
Gao, J.-X. **19**-956
Gao, J. **4**-286, **10**-21, **14**-300, **18**-704, **19**-179, **19**-800
Gao, J.J. **16**-820
Gao, K. **13**-579

Gao, L. **10**-858, **13**-495, **15**-1721, **16**-1173, **16**-1206
Gao, L.-X. **13**-514, **15**-210, **19**-180
Gao, Q. **15**-945, **16**-1094, **16**-1490
Gao, S. **15**-1444, **15**-1445, **19**-269
Gao, W.-Z. **15**-244
Gao, W. **15**-249, **15**-411
Gao, X. **15**-1741
Gao, Y.-H. **15**-351
Gao, Y. **10**-529, **10**-842, **10**-1074, **15**-449, **15**-1971, **16**-1201, **16**-1582, **19**-866, **19**-892
Gao, Z.-R. **13**-497
Gaoni, Y. **2**-300, **2**-301, **2**-315, **2**-354
Gapinski, R.E. **16**-1839
Garapon, J. **15**-1691
Garau, C. **13**-23
Garavelas, A. **15**-267
Garavelli, M. **18**-906
Garay, R.O. **17**-55
Garbarino, G. **17**-60
Garbarino, J.A. **16**-2175
Garber, S.B. **18**-846
Garbisch Jr., E.W. **12**-151, **13**-13, **19**-1347
Garcia-Garibay, M. **4**-146
Garcia-Ochoa, S. **10**-1611
Garcia-Slanga, B.J. **13**-823
García-Río, L. **3**-184
García-Granda, S. **10**-1236
García-Delgado, N. **10**-736
García-Ruano, J.L. **11**-269
García-Cuadrado, D. **13**-445
García-Gómez, G. **15**-1038
García-Expósito, E. **15**-2454
García-Granda, S. **15**-2500, **15**-2527
García-Garrido, S.E. **15**-2683
García-Ruiz, J.M. **16**-575
García Ruano, J.L. **10**-518
García Ruano, J.L.G. **19**-1482
Garcia, A. **15**-482, **15**-593
García, B. **8**-131, **12**-509
Garcia, B.A. **10**-1107
García, C. **16**-666, **16**-675, **16**-681
Garcia, E. **10**-1806
García, G.V. **15**-909
Garcia, H. **16**-1516, **19**-128
García, I. **15**-163
Garcia, I.F. **16**-638
García, J.-I. **15**-2238
Garcia, J. **16**-754, **16**-1969
García, J.I. **15**-2238, **15**-2244, **15**-2524
García, J.M. **11**-326, **15**-1407
Garcia, L. **10**-1179
Garcia, L.A. **15**-2120
García, M.C. **15**-1451
García, T. **16**-1773, **19**-459
Garcias, X. **13**-244
Gard, M.N. **2**-319
Gardelli, C. **10**-683, **10**-1219, **10**-1647, **10**-1744
Gardette, M. **15**-979
Gardiner Jr., W.C. **6**-49
Gardiner, J.M. **15**-662
Gardiner, S.D. **10**-639
Gardini, G.P. **14**-174, **14**-382
Gardlik, J.M. **4**-89
Gardner, H.C. **15**-885
Gardner, J.N. **19**-1594
Gardner, P.D. **4**-504
Gardossi, L. **17**-158
Gareau, Y. **10**-839, **15**-302
Gareev, G.A. **10**-680
Garg, N.K. **13**-513, **13**-548
Garg, P. **18**-144
Gargalak Jr., J. **12**-300
Gargo, J.V.S. **19**-223
Gariano Jr., P. **10**-755
Gariano, A. **10**-755
Garibina, V.A. **16**-1364
Garigipati, R.S. **16**-421
Garima. **18**-342
Garley, M. **10**-777
Garlyauskayte, R.Yu. **11**-453
Garner, C.M. **15**-709
Garner, C.S. **12**-8
Garner, J. **10**-974
Garner, L.A. **18**-934
Garner, P. **10**-905
Garnett, J.L. **11**-120, **11**-121, **11**-122
Garnier, B. **18**-217
Garnier, J. **11**-697
Garnier, J.M. **15**-1717
Garnier, L. **10**-1966
Garofalo, A. **16**-92
Garratt, D.G. **15**-1, **15**-21, **15**-27, **15**-88
Garratt, P.G. **2**-300
Garratt, P.J. **2**-99, **2**-115, **2**-275, **2**-300, **2**-316, **2**-334, **2**-385, **4**-537
Garrell, R.L. **3**-195
Garrett, C.E. **14**-22, **15**-724
Garrido, F. **13**-666
Garrido, G. **8**-86
Garrido, N.P. **18**-781
Garrison, B.J. **7**-17
Garrone, A. **19**-125
Garst, J.F. **10**-1398, **12**-460, **12**-640, **15**-1620, **16**-525, **16**-2145, **18**-446, **18**-447
Garst, M.E. **15**-2665, **19**-1390
Garver, L.C. **12**-218
Garvey, D.S. **4**-136, **10**-991, **19**-150
Garwood, D.C. **10**-9
Garza, T. **15**-2374
Garzya, V. **11**-216
Gasc, M.B. **15**-325, **15**-329
Gasch, C. **19**-292
Gaset, A. **10**-842, **16**-1384
Gash, D.M. **4**-221
Gasol, V. **10**-1944, **15**-1671
Gaspar, P.P. **12**-51, **15**-2538
Gaspard-Iloughmane, H. **10**-1152
Gaspari, M. **10**-974, **16**-136
Gasparrini, F. **4**-62, **19**-1494
Gassman, P.G. **4**-242, **5**-443, **5**-444, **10**-145, **10**-151, **10**-153, **10**-156, **10**-161, **10**-164, **10**-297, **10**-316, **10**-1017, **10**-1675, **11**-553, **11**-554, **12**-247, **12**-713, **15**-319, **15**-2285, **15**-2413, **15**-2414, **15**-2416, **16**-1641, **16**-1691, **17**-193, **18**-371, **18**-905, **19**-1303
Gastaldi, S. **17**-144, **19**-1293
Gasteiger, J. **1**-100, **2**-60, **2**-219, **15**-579
Gastner, T. **16**-912
Gaston, L.K. **19**-1706
Gatehouse, B.M. **12**-290
Gates, M. **10**-184
Gath, S. **2**-372
Gati, A. **15**-2589
Gati, E. **4**-195
Gatti, M. **15**-1269
Gatto, V.J. **3**-153
Gau, G. **8**-17
Gau, H.-M. **16**-603, **16**-653
Gaudemar, M. **10**-1750, **10**-1801, **16**-830
Gauder, S. **19**-1233
Gaudry, M. **16**-383
Gaugler, R.W. **8**-29
Gaul, J.M. **19**-1488
Gäumann, T. **15**-478
Gaumont, A.C. **9**-137
Gaunt, M.J. **11**-429, **13**-220, **15**-150, **15**-1077, **15**-1081, **15**-1420, **15**-2523, **18**-965
Gaur, S. **12**-104
Gausepohl, R. **16**-960
Gautam, V.K. **15**-729
Gauthier Jr., D.R. **13**-273
Gauthier, D. **10**-1309
Gauthier, D.A. **15**-2686
Gauthier, D.R. **12**-759
Gauthier, J.Y. **16**-1840
Gauthier, R. **16**-995
Gauthier, S. **13**-229
Gautier, A. **10**-575
Gautier, J. **16**-418
Gavard, J. **11**-587
Gavaskar, K.V. **15**-921
Gavazza, F. **16**-2104
Gavezzotti, A. **1**-9, **1**-77
Gavi, T. **10**-812
Gaviña, F. **13**-50
Gavrilenko, V.V. **12**-504, **19**-1099
Gavrilov, K.N. **10**-882
Gavryushin, A. **13**-211
Gavuzzo, E. **4**-69
Gawande, M.B. **16**-1872
Gawienowski, J.J. **7**-85
Gawinecki, R. **12**-84

Gawley, R.E. **9**-82, **12**-3, **12**-441, **13**-305, **16**-1112, **17**-453, **18**-335
Gawronska, K. **5**-382
Gawronski, J. **4**-115, **5**-382
Gayathri, K.U. **14**-336
Gaye, M. **19**-181
Gaylord, N.G. **19**-1051, **19**-1064, **19**-1472
Gázguez, J.L. **8**-173
Gazit, A. **10**-259, **10**-260
Gazzolo, F.H. **13**-7
Ge, C.-S. **15**-2478
Ge, H.-Q. **15**-1906
Ge, H. **13**-578
Ge, J. **15**-2061
Ge, Z. **16**-1085
Gealageas, R. **18**-269
Geary, L.M. **16**-1074
Gebicki, J. **3**-174
Gebicki, J.M. **5**-220
Gebreyes, K. **17**-351
Gebrian, J.H. **2**-284
Gedanken, A. **15**-2204, **19**-147
Gedye, R. N. **7**-105
Gee, K.R. **18**-634, **18**-713
Geels, E.J. **12**-751
Geerlings, P. **13**-52, **14**-113
Geetha, V. **15**-1058
Geib, A.D. **15**-1565
Geib, G.D. **16**-1410
Geib, S.J. **13**-435, **15**-1351, **15**-1564
Geiger, M. **4**-120
Geise, H.J. **4**-329, **19**-1687, **19**-1689
Geise, H.Y. **19**-1699
Geisel, M. **14**-475, **17**-411
Geiss, W. **5**-343
Geissler, M. **5**-138
Geissman, T.A. **19**-1725
Gelalcha, F.G. **15**-1885
Gelas-Mialhe, Y. **10**-1283
Gelder, E.A. **19**-1182
Geletii, Y.V. **19**-489
Geller, B.A. **10**-953, **11**-612
Geller, L.E. **18**-929
Geller, T. **15**-1958, **15**-1961
Gellert, E. **13**-827
Gellman, A.J. **19**-1299
Gellman, S.H. **15**-1107, **15**-1033, **15**-1056, **16**-1842, **16**-1966
Gelman, D. **11**-364, **13**-360, **16**-1366
Gelman, S.H. **3**-74
Gelpke, A.E.S. **13**-244
Geltz, Z. **8**-132
Gendrineau, T. **15**-1280
Genesio, E. **15**-561
Geneste, J. **15**-1706
Genêt, J.-P. **4**-155, **10**-240, **10**-1893, **12**-346, **13**-381, **12**-537, **13**-571, **13**-814, **13**-815, **13**-816, **15**-1279, **15**-1280, **15**-1008, **15**-242, **15**-972, **16**-760, **19**-1600, appendixa-27
Geng, B. **16**-736
Geng, F. **18**-438, **18**-440
Geng, X.-L. **15**-1903
Geng, Z. **16**-1122
Genin, E. **15**-242, **15**-972
Gennari, C. **16**-1488, **16**-943, **16**-1098, **16**-1125
Gennaro, A. **10**-1997
Gennet, D. **16**-1344
Genov, D.G. **18**-814
Genovese, S. **15**-1716
Gente, G. **14**-117
Gentile, A. **11**-182
Gentili, P. **10**-281, **13**-65, **13**-68, **19**-172
Gentilucci, L. **6**-36, **15**-1415
Gentric, E. **3**-19
Geoffroy, M. **19**-935
Geoffroy, O.J. **19**-1520
Geoghegan Jr., P.J. **15**-183
Georg, G.I. **13**-578, **16**-1895, **18**-856, **19**-1111, **19**-1118
Georgakilas, V. **11**-451
George, A.V. **15**-2208
George, M.V. **7**-66, **7**-67, **15**-1391, **18**-506, **19**-10
George, P. **2**-30, **15**-2335
George, R.S. **16**-506
George, T.G. **15**-1658, **15**-1729, **15**-1757
Georghiou, P.E. **13**-537, **19**-1281
Georgiadis, G.M. **18**-961
Georgiadis, R. **8**-255
Georgoulis, C. **10**-238, **19**-82
Georgy, M. **10**-1595
Geraci, C. **3**-128, **3**-144, **4**-69, **4**-95
Geraghty, N.W.A. **15**-752
Gérard, D. **18**-266
Gérard, L. **18**-14
Gerasimova, E.S. **18**-320
Gerber, G.E. **16**-1776
Gerdes, J.M. **16**-130
Gerdes, P. **15**-1463
Gerdil, R. **3**-162
Gerecs, A. **11**-583
Gerhardt, G. **6**-18
Gerhardt, H. **16**-1933
Geri, R. **15**-378
Géribaldi, S. **15**-39
Gerisch, M. **16**-986
Gerken, J.B. **18**-623
Gerlach, A. **15**-1833
Gerlach, H. **3**-213, **16**-1764
Gerlitz, O.O. **15**-2669
Germain, A. **5**-61, **11**-481
Germain, G. **4**-481
German, A.L. **16**-1806
German, L. **11**-308, **12**-111, **14**-151
German, L.S. **15**-73, **15**-1755
Germani, R. **10**-438, **10**-725, **15**-1817, **15**-1968, **19**-273
Germon, C. **10**-1605
Gernon, M. **12**-425
Gerrard, W. **8**-24, **8**-255, **12**-490, **17**-232
Gerratt, J. **2**-133, **15**-2129
Gerrits, P.J. **16**-1500
Gersch, B. **3**-121
Gersmann, H.R. **12**-319, **14**-249
Gerson, F. **5**-333, **5**-335, **5**-340, **5**-341, **5**-345
Gerstenberger, M.R.C. **14**-149
Gertrude Gutierrez, M. **2**-277
Gesche, P. **18**-515
Geslin, M. **19**-1234
Gessler, S. **18**-853
Gesson, J. **11**-567
Gestmann, D. **4**-455
Gettwert, V.J. **11**-133
Getzler, Y.D.Y.L. **10**-1632
Geuenich, D. **2**-107
Geurts, K. **10**-1370, **15**-1185
Geuss, R. **5**-178
Gevorgyan, G.A. **16**-372, **16**-373
Gevorgyan, V. **10**-1502, **10**-1928, **13**-318, **13**-609, **15**-244, **15**-371, **15**-563, **15**-777, **15**-860, **15**-880, **15**-2582, **15**-2596, **15**-2603, **16**-808, **19**-1429
Ghadir, K.D.F. **1**-45
Ghaemi, E. **11**-134, **12**-732
Ghaffarzadeh, M. **19**-1134
Ghambarian, M. **5**-372
Ghanbari, M. **16**-1007
Ghannam, A. **18**-960
Ghassemzadeh, M. **16**-54, **16**-127, **19**-114, **19**-130, **19**-248
Ghatak, A. **16**-2219
Ghatak, U.R. **19**-396
Ghazi, I. **10**-1233
Ghelfenstein, M. **18**-447
Ghelfi, F. **12**-115, **12**-117, **14**-23, **15**-1654, **15**-1732, **19**-804
Ghenciulescu, A. **19**-607
Gheorghiu, M.D. **15**-2420
Ghiaci, M. **11**-245
Ghirardelli, R.G. **17**-45
Ghiro, E. **15**-54
Ghiron, C. **15**-561
Ghiviriga, I. **5**-386
Ghobrial, M. **18**-389
Ghodrati, K. **16**-211
Gholap, A.R. **13**-592
Gholizadeh, M. **19**-81, **19**-835
Ghoneim, N. **7**-36
Ghorai, M.K. **10**-702
Ghorai, S. **18**-861
Ghoroku, K. **13**-711
Ghorpade, S.R. **16**-1847
Ghosal, S. **14**-429
Ghose, B.N. **14**-349
Ghosez, A. **14**-16

Ghosez, L. **8**-205, **10**-1150, **11**-356, **15**-2187, **15**-2195, **15**-2216, **15**-2338, **15**-2389, **15**-2390, **15**-2422, **15**-2423, **16**-1990
Ghosh, A.C. **16**-1236
Ghosh, A.K. **16**-29, **18**-876
Ghosh, K. **13**-562, **16**-862, **16**-2095, **19**-1096
Ghosh, M. **18**-754
Ghosh, P.K. **11**-294
Ghosh, R. **13**-495, **16**-1711, **16**-1714, **16**-1863
Ghosh, S. **11**-390, **12**-220, **17**-454, **18**-282, **18**-754, **19**-562
Ghosh, S.C. **10**-1045
Ghoshal, A. **19**-1037
Ghribi, A. **10**-1600
Ghribi, A. **10**-1600
Giacomelli, G. **7**-46, **12**-760, **12**-766, **16**-1811, **16**-1901, **16**-2064, **16**-2291, **17**-484, **19**-649
Giacomini, D. **15**-2241, **16**-1021, **19**-1044
Giagou T. **19**-149
Giamalva, D. **19**-340
Giambastiani, G. **10**-1523
Gianeti, T.R. **15**-322
Giang, Y.F. **17**-172, **17**-174
Giangiordano, M.A. **16**-883
Gianni, M.H. **4**-270, **4**-363
Giannis, A. **19**-656
Giannotti, C. **14**-373
Gianotti, M. **15**-1415
Giardello, M.A. **15**-2027
Giarlo, G. **10**-1056
Gibbard, H.C. **2**-295
Gibbons, C.S. **4**-471
Gibbs, D.E. **19**-1232
Gibbs, H.W. **11**-59
Gibbs, R.A. **10**-974, **16**-124, **16**-1517, **16**-1538
Gibbs, S.A. **15**-2161
Gibby, J.E. **15**-2682
Gibe, R. **12**-371
Giberson, C.B. **2**-298
Gibian, M.J. **5**-320
Giblin, G.M.P. **19**-662
Gibson, C.P. **14**-420
Gibson, D. **13**-282
Gibson, D.T. **15**-1864, **15**-1865, **15**-1866, **15**-1867
Gibson, M.S. **10**-877, **10**-1032
Gibson, S.E. **15**-1539, **15**-1539, **15**-1560
Gibson, T.L. **11**-383
Gibson, V.C. **18**-807
Gidaspov, B.V. **10**-1093, **11**-140, **12**-744, **18**-318, **18**-334
Gidley, G.C. **17**-88
Giebel, D. **11**-443
Gielen, M. **4**-28, **15**-2646
Gieren, A. **4**-488
Giersch, W. **19**-305
Giese, B. **5**-255, **5**-284, **5**-309, **5**-408, **14**-2, **14**-16, **14**-71, **14**-72, **14**-109, **14**-143, **14**-315, **15**-51, **15**-53, **15**-67, **15**-92, **15**-101, **15**-128, **15**-790, **15**-1283, **15**-1287, **15**-1306, **15**-1470, **15**-1474, **15**-2536, **18**-77
Giese, C.M. **15**-2540
Giese, R.W. **19**-326
Giese, S. **15**-1092, **15**-1530
Giesen, F.L.L. **11**-361
Gieson, V. **10**-1376
Giessert, A.J. **15**-848, **15**-2669, **18**-888, **18**-889, **18**-890
Giessner-Prettre, C. **5**-187, **8**-215
Gigante, B. **16**-1516
Giger, U. **15**-2554
Giglio, E. **3**-176
Giguere, R.J. **7**-106, **10**-502, **12**-664
Gil-Av, E. **4**-175
Gil, P. **13**-50
Gil, R. **10**-974, **11**-445
Gil, R. **15**-1234, **15**-2217
Gil, S. **12**-4, **19**-817
Gilabert, D.M. **19**-276
Gilardi, R. D. **16**-1879
Gilbert, A. **15**-2679, **18**-528
Gilbert, B. **8**-126
Gilbert, B.A. **10**-1263
Gilbert, B.C. **5**-369, **10**-1295, **14**-166, **14**-394, **15**-1347
Gilbert, D.P. **15**-319
Gilbert, E.E. **11**-195, **11**-207, **11**-673, **12**-260, **13**-103, **14**-292, **14**-402, **16**-365, **16**-433, **19**-769, **19**-772
Gilbert, H.F. **16**-10
Gilbert, J.C. **4**-499, **15**-2408, **15**-2418, **18**-92, **18**-746
Gilbert, K.E. **18**-666, **19**-744
Gilbert, L. **19**-1048
Gilbert, R.P. **10**-268
Gilbert, T.M. **15**-2417
Gilbertson, R.D. **5**-65
Gilbertson, S.R. **12**-286, **13**-436, **13**-436, **15**-2692, **18**-814, **18**-886
Gilchrist, J.H. **8**-220, **8**-222, **10**-1703
Gilchrist, M. **10**-377, **16**-21
Gilchrist, T.L. **5**-348, **13**-39, **15**-2053, **15**-2297, **15**-2371, **18**-506
Gilday, J.P. **7**-115, **12**-426, **12**-698, **12**-717, **12**-718
Giles, P.R. **16**-812
Gilheany, D.G. **16**-459, **15**-1983, **15**-1986, **16**-1325, **19**-767
Gilhespy, M. **19**-185
Gilkerson, T. **19**-1214
Gill, G. **4**-334
Gill, G.B. **15**-825, **15**-2297, **16**-1573
Gille, B. **16**-1559
Gilles, J. **2**-320, **2**-327, **2**-345, **2**-355, **18**-674
Gillespie, K.M. **15**-2045, **15**-2070
Gillespie, R.J. **5**-24, **8**-18, **8**-19, **11**-151
Gilley, C.B. **19**-663
Gillies, C.W. **19**-340, **19**-349
Gillies, J.Z. **19**-349
Gillingham, D.G. **10**-1450, **18**-846
Gillmore, A.T. **10**-627
Gillmore, J.G. **5**-331, **14**-81
Gilman, H. **4**-14, **10**-1350, **12**-1, **13**-45
Gilman, N.W. **14**-304
Gilmore, N.J. **19**-1020
Gilow, H.M. **11**-44
Gimbert, C. **15**-1044
Gimbert, Y. **15**-1540, **15**-1557, **15**-1572, **15**-1573, **16**-1379
Gimeno, J. **15**-205, **15**-2683
Gimisis, Z.T. **15**-1311
Gimzewski, J.K. **8**-251
Ginah, F.O. **10**-1292
Gingras, M. **10**-535, **10**-805, **10**-829
Ginodman, L.G. **13**-170
Ginos, J.Z. **16**-2266
Ginsburg, D. **4**-452, **15**-1032, **15**-2312
Ginzburg, B.M. **13**-72
Giordano, C. **11**-646, **14**-140, **14**-389, **18**-202, **19**-934
Giordano, F. **15**-2115
Giovani, E. **10**-837
Giovannini, P.P. **19**-223
Giovannini, R. **10**-1470, **19**-1254
Gipe, B.T. **15**-4, **15**-34
Gipson, J.D. **16**-749
Giralt, E. **13**-517
Girard, C. **15**-2552, **19**-1048
Girard, J.-P. **18**-157
Giri, R. **11**-537
Giri, S. **8**-182
Giri, V.S. **19**-1411, **19**-1465
Girichev, G.V. **2**-450
Giroux, A. **10**-2001
Girreser, U. **2**-342
Gisdakis, P. **15**-1877, **15**-1882, **15**-2107, **19**-123
Gissot, A. **13**-304, **13**-723, **15**-2112
Gitlin, L.F. **17**-96
Gitlitz, M.H. **12**-620
Giudicelli, M.B. **10**-1102
Giuffrida, D. **2**-342
Giuli, S. **16**-1229, **16**-1242, **19**-1254
Giuliani, A. **15**-1397, **16**-1229, **16**-1242
Giuliano, C. **10**-1222
Giumanini, A. **18**-418

Giumanini, A.G. **10**-1828, **12**-735, **13**-847, **16**-1821, **18**-411
Giunta, N. **15**-1821
Givens, R.S. **7**-54, **17**-499, **17**-515, **18**-678
Gjuranovic, Z. **10**-155
Gladfelter, W.L. **12**-778
Gladiali, S. **15**-1614
Gladys, J.A. **19**-875, **19**-1431
Gladysheva, F.N. **15**-2152
Gladysz, J.A. **17**-194, **19**-1047
Glänzer, B.I. **15**-535
Glapski, C. **15**-1118
Glaser, P.B. **15**-761
Glaser, R. **5**-69, **13**-6, **13**-25, **13**-29
Glasfeld, A. **4**-261
Glasovac, Z. **2**-88, **8**-93
Glass, L.E. **10**-189
Glass, R.S. **4**-367, **4**-400, **16**-425
Glass, T. **2**-405
Glatzhofer, D.T. **16**-1815
Glazer, E.A. **18**-374
Glazunova, E.M. **16**-541
Gleason, B.L. **15**-2161
Gleason, J.D. **16**-1540
Gleason, J.G. **12**-182, **19**-1405
Gleason, J.L. **15**-866
Gleave, D.M. **16**-1071
Glebova, E.V. **16**-415
Gledhill, A.P. **19**-1549
Gleich, A. **4**-252
Gleicher, G.J. **2**-39, **14**-123, **14**-141, **15**-102, **18**-117
Gleiter, R. **2**-55, **2**-199, **2**-372, **4**-258, **4**-448, **4**-511, **15**-1567, **15**-2116, **15**-2312, **16**-2045, **18**-668
Glendening, E.D. **2**-24
Glenn, A.G. **18**-75
Glick, A.H. **16**-2207
Glick, H.C. **5**-391
Glick, R. **9**-47
Glick, R.E. **9**-54
Glidewell, C. **2**-149
Glieder, A. **19**-993
Gligorich, K.M. **15**-226
Glöckner, H. **2**-261
Gloe, K. **3**-144
Gloor, B.F. **13**-631
Glorius, F. **10**-1463, **10**-1546, **13**-605
Glover, B. **13**-314
Glover, C. **16**-117
Glover, I.T. **18**-40
Glover, S.A. **15**-1352, **15**-1703
Glukhovtsev, M.N. **2**-234, **2**-316, **5**-348
Glushkov, R.G. **10**-410, **10**-710
Glyde, E. **2**-414
Gmouth, S. **11**-449
Gnaim, J.M. **11**-246
Gnanadesikan, V. **15**-1883, **16**-411, **16**-2199
Gnanapragasam, N.S. **11**-304
Gnedin, B.G. **16**-2273
Gnonlonfoun, N. **15**-818
Goblyos, A. **2**-486
Goda, K. **10**-1276, **15**-770
Godard, C. **15**-1621
Goddard III, W.A. **2**-241, **15**-2518, **19**-128, **19**-188, **19**-701
Goddard, J.-P. **15**-736
Goddard, J.D. **15**-2281
Godefroi, E.F. **19**-1377
Godel, T. **10**-1745
Godenschwager, P.F. **10**-1747, **10**-1748
Godet, T. **16**-2261
Godfrey, A.G. **17**-285, **19**-161
Godfrey, C.R.A. **19**-51, **19**-1390
Godfrey, I.M. **18**-401
Godfrey, M. **8**-186, **11**-87
Godfrey, P.D. **13**-43, **13**-51
Godin, B. **13**-442
Godjoian, G. **19**-1110
Godleski, S. **4**-214
Godleski, S.A. **18**-116
Godoi, M. **16**-666
Godovikova, T.I. **13**-772
Godschalx, J.P. **10**-1969
Godt, A. **3**-208
Goeddel, D. **15**-1932, **15**-1936
Goedecke, E. **2**-200
Goedken, V. **5**-382, **18**-19
Goel, A.B. **10**-100, **10**-801, **15**-978, **17**-181
Goel, O.P. **16**-2173
Goel, S.C. **18**-122
Goem G.L. **15**-258
Goering, H.L. **4**-151, **10**-230, **10**-74, **10**-78, **10**-79, **10**-229, **10**-1500, **10**-1586, **10**-1763, **14**-284, **15**-55, **15**-58
Goerlich, J.R. **12**-372
Goggiamani, A. **13**-163, **13**-238, **13**-667, **15**-907, **16**-2104, **18**-381
Goggiamani, AA. **13**-608
Gogia, A. **19**-304
Gogoi, B.J. **16**-922
Gogoi, N. **16**-1213
Gogoi, P. **16**-58, **18**-297, **19**-222, **19**-240
Gogoll, A. **13**-601
Gogonea, V. **2**-370
Gøgsig, T.M. **10**-1309
Goh, E.-L. **16**-560
Goh, J.-D. **16**-639
Goh, S.H. **11**-689
Gohain, M. **10**-1637
Gohain, M. **9**-114
Going, R. **12**-149
Gois, P.M.P. **19**-687
Goj, L.A. **15**-805
Gojo, T. **10**-834
Gök, Y. **13**-595
Gokcek, D.Y. **16**-1764
Gokel, G.W. **3**-94, **3**-106, **3**-109, **3**-122, **3**-153, **10**-484, **10**-628, **10**-720, **10**-812, **10**-1015, **10**-1106, **10**-1708, **10**-1932, **13**-776, **13**-823, **15**-2485, **16**-2253, **16**-2253, **16**-2262, **17**-481, **19**-1547
Göksu, S. **10**-985, **19**-379
Golan, O. **4**-339, **4**-357
Gold, H. **10**-550, **13**-397, **16**-453
Gold, V. **5**-6, **5**-72, **6**-53, **8**-26, **13**-10, **16**-1998, **19**-1001
Goldberg, B.J. **10**-222
Goldberg, G.M. **12**-455
Goldberg, I **1**-71, **3**-163
Goldberg, S.I. **17**-132
Gol'dberg, Yu.Sh. **15**-2485
Goldblum, A. **4**-74, **16**-2289
Golden, D.M. **5**-278, **15**-60
Golden, J.T. **11**-613
Golden, K.C. **10**-574, **15**-618, **16**-123
Goldenberg, W. S. **5**-185, **5**-190
Gol'dfarb, Ya.L. **4**-477
Goldfinger, P. **14**-206
Goldfuss, B. **5**-308, **19**-1027
Golding, B.T. **10**-924, **12**-687
Golding, G.M. **13**-548
Gol'ding, I.R. **13**-580
Golding, P. **10**-792
Golding, P.D. **11**-626
Goldman, A.S. **19**-44, **19**-56
Goldman, B.E. **16**-1571
Goldman, G. **11**-212, **11**-430
Goldman, G.K. **2**-417
Goldman, I.M. **15**-2453
Goldman, L. **19**-155, **19**-165
Goldman, M. **4**-175
Goldmann, A. **4**-458
Goldring, W.P.D. **18**-876
Gol'dshtein, I.P. **3**-3
Goldsmith, B. **19**-1283, **19**-1505
Goldsmith, M.D. **12**-387
Goldwhite, H. **15**-75, **11**-632
Golinski, J. **19**-757
Goll, J.M. **11**-329
Goller, A. **2**-430
Goller, E.J. **4**-141
Gollnick, K. **14**-250, **14**-263, **15**-2356
Golobish, T.D. **4**-449
Golobov, Y.G. **19**-1259
Golod, E.L. **11**-30, **11**-140
Gololobov, Yu.G. **16**-1471
Golovina, Z.P. **16**-33
Golse, R. **10**-1604
Golubeva, I.A. **16**-415
Golubkin, L.N. **11**-48
Gomaa, M.A.-M. **11**-173
Gomberg, M. **5**-3, **5**-241, **19**-1627
Gomes Jr., M. **14**-362
Gomes, A.K. **15**-1037
Gomes, P. **10**-1515
Gomez-Paloma, L. **4**-123

Gomez-Bengoa, E. **15**-2296
Gómez-López, M. **3**-201
Gómez-Parra, V. **10**-757
Gómez-Bengoa, E. **13**-141
Gómez-Benítez, V. **13**-150
Gómez-Lor, B. **13**-376
Gómez-Escalonilla, M.J. **13**-519
Gómez-Bengoa, E. **15**-1407
Gómez Aranda, V. **15**-2031
Gómez, A.M. **10**-1611, **15**-1319
Gómez, B. **15**-2298
Gómez, C. **15**-2572
Gómez, G. **19**-181
Gómez, J. **8**-138, **8**-144
Gómez, J.L. **17**-486
Gómez, M. **10**-1532
Gommermann, N. **16**-470, **16**-925
Gompper, R. **2**-246, **2**-247, **2**-249, **2**-261, **10**-515, **15**-2434, **18**-669
Goncalves, S.M.C. **10**-851, **12**-152
Gondi, V.B. **19**-1118
Gong, H. **16**-78
Gong, J.-F. **13**-197, **13**-503
Gong, L.-Z. **15**-1272, **16**-400, **16**-1082, **16**-1084
Gong, L. **19**-1255
Gong, M.-Z. **16**-545
Gong, W.H. **13**-433, **13**-467
Gong, Y. **7**-126, **7**-127
Gonikberg, E.M. **15**-998, **19**-1012
Gonthier, E. **13**-599, **18**-856
Gonzalez-Outeirino, J. **4**-361
González-Sierra, M. **2**-460
González-Nilo, F. **8**-90
González-Bobes, F. **13**-548, **14**-162
González-Zamora, E. **15**-441
González-Rodríguez, C. **15**-851, **18**-387, **19**-70, **19**-479, **19**-777
Gonzalez, D. **15**-1867, **15**-2441
González, E. **16**-1249
González, G. **11**-269
González, I. **10**-918, **13**-498
Gonzalez, J. **16**-1897
González, J.J. **13**-376
González, J.M. **10**-686, **14**-162, **15**-372, **15**-1672, **15**-1673
Gonzalez, M.A. **10**-1837
González, R.R. **10**-146, **19**-325, **19**-1535
Gonzalez, T. **10**-493
Gonzlez, A.M. **15**-602
Gooch, E.E. **12**-517
Good, G.M. **15**-1591
Goodacre, P.R. **14**-392
Goodale, J.W. **7**-83, **7**-92
Goodarzi, M. **19**-85
Goodby, J.W. **10**-1366
Goodchild, N.J. **14**-20
Goode, E.V. **1**-39
Goode, N.C. **4**-249
Goodenough-Lashua, D.M. **4**-324
Goodenough, K.M. **19**-1375
Goodhue, C.E. **10**-1887, **11**-237
Gooding, O.W. **16**-335, **16**-1857
Goodlett, V.W. **15**-2395
Goodman, J.L. **1**-107, **5**-404, **5**-416, **15**-2546
Goodman, J.M. **15**-1267, **16**-807, **16**-1077, **16**-1098
Goodman, L. **10**-1185, **17**-224
Goodman, M. **3**-213
Goodman, R.M. **16**-167
Goodman, S.N. **7**-131
Goodwin, T.H. **2**-4, **2**-7
Goon, S. **11**-493
Goosen, A. **14**-237, **15**-1703, **18**-927
Gooßen, L.J. **11**-658, **11**-663, **13**-562, **15**-277, **15**-409, **16**-162, **16**-862, **16**-1893, **16**-2095, **17**-230, **19**-1096
Gopalaiah, K. **18**-346
Gopalakrishnan, G. **16**-86
Gopalan, A.D. **9**-105
Gopalan, R. **12**-157
Gopalarathnam, A. **10**-930
Gopinath, R. **16**-131, **19**-682
Gopius, E.D. **18**-44, **18**-259
Goracci, L. **19**-273
Goralski, C.T. **10**-964, **15**-704, **19**-1141, **19**-1166, **19**-1510
Gorb, L. **12**-85, **17**-211
Görbitz, C.H. **3**-39
Gorczyca, A.M. **4**-230
Gordi, Z. **18**-353
Gordillo, Á. **13**-698
Gordillo, B. **4**-374
Gordillo, R. **15**-2290, **15**-2355, **16**-1074
Gordo, J. **16**-989
Gordon, A.J. **14**-245, **15**-130
Gordon, C.M. **16**-635
Gordon, G. **18**-721
Gordon, I.M. **16**-2270
Gordon, J.E. **10**-354
Gordon, J.R. **16**-2263
Gordon, K.M. **17**-293, **19**-588
Gordon, M. **17**-381
Gordon, M.D. **15**-2229
Gordon, M.S. **1**-11, **1**-12
Gordon, P.F. **7**-5, **11**-163
Gordon, R.J. **18**-534
Gordon, R.S. **13**-392, **13**-501
Gore, J. **10**-1504, **10**-1422, **15**-208, **15**-547, **15**-1745, **15**-2422
Gore, P.H. **11**-430, **11**-77, **11**-478, **11**-647
Gorecka-Kobylinska, J. **8**-100
Gorelik, M.V. **2**-99, **11**-621
Goren, A.C. **18**-678
Goren, Z. **4**-357
Gorenstein, D.G. **13**-32, **16**-32
Goretti Gomes, M. **16**-198
Gori, D. **16**-801
Gorin, D.J. **18**-330
Gorman, A.A. **14**-251, **15**-2361
Gorman, D.B. **15**-2285
Gorman, J.A. **4**-321
Gormisky, P.E. **10**-1895
Görner, H. **7**-58
Gornitzka, H. **5**-360
Gorsane, M. **15**-2015
Gorsuch, S. **10**-1336
Gorton, P.J. **15**-179
Gortva, A.M. **18**-604
Gosavi, R.K. **18**-235
Gosberg, A. **15**-1203
Goshaev, M. **13**-468
Gosmini, C. **10**-1515, **13**-450, **15**-1221, **16**-2036
Gosney, A.P. **11**-161
Gosney, I. **2**-96, **15**-16, **16**-1381
Gossage, R.A. **12**-420, **13**-732
Gosselain, P.A. **14**-206
Gosselin, F. **19**-1142
Gosselin, P. **10**-386
Gosser, L. **12**-30
Gössler, W. **7**-107
Goswami, A. **15**-1861
Goswami, P. **12**-127
Goswami, S. **19**-620
Gotanda, K. **12**-257, **14**-11
Gotebiowski, A. **4**-138
Gothelf, A.S. **11**-388
Gothelf, K.V. **13**-187, **16**-966, **16**-1221
Goti, A. **17**-452, **19**-298, **19**-745, **19**-752, **19**-1222
Goto, A. **16**-101
Goto, H. **4**-284, **19**-1646
Goto, K. **3**-140, **8**-203, **16**-695
Goto, M. **10**-183, **10**-472
Goto, N. **10**-471
Gotoh, H. **15**-1106, **16**-1085
Gotou, H. **2**-348
Gotou, T. **15**-973, **17**-389
Gott, P.G. **15**-2396
Gotta, M.F. **10**-375
Gottardi, W. **11**-255
Gottarelli, G. **4**-194
Gotteland, J. **15**-2164
Göttker-Schnetmann, I. **19**-38
Göttlich, R. **15**-1694
Gottlieb, H. **19**-147
Gottschalk, T. **16**-1487
Gottschling, S.E. **5**-254
Goubitz, K. **11**-654
Goud, P.R. **16**-299
Goudgaon, N.M. **12**-467, **12**-543, **12**-546
Goudmand, P. **18**-671
Gould, F.E. **19**-1169
Gould, I.R. **1**-107, **5**-356, **15**-2534, **17**-515
Gould, K.J. **18**-489
Goumont, R. **8**-188, **10**-399, **19**-193
Goumont, T. **13**-6
Goure, W.F. **10**-1969
Gourevitch, D.N. **15**-2142

Gouverneur, V. **10**-1179, **15**-1434, **15**-1688, **18**-839
Goux-Henry, C. **10**-1522
Goux, C. **10**-826
Govande, C.A. **19**-683
Gover, T.A. **14**-158
Govind, N. **18**-91
Govindachari, T.R. **11**-406
Govindan, C.K. **19**-343
Gowda, A.S.P. **19**-1194
Gowda, D.C. **19**-1140, **19**-1194, **19**-1196, **19**-1207, **19**-1720
Gowda, R.R. **19**-680
Gowda, S. **19**-1140, **19**-1194, **19**-1207
Gowenlock, B.G. **12**-740, **15**-1749
Gower, N.J. **13**-554
Gowland, F.W. **19**-1001
Gozzi, C. **13**-310, **16**-1889
Gozzo, A. **19**-1768
Gozzo, F.C. **11**-75, **18**-692
Grabner, G. **5**-380
Graboski, G.G. **16**-1199
Grabowski, E.J.J. **4**-204, **15**-1113, **18**-329, **19**-647, **19**-650
Grabowski, J. **10**-328
Grabowski, J.J. **17**-126, **18**-634
Grabowski, S. **7**-52
Grachan, M.L. **15**-1021
Gracheva, E.P. **15**-294
Gracheva, R.A. **4**-148
Gracias, V. **18**-324
Gradillas, A. **18**-820
Gradl, S.N. **18**-727, **18**-742
Graening, T. **10**-1727
Graf, N.A. **15**-2420
Graf, R. **16**-2234
Gragerov, I.P. **13**-834, **19**-606, **19**-734, **19**-1553
Graham, A. **12**-204
Graham, A.E. **10**-685, **10**-974, **16**-152, **18**-147, **18**-147
Graham, G.R. **15**-2663
Graham, J. **11**-151
Grahn, W. **15**-95
Graiver, D. **3**-204
Grajewski, J., **4**-115
Grakauskas, V. **12**-218, **12**-764, **14**-478
Gramaccioli, C.M. **2**-313, **13**-11
Gramain, J.-C. **10**-1283
Gran-Masse, H. **12**-106
Graña, P. **5**-195
Granados, P. **13**-506
Granander, J. **16**-488, **16**-491
Grand, A. **5**-275
Grand, E. **15**-2333
Grandander, J. **8**-225
Grandberg, I.I. **18**-761
Grandbois, E.R. **19**-1009
Grandclaudon, P. **16**-1379
Grandi, M. **11**-416
Grandi, R. **12**-117, **19**-804
Grandolini, G. **2**-165
Granger, M.-C. **16**-490
Granger, M.R. **16**-191
Granger, M.R. **8**-32
Granik, V.G. **4**-482, **10**-410, **10**-710, **10**-1785, **16**-418
Granito, C. **12**-769, **16**-2167
Granoth, I. **15**-525
Grant, A.A. **18**-126
Grant, C.D. **16**-930
Grant, D.M. **2**-243, **3**-83, **4**-168
Grant, E. H. **7**-112
Grant, G.M. **10**-685
Grant, H.M. **8**-45
Grant, J.L. **8**-82
Grant, R.W. **18**-428
Grant, T.N. **5**-254, **15**-1095
Gras, J. **15**-2393
Gras, J.L. **15**-2422
Grasa, G.A. **13**-195, **13**-328, **13**-641, **16**-1789, **16**-1803
Grass, F. **12**-703
Grasselli, P. **16**-484
Grätz, W. **10**-1617
Grau, G. **14**-352
Graul, S.T. **5**-107, **5**-114, **12**-671
Gravaatt, E.C. **18**-953
Gravel, D. **15**-54, **16**-1948
Gravel, M. **16**-750
Graves, C.R. **19**-143
Gravestock, M.B. **15**-820
Gray, D.L. **16**-894
Gray, P. **14**-130
Gray, T.A. **18**-517
Gray, W.K. **9**-113
Grayshan, R. **10**-1814
Grayson, J.I. **15**-2186
Grayston, M.W. **10**-1579, **18**-177
Graziani, M. **11**-505
Graziano, M.L. **15**-2115
Grazini, M.V.A. **12**-386
Grdina, M.J. **14**-263
Grdinic, M. **15**-96
Gream, G.E. **10**-147, **10**-183, **10**-186, **19**-423
Greaney, M.F. **15**-1088
Greasley. P.M. **11**-12
Greaves, T.L. **9**-119
Grebenik, P. **2**-190
Grech, E. **3**-16
Greck, C. **12**-537
Greco, G.E. **15**-2161
Grée, R. **19**-128, **19**-183
Greeley, R.H. **2**-278
Green, B. **19**-1450
Green, B.S. **4**-169, **4**-170, **9**-12
Green, D.L.C. **5**-105, **10**-513
Green, D.P. **5**-190, **12**-658
Green, G.M. **15**-2506
Green, J. **8**-162, **16**-1986
Green, L. **10**-1349, **13**-725
Green, M. **17**-460
Green, M.L.H. **2**-190, **5**-152
Green, M.M. **18**-931
Green, N.S. **12**-88
Green, R. **15**-1812
Green, R.D. **3**-51
Greenberg, A. **2**-229, **4**-418, **4**-427, **4**-444, **18**-114, **18**-683
Greenblatt, J. **4**-33
Greene Jr., J.L. **17**-145
Greene, A.E. **15**-1540, **15**-1557, **15**-1572, **15**-1573, **19**-1438
Greene, D.J. **15**-643
Greene, F.D. **10**-775, **17**-103, **18**-212
Greene, J.L. **18**-189
Greene, R.M.E. **18**-894
Greene, T.W. **10**-914, **10**-631, **16**-1874
Greenfield, H. **15**-489
Greenhalgh, C. **13**-21
Greenhall, M.P. **12**-143
Greenlee, K.W. **4**-430, **15**-539
Greenman, K.L. **15**-407
Greenspoon, N. **15**-591, **19**-893
Greenwald, R. **16**-1327
Greer, A. **15**-994
Greer, S. **19**-1045
Greeves, N. **10**-618, **16**-463, **16**-632, **16**-912, **16**-1515, **19**-1630
Grega, K.C. **19**-323
Gregg, B.T. **10**-574, **15**-618, **16**-123
Gregor, I.K. **11**-120
Gregory, B.J. **18**-362
Gregory, C.D. **10**-1402
Gregory, M.J. **11**-650
Gregory, P. **7**-5, **11**-163
Gregory, R.J. **18**-953
Gregson, M. **10**-1118, **10**-1324
Gregson, T. **16**-103
Grehn, L. **10**-1041
Greiciute, D. **15**-1731
Greico, P.A. **18**-715
Greig, C.C. **11**-62
Greiner, A. **17**-155, **18**-349
Greinert, R. **19**-353
Greisbeck, A.G. **16**-2211
Greisinger, R. **18**-593
Grekov, A.P. **10**-383
Grela, K. **18**-821, **18**-832, **18**-850, **18**-875, **19**-1712
Grelbig, T. **1**-102
Grelier, S. **13**-82
Grell, E. **3**-121
Grellier, M. **10**-904, **19**-1167
Grellier, P.L. **3**-19, **10**-474, **12**-2, **12**-448, **12**-455, **12**-505, **12**-533, **12**-579
Gremaud, D. **15**-2467
Grendze, M.P. **10**-202
Grenga, P.N. **16**-339
Gresser, M. **6**-95
Grenon, M. **16**-228, **16**-1959
Gretz, E. **14**-282
Greunig, H. **19**-353
Greuter, H. **15**-2384

Grev, R.S. **4**-290
Grey, R.A. **16**-2031
Grgurina, I. **10**-954
Gribanova, T.N. **4**-447
Gribble, G.W. **11**-690, **15**-526, **16**-104, **16**-330, **16**-1886, **19**-908, **19**-1335
Gribchenko, E.A. **13**-807
Gribkov, D.V. **10**-1890, **12**-691, **15**-352
Grice, P. **10**-613, **19**-1114
Gridnev, I.D. **15**-365, **15**-634, **15**-2088, **18**-584
Griebe, D. **3**-159
Griebenow, N. **16**-698
Grieco, C. **10**-283
Grieco, P.A. **10**-1118, **10**-1324, **12**-252, **12**-365, **13**-586, **15**-2216, **15**-2470, **16**-1476, **16**-1688, **18**-393, **18**-602, **18**-704
Griedel, B.D. **16**-776
Grieme, T. **16**-240
Griengl, H **16**-1212, **16**-1501, **16**-1544, **16**-2127
Griesbaum, K. **15**-31, **15**-107, **15**-111, **15**-296, **19**-337, **19**-353
Griesbeck, A. **15**-1994
Griesbeck, A.G. **5**-308. **12**-97, **16**-2208, **16**-2209, **16**-2212
Griesinger, C. **5**-193
Grieve, D.M.A. **16**-29
Griffin, D. **11**-197, **15**-417
Griffin, G.W. **4**-462, **18**-918
Griffin, R. G. **5**-234
Griffin, R.N. **12**-678
Griffith, J.R. **16**-175
Griffith, R.C. **4**-298
Griffith, W.P. **19**-117, **19**-380
Griffiths-Jones, C.M. **13**-506
Griffiths, D.V. **10**-998
Griffiths, D.W. **3**-183
Griffiths, J. **7**-5
Griffiths, P.A. **15**-2449
Grigg, R. **10**-1311, **15**-863, **15**-917, **15**-1592, **15**-2117
Grigina, I.N. **16**-541
Grignon-Dubois, M. **12**-312
Grigor, B.A. **8**-37
Grijzen, Y. **6**-36
Grill, J.M. **19**-651
Griller, D. **1**-95, **5**-211, **5**-218, **5**-369, **14**-64, **14**-92, **14**-115, **14**-166, **18**-73, **19**-1516
Grilli, S. **4**-90
Grillot, G.F. **11**-629
Grima, P.M. **7**-103
Grimaud, J. **18**-33
Grimaud, L. **16**-378, **16**-1845, **16**-2260
Grimeau, J. **12**-14
Grimes, K.D. **19**-1297
Grimes, P. **12**-430
Grimm, B. **18**-608
Grimm, R.A. **14**-449, **19**-1575
Grimme, S. **19**-173
Grimme, W. **4**-488, **18**-588
Grimmelikhuysen, J.C. **19**-337, **19**-356
Grimmond, B.J. **15**-2250
Grimster, N.P. **11**-429
Grinberg, N. **15**-452
Grinblat, J. **10**-29
Grinter, R. **2**-190
Grishin, Yu.K. **15**-279
Grisso, B.A. **16**-1077
Griswold, A.A. **18**-502
Grivas, J.C. **16**-420
Grob, C.A. **1**-46, **1**-47, **9**-41, **10**-186, **10**-188, **10**-190, **10**-266, **14**-121, **14**-475, **15**-35, **17**-405, **17**-406, **17**-408, **17**-410, **17**-411, **17**-413, **17**-455, **17**-459, **17**-460
Gröbel, B. **10**-579, **10**-1775
Groen, M.B. **4**-193
Grogan, M.J. **15**-1802
Gröger, H. **16**-1496, **16**-1522
Grohmann, K. **2**-300, **18**-679
Gromova, A. **16**-788
Grondin, R. **15**-401
Gronert, S. **5**-113, **5**-157, **5**-235, **10**-282, **10**-323
Gronheid, R. **5**-66, **5**-78, **12**-507
Gronowitz, S. **12**-541
Gros, C. **4**-99
Gros, E.G. **10**-571
Gros, P. **13**-739
Gros, P.C. **10**-1702
Grosjean, C. **16**-1531
Grosjean, D. **15**-69
Grosjean, M. **4**-277
Gross, A.W. **10**-1759, **12**-323, **15**-2089, **19**-732
Gross, B.A. **15**-2520
Gross, B.H. **19**-1297
Gross, E. **16**-1909, **16**-1929, **16**-2262
Gross, G. **4**-497, **4**-507
Gross, H. **10**-308, **11**-517
Gross, K.C. **8**-191
Gross, M.L. **11**-32
Groß, P. **11**-521
Grosse, D. **16**-2001
Grossert, J.S. **5**-151
Grossi, L. **5**-225, **13**-12, **15**-1238, **18**-931
Grossman, N. **18**-195
Grossman, R.B. **15**-1047
Grosu, I. **2**-485, **4**-79
Grote, D. **5**-434
Grotemeier, G. **10**-1744
Groth, P. **2**-381, **3**-112
Groth, U. **16**-720, **19**-892, **19**-1638
Grotjahn, D.B. **8**-214
Grotjahn, D.B. **15**-222, **17**-65
Grove, D.I. **2**-403
Grove, D.M. **10**-1507
Grovenstein Jr., E. **5**-152, **11**-304, **11**-661, **12**-722, **18**-94, **18**-121, **18**-121, **18**-122, **18**-123
Grover, R. **4**-316
Grover, V. **10**-748
Grover, V.K. **10**-621
Groves, E.E. **12**-311
Groves, J. T. **14**-97
Groves, J.K. **15**-1781
Groves, J.T. **2**-222, **19**-444, **19**-445
Groves, K. **18**-538
Grozinger, K. **11**-404
Grubber, M.J. **18**-543
Grubbs, E.J. **1**-44
Grubbs, R. **2**-251
Grubbs, R.H. **15**-2409, **16**-1409, **16**-1410, **18**-264, **18**-264, **18**-804, **18**-807, **18**-808, **18**-816, **18**-817, **18**-819, **18**-821, **18**-822, **18**-826, **18**-841, **18**-844, **18**-857, **18**-858, **18**-860, **18**-861, **18**-865, **18**-870, **18**-872, **18**-874, **18**-887, **18**-891, **18**-894, **18**-895
Gruber-Khadjawi, M. **16**-1212
Gruber, J.M. **19**-507
Gruber, K. **16**-1212
Gruber, W. **18**-11
Grubmüller, P. **12**-721
Gruen, L.C. **11**-113
Gruetzmacher, G. **11**-554
Grünanger, P. **15**-2105
Gründemann, E. **4**-40
Grundke, H. **18**-451
Grundmann, C. **19**-1538, **19**-1539
Grundon, M.F. **13**-863
Grundy, J. **10**-746
Grüner, H. **15**-2465, **18**-529
Grunewald, G.L. **10**-1042, **18**-678
Gruntz, U. **10**-753, **10**-875
Grunwald, E. **3**-12, **6**-7, **6**-49, **8**-237, **9**-16, **10**-458, **16**-139, **16**-140
Grunwell, J.R. **15**-1242
Gruszecka, E. **18**-800, **18**-951
Gruttadauric, M. **15**-229
Grutzner, J.B. **5**-141, **12**-214, **12**-105, **15**-1638
Gruzdneva, V.N. **9**-34, **18**-44
Grynszpan, F. **3**-129
Grzyb, J.A. **16**-1916
Gschwend-Steen, K. **18**-726
Gschwend, H.W. **10**-1349, **12**-409, **13**-725
Gschwind, R.M. **8**-98, **15**-1143
Gstöttmayr, C.W.K. **10**-1388
Gu, C. **19**-98
Gu, D. **19**-481, **19**-770
Gu, H. **19**-1104
Gu, J. **19**-1221
Gu, P.M. **19**-1036
Gu, S. **15**-899
Gu, Y. **16**-400
Gu, Z. **15**-870
Guan, B.-T. **10**-1607

Guan, B. **19**-115, **19**-128
Guan, J.T. **13**-594
Guan, X.-P. **16**-1879
Guan, X. **15**-1311
Guanti, G. **16**-2276
Guardeño, R. **15**-482
Guarezemini, A.S. **16**-240
Guarna, A. **10**-1875, **12**-295, **16**-680
Guarnieri, A. **5**-252, **13**-65
Guay, D. **15**-819, **16**-1435, **16**-2312
Gubelt, C. **12**-503
Gucciardo, G. **19**-1044
Guchhait, S.K. **13**-417, **15**-544, **17**-376, **19**-1321
Gudipati, M.S. **16**-2212
Gudkov, B.S. **15**-475, **15**-478
Gudmundsdottir, A.D. **5**-433, **16**-1408
Gudmundsson, B.Ö. **5**-185, **5**-190
Gudnason, P. I. **4**-384
Guebitz, G.M. **16**-362
Guérin, B. **15**-1339, **15**-1377
Guérin, C. **4**-27
Guerin, D.J. **15**-1416
Guérinot, A. **16**-2178
Guerra, C.F. **1**-6, **3**-22
Guerra, F.M. **14**-200, **15**-284, **15**-2098
Guerra, I.M. **15**-1851
Guerra, M. **1**-116, **15**-1311
Guerreiro, M.C. **19**-486
Guerrero, A. **10**-1944, **15**-1671
Guerrero, C. **10**-918
Guerrieri, F. **10**-1983
Guertin, K.R. **19**-512, **19**-786
Guest, J.M. **18**-704
Guette, C. **11**-229
Guetté, J. **4**-222, **11**-261
Gugel, H. **4**-493
Guggenberger, L.J. **5**-166
Guggisberg, A. **16**-1970
Guha, A. **16**-1900
Guha, S. **16**-52, **19**-939
Guha, S.K. **12**-116
Guibé-Jampel, E. **18**-762
Guibe, F. **10**-359, **10**-520
Guida, A.R. **10**-755
Guida, W.C. **10**-755, **19**-1071
Guido, G. **5**-339
Guihéneuf, G. **3**-19
Guijarro, A. **12**-647, **16**-472
Guijarro, D. **15**-791, **16**-897
Guilhem, J. **3**-218, **4**-253
Guillarme, S. **16**-534
Guillaumet, G. **10**-949, **13**-637
Guillemin, J.-C. **18**-848
Guillemin, J. **12**-758
Guillen, F. **9**-137
Guillena, G. **16**-1084
Guimet, E. **10**-1522
Guin, C. **11**-250, **12**-665
Guin, J. **19**-173
Guindon, Y. **5**-255, **10**-632, **10**-824, **15**-1339, **15**-1377
Guingant, A. **15**-1108
Guinn, V.P. **18**-64
Guinó, M. **13**-192
Guir, C. **10**-1600
Guirado, A. **17**-486
Guirado, G. **13**-8
Guiry, P.J. **12**-549
Guiry, P.J. **16**-691
Guisán-Ceinos, M. **10**-1463
Guisnet, M. **10**-807
Guiu, E. **10**-1532
Guixer, J. **15**-1959
Guizzetti, S. **16**-1081, **16**-1085, **19**-1156
Gujadhur, R. **13**-112
Guk, Yu.V. **11**-30, **11**-140
Gula, M.J. **17**-55
Gulevich, Yu.V. **10**-1988, **12**-555
Gulhane, R. **16**-1723
Gulias, M. **13**-220, **15**-2667
Gulino, F. **12**-685
Gulyaev, N.D. **16**-1967
Gulyukina, N.S. **12**-703
Gum, A. **7**-123
Gumaste, V.K. **10**-1083
Gumby, W.L. **5**-135, **10**-362
Gumienny, C. **11**-671
Gunanathan, C. **10**-927, **12**-382
Gunaratne, H.Q.N. **10**-595
Gunasekar, D. **10**-1266
Gunathilagan, S. **15**-1957
Gunaydin, H. **16**-1654
Gund, P. **4**-445
Gund, T.M. **4**-445, **5**-87, **18**-115
Gundersen, L.-L. **4**-406
Gündogan, B. **16**-1018, **16**-1045
Gung, B.W. **8**-213
Gunnar Müller, G. **15**-2255
Gunning, H.E. **18**-235
Gunnoe, T.B. **15**-965, **15**-1382
Gunsher, J. **15**-2548
Gunter, H.V. **14**-332
Günthard, H.H. **2**-202
Günther, B. **18**-42
Günther, H. **2**-111, **2**-291, **2**-305, **2**-350, **2**-352, **5**-155, **18**-674, **18**-679
Günther, W. **5**-192
Guo, B. **2**-458, **14**-453
Guo, C. **16**-400, **17**-177
Guo, D. **13**-218
Guo, G. **15**-693
Guo, H. **10**-855, **16**-999, **19**-800, **19**-1568
Guo, J. X. **12**-85
Guo, J. **16**-546, **16**-1106
Guo, L. **11**-258, **15**-1056, **15**-2061
Guo, M. **10**-1744, **13**-494, **19**-1017
Guo, Q.-X. **1**-115, **1**-117, **10**-1067, **13**-236, **13**-421, **13**-496, **14**-84, **14**-88, **15**-1346, **16**-400, **18**-185, **18**-242
Guo, Q. **15**-2604 **18**-136
Guo, R. **15**-1102
Guo, S. **10**-935, **16**-59, **16**-134
Guo, W.-r. **15**-315, **15**-643
Guo, X.-X. **15**-1223
Guo, X. **16**-1073
Guo, Y. **13**-510, **17**-287
Guo, Z.-R. **13**-168
Guo, Z. **15**-569, **16**-1942, **18**-193, **19**-619
Guofu, Q. **10**-709
Gupt, I. **15**-94
Gupta, A. **4**-142, **15**-605, **19**-583
Gupta, A.K. **15**-928
Gupta, B.D. **10**-620
Gupta, B.G.B. **10**-1200, **10**-1247, **16**-95
Gupta, D. **19**-334
Gupta, K. **8**-182
Gupta, L. **12**-421, **13**-734
Gupta, M. **10**-610, **11**-591, **11**-502
Gupta, M.K. **15**-1696, **15**-1736
Gupta, O.D. **12**-144
Gupta, R. **11**-447, **11**-502, **12**-119, **12**-120, **19**-601
Gupta, S.K. **15**-433, **15**-436, **15**-724
Gupta, V. **12**-120, **15**-193, **15**-1354
Gupta, V.K. **13**-19
Gupta, V.P. **4**-308
Guram, A.S. **11**-179, **19**-211
Gürbüz, N. **13**-595
Gurien, H. **17**-398
Gurka, D.F. **11**-49
Gurr, P.A. **11**-188
Gurskii, M.E. **10**-1879, **18**-584
Gurudutt, K.N. **10**-876, **17**-204
Gurumurthy, R. **10**-112
Gurunath, S. **11**-288, **19**-319
Gur'yanova, E.N. **3**-3
Guse, I. **10**-732
Guseinova, S.N. **11**-414
Gust, D. **1**-94
Gustafson, D.H. **18**-98
Gustafson, G. **10**-512, **15**-47
Gustin, D.J. **4**-126, **16**-1055
Gut, I. **2**-468
Gut, I.G. **2**-445
Guthikonda, K. **15**-2059, **15**-2068
Guthrie, D.B. **15**-1351
Guthrie, J.P. **8**-61, **8**-64, **8**-154, **12**-681, **12**-706, **12**-710, **16**-20, **16**-1032, **16**-1106, **16**-1615, **16**-1700, **16**-1701
Guthrie, R.D. **5**-208, **5**-243, part **2**-4, **10**-644, **12**-102, **16**-1651, **18**-4, **18**-17
Gutiérrez, A. **4**-525
Gutierrez, E. **10**-723
Gutiérrez, I. **15**-2500
Gutiérrez, L.G. **15**-2355
Gutman, A.L. **2**-302, **16**-1905
Gutman, D. **5**-288
Gutman, I. **2**-114, **2**-131, **2**-132

Gutmann, H. **15**-461
Gutmann, R. **11**-584
Gutnov, A.V. **16**-1518
Gutowski, F.D. **14**-418
Gutowsky, H S. **3**-77, **5**-245
Gutsche, C.D. **3**-106, **3**-128, **3**-132, **3**-136, **16**-1455, **17**-510, **18**-160, **18**-182, **18**-203, **18**-225, **18**-239, **18**-247
Gutteridge, J.M.C. **5**-317
Guttieri, M.J. **15**-462
Gutzwiller, J. **4**-211
Guy, A. **10**-1075, **11**-261, **12**-354
Guy, R.G. **10**-874
Guy, R.K. **13**-157
Guyon, R. **10**-70
Guyton, C.A. **15**-2432, **18**-625
Guzei, I. A. **5**-185
Guzei, I.A. **15**-346
Guzen, K.P. **16**-240
Guziec Jr., F.S. **10**-1253, **17**-516, **17**-526, **19**-81, **19**-1503, **19**-1521
Guzik, H. **14**-441, **19**-1562
Guzmán, I. **19**-972
Guzzi, U. **12**-270, **13**-487
Gybin, A.S. **15**-2205
Gyoung, Y.S. **19**-847
Gypser, A. **15**-1835

Ha, C. **14**-93, **15**-1313
Ha, D.-C. **19**-945
Ha, D. **16**-2220
Ha, D.S. **19**-709
Ha, H.-J. **15**-1834
Ha, H. **10**-260
Ha, J.D. **10**-1235
Ha, T. **2**-424
Ha, Y.-H. **16**-723
Haaf, W. **15**-1495
Haag, R. **13**-508
Haag, W. **17**-200
Haag, W.O. **17**-146
Haak, J.R. **10**-476
Haak, R.M. **10**-1891
Haake, M. **16**-85
Haaland, A. **2**-186
Haas, A. **14**-149
Haas, C.K. **15**-2480
Haas, J. **15**-1719
Haas, Y. **19**-348, **19**-350, **19**-368
Haase, K. **16**-2001
Habashita, H. **10**-249
Habashneh, A.Y. **13**-537
Habata, Y. **7**-62
Habaue, S. **16**-585
Haberaecker III, W.W. **12**-275
Haberfield, P. **7**-63, **7**-64, **10**-110, **10**-449, **10**-519, **10**-520, **11**-276
Haberl, U. **15**-2286
Haberland, H. **11**-360
Haberman, J.X. **16**-559
Haberman, L.M. **10**-1017
Habiak, V. **10**-1366
Habib, M.J. **15**-1539
Habibi, D. **10**-664
Habibi, M.F. **4**-251
Habibi, M.H. **14**-464, **15**-1981
Habibzadeh, S. **16**-127, **19**-114
Häbich, D. **10**-712
Habicher, T. **15**-1907
Habu, H. **10**-744
Haché, B. **15**-302
Hachiya, I. **11**-440, **11**-585, **15**-2194, **16**-1050, **16**-1133
Hachiya, I. **16**-1580
Hacker, N.P. **15**-2534
Hackett, P. **18**-909
Hackfeld, L. **19**-1125, **19**-1126
Hackler, U.E. **18**-668
Hackman, B.M. **16**-781
Hadad, C.M. **1**-114, **5**-317, **15**-2540, **18**-229
Haddach, A.A. **19**-1604
Haddach, M. **13**-558
Haddad, N. **15**-452, **15**-2429, **15**-2451, **15**-2459, **15**-2513
Haddad, T.D. **16**-560
Haddenham, D. **19**-973
Haddon, H.A. **18**-432
Haddon, R.C. **2**-107, **2**-125, **2**-297, **2**-383, **2**-407, **2**-419, **5**-25
Haddon, V.R. **2**-107, **10**-184
Haddow, M.F. **13**-554
Hadei, N. **10**-1309, **10**-1469
Hadži, D. **3**-11
Hadida, S. **12**-272
Hadj Ali Salem, M. **12**-729
Hadjieva, B. **4**-319
Hadjigeorgiou, P. **11**-202
Hadju, E. **2**-405, **15**-140
Hæffner, F. **12**-441
Haelg, P. **15**-1611
Haese, W. **15**-1462
Hafez, A.M. **12**-175, **15**-2386, **16**-2226, **16**-2228, **17**-322
Hafezi, N. **5**-99
Haffner, C.D. **18**-657
Häfliger, O. **17**-407
Häflinger, O. **8**-25, **8**-47
Hafner, A. **16**-663
Hafner, H. **11**-67
Hafner, K. **2**-195, **2**-198, **2**-199, **2**-200, **2**-351
Hafner, W. **19**-699
Haga, K. **18**-261
Hagaman, E. **15**-899
Hagan, S. **2**-401
Hage, R. **15**-1795
Hagège, A. **3**-141
Hageman, H.A. **10**-1261
Hagemann, B. **19**-929
Hagen, E.L. **5**-21, **18**-8, **18**-22
Hagihara, K. **15**-1056, **19**-1118
Hagihara, N. **13**-582
Hagihara, T. **15**-2528
Hagitani, A. **16**-1730
Hagiwara, E. **16**-388
Hagiwara, H. **10**-656, **10**-695, **13**-401, **13**-500, **16**-1062, **16**-1146, **16**-1202, **16**-1792, **18**-385
Hagiwara, I. **10**-1738
Hagiya, K. **10**-728
Hagler, A.T. **4**-314
Hahn, C.S. **19**-104
Hahn, F.E. **5**-366
Hahn, G. **19**-864
Hahn, J.-T. **19**-1204
Hahn, P. **19**-55
Hahn, S. **3**-34
Hahn, W. **11**-360, **11**-361
Hahn, Y.P. **18**-34
Hahnfeld, J.L. **5**-370
Hähnle, R. **10**-1137
Hai, A.K.M.A. **16**-2242
Haider, S.Z. **12**-489
Haidour, A. **17**-160
Haiduc, I. **12**-1
Haidukewych, D. **17**-359
Haigh, D. **16**-1490
Haight, A.R. **10**-621
Hailes, H.C. **15**-2206, **16**-798
Haines, A.H. **11**-567, **14**-288, **15**-1789, **15**-1869, **16**-88, **19**-11, **19**-12, **19**-252, **19**-301, **19**-609, **19**-614, **19**-633, **19**-646, **19**-668, **19**-669, **19**-716
Haines, A.J. **19**-40
Haines, A.M. **19**-63
Haines, R.J. **18**-807
Hair, C.M. **13**-504
Haire, D.L. **5**-221
Hajdu, C. **12**-332
Hájek, M. **15**-1472
Hájicek, J. **16**-1970
Hajipour, A.R. **9**-141, **10**-1066, **10**-1148, **10**-1167, **11**-142, **11**-198, **11**-298, **11**-455, **16**-66, **16**-67, **16**-70, **16**-72, **16**-80, **16**-286, **16**-1860, **19**-84, **19**-87, **19**-91, **19**-244, **19**-247, **19**-322, **19**-797, **19**-883
Hajos, A. **19**-879, **19**-847, **19**-1278
Hajos, Z.G. **15**-1117, **16**-1017, **16**-1120
Hajra, A. **15**-1204, **16**-554, **16**-1865, **17**-378
Hajra, S. **11**-322, **19**-200
Hakamata, W. **16**-133
Håkansson, M. **15**-1169
Håkansson, R. **4**-277
Hakim Lakmini, H. **13**-545
Haky, J.E. **15**-64
Halberstadt, M.L. **5**-407
Halbes, U. **12**-303
Halcomb, R.L. **19**-735
Halcour, K. **19**-1777
Halder, R. **15**-1407
Halek, G.W. **15**-2565
Hales J.L. **11**-529
Hales, N.J. **15**-1560

Hales, R.H. **13**-143
Halevi, E.A. **6**-76, **6**-82, **6**-84, **6**-85, **18**-667
Haley, M.M. **2**-87, **2**-213, **2**-317, **2**-318, **2**-331, **4**-487, **4**-512, **5**-65
Halgren, T.A. **4**-417, **5**-327
Halimjani, A.Z. **19**-897
Hall Jr., H.K. **15**-2293, **15**-2439
Hall, C.D. **16**-2107
Hall, D.G. **16**-750, **16**-751
Hall, D.M. **4**-52
Hall, G.E. **4**-265
Hall, G.G. **2**-10, **2**-83
Hall, J.A. **15**-2121, **18**-955
Hall, J.B. **10**-156
Hall, K.J. **16**-417
Hall, M.A. **13**-554
Hall, M.K. **13**-25
Hall, M.L. **15**-1934
Hall, N.D. **16**-1668
Hall, R.E. **6**-87, **10**-66, **10**-89
Hall, R.W. **3**-184
Hall, S.S. **16**-532, **16**-993
Hall, T.N. **13**-9
Halland, N. **12**-123, **12**-124, **13**-587, **15**-1036, **15**-1051, **16**-1607
Hallberg, A. **7**-123, **7**-125, **10**-781, **10**-1337, **12**-273, **12**-298, **12**-314, **13**-368, **13**-397, **13**-408, **13**-411, **13**-416, **13**-422, **13**-671
Hallé, J.-C. **13**-6, **15**-2295
Haller, G.L. **6**-42
Haller, I. **4**-450, **15**-1426
Haller, K.J. **1**-13
Halley, F. **14**-373
Halligudi, S.B. **15**-368
Hallissey, J. **19**-986
Halliwell, B. **5**-317
Hallman, P.S. **15**-445
Halloran, D.J. **17**-242
Hallouis, S. **16**-2050
Halpern, B. **4**-174, **4**-217
Halpern, J. **4**-150, **12**-13, **15**-456, **15**-502, **15**-636, **18**-896, **18**-898
Halpern, M. **10**-488, **17**-309
Halpern, Y. **10**-614
Halpern, Y. **5**-18
Halsall, T.G. **19**-66
Halstead, B. S. J. **7**-112
Halstenberg, M. **10**-1160
Halterman, R.I. **10**-1872, **15**-1978, **16**-752
Haltiwanger, R.C. **4**-93
Halton, B. **2**-85, **4**-485, **4**-487
Halton, B. **7**-1
Halupka, M. **5**-217
Halvorsen, A. **10**-318
Ham, G.E. **10**-525, **10**-698, **10**-901, **10**-998, **15**-2043, **17**-363, **18**-615
Hama, T. **13**-359, **13**-642
Hamachi, K. **19**-461
Hamada, F. **3**-65
Hamada, H. **15**-660, **19**-475
Hamada, N. **15**-2248
Hamada, T. **12**-499, **13**-663, **15**-1985, **16**-402, **16**-770, **16**-962, **16**-972, **16**-1172, **19**-461
Hamada, Y. **10**-1540, **16**-806, **19**-504
Hamadi, H. **16**-1872
Hamaguchi, H. **3**-114, **10**-1365
Hamaguchi, S. **16**-1372
Hamai, K. **9**-145
Hamanaka, K. **11**-104
Hamann, L.G. **19**-913
Hamaoka, T. **12**-517, **12**-519
Hamasaki, R. **16**-1143, **16**-2131
Hamashima, Y. **12**-147, **16**-1495
Hamatani, T. **17**-312
Hamaya, M. **16**-1582
Hamblin, G.D. **18**-206
Hamblin, M.C. **11**-384
Hambling, J.K. **14**-133
Hambly, A.N. **8**-24
Hamdani, M. **13**-82
Hamdouchi, C. **5**-206, **12**-450
Hamel, N. **10**-2002, **15**-1502
Hamelin, J. **15**-2150, **16**-267, **16**-1946
Hamelink, E. **7**-126
Hamer, J. **15**-2043, **15**-2356, **16**-1463, **16**-2197, **16**-2205 **16**-2216
Hamersma, J.W. **10**-160
Hamid, M.H.S.A. **10**-933
Hamill, H. **4**-51
Hamilton Jr., E.J. **18**-56
Hamilton, A.D. **3**-157
Hamilton, G.S. **16**-1642
Hamilton, J.A. **4**-183
Hamilton, T.P. **15**-11
Hamilton, W.C. **3**-3
Hamlet, Z. **9**-95
Hammadi, M. **19**-615
Hammarström, L. **4**-345
Hammerschmidt, F. **12**-439
Hammerton, D.A. **7**-75
Hammerum, S. **5**-322, **16**-49
Hammett, L.P. **5**-63, **5**-75, **6**-49, **6**-61, **8**-124, **8**-128, **8**-137, **11**-8, **16**-1663
Hammond, G.S. **4**-239, **5**-354, **6**-24, **7**-13, **7**-25, **7**-26, **7**-41, **11**-66, **11**-598, **15**-32, **15**-33, **15**-2449, **15**-2452, **17**-146, **18**-665
Hammond, M.E.W. **11**-277
Hammond, R.C. **14**-392
Hammond, W.B. **16**-45
Hammons, J.H. **8**-16, **8**-65, **18**-100
Hamoir, C. **10**-979
Hamor, T.A. **2**-181
Hampel, F. **5**-183, **8**-123, **15**-352
Hampel, M. **15**-25
Hampel, N. **10**-12, **10**-1784, **11**-346
Hamper, B.C. **13**-176
Hampl, F. **19**-800
Hampton, D.C. **13**-873
Hamrick Jr., P.J. **10**-1667, **19**-1738
Hamura, T. **13**-55
Hamze, A. **13**-704, **15**-781
Han, B.-H. **7**-84, **15**-174
Han, B. **10**-602, **15**-444, **16**-834, **16**-1206
Han, B.H. **7**-90, **7**-94, **10**-1296, **16**-2115
Han, F.-S. **13**-514
Han, H. **5**-299. **10**-1022, **10**-1265
Han, J. **15**-491, **15**-1485, **16**-1591, **19**-229
Han, J.H. **19**-1530
Han, J.L. **19**-1204
Han, J.W. **12**-71, **15**-503, **15**-1226, **15**-1859
Han, K.-J. **16**-1912
Han, L.-B. **10**-793, **15**-391, **15**-395, **15**-396, **15**-422
Han, M. **15**-855
Han, R. **16**-906, **19**-1186
Han, S.-Y. **17**-170
Han, S. **4**-54
Han, W. **12**-145, **12**-351
Han, X.-W. **15**-562
Han, X. **10**-1548, **15**-233, **15**-235, **15**-416, **15**-416, **15**-944
Han, Y. **10**-2001, **15**-1176, **15**-1228
Han, Z.-j. **16**-666
Han, Z. **16**-1035, **16**-1728
Hanack, H. **10**-263, **10**-264
Hanack, M. **4**-270, **5**-68, **5**-69, **10**-267, **10**-163, **10**-265, **10**-269, **10**-271, **10**-274, **10**-411, **10**-1137, **11**-498, **13**-29, **15**-36, **15**-107, **16**-2174, **17**-82
Hanada, S. **19**-1476, **19**-1479
Hanafusa, T. **6**-74, **10**-1019, **10**-1934, **15**-1671, **16**-519, **16**-524, **16**-528, **16**-1346, **16**-2162, **19**-958
Hanamoto, T. **13**-711, **14**-314
Hanamura, M. **10**-215
Hanano, T. **12**-186
Hanaoka, M. **15**-1562, **16**-61
Hanasaka, F. **10**-1585
Hanbing, T. **10**-709
Hancock, J.E.H. appendixa-1
Hancock, J.W. **10**-254
Hancock, M.T. **12**-794
Handa, S. **16**-411, **19**-1658
Handel, H. **16**-529, **19**-1000
Handoo, K.L. **16**-527
Handy, C.J. **13**-718
Handy, N.C. **4**-173, **4**-299
Handy, S.T. **9**-125, **9**-131, **13**-401, **13**-402, **13**-420, **15**-2216, **16**-457, **16**-990

Hane, J.T. **18**-677
Haneda, A. **19**-1317
Hanes, R.E. **8**-187
Hanessian, S. **4**-138, **10**-632, **10**-824, **10**-1418, **16**-1374, **19**-1659
Haney, W.A. **11**-104
Hanfusa, T. **19**-107
Hang, C. **15**-994, **15**-2280, **15**-2390
Hang, J.-F. **19**-1020
Hanissian, S.H. **9**-78
Hanley, J.A. **4**-36
Hanna Jr., J.M. **13**-828
Hanna, I. **10**-1621
Hanna, S.B. **19**-813
Hanna, S.Y. **18**-431
Hannan, J.J. **15**-752
Hannan, W. **11**-120
Hannick, S.M. **16**-856
Hannon, F.J. **15**-1167, **15**-1244
Hanold, N. **4**-492
Hansch, C. **9**-20, **9**-63, **9**-65, **9**-68
Hansch, M. **16**-1450
Hansell, D.P. **10**-387
Hansell, G. **10**-122
Hansen, B. **16**-1317
Hansen, D.E. **6**-54
Hansen, E.C. **15**-1030, **18**-890
Hansen, H.-J. **5**-340, **18**-613, **19**-550
Hansen, H. **15**-2309, **18**-691, **18**-740, **18**-745, **18**-758
Hansen, J. **13**-767
Hansen, J.F. **14**-376
Hansen, J.S. **10**-1092
Hansen, K.B. **10**-696
Hansen, L.K. **15**-452
Hansen, M.C. **19**-1155, **19**-1451
Hansen, M.M. **16**-1070
Hansen, T. **11**-388
Hansen, T. **15**-2521
Hansford, K.A. **16**-2079
Hanson, A.W. **2**-307
Hanson, G.C. **10**-225
Hanson, J. **10**-339
Hanson, J.R. **19**-1242
Hanson, K.R. **4**-263
Hanson, M.P. **10**-521
Hanson, P. **9**-59, **14**-392, **14**-394
Hanson, P.R. **10**-731, **16**-2192
Hanson, R.M. **15**-1971
Hansske, F. **19**-1382
Hansson, L. **4**-180
Hansson, S. **14**-274
Hanus, V. **13**-244
Hanzawa, Y. **8**-217, **10**-1964, **15**-1236, **15**-1457, **16**-580
Hanzlik, R.P. **10**-1578, **15**-1875
Hao, J. **16**-716, **16**-728
Hao, Q.-S. **10**-932
Hao, X.-S. **11**-237
Hao, X.-Q. **13**-503
Hapala, J. **17**-32
Hapiot, P. **13**-57
Happer, D.A.R. **2**-415, **9**-30, **9**-53
Haque, A. **15**-605
Haque, M.S. **16**-2105, **16**-2106, **19**-511
Haque, Sk.J. **16**-131
Hara Gopal, A.V. **16**-1555
Hara, H. **10**-1203
Hara, K. **13**-633
Hara, M. **14**-407
Hara, N. **12**-790
Hara, O. **10**-1540, **19**-504
Hara, R. **10**-1911, **15**-988, **15**-2604
Hara, S. **10**-1217, **10**-1102, **10**-1103, **12**-566, **15**-1259, **15**-1264, **15**-1646, **16**-735, **17**-416, **18**-473, **18**-479
Hara, Y. **15**-2116, **19**-1455
Harada, A. **3**-215
Harada, K. **4**-150, **16**-880, **16**-981, **16**-1533, **19**-1122
Harada, M. **12**-515, **15**-1712
Harada, R. **16**-1962
Harada, S. **2**-76, **15**-1034, **15**-2322, **16**-1326, **19**-48, **19**-1654
Harada, T. **2**-76, **3**-131, **11**-314, **11**-538, **12**-408, **12**-457, **15**-225, **15**-922, **15**-1132, **16**-467, **16**-680, **16**-1165, **16**-1173, **18**-124, **19**-963, **19**-994, **19**-996
Harada, Y. **15**-1276, **17**-165
Harang, J.E. **15**-419
Harano, K. **15**-995, **18**-649
Harano, Y. **15**-2221
Harayama, T. **11**-325
Harbison, K.G. **13**-30, **13**-32, **13**-806
Harbusch-Görnert, E. **10**-477
Hardacre, C. **9**-119, **9**-136, **16**-1327
Hardacre, J.M. **13**-654
Hardcastle, I.R. **11**-520
Harder, S. **15**-760
Hardie, B.A. **11**-26, **11**-28
Hardies, D.E. **10**-457
Hardin, J. **16**-787
Harding, C.E. **10**-271
Harding, D.R.K. **18**-755
Harding, K.E. **19**-75
Hardouin, C. **15**-600, **19**-872
Hardy, W.B. **12**-777
Hare, G.J. **6**-71
Harel, T. **19**-749
Hargaden, G.C. **16**-691
Hargett, J.L. **10**-920
Hargis, J.H. **14**-54, **14**-61
Hargittai, I. **5**-238
Hargreaves, M.K. **16**-1881
Hargreaves, R.T. **17**-64
Harich, K. **2**-405
Harikishan, K. **10**-705
Hariri, R. **10**-295
Haritha, Y. **15**-2071, **19**-1299
Harjani, J.R. **11**-592, **16**-1230
Harkat, H. **15**-2101
Harkema, S. **3**-118
Harker, R.L. **13**-576
Härle, H. **15**-2263
Harlow, K.J. **9**-123
Harlow, R.L. **5**-412, **15**-849, **19**-825
Harman, W.D. **15**-556, **15**-2260, **15**-2262
Harmata, M. **15**-1093, **15**-2670
Harmata, M.A. **18**-732
Harmon, C. **15**-2374
Harmon, K.H. **2**-174
Harmon, R.E. **15**-433, **15**-436
Harmony, J.A.K. **5**-310
Harmony, M.D. **1**-55
Harms, K. **5**-143, **12**-30, **15**-1487, **15**-2684, **16**-722, **18**-784
Harmsen, D. **19**-476
Harned, A.M. **10**-731
Harned, H.S. **8**-59
Harnett, J.J. **16**-1447
Harney, D.W. **10**-1582
Harnying, W. **10**-1678
Harper, D.J. **19**-196
Harper, J.J. **10**-177
Harper, R.W. **19**-58
Harpold, M.A. **19**-774
Harpp, D.N. **10**-805, **10**-829, **12**-182, **12**-500, **19**-770, **19**-1405
Harrack, Y. **10**-964
Harran, T. **9**-135
Harre, M. **19**-61
Harrelson Jr., J.A. **5**-259, **8**-208, **10**-1687
Harring, L.S. **15**-2573
Harris Jr., J.F. **15**-296, **16**-187
Harris, B.D. **16**-340
Harris, B.R. **10**-57
Harris, C.J. **4**-258
Harris, C.L. **10**-1031
Harris, C.M. **10**-513
Harris, D.O. **2**-37
Harris, H.P. **10**-493
Harris, J.C. **10**-89
Harris, J.M. **6**-87, **10**-45, **10**-61, **10**-66, **10**-175, **10**-296, **10**-324, **10**-345, **10**-460, **10**-463, **10**-479, **18**-62
Harris Jr., J.F. **18**-648
Harris, K.D.M. **3**-75
Harris, M.C. **13**-187
Harris, M.M. **10**-747
Harris, N.J. **2**-475
Harris, P.A. **2**-471, **16**-387
Harris, R.F. **16**-540
Harris, S.H. **14**-497, **14**-500
Harris, T.M. **10**-513, **16**-2153
Harris, W. **15**-955
Harrison, A.T. **8**-222
Harrison, C.L. **15**-1195
Harrison, C.R. **17**-462, **18**-489

Harrison, D.J. **19**-1516, **19**-1588
Harrison, I.T. **3**-204, **10**-1202, **15**-2553, **19**-585
Harrison, J.M. **15**-2425
Harrison, J.R. **10**-1280, **15**-586, **19**-1231
Harrison, K.N. **15**-734
Harrison, L.J. **5**-265
Harrison, R.G. **10**-551, **16**-288, **16**-1345, **17**-3, **17**-40, **17**-42, **17**-61, **17**-107, **19**-97
Harrison, S. **3**-204, **19**-585
Harrisson, P. **12**-588
Harrity, J.P.A. **15**-2096, **15**-2162, **15**-2296, **15**-2650, **18**-847, **19**-1375
Harrod, J.F. **19**-1676
Harrowfield, J.Mc B. **3**-129
Harrowven, D.C. **11**-585
Harshavardhan, S.J. **15**-1696
Hart, A.J. **5**-137
Hart, D.J. **14**-34, **15**-106, **15**-808, **16**-2220
Hart, H. **2**-448, **11**-568, **11**-631, **13**-342, **15**-1949, **15**-2310, **19**-702
Hart, L.S. **11**-581, **11**-589
Hart, P.A. **19**-67
Hart, P.W. **10**-1398
Hartan, H. **2**-183
Hartel, A.M. **12**-335
Hartemink, M.A. **16**-179
Hartenstein, J.H. **18**-677
Hartford, W.H. **19**-595
Hartgerink, R.L. **13**-691
Hartke, K. **2**-197
Hartley, C.R. **12**-320
Hartley, F.R. **3**-92, **4**-150, **4**-153, **5**-152, **5**-311, **10**-1317, **10**-1357, **10**-1518, **10**-1626, **10**-1983, **12**-1, **12**-2, **12**-49, **12**-409, **12**-448, **12**-455, **12**-456, **12**-505, **12**-533, **12**-579, **12**-594, **12**-604, **12**-611, **12**-623, **15**-428, **15**-490, **15**-635, **15**-671, **15**-801, **15**-884, **15**-977, **15**-1000, **15**-1494, **15**-1597, **15**-1598, **15**-1856, **15**-2586, **16**-3, **16**-451, **18**-451, **18**-807, **19**-927
Hartley, J.P. **11**-197, **11**-215, **11**-438
Hartley, R.C. **16**-1428, **18**-635
Hartman, A. **15**-1660
Hartman, A.F. **10**-752
Hartman, G.D. **17**-347
Hartman, J.W. **15**-241
Hartman, M.E. **18**-249
Hartman, R.D. **17**-347
Hartmann-Schreier, J. **19**-477
Hartmann, J. **12**-416, **12**-417
Hartmann, M. **15**-2318
Hartmanns, J. **15**-748
Hartner Jr., F.W. **16**-1427
Hartog, F.A. **12**-612, **16**-471
Hartschuh, A. **2**-480
Hartshorn, M.P. **9**-30
Hartshorn, S.R. **10**-1, **10**-80, **10**-461, **11**-45
Hartshorn, M.P. **11**-61, **11**-110, **15**-614
Hartung, C.G. **15**-325, **15**-357, **15**-363, **15**-366
Hartung, J. **14**-71, **15**-1379, **15**-1830, **15**-1832, **15**-1843
Hartung, W.H. **19**-1498
Hartwig, J. **16**-920
Hartwig, J.F. **10**-623, **10**-930, **10**-1309, **10**-1544, **10**-1727, **10**-1786, **10**-1838, **11**-265, **12**-345, **13**-147, **13**-186, **13**-187, **13**-217, **13**-296, **13**-349, **13**-359, **13**-366, **13**-642, **13**-658, **15**-330, **15**-334, **15**-342, **15**-346, **15**-347, **15**-402, **15**-949
Hartwig, W. **19**-1389
Harusawa, S. **16**-1494
Harutyanyan, S.R. **15**-1181, **15**-1185
Harvey, G.R. **15**-423
Harvey, J.N. **16**-792, **16**-1382, **16**-1383, **16**-1452, **17**-292, **18**-558
Harvey, K.A. **13**-314
Harvey, R.G. **11**-23, **19**-12, **19**-554
Harvey, S. **12**-609
Harwood, H.J. **12**-174
Has-Becker, S. **16**-1363
Hasan, S.K. **10**-1038
Hasan, T. **17**-62
Hasanayn, F. **10**-3, **10**-244
Hase, E. **16**-963
Hase, T.A. **10**-833, **10**-1775, **10**-1776, **10**-1805, **10**-1812
Hase, W.L. **10**-2
Hasebe, M. **14**-477
Hasegawa, A. **15**-1686, **16**-132
Hasegawa, E. **18**-254
Hasegawa, H. **16**-1847
Hasegawa, K. **11**-104, **15**-1797
Hasegawa, M. **14**-164, **18**-130, **18**-159
Hasegawa, T. **16**-1793
Hasegawa, Y. **12**-792, **16**-1536
Hasek, R.H. **15**-2396
Haselbach, E. **5**-341, **7**-36
Hasenfratz, Ch. **8**-94
Hasenfratz, H. **16**-2150
Hasha, D.L. **15**-704
Hashem, Md.A. **15**-2087
Hashemi, M. **13**-591
Hashemi, M.M. **2**-399, **13**-99, **16**-64, **19**-256
Hashemsadeh, M. **16**-499
Hashida, Y. **11**-166
Hashidzume, H. **18**-950
Hashiguchi, B.G. **15**-1613
Hashiguchi, S. **15**-645
Hashimoto, H. **13**-127, **16**-1336
Hashimoto, I. **15**-1459
Hashimoto, K. **19**-613
Hashimoto, M. **12**-686, **18**-341
Hashimoto, N. **16**-382, **16**-384
Hashimoto, N. **16**-1582
Hashimoto, S. **12**-390, **16**-1940, **16**-1944, **19**-405
Hashimoto, T. **12**-377, **13**-554, **15**-2141, **15**-2148
Hashimoto, Y. **2**-442, **2**-464, **11**-301, **16**-579, **16**-842, **16**-843, **18**-130, **19**-1640
Hasiak, B. **18**-413
Haskins, C.M. **15**-402
Haslam, E. **16**-1736
Hass, H.B. **12**-210, **14**-78, **16**-1200
Hassan, H.A. **16**-505
Hassan, J. **13**-310
Hassdenteufel, J.R. **10**-267
Hassel, T. **19**-1269
Hasselmann, D. **18**-597
Hassenrück, K. **18**-679, **18**-684
Hassfeld, J. **16**-343
Hassine, B.B. **15**-2015
Hassner, A. **10**-511, **10**-1078, **12**-205, **15**-20, **15**-424, **15**-1757, **15**-1760, **15**-1762, **15**-1763, **15**-1764, **15**-1765, **15**-1766, **16**-1103, **16**-2234, **17**-458
Hassouna, F. **13**-696
Hasvold, L.A. **15**-414
Haswell, S.J. **7**-109, **7**-110
Haszeldine, R.N. **18**-528
Hata, E. **15**-1991
Hata, K. **18**-551
Hata, N. **4**-7
Hata, S. **14**-227, **16**-405
Hata, T. **14**-95, **15**-919, **15**-2042, **16**-1825
Hatada, K. **4**-90
Hatajima, T. **16**-511
Hatakeda, K. **18**-128
Hatakeyama, S. **15**-1005, **16**-650
Hatakeyama, T. **10**-1770, **13**-554, **15**-844
Hatanaka, A. **10**-70, **10**-84
Hatanaka, K. **16**-885
Hatanaka, T. **16**-462
Hatanaka, Y. **10**-1269, **10**-1276, **12**-558, **13**-688, **15**-770
Hatano, B. **11**-347, **19**-1437
Hatano, K. **10**-1540
Hatano, M. **15**-857, **16**-458, **16**-458, **16**-666, **16**-671, **16**-716, **16**-728, **16**-893
Hatayama, Y. **19**-53
Hatch, L.F. **15**-2279
Hatch, M.J. **18**-284
Hatch, R.P. **16**-1839
Hatcher, P.G. **5**-317
Hatem, J. **19**-1326
Hathaway, S.J. **15**-2363
Hatlevik, O. **11**-239
Hato, Y. **16**-397

Hatta, G. **15**-1995
Hatta, T. **15**-2105
Hattori, G. **15**-643
Hattori, H. **13**-503, **19**-1741, **19**-1749
Hattori, K. **5**-301, **11**-686, **11**-694, **13**-496, **15**-438, **15**-2610, **18**-367
Hattori, T. **19**-1017
Hatz, E. **10**-751
Hatzakis, N.S. **19**-226
Haubenstock, H. **5**-60, **19**-1002, **19**-1009
Haubrich, J.E. **18**-498
Hauck, B.J. **15**-625
Hauck, S.I. **15**-400
Haudrechy, A. **15**-1844, **16**-534
Hauer, B. **15**-1907, **18**-156
Haufe, G. **4**-73
Haumann, T. **2**-58, **18**-87
Haupt, F.C. **10**-130
Hauptman, E. **13**-239
Hauptmann, H. **14**-439, **19**-1559
Haurena, C. **16**-399
Hauri, R.J. **10**-354
Hause, N.L. **17**-12, **17**-17
Hauser, C.R. **10**-513, **10**-1667, **10**-1690, **13**-848, **13**-849, **13**-852, **13**-853, **16**-86, **16**-2126, **16**-2153, **16**-2154, **17**-46, **17**-447, **19**-1738
Hauser, F.M. **15**-1853
Hauske, J.R. **16**-1380
Hausser, J.W. **10**-335, **18**-542, **18**-543, **18**-543
Haustedt, L.O. **15**-2671
Haut, S.A. **19**-1444
Hautala, R. **7**-48
Hautala, R.T. **7**-44
Hautefaye, P. **10**-995
Havel, J.J. **12**-625
Havel, M. **17**-382
Havelka, F. **16**-1829
Havenith, R.W.A. **2**-89, **2**-106, **2**-265
Havinga, E. **4**-378, **13**-62, **19**-1210
Havlas, Z. **10**-363
Havlin, R. **16**-2010
Havránek, M. **15**-958
Hawari, J.A. **14**-166
Hawkins, C.M. **18**-658
Hawkins, E.G.E. **14**-319
Hawkins, J.D. **15**-421
Hawkins, J.M. **15**-1098, **15**-2249, **15**-2251
Hawkins, J.M. **2**-393
Hawkinson, D.C. **10**-470
Hawks III, G.H. **16**-2120
Hawthorne, M.F. **11**-66, **13**-104, **16**-89
Haxell, T.F.M. **16**-825
Hay, A S. **14**-334
Hay, B.P. **16**-9
Hay, D.R. **13**-728
Hay, J.M. **5**-211, **5**-237
Hay, J.V. **17**-381
Haya, M. **16**-1243
Hayakawa, K. **15**-49
Hayakawa, R. **16**-1163, **19**-946, **19**-1131, **19**-1646
Hayakawa, Y. **15**-2168, **19**-1307
Hayama, N. **10**-1097, **13**-482
Hayami, J. **6**-88, **17**-73
Hayasaka, S. **19**-802
Hayasaka, T. **16**-679
Hayase, S. **18**-578
Hayashi, C. **19**-1035
Hayashi, H. **7**-37
Hayashi, J. **15**-1246
Hayashi, K. **16**-1038
Hayashi, M. **4**-200, **10**-577, **10**-1818, **10**-1918, **10**-1943, **15**-386, **15**-659, **15**-661, **16**-674, **19**-1414
Hayashi, N. **4**-122, **4**-125, **18**-231, **19**-1295
Hayashi, R. **11**-355. **12**-492, **15**-1315, **16**-2141
Hayashi, S. **10**-1539, **10**-1576, **15**-225, **16**-352
Hayashi, T. **10**-715, **10**-1375, **10**-1382, **10**-1387, **10**-1389, **10**-1529, **10**-1614, **10**-1810, **11**-330, **11**-432, **11**-535, **12**-71, **15**-369, **15**-503, **15**-852, **15**-894, **15**-1072, **15**-1199, **15**-1209, **15**-1211, **15**-1223, **15**-1226, **15**-1263, **15**-1269, **15**-1275, **15**-1281, **15**-1859, **16**-899, **16**-921, **16**-932, **16**-1096, **16**-1578, **16**-2122, **18**-746, **19**-1035, **19**-1153
Hayashi, Y. **10**-235, **10**-1630, **11**-552, **12**-354, **15**-1106, **15**-2210, **15**-2352, **16**-395, **16**-916, **16**-1085, **19**-515, **19**-517
Hayashida, J. **16**-1838
Hayashida, M. **10**-1203
Hayat, S. **10**-890, **10**-1142
Hayday, K. **14**-115
Hayden, W. **16**-2127
Hayen, A. **15**-1285
Hayer, M.F. **15**-2063
Hayes, A.M. **19**-989
Hayes, B.L. **7**-110
Hayes, C.J. **19**-1320
Hayes, D. **12**-322, **16**-1155
Hayes, J.-F. **10**-261
Hayes, J.M. **18**-332
Hayes, P.D. **16**-63, **16**-154
Hayes, R. **18**-517
Hayes, R.A. **18**-236
Hayes, R.L. **18**-91
Hayes, W. **3**-201
Haymore, B.L. **3**-113
Haynes, L.W. **16**-259, **19**-42
Haynes, R.K. **16**-746
Häyri, L. **10**-833
Hays, D.S. **15**-1369, **16**-1595, **19**-1382, **19**-1385
Hayshi, T. **16**-1136
Hayter, B.R. **15**-1933
Hayward, R.C. **12**-169, **14**-473, **15**-1759, **15**-1822
Haywood-Farmer, J. **10**-158, **10**-159, **10**-162, **10**-163, **10**-164, **10**-451
Hazari, N. **19**-15
Hazarika, P. **16**-58
Hazarkhani, H. **10**-835, **10**-1177, **17**-161
Hazell, R.G. **15**-1172, **15**-2336, **16**-987, **16**-1213
Hazimeh, H. **16**-527
He, B. **16**-1497, **16**-1502, **16**-1512, **16**-1515
He, C. **10**-1011, **12**-242, **13**-648, **14**-343, **15**-228, **15**-237, **15**-339, **15**-2069, **15**-2076
He, H. **4**-155, **7**-128, **13**-356
He, H.S. **10**-731
He, H.-Y. **10**-1270
He, J. **10**-1904, **16**-239
He, L. **15**-1289, **19**-83, **19**-324, **19**-1262
He, L.-N. **19**-179
He, M.-Y. **16**-132
He, M. **15**-2340, **19**-1017
He, P. **4**-155
He, R. **13**-494, **16**-744
He, S.-L. **5**-330, **14**-82, **14**-89
He, W. **7**-126, **7**-127, **10**-1522
He, X. **12**-108, **13**-321, **14**-98, **18**-59
He, Y. **10**-625, **19**-1198
He, Y.-M. **15**-452
He, Y.-P. **19**-1605
He, Z. **19**-1255
Head, A.J. **17**-130
Head, N.J. **5**-86
Headley, A. **15**-370, **16**-787
Headley, A.D. **8**-180, **8**-240, **8**-252, **15**-1747
Healy, E.F. **2**-18, **6**-86, **19**-861
Heaney, H. **12**-611, **13**-177, **18**-412
Heard, G.L. **18**-414
Hearn, M.J. **18**-374
Heasley, G.E. **15**-4, **15**-34
Heasley, V.L. **15**-4, **15**-34
Heath, J.R. **2**-392
Heathcock, C.H. **4**-157, **10**-1184, **10**-1602, **12**-330, **15**-425, **15**-1060, **15**-1062, **15**-1097, **15**-1115, **15**-1131, **16**-1058, **16**-1063, **16**-1070, **16**-1113
Heaton, N.J. **3**-169
Hebbe, V. **16**-368
Hebel, A. **13**-508
Hebel, D. **11**-571, **15**-1709
Héberger, K. **15**-52

Hebert, E. **18**-444, **18**-447
Hebrard, P. **10**-1040
Hecht, R. **18**-74
Hecht, S.M. **19**-892
Hecht, S.S. **19**-610
Heck, H. d'A. **16**-26
Heck, M.-P. **10**-1277, **17**-475
Heck, R. **10**-63
Heck, R.F. **2**-50, **10**-1487, **10**-1520, **10**-1983, **10**-1988, **10**-1995, **12**-67, **12**-313, **13**-367, **13**-368, **13**-404, **13**-418, **13**-425, **13**-432, **13**-438, **13**-439, **13**-440, **13**-466, **13**-467, **13**-672, **14**-281, **15**-828, **15**-1499, **15**-2505, **15**-2661, **17**-234, **19**-49, **19**-698, **19**-929, **19**-1193
Heckrodt, T. **19**-61
Heckroth, H. **5**-308, **12**-97
Hedaya, E. **11**-597
Hedayatullah, M. **19**-727
Hedberg, C. **15**-452. **19**-928
Hedberg, K. **2**-265, **3**-56, **4**-294, **4**-295, **4**-462
Hedberg, L. **2**-265, **4**-462
Hedegaard, B. **18**-752
Hederich, V. **10**-767
Hedhli, A. **10**-961
Hedley, S.J. **12**-384, **15**-2162
Heemstra Jr., J.R. **16**-708, **16**-1029, **16**-1091, **16**-1154, **16**-1158
Heemstra, J.M. **8**-234
Heermann, D. **16**-1764
Heesing, A. **19**-24
Hefter, G. **10**-64
Hegarty, A.F. **2**-453, **5**-250, **10**-420, **10**-523, **11**-162, **12**-87, **12**-446, **13**-772, **16**-32
Hegbom, I. **11**-145
Hegde, S.G. **12**-172
Hegde, V.R. **15**-300
Hegedus, L.S. **3**-89, **10**-1318, **10**-1321, **10**-1322, **10**-1402, **10**-1508, **10**-1520, **10**-1983, **10**-1984, **13**-425, **14**-485, **15**-341, **15**-433, **15**-1458, **15**-1597, **15**-1599, **15**-2642, **16**-2122, **16**-2221, **16**-2222, **18**-893
Hegeman, A.D. **18**-736
Hegenberg, P. **2**-382
Hehre, W.J. **1**-55, **2**-14, **2**-219, **2**-414, **4**-297, **4**-412, **5**-79, **6**-76, **6**-79, **6**-83, **8**-252, **15**-2229
Hei, S. **12**-81
Heibel, G.E. **15**-2464
Heiber, M. **18**-668
Heiermann, J. **13**-329
Heikens, D. **16**-1806
Heilbronner, E. **2**-241, **2**-367, **4**-249, **4**-250
Heiliger, L. **5**-59
Heilmann, S.M. **16**-1494
Heim, P. **19**-851, **19**-854, **19**-858
Heimbach, H. **16**-1260
Heimbach, P. **15**-2661
Heimgartner, H. **4**-481, **15**-2309, **16**-1467, **18**-745
Hein, G.E. **12**-735
Hein, J.E. **16**-1086
Heine, H.W. **17**-366, **18**-615
Heine, T. **2**-9
Heinecke, U. **18**-608
Heinich, A.M. **10**-814
Heinisch, G. **14**-378, **14**-388
Heinrich, N. **18**-77
Heinsohn, G. **15**-1217
Heinz, W. **2**-282
Heinzman, S.W. **15**-527, **19**-1163
Heiser, B. **15**-636
Heitmann, P. **13**-180
Heitz, M. **10**-1161
Hekmatshoar, R. **19**-1639
Helbert, M. **1**-54, **3**-19, **8**-101, **8**-104
Held, G. **10**-1701
Helder, R. **15**-1911
Heldrich, F.J. **13**-472
Heldt, W.Z. **18**-361
Helgeson, R. **15**-2309
Helgeson, R.C. **4**-168
Helgren, P.F. **16**-1962
Hélion, F. **16**-570, **16**-2103, **19**-1629
Hell, Z. **13**-591
Helland, I. **14**-483, **16**-351
Hellbach, B. **2**-372
Heller, B. **15**-647, **15**-2632
Heller, D. **15**-647, **15**-648
Hellgardt, K. **13**-395
Hellin, M. **16**-1547, **16**-1550, **16**-1552
Helliwell, M. **15**-568, **15**-1816
Helliwell, S. **19**-389
Hellmann, H. **15**-2466, **15**-2469, **16**-374
Hellou, J. **16**-2148
Hellrung, B. **2**-445, **12**-97
Hellwinkel, D. **5**-246
Helm, M.D. **15**-2296
Helmchen, G. **4**-101, **4**-234, **10**-1513, **10**-1744, **15**-1070, **15**-2243
Helmkamp, G.K. **17**-228
Helms, A.M. **5**-303
Helquist, P. **15**-979, **15**-2498, **16**-1370
Helsby, P. **11**-146
Hembre, R.T. **19**-439
Hembury, G.A. **3**-75
Hemesley, P. **16**-1302
Hemingway, A. **4**-262
Hemmerling, M. **15**-1376
Hemminger, J.C. **19**-17
Hems, W. **19**-1036
Hems, W.P. **9**-108, **16**-849
Henbest, H.B. **15**-114, **19**-811
Henchman, M. **10**-365
Henderson, D.A. **11**-438, **19**-600
Henderson, G.N. **11**-58, **18**-34
Henderson, J.C. **19**-731
Henderson, J.L. **16**-556
Henderson, K.W. **12**-108, **16**-1155
Henderson, S. **16**-1066
Hendley, E.C. **18**-945, **18**-948
Hendrick, M.E. **5**-361, **15**-2535
Hendricks, R.T. **15**-1026
Hendrickson, J.B. **6**-2, **10**-645, **10**-743, **10**-945, **10**-1824, **15**-134, **15**-137, **16**-2295, **17**-209, **17**-352, **19**-1549
Hendriks, A.H.M. **19**-1377
Hendrix, J.P. **12**-419
Hendry, D.G. **14**-73
Hendry, J. **19**-645
Hendry, J.B. **11**-113
Hengst, C. **14**-338
Henis, J.M.S. **12**-51
Henke, B.R. **16**-1067
Henke, H. **19**-353
Henkel, J.G. **18**-677
Henkelmann, J. **16**-2045
Henley, R.L. **15**-509, **15**-1792
Henne, A.L. **15**-539
Hennemann, M. **14**-101
Hennessy, A.J. **13**-436
Hennessy, E.J. **13**-646
Hennessy, M.J. **12**-221
Hennigar, K.H.R. **15**-2305
Henning, R. **10**-712
Hennion, G.F. **10**-1355, **10**-1356, **18**-421
Henri-Rousseau, O. **15**-2253
Henrichs, P.M. **10**-128
Henrick, C.A. **15**-1133, **16**-2097
Henriksen, S.T. **13**-438, **14**-355
Henriksson, U. **19**-1002, **19**-1003
Henry, B.R. **1**-78
Henry, C.E. **16**-1357
Henry, D.J. **12**-643
Henry, J.P. **18**-665
Henry, J.R. **19**-381
Henry, L. **16**-1200
Henry, P.M. **15**-1660, **16**-1807, **19**-374, **19**-698
Henseler, A. **15**-1485
Henshilwood, J.A. **15**-2677
Hensley, M. **15**-1866
Henze, D.K. **18**-676
Henze, W. **15**-1143
Henzel, R.P. **18**-899, **18**-904
Heo, C.K.M. **17**-56
Hepler, L.G. **8**-255, **8**-256, **9**-26
Hepp, H.J. **15**-747
Heppenstall, T.J. **15**-2220
Heras, Md.R.C. **10**-1488
Herath, A. **15**-1225
Heravi, M.M. **16**-54, **16**-127, **19**-34, **19**-72, **19**-114, **19**-130, **19**-248, **19**-249, **19**-1639
Herbert, J.M. **10**-1492

Herbert, M. **19**-465
Herbst, M.D. **10**-755
Herbstein, F.H. **3**-175
Hercourt, A. **19**-1468
Hercules D.M. **11**-601
Herd, A.K. **16**-1922
Herderich, M. **15**-1980, **19**-200
Herdle, W.B. **2**-360
Herges, R. **2**-107, **2**-345, **2**-374, **2**-375, **15**-1651
Heribanová, A. **19**-557
Hering, N. **10**-375
Hérion, H. **17**-267
Herlem, M. **5**-18
Herlihy, K.P. **18**-150
Hermann, H.L. **12**-428
Hermann, W.A. **10**-1388
Hermanns, N. **19**-794
Hermans, B. **15**-2009
Hermans, I. **19**-408
Hermawan, I. **12**-140
Hermeling, D. **15**-2180
Hernán, A.G. **15**-1328
Hernández, A. **17**-151
Hernández, J.E. **19**-307
Hernandez, S.M. **4**-409
Herndon, J.W. **15**-2649, **15**-2653
Herndon, W.C. **2**-4, **2**-11, **2**-120, **2**-143, **2**-145, **2**-366, **15**-2303, **15**-2445, **18**-512
Herod, A.A. **14**-130
Herold, L.R. **10**-565
Herold, M. **15**-1206
Heron, N.M. **15**-2096
Herr, M.L. **2**-251
Herr, R.J. **13**-567, **16**-416
Herradua, P.S. **13**-157
Herranz, E. **15**-2014
Herrera-Álvarez, C. **13**-150
Herrera, R.P. **12**-647
Herrerías, C.I. **15**-2524
Herrero, L.A. **8**-131
Herrero, M.T. **15**-2099
Herring, A.P. **13**-493
Herring, L.E. **15**-2256
Herrlich, M. **11**-346
Herrmann, A.W. **13**-425
Herrmann, J.L. **10**-1699, **10**-1810, **15**-1464
Herrmann, P. **16**-775
Herrmann, R. **10**-134, **17**-482
Herrmann, W.A. **5**-374, **13**-584, **15**-1882
Herron J.T. **19**-373
Herscheid, J.D.M. **11**-310
Herschlag, D. **10**-387
Herse, C. **13**-414
Hershberger, J. **15**-1242
Hershberger, S.S. **12**-559, **14**-431
Hershenson, F.M. **4**-175
Hershey, B. **16**-1066
Hertas, I. **13**-173
Hertwig, R.H. **2**-349
Hervas', M. **5**-226
Hervé, G. **15**-877
Herweh, J.E. **16**-2301
Herz, A.H. **11**-41
Herzberg, G. **5**-367
Herzberg, G. **5**-289
Herzig, D. **19**-269
Herzog, K.J. **15**-2177
Herzon, S.B. **15**-334
Hesp, K.D. **15**-335
Hess Jr., B.A. **2**-119, **2**-248, **5**-47, **10**-205, **10**-210, **13**-41, **18**-573, **18**-583
Hess, G.P. **16**-1908
Hess, H. **4**-179
Hess, H.M. **15**-608
Hess Jr., B.A. **18**-579
Hess, K. **2**-107
Hess, T.C. **18**-236
Hess, W. **15**-2609
Hess, W.W. **19**-80
Hesse, D.G. **4**-483
Hesse, M. **12**-702, **15**-161, **16**-1970, **16**-1971, **18**-160
Hesse, R.H. **12**-765, **14**-153, **18**-928
Hessen, B. **15**-1269
Hessler, D.P. **14**-179
Hester, K.C. **3**-19, **3**-164
Hester, N.B. **19**-694
Heubes, M. **18**-678
Heuft, M.A. **10**-1123, **14**-359
Heuman, P. **19**-1505
Heumann, A. **14**-274
Heumann, K.G. **3**-116
Heuring, D.L. **18**-412
Heus-Kloos, Y.A. **16**-2010
Heusler, K. **14**-230, **19**-1005
Hevesi, L. **5**-52, **10**-800, **15**-2009, **19**-547
Hevia, E. **13**-733
Hewitt, C.D. **11**-308
Hewitt, G.W. **15**-796
Hexter, R.M. **15**-2658
Hey, D.H. **13**-822, **14**-125, **14**-127, **14**-365, **14**-369
Hey, J.P. **4**-244, **4**-255
Heyd, W.E. **10**-265
Heydari, A. **10**-968, **16**-338, **16**-1872
Heydari, R. **11**-140
Heydkamp, W.R. **12**-544
Heyer, D. **19**-589
Heymer, B. **13**-360
Heyn, A.S. **15**-886
Hiatt, R. **10**-768, **10**-773, **15**-1869, **15**-1884
Hiatt, R.R. **19**-747
Hibbert, F. **3**-49, **8**-68, **8**-108, **8**-114, **8**-196, **16**-450, **16**-1692, **16**-1998
Hibert, M. **15**-2335
Hiberty, P.C. **1**-51, **2**-6, **2**-44, **16**-12
Hibino, H. **10**-1562
Hibino, K. **16**-395, **19**-515, **19**-517
Hibino, S. **15**-2319, **19**-1271
Hickey, E.R. **15**-2240
Hickey, M. **15**-1936
Hickey, M.J. **4**-308
Hickinbottom, W.J. **19**-407
Hickmott, P.W. **10**-1785, **10**-1790
Hicks, F.A. **15**-1536, **15**-1581
Hicks, R. **7**-109, **11**-247, **15**-1889
Hicks, R.G. **5**-213
Hida, T. **10**-1195
Hidai, M. **10**-819, **11**-332, **15**-865, **19**-1233
Hidaka, T. **10**-1373, **16**-2081
Hideki, H. **10**-1576
Hideura, D. **15**-840
Hiebert, J.D. **19**-23
Hiebert, S. **10**-1615
Hiegel, G.A. **10**-1133, **19**-663
Hiel, G.P. **15**-2675
Hiemstra, H. **10**-917, **11**-409, **13**-244, **15**-934, **16**-1220, **16**-1844, **18**-834
Hienuki, Y. **4**-442
Hierl, P.M. **10**-365
Hiersemann, M. **18**-436, **18**-690, **18**-703, **18**-727, **18**-738
Hierso, J.-C. **13**-590
Higa, S. **16**-2139
Higashi, K. **19**-1182
Higashijima, M. **15**-557
Higashimae, Y. **10**-1991
Higasi, K. **2**-28
Higginbotham, H.K. **1**-59
Higgins, D. **10**-1501
Higgins, J. **13**-259
Higgins, R. **14**-172, **14**-227, **14**-256
Higgins, R.J. **11**-159, **11**-160
Higgins, S.D. **19**-1774
Higgins, W. **17**-294
High, K.G. **15**-741
Highcock, R.M. **15**-16
Highet, R.J. **2**-469
Hightower, T.R. **15**-274, **15**-414, **19**-55
Higley, D.P. **19**-360
Higuchi, H. **2**-353
Higuchi, T. **10**-1387, **12**-762, **16**-1922
Hii, K.K. **13**-192, **13**-386, **13**-448
Hiickel, E. **2**-64
Hiiragi, M. **10**-828
Hikida, T. **15**-225
Hilbert, J.M. **17**-50
Hildebrandt, B. **16**-462
Hilderbrandt, R.L. **1**-65
Hill, A.F. **2**-45, **9**-123
Hill, C.L. **12**-356, **12**-634, **12**-635, **14**-146, **14**-309, **19**-434
Hill, D.G. **16**-2154
Hill, D.R. **16**-1740, **19**-489
Hill, D.T. **15**-2548
Hill, E.A. **12**-581, **15**-899

Hill, H.A.O. **13**-263
Hill, H.D.W. **14**-367
Hill, H.W. **4**-220
Hill, J.A. **12**-23
Hill, K.A. **12**-162
Hill, M.S. **15**-355, **19**-1746
Hill, R. **2**-261
Hill, R.H. **19**-1502
Hill, R.K. **2**-298, **4**-15, **10**-1122, **17**-457, **18**-425, **18**-662
Hill, R.L. **16**-1929
Hill, T.A. **10**-974
Hiller, G. **16**-184, **19**-1433
Hillhouse, G.L. **19**-1555
Hillier, I.H. **2**-474, **18**-704, **18**-708
Hillier, M.C. **9**-112
Hillman, M.E.D. **16**-790
Hillmyer, M. **10**-831
Hills, I.D. **13**-532
Hilmersson, G. **8**-225, **8**-226, **10**-1189, **15**-504, **15**-964, **15**-2206, **16**-488, **16**-491, **16**-495, **19**-942, **19**-1188, **19**-1677
Hilpert, H. **4**-41
Hilt, G. **14**-338, **15**-833, **15**-1007, **15**-2242, **15**-2266, **15**-2404, **15**-2609, **15**-2684, **16**-917
Hilty, T.K. **16**-1124
Himabindu, K. **16**-1713
Himeshima, Y. **13**-24
Himoe, A. **11**-49, **11**-51
Hin, Q.-H. **19**-1309
Hinakubo, Y. **19**-1650
Hindley, N.J. **16**-812
Hine, J. **3**-34, **8**-56, **8**-175, **9**-16, **9**-22, **9**-24, **9**-25, **10**-546, **11**-512, **12**-58, **15**-579, **17**-45
Hinkley, J.M. **10**-512
Hinman, R.L. **16**-2207
Hino, F. **18**-369
Hinsley, J. **15**-863
Hintermann, L. **10**-1362, **15**-221
Hinton, J. **6**-45
Hintze, H. **19**-24
Hinze, J. **1**-29, **1**-31
Hinzen, B. **19**-120
Hioe, J. **5**-213
Hioki, H. **10**-729
Hioki, K. **16**-1938, **18**-778
Hipperson, W.C.P. **19**-316
Hirab, T. **10**-234
Hirabayashi, K. **10**-1269, **13**-380, **13**-715, **14**-358
Hirabayashi, R. **15**-2108, **16**-952
Hirabayashi, T. **10**-621, **15**-204, **16**-2181
Hirabayashi, Y. **16**-1835
Hiraga, Y. **16**-1285
Hirai, A. **10**-1949
Hirai, C. **3**-143, **10**-1762
Hirai, H. **11**-56
Hirai, K. **5**-357, **5**-359, **15**-1613
Hirai, T. **11**-577
Hirai, T. **14**-193, **15**-422
Hirai, Y. **19**-790
Hiraike, H. **12**-791
Hiraiwa, N. **2**-353
Hiraiwa, Y. **10**-1186, **16**-1144
Hirakawa, A.Y. **7**-14
Hirakawa, T. **12**-154
Hirama, M. **15**-650, **15**-1112, **15**-1836, **15**-1839, **16**-1071, **16**-1393
Hiramatsu, H. **16**-1227
Hiramatsu, K. **10**-1635
Hiramoto, K. **16**-1770
Hirano, J. **16**-1818
Hirano, K. **10**-1576, **10**-1715, **15**-1261, **16**-739, **16**-869, **16**-947
Hirano, M. **11**-350, **15**-156, **15**-523, **15**-845, **18**-271
Hirano, S. **15**-976, **16**-690
Hirano, Y. **19**-370
Hirao, H. **15**-2234
Hirao, I. **11**-530, **16**-2082
Hirao, K. **6**-4
Hirao, T. **10**-1281, **10**-1971, **11**-427, **13**-721, **15**-961, **15**-1210, **15**-1580, **15**-1597, **19**-1291, **19**-1574, **19**-1637
Hirao, Y. **14**-213
Hiraoka, M. **12**-329
Hiraoka, Y. **16**-680
Hirasawa, M. **16**-547
Hirasawa, S. **15**-633
Hirase, K. **15**-1302
Hirase, M. **15**-1565
Hirashima, T. **15**-2089
Hirashita, T. **10**-235, **10**-1630, **15**-987, **16**-916
Hirata, F. **15**-2221
Hirata, K. **16**-612, **16**-1766
Hirata, R. **16**-2269
Hirata, T. **12**-186, **16**-1649
Hirata, Y. **19**-1414
Hiratani, K. **18**-261
Hirayama, K. **15**-1509, **15**-2377
Hirayama, L.C. **16**-560
Hird, A.W. **15**-1205
Hird, M. **10**-1366, **10**-1367, **10**-1368
Hirner, S. **16**-1436
Hirobe, M. **10**-817
Hiroi, K. **12**-258, **17**-297, **19**-144
Hirooka, S. **2**-332, **2**-333, **2**-335
Hirosawa, C. **15**-1533, **15**-1534, **15**-1549, **16**-825
Hirose, T. **16**-546
Hirose, Y. **10**-676
Hirota, E. **4**-285, **5**-289
Hirota, K. **10**-614, **10**-958, **10**-1433, **11**-686, **15**-438, **19**-1355
Hirota, M. **9**-76
Hirota, N. **5**-218
Hirota, T. **13**-872
Hirotsu, K. **1**-72, **3**-171, **10**-1387
Hiroya, K. **16**-1850
Hirsch, A. **2**-390, **2**-395, **2**-396, **2**-398
Hirsch, J.A. **4**-352
Hirsch, R. **5**-145
Hirschmann, H. **4**-263
Hirshfeld, F.L. **2**-321
Hirst, D.M. **2**-2
His, S. **18**-349
Hisano, T. **15**-2105
Hiscocks, S.P. **2**-483
Hiskey, R.G. **19**-774
Hisler, K. **16**-1334
Hita, M.d.C. **16**-1084
Hitchcock, P.B. **13**-493
Hitchcock, S.R. **12**-492, **16**-666, **16**-668
Hites, R.A. **16**-2169
Hiti, J. **5**-293
Hitzler, M.G. **9**-113
Hixson, S.S. **18**-908
Hiyama, R. **15**-623
Hiyama, T. **10**-1269, **10**-1276, **10**-1415, **10**-1729, **10**-1913, **10**-1914, **11**-543, **12**-299, **12**-558, **13**-380, **13**-688, **13**-705, **13**-715, **14**-358, **15**-623, **15**-770, **15**-1669, **16**-690, **16**-693, **16**-1650, **19**-1031
Hiyashi, M. **19**-20
Hlasta, D.J. **16**-2080
Ho, C.-M. **15**-1809, **19**-623
Ho, C.-Y. **15**-803, **16**-326, **16**-694, **16**-1953
Ho, C.-J. **18**-90
Ho, D.M. **2**-80, **2**-141, **3**-210, **15**-2140
Ho, G. **5**-416
Ho, H.C. **16**-207
Ho, I. **17**-86
Ho, J. J. **12**-85
Ho, K.M. **14**-443
Ho, L.L. **17**-346
Ho, M.M. **19**-1208
Ho, P.-S. **10**-1920
Ho, P.T. **15**-1835
Ho, S. **10**-384
Ho, S.P. **3**-126
Ho, T.-I. **14**-375
Ho, T. **8**-164, **10**-1798, **16**-69
Ho, T.-L. **16**-207, **19**-10, **19**-1343, **19**-1344
Hoa, K. **11**-120
Hoang, H. **16**-1413
Hoang, L. **16**-1108
Hoashi, Y. **15**-1053
Hobbs, D. **15**-1362
Hobza, P. **3**-77
Hoch, H. **10**-1790
Hochrein, L. **19**-500
Hochstrasser, R. **12**-160
Hocker, J. **16**-2296

Hocking, M.B. **19**-412, **19**-414, **19**-415
Hocquemiller, R. **13**-317
Hodačová, J. **19**-800
Hodder, A.S. **18**-876
Hodek, W. **17**-478
Hodge, C.N. **3**-67, **4**-255
Hodge, J.D. **5**-35, **5**-49
Hodge, P. **12**-715, **16**-1930, **16**-1935, **17**-462
Hodges, F.W. **11**-627
Hodgson, D.M. **10**-979, **10**-1279, **10**-1619, **16**-256, **16**-497, **17**-214, **17**-367, **18**-145
Hodgson, P.B. **12**-387
Hodgson, P.K.G. **16**-1691, **18**-32
Hodnett, N. **15**-1434
Hodous, B.L. **16**-370, **16**-2227
Hodson, D. **16**-2165
Hoefnagel, A.J. **9**-64
Hoefnagel, M.A. **11**-156
Hoefs, C.A.M. **17**-231
Hoeg, D.F. **12**-650
Hoegerle, R.M. **17**-413
Hoekstra, A. **11**-310
Hoekstra, M.S. **16**-2124
Hoem, A.B. **18**-736
Hoen, R. **15**-643
Hoepker, A.C. **12**-421
Hoerter, J.M. **16**-1966
Hoesch, L. **4**-41
Hofelich, T.C. **5**-2, **5**-74, **10**-190
Hofer, E. **4**-223
Hoff, C.D. **2**-473
Hoff, D.J. **16**-1376
Hoff, W.S. **19**-396
Hoffman Jr., J.M. **2**-260
Hoffman Jr., L. **16**-1443
Hoffman, B.C. **5**-415
Hoffman, C. **15**-106
Hoffman, D.H. **12**-31
Hoffman, D.K. **18**-568
Hoffman, D.M. **15**-1875
Hoffman, N.W. **10**-1959
Hoffman, R.V. **18**-371, **18**-373
Hoffman, T.D. **12**-28, **12**-716
Hoffmann-Röder, A. **15**-1099
Hoffmann, D. **5**-191, **6**-37
Hoffmann, E. appendixa-23
Hoffmann, F. **19**-513
Hoffmann, H. **16**-1360
Hoffmann, H.M.R. **10**-1237, **15**-991, **15**-2664, **16**-2001, **19**-1117
Hoffmann, K.J. **11**-279
Hoffmann, M.R. **7**-73, **7**-77, **7**-78
Hoffmann, N. **15**-1118
Hoffmann, P. **16**-2249, **16**-2253, **16**-2262, **17**-481
Hoffmann, R. **1**-1, **1**-74, **2**-12, **2**-216, **4**-77, **4**-439, **5**-351, **12**-289, **15**-1796, **15**-2237, **15**-2297, **15**-2300
Hoffmann, R. **15**-2311, **17**-358, **18**-424, **18**-509, **18**-511, **18**-559, **18**-565, **18**-574, **18**-657, **18**-659, **18**-676
Hoffmann, R.W. **5**-145, **5**-146, **10**-1376, **12**-637, **12**-643, **12**-652, **13**-39, **13**-84, **13**-104, **13**-221, **13**-638, **14**-403, **15**-2262, **16**-437, **16**-460, **16**-462, **16**-526, **16**-736, **16**-752, **16**-1064, **18**-774, **18**-786
Hoffmann, S. **8**-119, **10**-1787, **16**-358
Hoffmann, V.T. **4**-467
Hofinger, A. **16**-349
Höfle, G. **16**-1727
Höfle, G.A. **12**-432, **16**-1259
Höfler, C. **19**-24
Hofman, P.S. **11**-635
Hofmann, A.W. **17**-252
Hofmann, H.-J. **11**-169
Hofmann, J.E. **11**-385, **17**-289, **17**-291
Hofmeyer, L.J.F. **7**-128
Hofsløkken, N.U. **11**-499
Hofstetter, K. **15**-1907
Hofstraat, R. **16**-2203
Höft, E. **10**-308
Högberg, H.-E. **15**-2104
Högberg, T. **16**-1941
Hoge, G. **15**-641, **15**-643
Hoge, G.S. **18**-814, **18**-886
Hogen-Esch, T.E. **5**-134
Höger, E. **19**-315
Hogeveen, H. **5**-31, **12**-109, **12**-358, **15**-135, **15**-1510, **15**-2444, **16**-1305, **18**-7, **18**-29, **18**-96, **16**-1701
Hogg, J.L. **16**-86, **16**-1661
Hogg, L.M. **13**-733
Hoggett, J.G. **11**-34, **11**-44, **11**-54
Hoggett, J.H. **11**-123
Hogrefe, F. **2**-194
Hohlneicher, G. **4**-424
Hohn, A. **15**-1497
Hoiness, C.M. **15**-2549
Høj, B. **15**-1454
Hojatti, M. **2**-438, **8**-110, **8**-118, **12**-93, **15**-219
Hojo, K. **2**-278
Hojo, M. **10**-80, **15**-911, **19**-1372
Hoke, D. **19**-1282, **19**-1329, **19**-1376
Holbrey, J.D. **9**-119, **9**-123
Holcomb, A.G. **2**-231, **10**-154
Holczknecht, O. **15**-2514, **19**-179
Holden, D.A. **14**-60
Holder, R.W. **15**-2420
Holeman, D.S. **15**-1047
Hölemann, A. **16**-696, **16**-732
Holland, H.L. **19**-773, **19**-801
Hollander, F.J. **15**-2250
Hollander, L.B. **15**-2161
Höller, B. **19**-993
Holler, E.R. **19**-1337
Holliday, R.E. **13**-35
Hollingsworth, C.A. **1**-3
Hollinshead, D.M. **19**-1390
Hollis, R. **14**-90
Hollis, T.K. **16**-1129
Hollist, G.O. **19**-671
Hollister, K.R. **10**-1825
Hollmann, D. **10**-909, **10**-933
Hollmann, F. **15**-1907, **19**-93
Holloway, R.L. **2**-235
Hollowell, C.D. **1**-79
Hollyhead, W.B. **8**-66, **8**-71
Holm, A. **10**-510
Holm, T. **16**-477, **16**-512, **16**-519, **16**-521, **16**-530
Holman, R.W. **11**-32
Holmberg, B. **16**-1658
Holme, D. **15**-473
Holmes, A.B. **9**-108, **13**-175, **13**-189, **13**-392, **13**-501, **15**-2126
Holmes, D. **4**-54, **13**-107
Holmes, I.P. **16**-1496
Holmes, J. **18**-443
Holmes, J.L. **5**-77, **5**-278, **10**-197
Holmes, R.R. **19**-728
Holmes, S.A. **4**-395
Holmgren, A. **10**-99
Holmquist, C.R. **12**-343
Holness, N.J. **4**-360
Holsboer, F. **2**-249
Holt, G. **16**-2165
Holt, J. **8**-125
Holt, R.J. **15**-2494
Holthausen, M.C. **2**-349
Holton, J. **10**-1974, **12**-67
Holton, R.A. **15**-1116
Holtz, H.D. **10**-331
Holubka, J.W. **12**-215
Holy, N.L. **5**-333, **10**-301, **15**-574
Holz, J. **15**-648, **19**-1150
Hölzer, B. **12**-643, **16**-526
Homer, R.B. **8**-31, **8**-62
Homma, K. **19**-1421, **19**-1446
Hommeltoft, S.I. **5**-232
Hommes, H. **10**-1839
Hommes, N.J.R.v.E. **2**-116, **2**-117
Homsi, F. **15**-1713
Hon, M. **4**-428, **15**-129, **18**-162, **18**-606, **18**-615, **18**-650
Hon, Y. **10**-51, **10**-339
Hon, Y.-S. **19**-332
Honaker, M.T. **10**-920
Honda, H. **15**-699
Honda, K. **13**-861, **18**-775
Honda, M. **16**-1167
Honda, T. **12**-338, **16**-851, **18**-375, **18**-962
Honda, Y. **19**-819
Hondo, T. **15**-230, **15**-398
Hondrogiannis, G. **15**-1675, **15**-2224
Honegger, E. **4**-250

Honeyman, G.W. **13**-733
Hong, B. **16**-350
Hong, D.J. **10**-532
Hong, F.-E. **13**-495
Hong, J.-I. **13**-146
Hong, J.-B. **16**-1154
Hong, M.-L. **16**-590
Hong, R.-K. **13**-201
Hong, R. **11**-314
Hong, S. **15**-344, **15**-353, **15**-2024, **15**-2027, **15**-2028
Hong, S.-H. **10**-1045, **18**-857, **18**-860, **18**-895
Hong, S.-p. **4**-127, **18**-731
Hong, W.S. **19**-1496
Hong, Y.-T. **10**-1714, **13**-555, **13**-622
Hong, Y. **16**-2086
Hongo, H. **10**-1537
Hongoh, Y. **4**-182
Hongwen, H. **10**-1041
Hongxun, D. **18**-462
Honma, M. **15**-2528
Honma, S. **15**-1282
Honma, T. **15**-1953
Honma, Y. **15**-1050, **15**-1229, **15**-1250
Honwad, V.K. **16**-2010
Honzatko, R. **4**-129, **4**-150, **15**-635
Hoobler, M.A. **10**-1855
Hoogenboom, R. **7**-114
Hoogzand, C. **15**-2646
Hoole, D. **11**-241
Hoover, D.J. **4**-215
Hooz, J. **10**-603, **10**-662, **10**-1880, **10**-1881, **12**-161, **12**-435, **12**-436, **16**-1039
Hope, E.G. **15**-1610
Hopf, H. **2**-52, **2**-53, **10**-74, **15**-107, **15**-2256, **15**-2389, **15**-2488, **17**-18
Hopff, H. **9**-94, **15**-2589
Hopkins, A. **16**-2276
Hopkins, P.B. **2**-449, **17**-343, **18**-733
Hopkins, T.E. **12**-753
Hopkinson, A.C. **3**-53, **10**-312, **10**-317
Hoppe, D. **16**-1254, **16**-1262, **16**-1263
Hoppen, V. **4**-343, **4**-354
Hopperdietzel, S. **15**-1674
Hor, T.S.A. **13**-510
Horaguchi, T. **12**-116, **19**-482
Horan, C. J. **5**-69, **13**-25, **13**-29
Hore, P.J. **5**-230
Horeau, A. **4**-208, **4**-222
Horeis, G. **7**-107
Horgan, A.G. **18**-799
Horgan, A.J. **18**-795
Horgan, S.W. **19**-258
Hori, H. **18**-849
Hori, I. **10**-1810
Hori, K. **15**-2639, **16**-1695
Hori, M. **15**-2639
Hori, T. **12**-226, **12**-227, **14**-198, **15**-643
Hori, Y. **15**-280
Horibe, I. **11**-690
Horie, T. **13**-171
Horiguchi, J. **15**-1486
Horiguchi, Y. **15**-1139, **19**-507
Horikawa, Y. **14**-137
Horino, H. **19**-1744
Horiuchi, C.A. **12**-130, **12**-170, **12**-183, **15**-1684, **15**-1704, **15**-1821, **19**-324, **19**-993
Horiuchi, M. **16**-1431
Horiuti, I. **15**-480
Horler, H. **18**-77
Hormi, O. **15**-1972
Hormi, O.E.O. **15**-1833, **15**-1850
Horn, A.H.C. **14**-91
Horn, U. **17**-426
Hornaman, E.C. **17**-276
Hornbuckle, S.F. **2**-92
Horner, J.H. **5**-326, **5**-327, **5**-330, **14**-53, **14**-85, **14**-143, **15**-1313, **15**-1314, **15**-1367
Horner, L. **4**-47, **16**-1311, **16**-1360, **18**-230, **19**-1404
Hornfeld, H.L. **11**-33
Hörnfeldt, A. **16**-2085
Horning, D.E. **13**-787
Horning, E.C. **19**-655
Horspool, W.M. **7**-1, **15**-2448, **15**-2679, **16**-2205, **18**-917
Horst, L. **10**-840
Horstmann, T.E. **15**-1416
Horton, D. **4**-376, **16**-280
Horton, J.L. **9**-78
Horváth, I.T. **19**-126
Hosaka, K. **16**-2140
Hoshi, M. **12**-522, **12**-574
Hoshi, T. **10**-695, **13**-401, **13**-500, **16**-1146, **16**-1202, **16**-1792, **18**-385
Hoshino, E. **15**-1797
Hoshino, M. **12**-272, **17**-373, **19**-819, **19**-864
Hoshino, O. **10**-1203, **15**-1556
Hoshino, Y. **13**-861
Hosie, L. **16**-31
Hosmane, R.S. **2**-162
Hosoi, K. **11**-543
Hosokawa, H. **15**-1684, **15**-1704
Hosokawa, S. **16**-1149
Hosomi, A. **10**-1325, **15**-230, **15**-398, **15**-626, **15**-814, **15**-911, **15**-1246, **16**-1062, **16**-1126, **16**-1127, **16**-2057, **16**-2068, **19**-1290, **19**-1372
Hosoya, H. **2**-149, **2**-163
Hossain, D. **13**-509
Hossain, I. **15**-654
Hossain, K.M. **10**-1456, **13**-330
Hossain, M.A. **12**-276
Hossain, M.M. **15**-2063
Hosseini-Sarvari, M. **16**-1903, **17**-437
Hosseini, M. **18**-353
Hosseini, M.W. **3**-160, **4**-252
Hosseinnia, A. **15**-1392
Hosseinzadeh, R. **10**-1135, **13**-123, **13**-235, **19**-598, **19**-832
Hossenlopp, J.M. **7**-50
Hostyn, S. **13**-196
Hotokka, M. **8**-83
Hotta, Y. **19**-416
Hou, D.-R. **17**-234
Hou, G.-H. **15**-470, **15**-643
Hou, G. **15**-452, **19**-1014, **19**-1142
Hou, I.-J. **10**-304
Hou, K. **19**-494
Hou, R.-S. **19**-503
Hou, S.-J. **10**-288
Hou, X.-L. **10**-598, **10**-699, **10**-700, **10**-1003, **10**-1243, **10**-1657, **10**-1659, **10**-1719, **13**-434, **15**-646, **16**-880
Hou, X. **10**-1905
Hou, Z. **15**-769, **15**-861, **16**-1529, **19**-1632
Hough, R.E. **15**-23
Houghton, T.J. **2**-73
Houk, K.N. **2**-43, **2**-388, **3**-3, **3**-72, **4**-307, **5**-131, **5**-284, **5**-389, **6**-46, **7**-1, **7**-13, **8**-210, **11**-29, **12**-88, **12**-433, **14**-72, **15**-81, **15**-104, **15**-270, **15**-994, **15**-998, **15**-999, **15**-1028, **15**-1029, **15**-1305, **15**-1321, **15**-1835, **15**-1880, **15**-1941, **15**-2000, **15**-2106, **15**-2112, **15**-2119, **15**-2120, **15**-2121, **15**-2127, **15**-2131, **15**-2135, **15**-2188, **15**-2255, **15**-2256, **15**-2271, **15**-2272, **15**-2280, **15**-2283, **15**-2291, **15**-2297, **15**-2301, **15**-2315, **15**-2421, **15**-2665, **15**-2699, **16**-256, **16**-395, **16**-1057, **16**-1067, **16**-1074, **16**-1654, **18**-493, **18**-495, **18**-513, **18**-518, **18**-567, **18**-605, **18**-619, **18**-638, **18**-639, **18**-676, **18**-694, **18**-712, **18**-734, **18**-784, **18**-911, **18**-915, **19**-924
Houk, R.J.T. **8**-116
Houle, F.A. **5**-76
Houlihan, W.J. **16**-1017
Houmam, A. **14**-5
Hourigan, M.J. **10**-225
House, D. **15**-566
House, H.O. **10**-1423, **10**-1661, **10**-1753, **10**-1755, **10**-1756, **10**-1759, **10**-1785, **12**-110, **12**-341, **12**-590, **15**-182, **15**-1136, **15**-1156, **15**-1158, **15**-1239, **15**-1637, **16**-372, **16**-1014, **16**-1042, **16**-1311, **16**-1441, **16**-1805, **16**-2002, **16**-2123, **16**-2150, **17**-403,

18-286, **18**-379, **19**-12, **19**-64, **19**-301, **19**-846, **19**-879, **19**-932, **19**-934, **19**-1209
Houser, H.J. **5**-49
Houser, J.J. **5**-35, **17**-44
Houser, R.W. **12**-195
Houson, I. **19**-1034
Housseman, C. **16**-812m **16**-959
Houston, D. **18**-100
Houston, T.A. **16**-1743
Hout, F.A.S. **7**-128
Hovanes, B.A. **10**-45
Höver, H. **2**-223
Hoveyda, A.H. **10**-1450, **10**-1517, **16**-672, **10**-1371, **15**-731, **15**-740, **15**-891, **15**-900, **15**-1170, **15**-1205, **15**-1208, **16**-672, **16**-776, **16**-899, **16**-1515, **16**-1540, **17**-191, **18**-804, **18**-821, **18**-829, **18**-843, **18**-845, **18**-846, **18**-847, **18**-854, **18**-892
Howard, A.E. **4**-370
Howard, J.A. **5**-312, **14**-60, **14**-73, **14**-241
Howard, J.A.K. **3**-14, **3**-76, **4**-460, **18**-953
Howard, S.I. **19**-1009
Howard, S.T. **8**-201
Howard, W.G. **14**-237
Howe, C.A. **13**-821
Howe, G.R. **19**-747
Howe, R. **10**-187
Howe, R.S. **10**-1049
Howell, A.R. **16**-499, **16**-1414, **16**-1416, **16**-2213, **19**-232
Howell, C.F. **17**-260
Howell, G.P. **16**-410, **16**-412
Howell, H.G. **19**-1159
Howell, R. **18**-400
Howells, R.D. **10**-411
Howk, B.W. **15**-326
Howlett, K.E. **17**-142
Howley, P.M. **15**-2535
Hoy, V.J. **3**-14, **3**-76
Hoye, T.R. **15**-1538, **17**-311, **19**-881
Hoyle, J. **5**-151
Hoyos, P. **19**-993
Hoyt Jr., E.B. **17**-350, **17**-356
Hoyt, H.M. **19**-1259
Hoz, S. **4**-456, **8**-146, **10**-27, **10**-28, **10**-29, **10**-117, **10**-336, **10**-338, **10**-382, **10**-385, **10**-386, **13**-838, **15**-598, **16**-17, **17**-59, **19**-147
Hoz, T. **10**-27, **10**-336, **10**-1579, **17**-404
Hrapchak, M.J. **16**-1509
Hrdlovic, P. **11**-594
Hrovat, D.A. **4**-542, **4**-543, **5**-251, **10**-55, **14**-31, **18**-575, **18**-578, **18**-678
Hrubiec, R.T. **10**-251, **10**-1166
Hruby, V.J. **15**-1176
Hrutfiord, B.F. **12**-719, **13**-221
Hsi, N. **18**-25
Hsiao, C.-N. **16**-1740
Hsiao, Y. **16**-251
Hsieh, W. **18**-101
Hsu, C.-Y. **16**-1747
Hsu, C.S. **10**-45
Hsu, H.C. **12**-517
Hsu, J.-L. **16**-309
Hsu, S.K. **12**-26
Hsu, Y.-C. **10**-930
Hsung, R.P. **10**-1051, **15**-2563, **15**-2670, **19**-720
Hu, A.-G. **15**-643
Hu, A. **9**-128, **19**-1014, **19**-1018
Hu, B. **10**-765, **18**-267, **19**-168, **19**-652
Hu, C. **16**-1084
Hu, C.-M. **16**-445
Hu, H. **15**-1154
Hu, J.-b. **10**-1476, **19**-1024, **19**-1033
Hu, J. **3**-94, **16**-1044, **19**-555
Hu, K.-N. **5**-234
Hu, L.-m. **19**-830
Hu, L. **10**-1373, **18**-304, **19**-1261
Hu, Q. **10**-1630
Hu, R.-J. **19**-175
Hu, S.-R. **13**-841
Hu, S. **19**-223
Hu, W. **15**-2250, **15**-2580
Hu, X. **15**-453, **19**-168, **19**-171 **19**-1221
Hu, W.-X. **10**-1253, **13**-134, **15**-1387, **15**-1424
Hu, X.E. **10**-407
Hu, Y. **10**-900, **10**-1550, **10**-1905, **11**-243, **13**-106, **13**-398, **13**-665, **15**-1610, **15**-2131, **16**-1822, **16**-1823, **16**-1884, **16**-2027, **16**-2041, **16**-2046, **16**-2047
Hu, Z. **14**-97
Hu, Y.-H. **16**-1419
Hu, Y.-Q. **10**-932
Hu, Y.-Z. **15**-852
Hua-ming, Z. **15**-2298
Hua, G. **19**-1593
Hua, I. **7**-73
Hua, J.C. **15**-2018
Hua, L. **16**-103, **19**-993
Hua, R. **11**-137, **13**-588, **13**-591, **15**-223, **15**-277, **15**-465, **15**-764, **15**-1266, **15**-1476, **15**-1785, **15**-1788
Hua, W.-T. **19**-1021
Hua, X.J. **16**-1406
Hua, Z. **15**-453, **15**-1208, **19**-302
Huang-Minlon **19**-1410
Huang, C.-W. **13**-456
Huang, C.-H. **15**-1310
Huang, C.-W. **15**-2613, **15**-2616
Huang, C. **8**-121, **16**-1364
Huang, D. **6**-73, **10**-858, **16**-2046
Huang, F. **10**-871, **15**-2697, **17**-330
Huang, G. **19**-529
Huang, H. **4**-304, **10**-602, **11**-311, **13**-218, **14**-150, **15**-453, **15**-643, **15**-1056, **19**-1014
Huang, H.-L. **17**-189
Huang, H.-Y. **19**-503
Huang, I.-w. **15**-2605
Huang, J. **4**-294, **8**-219, **10**-1051, **13**-98, **13**-195, **15**-444, **15**-1096, **15**-2670, **16**-1497, **16**-1534
Huang, J.-M. **15**-331
Huang, J.-S. **15**-2509, **19**-536, **19**-537
Huang, K.-H. **15**-2068
Huang, K. **15**-452, **19**-1158, **19**-1234
Huang, L.-F. **10**-1347
Huang, L.-H. **19**-68
Huang, L. **16**-893, **16**-1434
Huang, L.W. **7**-55
Huang, M. **4**-42, **13**-697
Huang, N.Z. **2**-270
Huang, P.-C. **16**-1421
Huang, P.-Q. **16**-469, **16**-1963
Huang, Q. **13**-428, **15**-373, **15**-959, **15**-2625
Huang, R. **19**-695
Huang, S. **13**-494, **15**-624
Huang, S.L. **19**-157
Huang, T.-B. **10**-923
Huang, T.-S. **15**-1252
Huang, T.-Y. **16**-1074
Huang, T.T. **10**-1160
Huang, W.-l. **5**-271
Huang, W.-J. **15**-1440
Huang, W.-S. **15**-941
Huang, W. **11**-472, **16**-1512
Huang, X.-R. **16**-691
Huang, X. **10**-1380, **10**-1995, **13**-130, **13**-131, **13**-187, **13**-189, **13**-200, **13**-236, **13**-675, **15**-315, **15**-467, **15**-1337, **15**-1380, **16**-1327, **16**-1358, **16**-1497, **18**-296, **18**-298, **19**-1234, **19**-1625
Huang, Y.-P. **19**-780
Huang, Y.-T. **13**-500
Huang, Y.-Y. **15**-452
Huang, Y.-Z. **15**-1228, **16**-1358
Huang, Y. **15**-2186, **15**-2326, **16**-129, **16**-546, **16**-571, **16**-832, **16**-854, **16**-1358, **19**-1253
Huang, Y.C.J. **15**-2283
Huang, Z.-Z. **16**-1358, **16**-1359, **16**-855
Huang, Z. **10**-602, **10**-1788, **13**-100, **16**-675, **16**-897
Huard, K. **15**-2056, **16**-1435
Huba, F. **13**-85
Hubbard, J.L. **8**-195, **18**-469
Hubbard, R. **18**-528
Hubbard, S.C. **7**-27

Huber-Buser, E. **4**-473
Huber-Emden, H. **10**-957
Huber, E.W. **16**-339
Huber, F.A.M. **16**-2073
Huber, G. **16**-1443, **19**-315
Huber, H. **4**-249, **18**-532
Huber, M.B. **15**-1237
Huber, W. **2**-334, **2**-336, **5**-333
Hubert, A.J. **10**-659, **12**-57, **17**-326
Hubig, S.M. **11**-19, **15**-2209, **16**-2205
Hübner, G. **3**-212
Hübner, S. **11**-521
Hübner, T. **4**-488
Hückel, E. **2**-397
Hückel, W. **17**-82, **19**-10
Huckin, S.N. **16**-1228
Huddleston, R.R. **16**-741
Hudec, J. **4**-277, **15**-1511, **18**-601
Hudlicky, M. **10**-542, **10**-1094, **10**-1099, **10**-1100, **10**-1138, **12**-709, **14**-149, **15**-165, **15**-440, **15**-1789, **15**-1869, **17**-497, **18**-379, **19**-9, **19**-11, **19**-63, **19**-374, **19**-401, **19**-609, **19**-634, **19**-646, **19**-669, **19**-717, **19**-773, **19**-843, **19**-847, **19**-848, **19**-878, **19**-1277, **19**-1287
Hudlicky, T. **4**-428, **10**-1094, **10**-1190, **15**-129, **15**-1864, **15**-1865, **15**-1867, **15**-2441, **15**-2493, **18**-162, **18**-606, **18**-615, **18**-650
Hudrlik, A.M. **15**-722, **15**-744, **15**-977, **16**-1290
Hudrlik, P.F. **5**-197, **15**-722, **15**-744, **15**-977, **16**-1290
Hudson, A. **14**-59
Hudson, C.E. **18**-570
Hudson, H.R. **10**-216, **18**-48
Hudson, R.F. **10**-345, **10**-387, **16**-1616
Hudspeth, J.P. **18**-649
Huerta, F.F. **10**-1506, **16**-1178
Huerta, M.. **17**-171
Huertas, R.E. **19**-1020
Huet, F. **10**-571, **16**-2055, **16**-881
Huffman, J.C. **10**-202
Huffman, J.W. **13**-800, **19**-933
Huffman, M.A. **10**-1146, **16**-1995, **19**-955
Huffman, R.W. **16**-1956
Hufton, R. **15**-913, **15**-2105
Hug, G.L. **7**-37, **7**-38
Hug, M. **15**-1992
Hug, S. **10**-1463
Huggins, M.L. **3**-3
Huggins, M.T. **3**-70
Hughes, C.O. **15**-2608
Hughes, D. **16**-998, **19**-1135
Hughes, D.D. **15**-2637
Hughes, D.E.P. **15**-169
Hughes, D.L. **4**-204, **9**-112, **10**-350, **10**-352, **10**-727, **16**-251, **18**-767
Hughes, E.D. **9**-3, **10**-6, **10**-17, **10**-42, **10**-43, **10**-46, **10**-347, **11**-149, **11**-151, **11**-610, **12**-10, **12**-17, **13**-782, **16**-1667, **17**-13, **17**-37, **17**-93, **17**-109, **17**-110, **17**-112, **17**-124, **17**-127, **18**-5, **18**-794
Hughes, G. **15**-632
Hughes, K. **16**-325
Hughes, L. **5**-296, **14**-90
Hughes, M.L. **17**-111
Hughes, N. **12**-610, **12**-626, **13**-80
Hughes, R. **14**-437
Hughes, R.L. **18**-122
Hughes, W.B. **18**-806, **18**-812
Hughmark, P.B. **18**-356
Huh, C. **5**-334
Huh, H. **10**-1764, **15**-1404
Huh, K. **10**-926
Huh, S.C. **15**-1063
Huheey, J.E. **1**-28, **8**-251
Hühnerfuss, H. **4**-234
Hui, A. **16**-666
Hui, R.A.H.F. **19**-51
Hui, R.C. **15**-1460, **15**-1461, **16**-503, **16**-504
Huie, E.M. **15**-2105
Huisgen, R. **13**-93, **13**-258, **15**-2105, **15**-2120, **15**-2128, **15**-2153, **15**-2391, **15**-2422, **15**-2426, **15**-2433, **15**-2435, **15**-2437, **15**-2438, **18**-312, **18**-532, **18**-541, **19**-1268
Hulce, M. **2**-54, **15**-1165
Hulin, B. **16**-336
Hull, K. **13**-586
Hull, K.I. **14**-197, **19**-463, **19**-525
Hull, W. **4**-302
Hüllmann, M. **16**-608
Hulshof, L.A. **19**-209
Hult, K. **15**-1110
Hultin, P.G. **16**-1086, **16**-1074
Hultzsch, K.C. **15**-324, **15**-338, **15**-352, **18**-854
Hum, G.P. **19**-98
Humbel, S. **16**-1107
Hummel, K. **10**-271, **15**-2419, **15**-2431
Hummel, K.F. **15**-2535
Hummelen, J.C. **15**-1911
Humpf, H.-U. **19**-477
Humphrey, G.R. **18**-329
Humphries, M.E. **10**-1535
Humphries, R.E. **2**-81, **12**-603
Humski, K. **10**-147, **10**-230
Hundertmark, T. **16**-75
Hung, C.-W. **4**-84
Hung, C.-C. **15**-2317
Hung, J.C. **10**-1798
Hung, W.-C. **13**-495
Hungate, R. **13**-473
Hunger, J. **19**-59
Hunger, M. **17**-180, **17**-319
Hünig, S. **10**-955, **10**-1771, **10**-1773, **10**-1790, **12**-62, **15**-508, **16**-1261, **16**-1982, **16**-2158, **17**-257, **19**-4
Hunkler, D. **4**-468
Hunsen, M. **19**-233
Hunt, D.A. **15**-1186
Hunt, I.R. **8**-159
Hunt, J. **16**-1284
Hunt, J.C. **16**-1877
Hunt, J.D. **14**-414
Hunt, KW. **18**-393
Hunter, C.A. **3**-46, **3**-75, **3**-85
Hunter, D.H. **5**-132, **12**-670, **17**-40, **18**-94, **18**-203
Hunter, J.A. **15**-373, **15**-2625
Hunter, J.E. **12**-433
Hunter, W.E. **19**-1621
Huntley, D.R. **1**-74
Huntress, E.H. appendixa-23
Huntsman, W.D. **12**-75, **18**-654
Huo, M. **16**-313, **18**-878
Huo, S. **15**-838, **15**-2643
Huo, X.-H. **19**-1014
Huo, Z. **15**-405
Huple, D.B. **19**-197
Hupperts, A. **19**-1694, **19**-1695
Hurd, C.D. **16**-138
Hurley, P.B. **18**-135
Hurst, J.J. **4**-241
Hursthouse, M.B. **3**-32, **15**-1167, **15**-1362, **19**-1113
Hurtado, G.R. **15**-322
Husain, A. **16**-1626
Huser, D.L. **15**-576, **15**-578
Husfeld, C.O. **18**-612
Hush, N.S. **2**-465
Husk, G.R. **15**-2499
Huskey, W.P. **16**-1661
Hussain, A. **12**-762
Hussain, K.A. **18**-876
Hussain, N. **19**-610
Hussain, R.K. **15**-863
Hussain, S. **16**-631, **15**-1398
Hussain, S.M.S. **16**-676
Hussénius, A. **12**-64
Hussoin, M.S. **10**-645
Hussoin, Md.S. **17**-209
Huston, S.E. **10**-81
Huszthy, P. **4**-182
Hutchings, M.G. **18**-460, **18**-465
Hutchins, M.G.K. **15**-461
Hutchins, R.O. **4**-372, **10**-531, **10**-827, **15**-461, **15**-673, **16**-339, **19**-1138, **19**-1141, **19**-1282, **19**-1283, **19**-1316, **19**-1329, **19**-1363, **19**-1376, **19**-1397, **19**-1438, **19**-1471, **19**-1505, **19**-1721
Hutchins, R.R. **14**-454
Hutchinson, E.G. **12**-725
Hutchinson, J. **12**-143, **17**-351

Hutchinson, J.H. **19**-1701
Hutchinson, M. **15**-905
Hutchinson, P.H. **4**-321
Hutchison, J.D. **10**-352
Hutchison, R.J. **12**-740
Huthmacher, K. **11**-214
Hutta, D.A. **18**-325
Hüttel, R. **19**-698
Hüttl, M.R.M. **12**-138
Hüttmann, G. **15**-1606
Hutton, J. **19**-950, **19**-1719
Hutton, R.S. **2**-260, **5**-303, **5**-365
Huuskonen, J. **3**-179
Huwe, M. **13**-554
Huybrechts, G. **15**-2284
Huyffer, P.S. **18**-921
Huynh, C. **18**-785
Huynh, T. **10**-912
Huynh, V.A. **15**-529
Huyser, E.S. **14**-2, **14**-30, **14**-55, **14**-131, **14**-134, **14**-145, **15**-51, **18**-54, **19**-1664
Hwang-Lee, S. **15**-710
Hwang, C.-D. **16**-1515
Hwang, D.-R. **16**-1515
Hwang, G.-S. **16**-1173
Hwang, H.-J. **19**-1308
Hwang, H.H. **19**-341
Hwang, H.Y. **13**-795
Hwang, J.-W. **15**-1589
Hwang, J.P. **11**-434
Hwang, L.K. **15**-1493
Hwang, S.H. **15**-1528
Hwang, Y.C. **16**-533
Hwu, J.R. **7**-55, **10**-1263, **16**-314, **16**-1747
Hyatt, J.A. **11**-220, **19**-286
Hyde, A.J. **10**-3
Hyde, A.M. **13**-268
Hyeon, T. **7**-74, **15**-1550, **15**-1551
Hylarides, M.D. **12**-521
Hylton, T. **10**-1809, **10**-1814
Hyma, R.S. **16**-790
Hymel, E. **16**-1066
Hynd, G. **16**-988, **16**-1286, **16**-1448
Hynes, M.J. **2**-442
Hyoda, S. **3**-171
Hyodo, M. **19**-677
Hyuga, S. **12**-566, **15**-1259, **18**-479

Iacono, S.T. **15**-1564
Iannece, P. **15**-1883
Ianni, J.C. **16**-666
Ianskanen-Lehti, K. **10**-652
Ibarbia, P.A. **15**-109
Ibatullin, U.G. **16**-1546
Ibazizene, M. **16**-430
Ibbitson, D.A. **1**-38
Ibdah, A. **13**-428
Ibers, J.A. **3**-3, **3**-92
Ibne-Rasa, K.M. **10**-372, **11**-656, **13**-845, **15**-1948
Ibragimov, A.G. **15**-889
Ibrahem, I. **15**-1402, **15**-2078, **16**-392, **16**-394, **16**-1084
Ibrahim-Ouali, M. **10**-1706, **15**-2373
Ibrahim, I.T. **16**-2187, **17**-487
Ibrahim, S. **12**-697
Ibuka, T. **10**-249, **15**-410, **16**-1393
Ibukuro, F. **3**-203, **3**-207
Ibusuki, Y. **13**-55
Ichige, T. **10**-697
Ichihara, A. **15**-2278
Ichihara, J. **10**-1934, **15**-1671
Ichikawa, H. **10**-665, **19**-143
Ichikawa, J. **10**-711
Ichikawa, K. **11**-381, **12**-648, **13**-298, **14**-124, **18**-810
Ichikawa, T. **15**-1170
Ichimura, K. **10**-944
Ichinari, D. **15**-567
Ichinohe, M. **5**-337
Ichinohe, M. **5**-337
Ichinose, N. **5**-303
Ichiyanagi, T. **15**-2513
Ida, H. **2**-75
Idacavage, M.J. **10**-1862, **18**-451
Ide, N.D. **16**-1963
Ide, W.S. **16**-1581
Ideda, S. **12**-329
Idemoto, T. **14**-406
Iding, H. **16**-1590
Idoux, J.P. **9**-71
Ie, Y. **11**-490
Ie, Y. **19**-1492
Ielmini, A. **13**-487
Iesato, A. **15**-846, **15**-2033
Iesce, M.R. **15**-2115
Iffland, D.C. **10**-517, **13**-777
Igami, M. **19**-1103
Igarashi, E. **15**-843
Igarashi, K. **19**-1640
Igarashi, M. **19**-1475
Igdir, A.C. **16**-1031, **19**-527
Iggo, J.A. **12**-347
Igi, K. **11**-424
Iglesias, Á. **15**-2038
Iglesias, B. **13**-569
Iglesias, E. **2**-437, **2**-446, **12**-82, **12**-204, **12**-734
Ignatenko, A.V. **16**-2083, **18**-584
Ignatov, S.M. **4**-43
Igonin, V. **5**-276
Iguchi, M. **15**-1395, **16**-405
Iguchi, Y. **15**-1070
Ihara, M. **10**-758, **10**-1886, **15**-809, **15**-973, **15**-1384, **15**-2372, **15**-2397, **17**-389, **19**-643
Ihara, Y. **16**-1695
Ihrig, A.M. **19**-19
Iida, A. **10**-1389, **12**-328
Iida, H. **12**-189, **15**-510
Iida, K. **15**-1839
Iida, S. **10**-1588, **19**-266, **19**-272
Iida, T. **15**-1694
Iida, Y. **19**-499
Iijima, T. **1**-61, **1**-90, **2**-32
Iimori, T. **17**-163
Iimura, S. **16**-1782, **17**-368
Iio, M. **9**-135
Ikagawa, A. **15**-1052
Ikai, K. **10**-70, **10**-84
Ikariya, T. **12**-274, **13**-392, **13**-535, **15**-1052, **15**-1072, **15**-1514, **18**-268, **19**-664, **19**-1034
Ikawa, T. **10**-1027, **13**-98, **13**-188, **19**-1355, **19**-1356
Ikebe, M. **16**-2004
Ikeda, A. **15**-1684
Ikeda, H. **18**-577
Ikeda, M. **10**-1995, **15**-1312, **15**-1334, **15**-1347, **18**-386
Ikeda, R. **19**-685
Ikeda, S.-i. **15**-643, **15**-1201, **15**-2591, **15**-2599
Ikeda, S. **7**-87, **15**-343, **15**-2598
Ikeda, T. **11**-329, **12**-771, **16**-602
Ikeda, Y. **13**-298, **13**-461, **13**-465, **15**-1666
Ikegami, S. **10**-192, **11**-556, **12**-390, **19**-862
Ikegashira, K. **10**-1913, **10**-1914, **12**-299, **14**-358
Ikehara, T. **15**-1428
Ikekawa, N. **4**-120
Ikeno, T. **15**-612, **15**-2046, **15**-2324, **19**-27, **19**-896
Ikeshita, K.-i. **19**-1564
Ikeshoji, T. **18**-347
Ikonnikov, N.S. **16**-1518
Ikorskii, V.N. **5**-275
Ikumi, A. **10**-1362, **10**-1388, **10**-1470
Ikushima, Y. **9**-102, **13**-399, **18**-128
Ikuta, S. **3**-58, **8**-242, **10**-447
Ila, H. **11**-340, **18**-257
Ilangovan, P. **16**-1778
Ilankumaran, P. **16**-1798, **16**-1802
Ilao, M.C. **18**-88
Iley, J. **12**-743
Ilias, Md. **19**-1537
Il'ichev, Y.V. **18**-584
Ilieva, S. **4**-319, **11**-35, **16**-1955
Il'ina, G.P. **14**-24
Illa, O. **16**-1450
Illi, V.O. **16**-1712
Illuminati, G. **6**-15, **10**-408, **11**-231, **13**-9, **13**-75
Ilyashenko, G. **10**-998
Ilyin, M. **16**-1285
Ilyushin, M.A. **11**-140
Imada, Y. **10**-1063, **10**-1065, **12**-787, **15**-510, **15**-1802, **16**-981, **18**-390
Imade, M. **15**-2234
Imagawa, H. **11**-329, **15**-872, **15**-1578, **15**-2595, **16**-1634

Imagire, J.S. **16**-173
Imai, E. **19**-580
Imai, H. **15**-1632
Imai, M. **15**-1481
Imai, N. **15**-2249
Imai, T. **10**-1325, **15**-715, **18**-473, **18**-474, **18**-475
Imai, Y. **16**-395
Imaizumi, J. **12**-189
Imaizumi, S. **19**-1347, **19**-1348
Imamoto, T. **5**-167, **15**-452, **15**-634, **15**-1206, **15**-2573, **16**-426, **16**-501, **16**-511, **16**-611, **16**-1157, **16**-1306, **16**-1837, **17**-365, **17**-476, **18**-300, **19**-1541
Imamura, P.M. **19**-355
Imamura, T. **16**-1174
Imamura, Y. **13**-465
Imanaka, H. **13**-705
Imanari, M. **3**-203
Imanzadeh, G. **16**-286
Imanzadeh, G.H. **16**-66
Imao, D. **13**-198, **19**-681
Imaoka, K. **10**-495
Imashev, U.B. **10**-559
Imashiro, R. **16**-1172
Imbeaux, M. **10**-2006
Imboden, C. **17**-299
Imbos, R. **16**-822
Imbriglio, J.E. **15**-1487, **16**-722, **16**-815
Imhof, W. **15**-1596
Imhoff, M.A. **10**-221, **18**-18
Imi, K. **15**-793
Imm, S. **10**-927
Imori, S. **16**-1748
Imoto, T. **2**-324
Imper, V. **10**-147
Imperato, G. **15**-2225
Imwinkelried, R. **4**-139, **16**-1787, **16**-2222
Inaba, S. **13**-481, **19**-824
Inaba, Y. **15**-658, **15**-661
Inada, Y. **10**-819, **11**-332
Inagaki, M. **12**-238
Inagaki, S. **5**-301, **18**-501, **18**-577
Inagaki, T. **10**-1217, **19**-1037
Inagaki, Y. **19**-499
Inaki, K. **19**-580
Inamoto, K. **13**-452, **16**-1850
Inamoto, N. **1**-32, **16**-222
Inamoto, Y. **11**-373
Inanaga, J. **14**-314, **15**-1403, **16**-636, **16**-1575, **16**-1576, **16**-1766, **17**-207, **19**-864, **19**-1339, **19**-1398
Inanaga, K. **15**-2372, **15**-2397
Inasaki, T. **13**-192
Inazu, T. **3**-134, **8**-203
Inbar, S. **7**-37
Inbasekaran, M. **12**-196
Incremona, J.H. **14**-208, **15**-143
Indolese, A.F. **11**-543, **13**-676, **15**-931
Inesi, A. **12**-783, **12**-789
Ing, H.R. **10**-1035
Ingalls, C.L. **15**-601
Ingemann, S. **11**-409
Ingham, R.K. **14**-467
Ingham, S. **18**-517
Inglesby, P.A. **15**-2668
Inglis, G.G.A. **10**-760
Ingold, C.F. **15**-1811
Ingold, C.K. **4**-101, **7**-15, **9**-42, **10**-6, **10**-42, **10**-43, **10**-46, **10**-347, **10**-436, **11**-149, **11**-150, **11**-151, **12**-11, **12**-17, **12**-26, **13**-782, **15**-28, **16**-1652, **16**-1659, **16**-1665, **16**-1667, **17**-13, **17**-37, **17**-89, **17**-93, **17**-109, **17**-110, **17**-111, **17**-112, **17**-124, **17**-127, **18**-793, **18**-794
Ingold, E.H. **16**-1659
Ingold, K.U. **2**-26, **2**-413, **4**-303, **5**-211, **5**-218, **5**-248, **5**-296, **5**-330, **14**-180, **14**-31, **14**-64, **14**-69, **14**-82, **14**-89, **14**-90, **14**-92, **14**-136, **14**-139, **14**-142, **14**-237, **14**-238, **14**-241, **15**-1304, **15**-1319, **18**-54, **18**-73, **18**-78, **18**-82, **18**-89, **19**-961, **19**-1084
Ingrosso, G. **15**-37
Inhoffen, E. **14**-352
Inman, C.G. **15**-2454
Inners, R.R. **16**-1355
Innes, K.K. **7**-14
Inoguchi, H. **16**-1146
Inoh, J.-I. **13**-329
Inokawa, S. **10**-1097, **10**-1312
Inokuchi, T. **15**-1371, **16**-144, **19**-387
Inokuma, S. **2**-75
Inomata, K. **10**-1509, **19**-581
Inoue, A. **13**-346, **15**-2487
Inoue, E. **13**-568
Inoue, H. **11**-329, **15**-813, **15**-873, **15**-874, **15**-960, **15**-1948, **15**-2006, **16**-1087, **19**-1458
Inoue, K. **3**-51, **5**-305, **16**-222, **16**-2032, **19**-1085, **19**-1285
Inoue, R. **2**-137, **16**-601, **10**-1484, **10**-1626, **15**-936
Inoue, S. **5**-337, **10**-1947, **11**-551, **13**-861, **15**-929, **15**-1990, **16**-1587, **18**-775, **19**-1016
Inoue, T. **12**-186, **12**-661, **15**-1718, **15**-2352, **16**-1030, **19**-1017
Inoue, T.C. **16**-1676
Inoue, Y. **3**-109, **4**-186, **11**-104, **12**-309, **14**-360, **15**-288, **15**-532, **15**-969, **15**-1050, **15**-1229, **15**-1250, **15**-2603, **16**-931, **16**-2022
Inubushi, T. **7**-98
Inukai, T. **9**-20
Invergo, B.J. **19**-637, **19**-988
Ioffe, A. **10**-879
Ioffe, B.V. **5**-427, **17**-449, **19**-1267
Ioffe, S.L. **19**-1180
Iogansen, A.V. **8**-234
Ionin, B.I. **15**-1413, **16**-1364
Ionita, L. **16**-406
Iovel, I. **11**-349
Ipaktschi, J. **18**-915, **19**-1397
Ippen, J. **2**-194
Ipposhi, J. **10**-929
Iqbal, J. **10**-1237, **12**-326, **14**-119, **16**-1720, **16**-1834
Iqbal, M. **15**-1555
Irandoost, M. **10**-674
Iranpoor, N. **10**-683, **10**-734, **10**-835, **10**-844, **10**-873, **10**-983, **10**-1151, **10**-1169, **10**-1176, **10**-1177, **10**-1945, **10**-1951, **11**-140, **11**-296, **13**-386, **13**-401, **15**-1705, **15**-2001, **15**-2659, **16**-197, **16**-1464, **16**-1759, **17**-161, **17**-468, **19**-740, **19**-796
Irelan, J.R.S. **19**-1705
Ireland, J.F. **7**-18
Ireland, R.E. **10**-950, **10**-1354, **18**-730, **19**-196
Iretskii, A.V. **11**-671
Iri, K. **12**-727
Irie, R. **15**-1978, **15**-1985, **15**-2145, **19**-214, **19**-461
Irie, T. **10**-159
Iriuchijima, S. **12**-188, **12**-193
Irngartinger, H. **4**-448, **4**-458, **18**-530
Irrgang, B. **10**-375
Irsa, P. **15**-476
Irvine, J.L. **18**-760
Irwin, R.S. **15**-2457
Isa, M. **19**-1773
Isaac, M.B. **16**-561
Isaacs, E.S. **6**-66
Isaacs, L. **3**-222
Isaacs, N.S. **5**-1, **6**-66, **9**-87, **10**-507, **10**-1227, **12**-39, **14**-479, **15**-2208, **15**-2386, **15**-2427, **16**-616, **16**-1335, **16**-1676, **16**-2216
Isaev, I.S. **11**-644
Isaev, S.D. **18**-354
Isaeva, Z.G. **18**-96
Isagulyants, G.V. **16**-1553
Isagulyants, V.I. **16**-1545, **16**-1549, **16**-1553
Isaka, M. **16**-699
Isakov, V.E. **10**-1570
Isakova, A.P. **11**-525
Isaksson, R. **4**-180
Isbister, R.J. **15**-1765
Isborn, C. M. **2**-373
Isborn, C. **14**-31
Ischay, M.A. **15**-2412
Iseki, K. **16**-779
Isenberg, N. **15**-96

Isenberger, K.M. **10**-1701
Ishar, M.P.S. **15**-2345
Ishi-i, K. **15**-1646
Ishiba, A. **16**-622
Ishiba, A. **16**-645
Ishibashi, H. **11**-555, **15**-1312, **15**-1333, **15**-1334, **16**-1316
Ishibashi, Y. **10**-1189
Ishibe, N. **3**-66
Ishida, A. **19**-1421, **19**-1446
Ishida, K. **19**-56
Ishida, M. **16**-170, **16**-230
Ishida, N. **18**-725
Ishida, S. **5**-337
Ishida, T. **2**-171, **15**-1845, **15**-1912, **16**-1277, **16**-1287, **19**-1479
Ishida, Y. **5**-263, **10**-1511
Ishigedani, M. **16**-932, **19**-1153
Ishiguro, K. **19**-370
Ishihara, H. **15**-2048, **16**-170
Ishihara, K. **10**-1186, **10**-1602, **15**-224, **15**-822, **15**-2192, **15**-2252, **15**-2402, **16**-132, **16**-458, **16**-666, **16**-671, **16**-893, **16**-1091, **16**-1094, **16**-1142, **16**-1144, **16**-1490, **16**-1727, **16**-1742, **16**-1778, **16**-1791, **16**-1896, **16**-1915, **16**-2133, **18**-344, **19**-206
Ishii, A. **15**-2000
Ishii, H. **14**-164, **18**-761
Ishii, J.-i. **15**-2594
Ishii, K. **10**-1012
Ishii, T. **10**-758, **15**-1052, **16**-2140
Ishii, Y. **5**-291, **10**-621, **10**-1574, **11**-536, **11**-577, **12**-216, **12**-217, **13**-386, **13**-407, **15**-173, **15**-204, **15**-388, **15**-656, **15**-794, **15**-1302, **15**-1521, **15**-1686, **15**-1692, **15**-1955, **15**-1995, **16**-326, **16**-1518, **16**-2181, **18**-341, **19**-132, **19**-138, **19**-306, **19**-546, **19**-1233
Ishikawa, A. **16**-688
Ishikawa, F. **18**-375
Ishikawa, H. **10**-1616, **16**-342, **16**-1882
Ishikawa, K. **10**-1466
Ishikawa, M. **10**-1877, **15**-2643
Ishikawa, N. **4**-174, **16**-1259, **16**-1992
Ishikawa, S. **13**-347
Ishikawa, S. **16**-1172
Ishikawa, T. **10**-993, **11**-329, **15**-2275, **16**-1105
Ishikawa, Y. **9**-135
Ishikura, M. **13**-698, **13**-701, **17**-390
Ishimaru, K. **16**-964
Ishimori, T. **3**-114
Ishimoto, K. **19**-1425
Ishimoto, M. **12**-792
Ishino, Y. **10**-648, **13**-570, **15**-1452, **16**-688
Ishino, Y. **16**-1424
Ishitani, H. **8**-204, **15**-2108, **15**-2194, **15**-2327, **16**-355, **16**-912, **16**-913, **16**-1172, **16**-1536
Ishiwata, F. **16**-1023
Ishiyama, T. **10**-1877, **10**-1878, **12**-475, **13**-694, **16**-920
Ishizaki, K. **10**-1358
Ishizaki, M. **10**-1203, **15**-1556
Ishizuka, T. **15**-626
Iskander, Z. **12**-86
Iskra, J. **14**-187, **15**-1897
Islam, I. **19**-712
Islam, M. **13**-509
Islam, Md.N. **15**-2256
Isler, M.P. **16**-1515
Ismagilova, G.S. **16**-2164
Isobe, H. **17**-210
Isobe, K. **13**-401, **16**-1792
Isobe, Y. **10**-1433
Isoe, S. **19**-327
Isola, M. **16**-2274
Isolani, P.C. **8**-248
Isomura, E. **15**-783
Ison, E.A. **19**-980
Isotani, S. **15**-649
Isozaki, S. **12**-216
Israel, G. **13**-806
Issa, F. **19**-1487
Issacs, N.S. **16**-616
Isse, A.A. **10**-1997
Istrate, F.M. **18**-277
Itagaki, Y. **10**-665, **19**-143
Itai, A. **4**-313
Itami, K. **10**-1271, **10**-1343, **13**-703, **15**-1527, **15**-1542, **16**-750
Itano, H.A. **19**-288
Ito, A. **16**-612
Ito, H. **8**-217, **10**-1497, **15**-626, **15**-814, **15**-1229, **16**-656, **16**-908, **16**-1088, **16**-1090, **16**-1126, **16**-2265, **18**-737
Ito, J.-i. **16**-1087, **19**-1037
Ito, K. **10**-1539, **15**-1206, **16**-1423, **16**-1709, **18**-390
Ito, M. **2**-377, **18**-268, **19**-664, **19**-1034
Ito, O. **16**-458
Ito, R. **12**-449
Ito, S. **2**-225, **5**-45, **5**-46, **10**-729, **10**-1770, **12**-329, **13**-871, **14**-223, **14**-227, **15**-1836, **16**-1071, **16**-1328, **18**-736, **19**-611, **19**-1645
Ito, T. **10**-1896, **13**-570, **15**-563, **16**-612, **16**-688, **19**-1744
Ito, T.I. **19**-1595
Ito, Y. **15**-849, **16**-704, **10**-713, **10**-715, **10**-958, **10**-1918, **13**-198, **15**-563, **15**-1527, **15**-1632, **15**-1978, **15**-2576, **16**-745, **16**-2252, **16**-2264, **16**-2265, **18**-883, **19**-820
Ito, Y.N. **15**-1982, **15**-2048
Itoh, A. **10**-676, **19**-220, **19**-239
Itoh, A. **19**-405
Itoh, H. **15**-123
Itoh, I. **11**-214
Itoh, J.-i. **15**-642
Itoh, J. **16**-400
Itoh, K. **10**-1543, **10**-1620, **10**-838, **10**-1544, **12**-528, **15**-856, **15**-1137, **15**-1402, **15**-1588, **15**-1593, **15**-2594, **15**-2629, **19**-1245
Itoh, M. **12**-515, **15**-1256, **15**-1282, **16**-1276, **18**-484, **19**-327
Itoh, O. **19**-1762
Itoh, T. **11**-417, **16**-342
Itoh, T. **5**-357, **5**-359, **15**-946
Itohara, S. **16**-963
Itooka, R. **15**-1070
Ittah, Y. **10**-1073
Ittel, S.D. **3**-92
Iuliano, A. **16**-746
Iura, T. **19**-1078
Ivakhnenko, E.P. **16**-1712
Ivan, S. **16**-1084
Ivanic, J. **4**-228
Ivanov, D. **12**-422
Ivanov, R. **12**-412
Ivanov, S.N. **16**-2273
Ivanov, V.V. **13**-590
Ivanova, T.M. **4**-273
Ivanyk, G.D. **10**-1137
Ives, D.A.J. **19**-1419
Ives, J.L. **12**-727
Ives, J.L. **14**-250, **15**-2356, **19**-548
Ivey, R.C. **5**-368
Ivin, K.J. **18**-807, **18**-894
Iwabuchi, Y. **16**-650, **19**-654
Iwadare, T. **18**-932
Iwahama, T. **15**-388, **15**-794, **15**-1302, **15**-1995
Iwahara, K. **15**-1556
Iwahara, T. **10**-712
Iwai, H. **16**-1165
Iwai, I. **12**-74, **18**-411
Iwai, J. **16**-907
Iwai, N. **19**-995
Iwai, T. **4**-78, **12**-686, **13**-570, **15**-1480, **16**-2044
Iwaki, S. **4**-347
Iwakura, Y. **16**-1871
Iwama, T. **15**-2186, **17**-519
Iwamoto, C. **16**-1301
Iwamoto, H. **4**-279, **10**-496
Iwamoto, K. **16**-1582
Iwamoto, S. **16**-905
Iwamoto, T. **5**-337
Iwamura, H. **4**-526, **5**-304, **5**-305, **15**-1269
Iwamura, H.I. **18**-427

Iwamura, M. **18**-427
Iwanaga, K. **10**-1741
Iwanami, K. **19**-1449
Iwanami, T. **16**-704
Iwanek, W. **4**-94
Iwao, M. **13**-741
Iwaoka, M. **11**-40
Iwasa, S. **15**-2518
Iwasaki, F. **19**-984, **19**-1156
Iwasaki, M. **16**-1972
Iwasaki, N. **16**-1420
Iwasawa, H. **10**-1675, **16**-1228
Iwasawa, N. **11**-330, **15**-954, **15**-1499, **15**-1798, **15**-2116, **16**-144, **16**-866, **16**-867, **16**-1061
Iwasawa, T. **16**-405, **19**-48
Iwashima, K. **3**-114
Iwata, A. **10**-1192
Iwata, K. **16**-1560
Iwata, N. **14**-416
Iwatani, K. **19**-1171
Iwaya, M. **13**-768
Iwazaki, K. **15**-922
Iwazaki, Y. **15**-595
Iwebuchi, Y. **15**-1976
Iyanar, K. **15**-1889
Iyengar, D.S. **10**-947, **16**-2284, **19**-868, **19**-1199, **19**-1248, **19**-1250, **19**-1257, **19**-1362, **19**-1529, **19**-1619, **19**-1622
Iyengar, N.R. **11**-109, **11**-272
Iyer, K. **18**-821
Iyer, M.R. **15**-2138
Iyer, P.S. **18**-73
Iyer, R. **17**-351
Iyer, V.S. **16**-2072
Iyigün, C. **19**-528
Iyoda, M. **13**-479
Iyoda, M. **2**-330, **15**-783, **15**-2544, **18**-505
Izatt, R.M. **3**-106, **3**-110, **3**-113, **3**-155, **4**-168, **4**-182
Izawa, K. **15**-108
Izawa, K. **15**-1730
Izawa, M. **15**-2275
Izawa, Y. **5**-401, **5**-410, **18**-231, **18**-237
Izgü, E.Ç. **16**-667
Izmailov, F.F. **1**-32
Izquierdo, M.A. **16**-2203
Izumi, K. **19**-1670, **19**-1674
Izumi, M. **15**-1193
Izumi, Y. **4**-1, **11**-229, **15**-640, **16**-1336
Izutsu, M. **18**-369

Jaber, J.J. **16**-1565
Jablonski, R.J. **10**-173
Jabri, N. **15**-1134
Jachiet, D. **10**-1624
Jackman, L.M. **2**-107, **5**-134, **5**-198, **5**-199, **8**-230, **8**-231, **10**-184, **10**-360, **10**-515, **18**-679
Jackson, A.C. **16**-1570, **16**-1571
Jackson, A.E. **19**-1193
Jackson, C.L. **13**-7
Jackson, F.L. **16**-1991
Jackson, H.L. **10**-1936
Jackson, J.E. **5**-416, **19**-1607
Jackson, L.L. **10**-895
Jackson, P.M. **11**-89
Jackson, R.A. **14**-59, **14**-68, **14**-495, **19**-1394
Jackson, R.F.W. **10**-650, **12**-139
Jackson, R.W. **16**-1643
Jackson, S.D. **19**-1182
Jackson, T.C. **19**-911
Jackson, T.J. **15**-2649
Jackson, W. F. **5**-325, **18**-606
Jackson, W.M. **7**-47
Jackson, W.R. **15**-1607, **15**-1616, **15**-1627, **15**-1628, **15**-1821
Jackstell, R. **15**-330, **16**-278
Jacob, M. **5**-329
Jacob, P. **1**-100
Jacob III, P. **16**-536
Jacob, R.G. **15**-314, **16**-701
Jacobi von Wangelin, A. **10**-1495
Jacobi, P.A. **15**-400
Jacobs, H.K. **9**-105
Jacobs, P.A. **19**-408
Jacobs, T.L. **10**-307, **15**-107, **15**-110, **15**-1678, **15**-1963
Jacobsen, E.N. **7**-131, **10**-601, **10**-696, **10**-1634, **10**-1658, **10**-1950, **11**-409, **15**-800, **15**-1020, **15**-1021, **15**-1043, **15**-1056, **15**-1105, **15**-1830, **15**-1840, **15**-1841, **15**-1978, **15**-2354, **15**-1981, **16**-1497, **18**-710
Jacobsen, H. **15**-1987, **15**-1988
Jacobsen, M.F. **16**-406
Jacobsen, W.N. **13**-651
Jacobson, A.E. **16**-130
Jacobson, B.M. **10**-114
Jacobson, E. N. **15**-1942
Jacobson, G.B. **9**-104, **9**-115
Jacobson, M. A. **8**-228, **12**-421
Jacobson, R.A. **4**-129, **4**-150, **15**-635
Jacobus, J. **14**-44, **15**-517, **15**-687, **4**-210, **4**-220
Jacox, M.E. **5**-212, **5**-290
Jacques, J. **4**-10, **4**-99, **4**-160, **4**-189
Jacquesy, J. **11**-266, **11**-567, **11**-570, **11**-679
Jacquier, R. **11**-491, **16**-1929
Jacquier, Y. **15**-2066
Jacquot, R. **10**-941, **11**-393
Jaculi, D. **19**-263
Jadhav, D.N. **12**-129, **13**-362
Jadhav, P.K. **15**-709, **15**-710, **15**-711, **15**-714
Jadhav, V. **4**-187
Jadhav, W.N. **10**-611, **18**-395
Jaegar, D.A. **9**-124
Jaeger, C.D. **14**-458
Jaeger, D.A. **15**-2215
Jaenicke, S. **19**-953
Jafarpour, M. **10**-1151
Jaffe, A. **2**-260
Jaffé, H.H. **1**-29, **2**-13, **7**-12, **9**-17, **9**-20, **11**-74
Jaffe, M.H. **18**-27
Jaffe, R.L. **4**-305
Jagadeshwar, N.V. **16**-1472
Jagadeshwar, V. **10**-866
Jaganathan, A. **15**-1720
Jäger, C.M. **14**-101
Jager, W.F. **7**-65
Jager, W.W. **15**-1497
Jagner, S. **15**-1169
Jagodzinski, T. **11**-540
Jagodzinski, T.S. **15**-1400
Jagoe, C.T. **18**-602
Jagow, R.H. **6**-90
Jagt, R.B.C. **16**-746
Jagtap, H.S. **19**-730
Jahn, R. **4**-458
Jahngen Jr., E.G.E. **16**-2157
Jahnke, E. **17**-318
Jain, A. **4**-475
Jain, A.K. **13**-19
Jain, A.L. **19**-693
Jain, M.L. **16**-1747
Jain, N. **13**-115, **19**-103
Jain, R.P. **10**-653
Jain, S.L. **15**-2064, **15**-2077, **15**-2561, **16**-369, **19**-123, **19**-237, **19**-761, **19**-762, **19**-764
Jaipetch, T. **19**-267
Jaisankar, P. **19**-1411
Jäkel, C. **15**-956
Jalali-Araghi, K. **19**-335
Jalil, A.A. **13**-460
Jalili, F. **19**-88
James, B. **10**-1440, **15**-1140
James, B.G. **10**-746
James, B.R. **15**-433, **15**-554
James, D.R. **18**-675
James, L.L. **11**-11
James, R.A. **10**-745, **10**-1043
James, T.D. **4**-112
Jamieson, J.Y. **18**-843
Jamil, Z. **19**-212
Jamison, T.F. **15**-803, **16**-694, **16**-703,**16**-704, **16**-711, **16**-707, **19**-1649
Jammi, S. **13**-149, **16**-1214
Jammot, J. **16**-105
Jamode, V.S. **16**-158
Jan, D. **15**-2142
Jan, G. **17**-26
Jan, S. **15**-1978
Jana, R. **10**-1149, **17**-383, **19**-1312
Jana, S. **19**-620
Jana, S.K. **11**-438
Jana, U. **10**-1046, **18**-138
Janardanan, D. **16**-984

Janda, K.D. **12**-340, **15**-1847, **15**-1973, **15**-2131, **16**-1795, **16**-1936
Jandu, K.S. **14**-48, **14**-368
Jang, D.O. **10**-852, **10**-1059, **10**-1162, **11**-446, **14**-217, **15**-1295, **16**-1609, **16**-1826, **16**-1861, **16**-1865, **16**-1987, **19**-1383, **19**-1384, **19**-1395, **19**-1445, **19**-1453
Jang, E.G. **15**-2478
Jang, H.-Y. **15**-850, **16**-1154
Jang, M. **16**-869
Jang, T.-S. **16**-641
Jang, Y.-J. **13**-841, **15**-1220
Jani, A. **16**-2006
Janik, D.S. **15**-1947
Janikowski, J. **15**-2242
Janke, N. **12**-608
Janke, R.H. **4**-73
Janker, B. **10**-375
Jankowska, J. **16**-1152, **16**-1153
Jankowska, R. **19**-871
Jankowski, C.K. **15**-2203
Jannini, M.J.D.M. **19**-486
Janosi, A. **17**-267
Janoski, E.J. **18**-117
Janousek, Z. **5**-256, **5**-258, **15**-2388, **15**-2432
Janowski, W.K. **5**-86
Jansat, S. **10**-1532
Jansen, B.J.M. **17**-298
Janssen, C.G.M. **19**-1377
Janssen, E. **15**-898, **19**-1695
Janssen, M.H.M. **17**-5
Janssen, M.J. **15**-301, **16**-2, **19**-1778
Janssen, S.J. **15**-1733
Janura, M. **13**-244
Januszkiewicz, K. **19**-706
Januszkiewicz, K.R. **15**-552
Janzen, E.G. **5**-221, **5**-224, **5**-273
Jaouen, G. **16**-487, **16**-2175, **19**-923, **19**-998
Jaques, D. **10**-552
Jaratjaroonphong, J. **16**-404
Jardine, F.H. **2**-46, **4**-150, **14**-488, **15**-435, **15**-437, **15**-445, **15**-490, **15**-635, **15**-1598
Jaric, M. **10**-1456
Jarikote, D.V. **11**-242
Jarowski, P.D. **2**-43
Jarrahpour, A.A. **19**-111
Jarvis, B.B. **17**-350, **17**-356
Jasat, A. **3**-181
Jaskot, K. **10**-608
Jasne, S.J. **10**-238
Jason, M.E. **4**-540
Jasoni, R.L. **16**-1044, **19**-555
Jasor, Y. **16**-383
Jaspars, M. **15**-195
Jasperse, C.P. **15**-1119, **15**-1287, **15**-2110, **15**-2146, **15**-2147, **15**-2251
Jasra, R.V. **15**-1979
Jasti, R. **16**-1554, **18**-640
Jastrzebski, J.T.B.H. **12**-420, **13**-732
Jászay, Z.M. **16**-1921, **17**-489
Jaszberenyi, J.C. **19**-1395
Jaszberenyi, J.Cs. **19**-1381, **19**-1383, **19**-1384
Jatczak, M. **10**-1200, **10**-1819, **16**-1443
Jawdosiuk, M. **4**-518, **4**-519
Jayakumar, K.N. **13**-660, **13**-751
Jayakumar, S. **15**-2345
Jayanth, T.T. **15**-1013
Jayaprakash, K. **13**-838
Jayaram, R.V. **16**-1872
Jayaraman, H. **16**-22, **16**-1699
Jayashankaran, J. **19**-1037
Jayasree, E.G. **10**-232, **10**-244
Jean-Gérard, L. **13**-464, **13**-570
Jean, A. **15**-834
Jean, H.-J. **15**-2073
Jean, T.-S. **15**-1340
Jedrzejczak, M. **16**-1856
Jedziniak, E.J. **14**-170, **19**-442
Jeevanandam, A. **15**-2605, **16**-146
Jefferson, A. **18**-691
Jefferson, E.A. **2**-443, **15**-2478
Jeffery-Luong, T. **10**-1355
Jeffery, E.A. **11**-561, **16**-654, **19**-1351
Jeffery, T. **10**-1899, **13**-412, **13**-415, **13**-467, **13**-815
Jefford, C.W. **4**-444, **10**-335, **14**-267, **15**-2303, **15**-2548, **18**-512
Jeffrey S. **16**-1594
Jeffrey W. **15**-23
Jeffrey, G.A. **3**-33, **3**-172, **18**-674
Jeffs, P.W. **14**-376
Jeganathan, A. **19**-523
Jeganathan, S. **16**-1384
Jeganmohan, M. **13**-621, **15**-927, **15**-1013, **15**-1069, **15**-2613
Jeger, O. **15**-817, **18**-113
Jeko, J. **12**-332
Jellison, K.M. **17**-174
Jemison, R.W. **18**-417
Jemmis, E.D. **1**-84
Jen, M. **1**-63
Jencks, W.P. **3**-23, **6**-42, **6**-49, **8**-154, **8**-155, part**2**-4, **10**-85, **10**-94, **10**-99, **10**-295, **10**-376, **10**-383, **10**-387, **10**-558, **10**-564, **10**-777, **12**-157, **12**-672, **16**-1, **16**-10, **16**-16, **16**-19, **16**-21, **16**-22, **16**-46, **16**-47, **16**-84, **16**-234, **16**-287, **16**-289, **16**-417, **16**-1614, **16**-1875, **16**-1957, **16**-1959, **16**-1960, **16**-2053, **17**-47, **17**-52
Jenck, J. **15**-1597
Jendza, K. **16**-555
Jenkins, I.D. **4**-45, **10**-644, **10**-726
Jenkins, I.L. **13**-228
Jenkins, P.R. **5**-149, **12**-35
Jenkins Jr., R.H. **4**-29
Jenkins, S.R. **19**-1297
Jenks, W.S. **16**-1439, **13**-428, **17**-287
Jennequin, T. **16**-645
Jenner, G. **9**-85, **9**-88, **10**-666, **12**-767, **15**-998, **15**-1390, **16**-1239, **16**-1505, **16**-1525, **16**-1568, **16**-1569, **16**-2257, **18**-493
Jenner, P.J. **18**-22, **18**-102
Jenneskens, L.W. **2**-67, **2**-68, **2**-89, **2**-265, **17**-231, **18**-553, **18**-553
Jennings, C.A. **13**-724
Jennings, H.J. **12**-731
Jennings, M.C. **5**-254
Jennings, W.B. **4**-259, **19**-805
Jenny, E.F. **18**-423
Jensen, A.E. **10**-1470, **10**-1477
Jensen, D.R. **19**-141, **19**-211
Jensen, F. **17**-6, **15**-2291
Jensen, F.R. **2**-418, **4**-328, **4**-338, **4**-341, **4**-343, **4**-344, **4**-364, **11**-212, **11**-430, **12**-7, **12**-11, **12**-12, **12**-14, **12**-17, **12**-19, **12**-22, **12**-41, **12**-533, **12**-534, **12**-579, **17**-145, **18**-94
Jensen, H.B. **15**-495
Jensen, H.P. **19**-450, **19**-711
Jensen, J.F. **15**-775
Jensen, J.L. **2**-27, **10**-565
Jensen, K.B. **15**-1172
Jensen, K.H. **15**-2341
Jensen, P. **10**-880
Jensen, R.M. **5**-157
Jensen, R.S. **12**-263
Jensen, S.D. **16**-169
Jensen, T.A. **13**-196
Jensen, V.R. **19**-1535
Jensen, W.B. **8**-158
Jenson, T.M. **10**-164
Jentzsch, J. **14**-321, **16**-184, **19**-1433
Jeon, D.J. **10**-641
Jeon, M. **16**-650
Jeon, S.-J. **16**-675
Jeon, S. **19**-485
Jeong, B.-s. **10**-1764
Jeong, B.S. **15**-1404
Jeong, H.-J. **10**-1114, **16**-1640
Jeong, J.M. **19**-1190
Jeong, K.-S. **15**-1793, **15**-1832, **15**-1843
Jeong, M. **13**-683
Jeong, N. **15**-1528, **15**-1559
Jeoung, M.K. **19**-1095, **19**-1098, **19**-1178
Jereb, M. **12**-133
Jeremic, D. **14**-233, **14**-234, **14**-235
Jeremy N. **16**-792
Jerkunica, J.M. **10**-189

Jernberg, N. **16**-1932
Jernelius, J.A. **18**-854
Jeromin, G.E. **5**-264
Jerphagnon, T. **15**-453
Jerussi, R.A. **19**-45, **19**-448
Jesberger, M. **16**-218
Jeske, M. **16**-720, **19**-1638
Jesson, J.P. **15**-492
Jessop, P.G. **12**-274, **15**-554, **15**-651
Jeuell, C.L. **5**-41
Jevalainen, V. **19**-1751
Jew, S.-s. **10**-1764, **15**-1404
Jew, S. **16**-1198
Jewett, R. **10**-954
Jeyakumar, K. **19**-793
Jeyaraj, D.A. **16**-8
Jeyaraman, R. **5**-443, **10**-878, **16**-236, **19**-1270
Jézéquel, M. **10**-1416
Jha, S. **13**-204, **13**-504
Jha, S.C. **10**-612, **15**-1111
Jhaveri, S.B. **13**-363
Jhurry, D. **13**-82
Ji, G.Z. **8**-94
Ji, H.-B. **19**-235
Ji, J. **15**-1119
Ji, J.-X. **16**-746
Ji, L. **16**-311
Ji, M. **19**-778
Ji, R.Y. **15**-1976
Ji, S.-J. **15**-1185, **16**-1159, **16**-1508, **16**-1527, **16**-590, **16**-637, **16**-639, **19**-722
Ji, S. **16**-546
Ji, W.-H. **10**-1213
Ji, X. **19**-163
Jia, G. **15**-2136
Jia, J.H. **2**-270
Jia, L. **15**-1515
Jia, X. **13**-698, **14**-344, **15**-1218, **16**-572, **16**-600, **16**-670, **16**-893, **16**-1862, **19**-1087
Jia, Y.-X. **16**-943, **19**-83
Jia, Y. **16**-591
Jia, Z.S. **10**-71, **17**-48
Jiaang, W.-T. **15**-1364
Jian, F. **13**-494
Jian, S. **19**-1349
Jiang, B. **13**-287, **16**-542, **16**-544, **16**-902, **19**-1020, **19**-1032
Jiang, D. **13**-205
Jiang, F. **16**-1082
Jiang, G.J. **4**-398
Jiang, H.-F. **14**-342, **15**-375
Jiang, H.-y. **19**-1014
Jiang, H. **10**-1927, **10**-2000, **13**-218, **14**-335, **15**-1515, **15**-1520, **15**-1862, **15**-2648, **19**-1304
Jiang, H.L. **15**-1976
Jiang, J.-K. **16**-793, **16**-820
Jiang, J. **5**-307, **16**-612
Jiang, J.-X. **16**-165, **16**-667
Jiang, K.-Z. **4**-155
Jiang, L. **13**-189, **16**-1366
Jiang, L.H. **16**-2244
Jiang, M.X.-W. **15**-2651
Jiang, N. **10**-1630, **13**-503, **17**-436, **19**-128, **19**-128
Jiang, R. **15**-1829
Jiang, S.A. **12**-298
Jiang, T. **15**-444, **16**-1206
Jiang, W.-T. **15**-1310
Jiang, W. **10**-1921, **15**-1106
Jiang, X. **5**-261, **14**-186, **14**-212, **15**-1720
Jiang, Y. **16**-1515
Jiang, Y.-L. **10**-932
Jiang, Y.-Z. **15**-1272, **16**-1082, **16**-1084
Jiang, Y. **11**-138, **13**-100, **13**-205, **14**-298, **15**-2326, **16**-1364, **16**-1503, **18**-304, **19**-1014
Jiang, Z. **13**-69, **13**-223, **14**-282, **16**-1085
Jiao, H. **2**-106, **2**-116, **2**-117, **2**-279, **2**-289, **2**-338, **2**-340, **2**-370, **2**-390, **2**-396, **15**-683, **15**-2123
Jiao, J. **12**-704
Jiao, L. **15**-2143, **15**-2697, **19**-1259
Jiao, N. **12**-355, **13**-431
Jiao, X. **10**-1910
Jiao, X.H. **13**-333
Jie, C. **18**-667, **18**-707
Jigajinni, V.B. **12**-514
Jiménez-Vázquez, H.A. **5**-2
Jiménez-Tenorio, M. **15**-284
Jiménez-Núñez, E. **16**-1562
Jiménez-Sanchidrián, C. **18**-383
Jiménez, C. **13**-643
Jiménez, J.L. **4**-5, **4**-312, **4**-315, **15**-2187, **15**-2193, **15**-2290, **18**-660
Jimenez, R.P. **18**-206
Jin, C.H. **10**-607
Jin, C.K. **16**-1640
Jin, E. **19**-184, **19**-202
Jin, J. **14**-84, **14**-100, **15**-837
Jin, K. **13**-148, **13**-205
Jin, L. **10**-1559, **10**-1992, **17**-290
Jin, M.-J. **13**-401, **13**-494
Jin, M. **16**-1605
Jin, Q.-H. **19**-1217
Jin, Q. **12**-370, **12**-394
Jin, R. **15**-1721
Jin, T. **12**-664
Jin, W. **15**-2520, **16**-546, **19**-1680
Jin, X. **15**-1576, **15**-2660
Jin, X.L. **15**-1403
Jin, Y. **19**-174, **19**-1255
Jin, Y.S. **19**-530
Jin, Y.Z. **16**-636
Jin, Z. **10**-1725, **15**-176, **16**-1378, **19**-302
Jindong, Z. **19**-1349
Jing, L. **13**-100
Jing, Q. **19**-1014
Jinguji, M. **7**-23
Jinnai, T. **17**-165
Jinnouchi, K. **10**-1012
Jintoku, T. **11**-534
Jira, R. **12**-67, **14**-281, **15**-828, **19**-698, **19**-699
Jirandehi, H.F. **19**-1617
Jiricny, J. **10**-1049, **16**-77, **16**-1541
Jirovetz, L. **16**-176
Jnaneshwara, G.K. **10**-679, **16**-1203
Jo, E.-A. **15**-1483
Joannetaud, M. **11**-570
Job, A. **16**-1429
Job, R.C. **4**-261
Jochims, J.C. **16**-427
Jochum, C. **15**-579
Jockusch, S. **5**-397
Jodhan, A. **5**-385, **16**-1700, **16**-1701
Jödicke, T. **16**-265
Jodry, J.J. **4**-64
Joerg, S. **3**-22
Joesten, M.D. **3**-3
Joffee, I. **10**-945
Jöge, T. **15**-543
Johannsen, M. **15**-775, **15**-2336
Johansen, J.E. **15**-801
Johansson, A. **16**-1024
Johansson, C.C.C. **13**-220, **15**-2523
Johansson, K. **12**-298
Johansson, K.M. **9**-140
Johansson, M. **15**-1807, **19**-794
John, K.C. **16**-2159
John, L. **18**-534
John, M.P. **16**-396
John, O.R.S. **19**-533
Johns, J.W.C. **5**-367
Johnson II, C.A. **2**-213
Johnson Jr., C.S. **5**-245
Johnson Jr., H.W. **4**-77
Johnson, A.L. **4**-112
Johnson, A.P. **4**-103
Johnson, A.W. **2**-92, **16**-1311
Johnson, C.A. **2**-317
Johnson, C.C. **14**-93
Johnson, C.D. **5**-408, **6**-20, **8**-31, **8**-62, **9**-16, **9**-38, **11**-72
Johnson, C.N. **15**-2650
Johnson, C.R. **4**-48, **10**-1417, **12**-269, **15**-121, **15**-1853, **16**-1274, **16**-1453, **16**-1454, **16**-1474, **16**-2007, **19**-624
Johnson, D.R. **16**-322
Johnson, E. **15**-537
Johnson, F. **4**-362, **10**-1196, **16**-1304, **16**-2170
Johnson, G. **15**-1690
Johnson, G.L. **14**-184
Johnson, G.S. **19**-1169
Johnson, H. **16**-1066

Johnson, J.B. **15**-1505
Johnson, J.E. **4**-230
Johnson, J.R. **12**-471, **15**-1603, **16**-1265
Johnson, J.S. **13**-215, **13**-216, **15**-1076, **15**-2249, **16**-1593, **16**-1594
Johnson, K. **19**-1240
Johnson, L.A. **5**-421
Johnson, L.K. **4**-89
Johnson, M.D. **9**-35, **14**-68
Johnson, M.J.A. **18**-880
Johnson, M.R. **19**-903
Johnson, N.B. **15**-644
Johnson, P.L. **13**-368
Johnson, R.A. **10**-770
Johnson, R.D. **2**-393
Johnson, R.E. **19**-1456
Johnson, R.G. **14**-467
Johnson, R.L. **15**-2079
Johnson, R.P. **4**-409, **4**-484, **4**-502, **4**-503, **4**-507, **4**-509, **7**-58, **15**-2583
Johnson, S.A. **10**-194, **10**-219
Johnson, S.L. **16**-16, **16**-22, **16**-33
Johnson, S.M. **2**-356
Johnson, T.A. **18**-759
Johnson, T.J. **15**-2645
Johnson, T.R. **14**-350
Johnson, W.L. **19**-720
Johnson, W.S. **10**-655, **15**-818, **15**-819, **15**-820, **15**-821, **16**-1186, **19**-386, **19**-891
Johnsson, B. **3**-63
Johnsson, R. **11**-291
Johnston, B.H. **16**-1741
Johnston, E.R. **3**-83
Johnston, G.F. **12**-20
Johnston, J.F. **11**-104
Johnston, J.N. **15**-1374, **15**-2055, **16**-965, **16**-986, **16**-1222, **18**-129
Johnston, K P. **9**-104
Johnston, K.M. **11**-628, **14**-317
Johnston, K.P. **9**-104
Johnston, L.J. **5**-299, **5**-318, **7**-1
Johnston, R.D. **15**-258
Johnstone, R.A.W. **10**-1668, **15**-506, **15**-1931, **15**-2178, **18**-415, **18**-429, **19**-1086, **19**-1193, **19**-1214
Johri, K.K. **14**-478
Jolicoeur, E. **15**-2566
Jolidon, S. **18**-740
Jolley, K.W. **17**-69
Jon, S.Y. **10**-1973, **16**-1601
Jona, H. **15**-306
Jonas, K. **15**-829
Jonas, L. **11**-239
Jonas, M. **4**-322
Jonassen, H.B. **15**-1622
Jonasson, C. **16**-938
Jonczyk, A. **10**-911
Jone, P.G. **17**-18
Jones, A. **14**-130
Jones, A.C. **5**-181
Jones, A.J. **2**-101, **2**-106
Jones, B.A. **4**-168, **16**-223
Jones, C.D. **19**-726
Jones, C.W. **13**-167, **13**-263
Jones, D.N. **17**-132, **17**-294
Jones, D.W. **2**-236, **14**-248
Jones, E. **16**-1448
Jones, E.R.H. **15**-473, **19**-66
Jones, G. **16**-1225
Jones, G.A. **15**-2270
Jones, G.B. **18**-524, **18**-526
Jones, G.C. **13**-849
Jones, G.I.L. **4**-307
Jones, G.O. **15**-2135, **15**-2255
Jones, G.T. **11**-610
Jones, J. **10**-587
Jones, J.B. **4**-156, **10**-1814
Jones, J.I. **11**-529
Jones, J.K.N. **10**-1226
Jones, J.M. **6**-78, **16**-1875
Jones, J.R. **5**-111, **8**-17, **11**-116, **12**-83, **14**-394
Jones, J.W. **9**-78
Jones, K. **15**-1329, **16**-2067
Jones II, M. **16**-2205
Jones III, F.M. **8**-237
Jones Jr., J. **15**-1037
Jones Jr., M. **5**-348, **5**-361, **5**-375, **5**-376, **5**-387, **5**-391, **5**-403, **5**-406, **5**-441, **12**-404, **15**-2483, **15**-2534, **15**-2538, **18**-226, **18**-677, **18**-683
Jones, M.B. **11**-415
Jones, M.E. **10**-522, **17**-126
Jones, M.G. **10**-175
Jones, M.L. **18**-145
Jones, M.R. **16**-2271
Jones, M.T. **15**-575
Jones, N. **15**-1782
Jones, N.D. **12**-227
Jones, N.R. **10**-1809
Jones, P.B. **7**-27
Jones, P.G. **1**-66, **4**-173, **4**-299, **15**-2690
Jones, P.M. appendixa-31
Jones, P.R. **10**-1810, **15**-690, **16**-685
Jones, R. **10**-1124
Jones, R.A. **16**-2119
Jones, R.A.Y. **2**-208, **8**-3, **8**-124, **8**-148, **9**-16, **9**-24, part**2**-2, **15**-2300, **18**-512
Jones, R.V.H. **16**-1448
Jones, S. **16**-1365, **19**-1020
Jones, S.R. **4**-32, **14**-287
Jones, W.D. **16**-2267
Jones, W.H. **16**-283
Jones, W.J. **10**-457, **19**-615, **19**-616, **19**-618
Jones, W.M. **5**-413, **5**-420, **17**-503
Jong, Y. **8**-121
Jonnalagadda, S.B. **16**-1232
Jonsäll, G. **18**-9
Jonsdottir, S. **4**-384
Jönsson, L. **13**-137
Jonsson, S.Y. **15**-1848
Joo, T.Y. **14**-217, **16**-1987
Joos, R. **17**-426
Jorapur, Y.R. **13**-307
Jordan-Hore, J.A. **13**-220
Jordan Jr., A.D. **16**-1385
Jordan, K.D. **15**-87
Jordan, M.R. **2**-405
Jordan, R.W. **15**-2376
Jorge-Robin, A. **15**-1949
Jorge, J.A.L. **10**-328
Jorge, Z.D. **15**-1851, **15**-2098
Jorge, Z.S. **14**-200
Jørgensen, C.K. **1**-23, **1**-25, **1**-28, **1**-31
Jørgensen, K.A. **10**-992, **10**-1915, **11**-314, **11**-388, **12**-123, **12**-124, **12**-156, **12**-230, **13**-635, **15**-1036, **15**-1049, **15**-1051, **15**-1172, **15**-1409, **15**-1439, **15**-1796, **15**-1920, **15**-1954, **15**-2331, **15**-2336, **16**-1213, **16**-1221, **16**-1607, **16**-364, **16**-966, **16**-983, **16**-987, **19**-281, **19**-538
Jorgenson, M.J. **16**-858, **16**-2207
Jorgensen, W.L. **10**-20, **10**-23, **10**-24, **10**-81, **13**-3, **15**-122, **15**-155, **15**-2291, **17**-263
Jose, A. **16**-871
José, S.M. **10**-12, **16**-1671
Joseph, D. **13**-378
Joseph, R. **10**-1132
Joseph, S.P. **15**-1350
Joseph, T. **15**-368
Josey, J.A. **15**-2318
Joshi, B.V. **19**-1523
Joshi, A.V. **19**-837
Joshi, G.C. **15**-546
Joshi, N.N. **10**-612, **10**-1228, **10**-1878, **15**-1111, **19**-1648, **19**-1652
Joshi, N.S. **10**-848, **16**-158
Joshi, U.M. **16**-1800
Joshikawa, M. **11**-332
Josien, H. **10**-1024
Joslin, C.G. **5**-230
Jost, R. **8**-18, **18**-35
Jothilingam, S. **15**-1425, **16**-145
Jouannetaud, M. **11**-266, **11**-567, **11**-679
Jouikov, V. **10**-1405
Joukhadar, L. **19**-1390
Joule, J.A. **10**-754
Joung, M.J. **16**-537
Jourdant, A. **15**-441
Journet, M. **15**-466, **18**-582
Jousseaume, B. **15**-888, **16**-2116
Jovan Jose, K.V. **3**-41
Jovanovic, M.V. **13**-85
Jovanovich, A.P. **10**-160

Joya, T. **15**-212
Jozwiak, A. **16**-260
Jroundi, R. **14**-242
Ju, J. **13**-683
Ju, Y. **10**-907, **16**-740
Juan, B. **2**-259, **8**-82
Juaristi, E. **4**-297, **4**-340, **4**-367, **4**-372, **4**-374, **4**-377, **8**-17, **8**-232, **10**-906, **16**-681, **16**-1130
Jubault, P. **16**-1448
Juchnovski, I.N. **9**-23
Judd, D.B. **16**-325
Judd, K.R. **11**-77
Judeh, Z.M.A. **11**-402
Judy, W.A. **18**-809, **18**-881, **18**-894
Juers, D.F. **18**-909
Jug, K. **2**-6, **2**-98, **2**-101, **2**-124
Juge, S. **19**-766
Jugie, G. **11**-496
Juhasz, M. **5**-8, **8**-119
Juhl, K. **16**-364, **16**-987, **16**-1213, **19**-538
Julia, M. **10**-431, **10**-1559, **10**-1825, **13**-353, **15**-53, **17**-290, **19**-518, **19**-818
Juliá, S. **15**-1959, **18**-785
Julian, R.R. **8**-92
Julin, S. **16**-1380
Julius, M. **15**-766
Juliusburger, F. **10**-17
Jullien, A. **13**-495
Jumbam, D.N. **19**-1696
Jumde, V.R. **16**-746
Jumonville, S. **14**-42
Jun, B.-H. **13**-150, **15**-970
Jun, C.-H. **15**-1483
Jun, P. **10**-609
Jun, Y. **16**-906
Jun, Y.M. **10**-1335, **12**-433, **19**-1186
Junchai, B. **18**-462
Junckers, T.H.M. **13**-204
Juneja, S.K. **12**-119
Jung, A. **15**-2087, **16**-1078
Jung, D.-S. **19**-558
Jung, G. **15**-1339
Jung, H.C. **19**-782
Jung, H.M. **13**-683
Jung, I.-H. **16**-1854
Jung, I.N. **10**-1265
Jung, J.-C. **11**-270
Jung, J.-Y. **13**-401, **13**-494
Jung, J. **16**-723, **16**-731
Jung, K.W. **10**-758, **10**-889, **10**-891, **10**-1021, **13**-491, **13**-546, **13**-566, **13**-712, **16**-180, **16**-1976, **17**-236
Jung, L.-j. **10**-233
Jung, M.E. **10**-1199, **15**-1305, **15**-1321, **15**-2112, **15**-2272, **16**-1112, **16**-1282, **18**-632, **18**-649, **19**-52, **19**-346
Jung, S.H. **13**-626
Jung, Y.-J. **11**-270
Jung, Y.C. **13**-491, **13**-546, **13**-712
Jung, Y.H. **10**-607, **15**-149, **15**-2018
Jung, Y.J. **19**-966, **19**-1308
Jung, Y.S. **15**-1399
Junga, H. **15**-1346, **18**-825
Junge, K. **17**-472, **17**-473, **19**-929, **19**-1037, **19**-1161, **19**-1478
Jungen, M. **4**-187
Jungk, H. **11**-315, **11**-378
Junjappa, H. **11**-340, **18**-257
Junttila, M.H. **15**-1850
Jurayj, J. **18**-713
Jurca, T. **19**-1123
Jurczak, J. **4**-138, **16**-624
Jurečka, P. **3**-77
Jurgeleit, W. **19**-1404
Juric, S. **10**-155
Jurkauskas, V. **15**-630
Jurlina, J.L. **12**-169, **14**-473, **15**-1764
Jurok, R. **19**-800
Jursic, B. **10**-629, **10**-1181, **17**-431, **19**-268
Jursic, B.S. **2**-161, **12**-122
Just, G. **11**-660, **15**-25, **16**-2288
Justicia, J. **5**-321, **16**-575
Jutand, A. **10**-1993, **12**-288, **13**-442, **13**-479, **13**-545
Jutz, C. **11**-492
Jutz, J.C. **18**-506
Jutzi, P. **1**-12
Juve Jr., H.D. **14**-275, **19**-507
Jyothi, K. **15**-1806
Jyothi, K. **16**-357
Jyothirmai, B. **10**-707, **10**-885, **10**-1003, **10**-1069

Kaandorp, A.W. **11**-203
Kaba, R.A. **5**-247
Kabalka, G.W. **8**-162, **10**-764, **10**-831, **10**-1547, **10**-1571, **10**-1859, **10**-1867, **10**-1874, **12**-296, **12**-466, **12**-467, **12**-469, **12**-508, **12**-516, **12**-517, **12**-520, **12**-521, **12**-543, **12**-546, **13**-232, **13**-417, **13**-504, **13**-576, **13**-598, **13**-717, **13**-800, **14**-337, **15**-517, **15**-604, **15**-687, **15**-730, **15**-1256, **15**-1265, **15**-1282, **15**-1675, **15**-1677, **15**-2224, **16**-109, **16**-438, **16**-740, **16**-758, **16**-1199, **16**-1820, **16**-1986, **18**-464, **19**-895, **19**-970, **19**-1008, **19**-1245, **19**-1485, **19**-1579
Kabbara, J. **15**-652, **15**-1128
Kabir, M.S. **10**-1465
Kablaoui, N.M. **15**-1001, **15**-1536, **15**-1581
Kaboudin, B. **10**-845, **10**-939, **16**-118
Kabuto, C. **4**-524, **4**-539, **15**-2377
Kabuto, K. **4**-109
Kachala, M.S. **19**-1658
Kacprzak, K. **16**-1883
Kacprzynski, M. **5**-421
Kacprzynski, M.A. **10**-1517
Kaczorowska, K. **19**-787
Kad, G.-L. **10**-505, **16**-1036, **19**-72, **19**-449
Kadaba, P.K. **15**-2124, **16**-1777
Kaderli, S. **14**-223
Kadib-Elban, A. **15**-43
Kadoh, Y. **15**-815
Kadokawa, J.-i. **10**-744
Kadoma, Y. **10**-385
Kadorkina, G.K. **4**-37
Kadota, I. **15**-370
Kadow, J.F. **11**-460
Kadowaki, S. **15**-1012, **15**-1565
Kadoya, R. **15**-2275
Kadri, M. **15**-2120
Kadyrov, R. **13**-98, **16**-317, **19**-1150
Kadzyauskas, P.P. **15**-1748
Kaeding, W.W. **14**-289, **19**-411
Kaeobamrung, J. **18**-709
Kafafi, S.A. **8**-240
Kaftory, M. **2**-452
Kagan, H. **4**-1, **4**-99
Kagan, H.B. **4**-104, **4**-153, **4**-277, **16**-2113, **18**-141, **19**-799, **19**-950
Kagan, J. **12**-666, **18**-127
Kagan, J.F. **4**-159
Kagarise, R.E. **4**-300
Kagawa, M. **10**-942
Kagayama, A. **2**-176, **19**-1640
Kagel, J.R. **15**-2283
Kagen, B.S. **11**-308, **14**-149
Kageyama, H. **16**-771
Kageyama, T. **19**-709
Kagoshima, H. **16**-390, **16**-579, **16**-842, **16**-843, **16**-907, **16**-1164
Kagramanov, N.D. **5**-238
Kahn, B.E. **19**-1683
Kahn, S.D. **15**-2229, **15**-2448
Kahne, D. **12**-348, **16**-1681
Kahr, B. **2**-78, **4**-525, **5**-242
Kahr, K. **19**-733
Kai, H. **15**-1594
Kai, Y. **2**-69, **2**-76
Kaida, T. **3**-211, **4**-136
Kaim, W. **2**-264
Kaiser, R. **2**-200
Kaiser, C. **4**-366
Kaiser, E.M. **15**-565, **15**-581, **16**-1708
Kaiser, E.T. **5**-333, **14**-459, **15**-575, **16**-1637, **16**-1929, **16**-2272
Kaiser, H.M. **13**-162, **13**-801
Kaiser, S. **19**-1594
Kajfez, F. **10**-910

Kaji, A. **6**-88, **10**-813, **15**-2230, **17**-73, **19**-1515, **19**-1518, **19**-1756
Kaji, M. **15**-649
Kajigaeshi, S. **10**-822, **12**-118, **12**-140, **12**-154, **12**-755, **12**-756
Kajimoto, T. **19**-399
Kajiro, H. **15**-623, **16**-1650
Kajita, S. **10**-1275
Kajiwara, K. **13**-496
Kakde, S.B. **18**-395
Kakehi, A. **15**-1435
Kakei, H. **15**-1883, **15**-1919, **16**-1480
Kakinami, T. **12**-118, **12**-140, **12**-154, **12**-756
Kakiuchi, F. **10**-1267, **11**-424, **11**-490, **13**-451, **13**-563, **13**-565, **15**-758, **15**-793, **16**-2092, **16**-2093, **19**-1492
Kakiuchi, K. **2**-69, **15**-1568
Kakiuchi, N. **19**-215
Kakiya, H. **10**-1484, **10**-1626, **16**-576
Kakkar, R. **4**-316
Kaku, H. **10**-1816, **16**-1328
Kakui, T. **10**-712
Kakumoto, K. **15**-1038, **15**-1073, **15**-1419, **16**-2040
Kakushou, F. **16**-626
Kakuuchi, A. **15**-1236, **15**-1457
Kalafer, M. **19**-1416
Kalani, M.Y.S. **18**-734
Kalani, Y.S. **18**-638
Kalchschmid, F. **11**-371
Kalck, P. **15**-1597
Kaldor, S.W. **15**-1827
Kale, R.R. **16**-1809
Kalek, M. **10**-633
Kalendra, D.M. **13**-48
Kalesse, M. **16**-1160
Kaleta, Z. **16**-218
Kalinin, A.V. **12**-390
Kalinkin, M.I. **15**-499, **19**-1341
Kalinovskii, I.O. **13**-580
Kalinowski, H. **10**-1833, **18**-689
Kalinowski, M.K. **8**-246
Kalir, A. **10**-1077
Kalita, B. **10**-989, **10**-1058, **15**-2019
Kalita, H.R. **16**-618
Kalivretenos, A.G. **15**-2351
Kalkote, U.R. **19**-1203
Kallel, E.A. **18**-493, **18**-518
Kallemeyn, J.M. **13**-698
Kallen, R.G. **16**-1519
Kallfass, D. **18**-530
Kallio, R.E. **15**-1864, **15**-1865
Källström, K. **15**-449, **15**-452, **19**-928
Kalman, J.R. **14**-371
Kalmus, C.E. **11**-601
Kaloustian, M.K. **4**-375, **16**-28
Kalow, J.A. **10**-1218
Kalsey, S. **15**-1234, **15**-2217
Kalt, W. **11**-684
Kalthod, V.G. **16**-1916
Kalvoda, J. **14**-230
Kalyanakumar, R. **17**-385
Kalyanam, N. **19**-1668
Kalyani, D. **13**-444
Kalz, W. **15**-1347
Kamai, G. **4**-45
Kamakura, T. **17**-390
Kamal, A. **9**-91, **10**-581, **10**-971, **10**-1172, **10**-1204, **15**-1442, **16**-74, **16**-200, **16**-2234, **16**-2292, **19**-1256
Kamal, F. **19**-1176
Kamal, M. **18**-221
Kamalova, F.R. **11**-171
Kamat, R.J. **10**-126
Kamat, S.K. **10**-586
Kamat, V.P. **10**-695
Kamata, K. **10**-1854, **11**-418, **15**-2136
Kamata, M. **19**-355
Kamata, T. **10**-915
Kambara, H. **4**-329
Kambe, N. **10**-1267, **10**-1309, **10**-1362, **10**-1382, **10**-1388, **10**-1470, **10**-1996, **12**-252, **13**-357, **14**-26, **14**-414, **15**-304, **15**-313, **15**-903, **16**-431
Kamble, R.M. **11**-341
Kamble, V.T. **10**-848, **16**-158, **16**-1707, **16**-1725
Kameda, Y. **15**-633
Kamego, A.A. **10**-346, **19**-694
Kamei, K. **12**-511
Kamei, T. **10**-1271, **10**-1343, **15**-987
Kamenka, J. **15**-713
Kamer, P.C.J. **15**-1604
Kametani T. **15**-821
Kametani, H. **4**-82
Kametani, T. **10**-828, **15**-2319
Kameyama, A. **10**-1240
Kameyama, H. **10**-630, **10**-1297
Kameyama, M. **11**-260
Kameyama, T. **13**-330
Kamienska-Trela, K. **11**-280
Kamigata, N. **11**-260, **13**-824, **14**-189
Kamijo, S. **15**-2630, **16**-480
Kamikawa, K. **10**-1739
Kamikawa, T. **10**-1375
Kamikawaji, Y. **15**-49
Kamimura, A. **10**-1552, **15**-1322, **15**-1435, **15**-2230, **16**-1695, **17**-145, **19**-1515, **19**-1525
Kamiñski, R. **16**-425
Kamitanaka, T. **15**-225, **19**-963
Kamitani, A. **15**-1590
Kamiura, K. **19**-975
Kamiya, I. **15**-323, **15**-1519, **19**-977
Kamiya, M. **19**-1077
Kamiya, N. **15**-173
Kamiya, Y. **16**-511
Kamiyama, M. **16**-1149
Kamkha, M.A. **10**-1395
Kamlet, J. **16**-1200
Kamlet, M.J. **3**-19, **3**-20, **10**-460, **10**-463, **10**-479
Kammann Jr., K.P. **16**-2054
Kammoun, M. **15**-1940
Kamo, O. **3**-203
Kamochi, Y. **15**-587, **15**-588, **19**-1060, **19**-1061, **19**-1062
Kampar, E. **3**-103
Kampar, V.E. **3**-98
Kämper, F. **14**-175
Kampf, J.W. **18**-880
Kamphuis, J. **19**-1463
Kampmeier, J.A. **14**-490, **14**-497, **14**-500, **14**-501
Kamyshova, A.A. **10**-1300
Kan Wang, K. **18**-711
Kan, R.O. **11**-541, **19**-1662
Kan, S. **11**-424, **13**-565
Kan, Y. **13**-287
Kanagasabapathy, S. **15**-299, **16**-1780
Kanagasabapathy, V.M. **10**-47, **10**-310
Kanai, F. **15**-2249
Kanai, K. **16**-851
Kanai, M. **10**-708, **15**-1171, **15**-1635, **15**-1694, **15**-2030, **15**-2328, **16**-403, **16**-737, **16**-780, **16**-942, **16**-1150, **16**-1495
Kanamathareddy, S. **3**-132
Kanamori, M. **15**-1684, **15**-1704
Kanatani, R. **10**-712
Kanaya, H. **10**-2005
Kanayama, T. **10**-1527
Kanazaki, S. **10**-1629
Kanazawa, C. **15**-2630
Kanazawa, Y. **15**-642
Kanbara, T. **3**-134
Kanbe, O. **12**-528
Kanchiku, S. **15**-2515
Kanda, K. **16**-680
Kanda, T. **15**-551, **15**-774
Kanda, Y. **10**-815
Kandall, L.C. **10**-743
Kandasamy, D. **4**-375, **19**-1283, **19**-1316
Kandhasamy, S. **14**-17
Kandpal, B.M. **19**-221, **19**-304, **19**-1305
Kandula, S.R.V. **19**-158
Kane, V.V. **12**-259
Kaneda, K. **15**-563, **15**-1890, **15**-1953, **15**-1955
Kaneko, C. **15**-1546
Kaneko, H. **5**-120
Kaneko, K. **16**-192
Kaneko, M. **11**-355

Kaneko, T. **15**-1525, **15**-1584, **15**-1585
Kaneko, Y. **16**-642, **16**-1098, **16**-1170
Kanemasa, S. **10**-1680, **15**-2105, **15**-2112, **15**-2132
Kanematsu, K. **15**-49, **18**-649
Kanemoto, K. **16**-1446
Kanemoto, S. **10**-1328
Kanerva, L.T. **16**-1662
Kanetaka, S. **16**-1118
Kanetani, F. **10**-1192
Kaneti, J. **9**-23
Kang, B. **18**-888, **18**-889
Kang, C.H. **5**-334, **14**-41
Kang, D.H. **14**-217, **16**-1987
Kang, E.J. **15**-416
Kang, H.-Y. **14**-14, **19**-1496
Kang, H. **13**-150
Kang, H.K. **10**-82, **16**-2273
Kang, H.R. **12**-530
Kang, J. **15**-582, **15**-887, **15**-2206
Kang, K.H. **19**-1213
Kang, L. **16**-2041
Kang, Q. **11**-314
Kang, S. **17**-170
Kang, S.B. **16**-641
Kang, S.B. **17**-170
Kang, S.B. **19**-1310
Kang, S.B. **19**-1633
Kang, S.-H. **10**-1265, **15**-240, **15**-265
Kang, S.-K. **10**-1268, **10**-1458, **10**-1714, **10**-1910, **10**-1920, **10**-1235, **13**-201, **13**-202, **13**-242, **13**-324, **13**-333, **13**-334, **13**-339, **13**-555, **13**-556, **13**-622, **13**-627, **13**-692, **15**-248, **15**-876, **15**-1589, **16**-723, **16**-731, **16**-333, **19**-884
Kang, S.M. **16**-1511
Kang, T. **13**-150, **16**-2215
Kang, Y.-F. **16**-545, **16**-666, **16**-670
Kang, Y. **19**-302, **19**-1185
Kangani, C.O. **11**-456
Kanger, T. **19**-501
Kanishchev, M.I. **18**-2
Kankaanperä, A. **10**-617, **10**-677, **10**-776, **10**-1121, **16**-1767
Kannan, M.A. **19**-1612
Kannan, V. **16**-803, **16**-811
Kannemann, F.O. **3**-1
Kanner, B. **8**-206
Kanno, H. **2**-171, **19**-662
Kanno, K.-i. **15**-843, **15**-846
Kano, N. **16**-1406
Kano, S. **15**-1341, **19**-1271
Kano, T. **11**-213, **11**-420, **11**-421, **12**-126, **12**-135, **15**-1432, **15**-1433, **15**-2141, **15**-2148, **16**-397, **16**-397
Kanofsky, J.R. **19**-485
Kanoh, S. **4**-182
Kantam, M.L. **10**-779, **10**-937, **11**-223, **13**-205, **13**-494, **13**-509, **15**-1398, **15**-1806, **15**-2071, **16**-315, **16**-357, **16**-1087, **19**-212, **19**-759, **19**-1299
Kantchev, E.A.B. **10**-1469
Kanter, J.P. **8**-51, **17**-56
Kanters, J.A. **3**-29, **3**-54
Kanth, J.V.B. **12**-477, **13**-178, **19**-1466
Kantlehner, W. **11**-495
Kantner, S.S. **4**-151, **10**-230, **10**-1500
Kantor, E.A. **5**-53, **10**-559
Kantor, S.W. **13**-853
Kanyonyo, M.R. **19**-1768
Kao, J. **4**-242
Kapadia, S.R. **16**-452
Kapdi, A.R. **13**-493, **13**-494
Kapeller, D.C. **12**-439
Kaplan, E.P. **16**-2060
Kaplan, F. **12**-599
Kaplan, L. **4**-461, **5**-211, **5**-283, **10**-1305, **14**-56
Kaplan, L.A. **19**-1202
Kaplan, M.L. **3**-12
Kapon, M. **16**-1013
Kapoor, K.K. **15**-530
Kapoor, R. **10**-642
Kapp, D.L. **15**-2367
Kappe, C.O. **7**-108, **7**-110, **7**-123, **7**-126, **7**-127, **7**-129, **9**-98, **10**-727, **13**-248, **13**-332, **15**-2203
Kappos, J.C. **15**-1797, **17**-328
Kaprinidis, N.A. **15**-2448
Kaptein, B. **15**-934, **16**-895, **16**-1844, **19**-1463
Kaptein, R. **5**-229, **14**-367
Kapur, N. **15**-2102
Kapxhiu, E.A. **17**-236
Kar, A. **10**-1372, **13**-162, **15**-152
Kara, Y. **10**-1173
Karabal, P.U. **15**-2061
Karabatsos, G.J. **4**-307, **18**-21, **18**-23, **18**-25, **18**-26, **18**-45, **18**-48
Karabelas, K. **13**-368
Karadakov, P.B. **15**-2129, **15**-2130
Karade, N.N. **11**-209, **19**-197
Karaev, S.F. **15**-264
Karafiat, U. **16**-300
Karakhanov, E.A. **14**-221, **15**-549
Karaman, R. **10**-463, **16**-2289, **19**-1714
Karamé, I. **18**-143
Karami, B. **19**-29
Karasu, M. **10**-744
Karatekin, E. **5**-218
Karatjas, A.G. **15**-721
Karchaudhuri, N. **16**-81
Kardak, B.G. **11**-326
Kardile, G.B. **19**-938
Kardon, F. **16**-264
Kardos, N. **7**-104
Karelson, M. **2**-124, **2**-126, **2**-129, **2**-462, **2**-471, **10**-228
Karen, W. **7**-109
Kargbo, R. **16**-911
Karge, R. **15**-2243
Karger, B.L. **4**-174, **4**-176
Karger, M.H. **10**-761, **10**-789, **16**-1831
Karikomi, M. **10**-695, **18**-261
Karimi, A.-R. **19**-113
Karimi, B. **10**-585, **13**-385, **16**-143, **16**-148, **16**-155, **16**-1515, **17**-161, **19**-111, **19**-246, **19**-602, **19**-834, **19**-1587
Karimi, M.H. **16**-1749
Karimi, S. **15**-669
Karimipour, M. **13**-472
Karjalainen, J.K. **15**-1833, **15**-1972
Karl, R. **14**-321
Karliga, B. **16**-1715
Karlin, K.D. **14**-223
Karlov, S.S. **15**-1641
Karlsson, S. **15**-2104
Karlström, A.S.E. **10**-1385, **10**-1506
Karmanova, I.B. **11**-411
Karnes, J. **16**-1066
Karney, W.L. **2**-373, **2**-214, **2**-277, **2**-345, **5**-429
Karni, M. **15**-1952
Karo, W. **10**-778
Karodia, N. **17**-267
Karoui, H. **5**-224
Karpaty, M. **16**-1552
Karpitskaya, L.G. **19**-719
Karpov, A.S. **16**-2042
Karpyuk, A.D. **5**-136
Karrick, G.L. **15**-570
Kartashov, A.V. **10**-787, **14**-155
Kartashov, V.R. **15**-279
Karthikeyan, G. **19**-204
Karty. J.M. **2**-38, **5**-33, **8**-125, **8**-209
Karur, S. **15**-370, **16**-787
Kasahara, A. **15**-427
Kasai, K. **15**-989, **18**-824
Kasai, N. **2**-69, **2**-76
Kasai, P.H. **1**-88
Kasai, T. **6**-47
Kasaura, T. **16**-1362
Kasei, A. **15**-1370
Kasei, N. **3**-177
Kaselj, M. **19**-1012
Kashdan, D.S. **16**-2157
Kashima, C. **16**-2057
Kashimura, K. **10**-70, **10**-84
Kashimura, S. **16**-1578
Kashimura, T. **13**-677
Kashin, A.N. **12**-34, **12**-37, **13**-644, **14**-419
Kashinatham, A. **15**-609

Kashino, S. **10**-1629
Kashino, S. **13**-872
Kashiwabara, M. **15**-560
Kashiwagi, H. **10**-676
Kashiwagi, M. **15**-1256
Kashiwagi, R. **10**-1539
Kashiwagi, Y. **19**-665
Kashmiri, M.A. **10**-1692, **10**-1693
Kasi, D. **15**-415
Kaska, W.C. **10**-1393, **15**-745
Kasmai, H.S. **2**-281
Kasner, M.L. **19**-694
Kaspar, L.T. **15**-332
Kasperczyk, J. **15**-158
Kasrayan, A. **19**-500
Kass, S.R. **2**-31, **2**-217, **4**-434, **5**-142, **5**-179, **8**-147, **10**-522, **15**-132, **15**-142, **19**-456
Kassab, D.J. **10**-638
Kassab, Y. **19**-128
Kassaee, M.Z. **5**-372
Kasshinath, D. **13**-486
Kassianidis, E. **15**-2213
Kasture, S.P. **11**-219, **16**-1725
Kasturi, T.R. **19**-1450
Kasu, P.V.N. **12**-136
Kasuga, Y. **19**-1171
Kasukhin, L.F. **10**-1399, **19**-1259
Kaszynski, P. **4**-518, **4**-519
Katafuchi, Y. **15**-1480
Katagiri, K. **15**-1206
Katagiri, T. **15**-845, **16**-520, **16**-522
Katampe, I. **15**-292
Katamura, M. **4**-200
Kataoka, O. **16**-61, **18**-846
Kataoka, T. **17**-519
Kataoka, Y. **16**-662, **16**-1425, **19**-1042
Katayama, A. **14**-406
Katayama, E. **15**-1577
Katayama, K. **12**-77
Katayama, R. **19**-611
Katayama, S. **19**-627
Katayama, T. **19**-533
Katcher, M.H. **10**-1105
Kate, S.S. **11**-209
Katebzadeh, K. **15**-1066
Kato, A. **2**-442, **2**-464, **18**-778
Kato, D. **10**-1709, **19**-198
Kato, H. **2**-324, **2**-376, **12**-575, **15**-1632, **19**-1260
Kato, J. **16**-144
Kato, K. **10**-1034, **17**-490, **18**-746
Kato, M. **1**-73, **10**-1589
Kato, N. **13**-871, **19**-993, **19**-1323
Kato, S. **10**-1644, **15**-774, **15**-1136, **16**-230, **16**-1182, **16**-1301
Kato, T. **2**-332, **2**-333, **2**-335, **5**-9, **12**-329, **13**-638, **15**-1712, **15**-1798
Katoh, A. **19**-709
Katoh, S. **4**-182
Katoh, T. **15**-1223
Katoh, Y. **15**-1130
Katohgi, M. **19**-1610
Katona, B.W. **13**-625
Katritzky, A.R. **1**-94, **2**-98, **2**-101, **2**-104, **2**-124, **2**-126, **2**-129, **2**-462, **2**-471, **4**-367, **9**-39, **10**-1, **10**-89, **10**-91, **10**-94, **10**-228, **10**-416, **10**-417, **10**-753, **10**-797, **10**-875, **10**-923, **10**-1084, **10**-1255, **10**-1270, **10**-1566, **10**-1692, **10**-1693, **10**-1788, **11**-2, **11**-69, **11**-70, **11**-72, **11**-73, **12**-427, **13**-76, **13**-765, **15**-2319, **15**-2352, **16**-248, **16**-260, **16**-387, **16**-426, **16**-876, **16**-2107, **17**-258, **17**-506, **19**-756, **19**-1506, **19**-1526, appendixa-31
Katsigras, G. **15**-1660
Katsoulos, G. **12**-413
Katsuki, T. **10**-1539, **12**-229, **12**-395, **15**-1206, **15**-1886, **15**-1978, **15**-1981, **15**-1982, **15**-1984, **15**-1985, **15**-2048, **15**-2074, **15**-2145, **15**-2513, **15**-2515, **15**-2563, **16**-692, **16**-1766, **18**-390, **19**-214, **19**-461, **19**-462, **19**-469, **19**-524, **19**-545, **19**-579, **19**-800
Katsumura, N. **16**-656
Katsumura, S. **18**-500
Katsuro, Y. **10**-1614
Katz, A.H. **13**-270, **13**-747
Katz, C.E. **18**-324
Katz, J. **10**-1864, **18**-459, **18**-480, **18**-482
Katz, R.B. **14**-381
Katz, S. **2**-56
Katz, T.J. **2**-203, **4**-461, **7**-44, **18**-548, **18**-807, **18**-821, **18**-894
Katzenellenbogen, J.A. **10**-1353, **15**-282, **16**-1250
Katzenelson, O. **4**-83
Katzin, M.I. **19**-420
Katzka, C. **18**-764
Kauffmann, T. **12**-594, **12**-654, **13**-54, **13**-767, **14**-414, **15**-2165, **15**-2166
Kaufman, D. **15**-537
Kaufman, D.H. **17**-440
Kaufman, M.J. **5**-157
Kaufmann, D. **18**-667
Kaukoranta, P. **13**-438
Kaupp, G. **1**-69, **7**-57, **10**-483, **12**-751, **15**-2309, **18**-97
Kaur, A. **12**-423
Kaur, G. **15**-828, **16**-295
Kaur, J. **11**-432, **19**-72
Kaur, K.P. **16**-1036
Kaur, P. **16**-567
Kaushik, M.P. **10**-859, **16**-221
Kaval, N. **7**-126, **7**-127, **15**-2203
Kavala, V. **10**-886, **10**-1156
Kavanagh, S.A. **16**-1441
Kavarno, G.J. **7**-31
Kavita, B. **15**-2071
Kawa, H. **4**-174
Kawa, S. **16**-1406
Kawabata, H. **13**-43, **19**-20
Kawabata, N. **15**-2549, **16**-685
Kawabata, T. **10**-1535, **10**-1724
Kawada, A. **11**-438, **11**-440
Kawada, K. **12**-167
Kawafuchi, H. **15**-1371
Kawafuji, Y. **16**-528
Kawaguchi, K. **5**-289
Kawaguchi, S.-i. **15**-384
Kawahama, R. **19**-1294
Kawahara, F. **15**-1435
Kawahara, N. **15**-1481
Kawahito, A. **10**-1816
Kawai, M. **16**-336
Kawai, T. **10**-495, **13**-87
Kawai, Y. **15**-658, **15**-659, **15**-661
Kawajiri, K. **16**-1727
Kawakami, J.-i. **15**-1519
Kawakami, J.H. **15**-117, **18**-105, **19**-862
Kawakami, T. **15**-1802, **16**-981
Kawakami, Y. **11**-327, **15**-212, **15**-1025
Kawaki, T. **13**-127
Kawamatsu, H. **13**-682
Kawamura, E. **13**-861
Kawamura, M. **11**-432, **11**-453, **11**-468, **15**-1437
Kawamura, S. **15**-1724, **19**-1761
Kawamura, T. **10**-1275
Kawamura, Y. **7**-60, **10**-729
Kawanami, Y. **15**-786, **15**-1830, **19**-1021
Kawanishi, M. **13**-111
Kawanishi, T. **16**-931
Kawanisi, M. **17**-179
Kawano, N. **19**-1758
Kawano, T. **16**-1649
Kawaragi, S. **11**-342
Kawasaki, A. **11**-513, **16**-1519
Kawasaki, I. **19**-1034
Kawasaki, K. **12**-229, **19**-462
Kawasaki, M. **15**-2343, **16**-840
Kawasaki, N. **10**-2011
Kawasaki, S. **15**-2596
Kawasaki, T. **10**-875, **15**-2615, **15**-2640
Kawasaki, Y. **16**-1518
Kawase, M. **19**-1137
Kawase, T. **1**-13, **2**-368, **15**-2544
Kawashima, J. **13**-715
Kawashima, T. **3**-140, **11**-418, **13**-591, **16**-1406
Kawasoe, S. **10**-1381
Kawata, A. **10**-1908, **16**-2137
Kawata, I. **11**-522
Kawate, T. **10**-1934, **16**-2162
Kawathar, S.P. **15**-2602
Kawatsura, M. **10**-1529

Kawauchi, T. **11**-522
Kawazoe, Y. **10**-372
Kay, K.-Y. **16**-1912
Kayagishi, S. **12**-329
Kayaki, Y. **13**-392, **13**-535
Kayaleh, N.E. **16**-1726
Kayama, M. **15**-2093
Kayano, A. **15**-57
Kaye, P.T. **16**-828
Kayser, F. **10**-1403
Kayser, M.M. **16**-1400, **18**-389, **19**-1001, **19**-1455, **19**-1459
Kazan, J. **10**-775
Kazankov, M.V. **13**-170
Kazankova, M.A. **12**-552, **15**-385, **15**-393, **15**-397
Kazantsev, A.V. **15**-797
Kazaraya, K. **16**-196
Kazemi, F. **10**-843, **10**-981, **10**-983, **16**-1464, **19**-954
Kazitsyna, L.A. **9**-34
Kazlauskas, R.J. **4**-186
Kazmaieer, U. **10**-1542
Kazmaier, P.M. **12**-237, **19**-1765
Kazmaier, U. **18**-737
Kazubski, A. **19**-1011
Kazuki, K. **15**-1635
Kdota, I. **19**-1322
Keaffaber, J.J. **18**-517
Kean, N.B. **12**-675
Keana, J.F.W. **5**-267
Keaney, G.F. **15**-2059
Kearley Jr., F.J. **13**-47
Kearney, P.A. **6**-71
Kearns, D.R. **14**-251, **14**-263, **15**-2361, **15**-2365
Keating, J.T. **10**-425
Keaveney, W.P. **19**-330
Keay, B.A. **4**-166, **8**-159
Keay, J.G. **15**-583
Kebarle, P. **3**-58, **8**-239, **8**-240, **8**-241, **8**-242, **8**-244, **8**-249, **10**-286, **10**-447
Keck, G.E. **10**-1327, **16**-461, **16**-774, **16**-810, **16**-1771, **16**-1774, **18**-912, **19**-940
Keck, R. **10**-1250
Kee, K. **13**-689
Kee, M. **19**-778
Keefer, L.K. **4**-228, **19**-10, **19**-1223
Keefer, R.M. **11**-271
Keeffe, J.R. **2**-436, **2**-437, **2**-438, **2**-443, **6**-42, **15**-26, **12**-91, **12**-93, **17**-47
Keegstra, K. **10**-422
Keegstra, M.A. **13**-69
Keehn, P.M. **2**-66, **19**-655
Keenan, M. **11**-335
Kees, K.L. **19**-1682, **19**-1691
Keese, R. **4**-512, **4**-536
Keevil, T.A. **8**-15
Kefalas, P. **16**-1027
Kegelaers, Y. **7**-84
Kehrli, S. **15**-1181
Keii, T. **15**-830
Keijsper, J.J. **15**-1497
Keiko, V.V. **4**-307
Keil, R. **15**-742
Keillor, J.W. **16**-1364, **18**-296, **18**-298
Keim, W. **9**-120
Keinan, E. **10**-945, **10**-1510, **15**-591, **15**-628, **16**-1985, **19**-435, **19**-743, **19**-893
Keirs, D. **19**-277
Keister, J.B. **18**-890
Keith, J.A. **19**-701
Keith, J.M. **12**-788
Keith, T.A. **4**-314
Keivanloo, A. **13**-591, **13**-602, **13**-614
Keliher, E.J. **18**-579
Kel'in, A. **15**-371
Kel'in, A.V. **10**-1779, **15**-244
Kelleher, S. **16**-2025
Kelleman, A. **19**-1604
Keller, M. **4**-468
Keller, T.H. **4**-404
Kellie, G.M. **4**-331
Kellogg, M.S. **18**-520
Kellogg, R.E. **7**-30
Kellogg, R.M. **4**-213, **4**-499, **10**-719, **14**-264, **16**-895, **17**-2
Kelly, A.M. **4**-112
Kelly, B.G. **16**-459
Kelly, D.P. **5**-95, **11**-15, **18**-797
Kelly, D.R. **18**-399
Kelly, E.G. **12**-563
Kelly, F.W. **12**-673, **17**-128, **18**-627, **18**-691
Kelly, J.F. **16**-2237, **16**-2239
Kelly, J.W. **10**-645
Kelly, P. **19**-800
Kelly III, R.A. **13**-540
Kelly, R.P. **11**-165
Kelly, R.V. **12**-401
Kelly, W.J. **10**-172, **10**-1553, **12**-352
Kelly, W.L. **10**-1712
Kelsey, D.R. **10**-270
Kelso, M. **15**-1407
Kelso, P.A. **7**-52
Kemmer, R. **10**-409
Kemnitz, C.R. **2**-451, **5**-429
Kemp-Jones, A.V. **2**-275
Kemp, M.I. **15**-1591
Kemp, N.R. **1**-19, **5**-69, **13**-28
Kemp, T.J. **13**-29
Kempf, B. **10**-12, **10**-375, **10**-397, **10**-1784, **15**-2
Kendall, J.T. **15**-1876
Kendall, P.E. **15**-1243
Kende, A.S. **15**-810, **19**-786, **19**-1215
Kendrick, R.D. **5**-80
Kenkre, S.L. **10**-1703, **16**-1022
Kennady, P.K. **13**-494
Kennard, O. **1**-55, **1**-68, **2**-33, **3**-27, **3**-29, **3**-33
Kennedy, A.R. **12**-108, **15**-1361
Kennedy, E.M. **11**-122
Kennedy, J.P. **10**-1449
Kennedy, J.W.J. **2**-73, **2**-74
Kennedy, K. **19**-688
Kennedy, L.E. **13**-570
Kennedy, R.M. **15**-1116
Kennedy, S.R. **18**-647
Kennerly, R.E. **15**-59
Kennedy-Smith, J.J. **15**-1009, **18**-742
Kennewell, P.D. **16**-1473, **16**-1474
Kenny, D.H. **10**-753
Kent, B.A. **13**-867
Kent, J.L. **15**-1570
Kenttämaa, H.I. **13**-53
Kenworthy, M.N. **13**-303
Kenyon, J. **10**-10, **18**-10
Keogh, B.P. **15**-1155
Keogh, J. **15**-1762, **15**-1760, **19**-1376
Kepler, K.D. **15**-166
Keppens, M. **19**-35
Keramane, E.-M. **10**-668
Kerber, R.C. **10**-301
Kercher, T. **16**-1491
Kerek, F. **16**-2191
Kerekes, A.D. **15**-1565
Kerekes, I. **10**-1146, **10**-1249, **15**-167, **15**-1671, **16**-444, **16**-1992, **16**-1995
Kereselidze, R.V. **14**-24
Keresztes, I. **12**-421, **16**-1022, **17**-306
Kergomard, A. **10**-761, **15**-1706
Kerlinger, H.O. **14**-289
Kern, A. **19**-993
Kerr, J.A. **1**-95, **14**-77
Kerr, M.A. **12**-371, **13**-5, **16**-277
Kerr, M.S. **15**-1487, **16**-721, **16**-722
Kerr, W.J. **12**-322, **15**-1548, **15**-1554, **15**-1591, **15**-2096, **16**-1155, **19**-120
Kerrigan, N.J. **15**-1983
Kershaw, N.M. **19**-936
Kershner, L. **16**-1699
Kershner, L.D. **16**-22
Kerton, F.M. **9**-116
Kerwin, S.M. **10**-1916, **18**-527
Kesavan, V. **10**-969, **14**-341, **19**-833
Kesenheimer, C. **19**-892
Keshavarz, E. **16**-2176
Kessar, S.V. **12**-423, **13**-638
Kesseler, K. **16**-1078
Kesselmayer, M.A. **15**-2265
Kessick, M.A. **10**-461
Kessler, H. **4**-273, **4**-280, **10**-65, **15**-2505, **15**-2545, **18**-244, **18**-665
Kesten, S. **16**-2173

Kester, F.L. **1**-98
Kester, J. **2**-259
Kestner, M.M. **10**-301, **10**-1553
Ketcham, R. **15**-2441
Ketley, A.D. **18**-609
Kettle, S.F.A. **1**-2
Keul, H. **19**-337, **19**-364
Keum, G. **16**-641, **17**-170, **19**-1310, **19**-1633
Keum, S. **18**-947
Keum, S.R. **19**-1581
Keumi, T. **11**-104, **11**-458, **11**-646, **16**-292
Keuper, R. **4**-223
Keusenkothen, P.F. **10**-503, **15**-1348
Kevan, L. **15**-575, **5**-333
Kevill, D.N. **10**-70, **10**-87, **10**-167, **10**-209, **10**-298, **10**-372, **10**-454, **10**-456, **10**-462, **10**-463, **10**-467, **10**-470, **16**-22
Keyerleber, M.A. **15**-853
Keykha, H. **4**-312
Keypour, H. **12**-739
Keyvan, A. **16**-2171
Kézdy, F.J. **16**-1637
Kezuka, S. **15**-2324
Khac, T.B. **16**-383
Khachatrian, A.G. **19**-100
Khadilkar, B.M. **11**-130, **11**-450, **11**-590, **13**-114, **16**-108, **16**-114, **18**-763, **19**-552
Khafizova, L.O. **15**-889
Khaimova, T.G. **16**-1545
Khairudinov, I.R. **16**-1553
Khaksar, S. **16**-338
Khakshoor, O. **19**-1134
Khalaf, A.A. **11**-313, **11**-367
Khalafi-Nezhad, A. **10**-1066, **10**-1193, **16**-1900
Khaledy, M.M. **18**-734
Khalfina, I.L. **19**-719
Khalili, D. **16**-1759
Khamsi, J. **13**-227
Khan, A.A. **16**-367
Khan, A.T. **10**-582, **10**-584, **12**-127, **16**-212, **16**-634, **19**-562
Khan, C. **11**-303
Khan, F. **19**-243
Khan, F.A. **16**-7, **16**-566
Khan, F.N. **15**-952
Khan, I.U. **3**-134
Khan, K.M. **10**-814, **10**-890, **10**-1142
Khan, M. I. **5**-404
Khan, M.A. **10**-1237, **12**-326
Khan, M.I. **15**-2546
Khan, M.M.T. **12**-67, **15**-201, **15**-2661, **19**-698
Khan, M.N. **10**-1036, **16**-505, **16**-1696
Khan, N.H. **15**-1979
Khan, S.A. **19**-811
Khan, S.I. **15**-1305
Khan, T.A. **11**-368
Khan, W.A. **10**-1828
Khananashvili, L.M. **15**-739
Khanapure, S.P. **13**-85, **13**-638
Khand, I.U. **15**-1539
Khandekar, A.C. **11**-299
Khanna, G.B.R. **10**-971
Khanna, I.K. **10**-1258
Khanna, R.K. **13**-776, **14**-399
Khanolkar, A.D. **15**-917, **15**-921
Khanthapura, P. **11**-303
Kharasch, M.S. **10**-1298, **10**-1357, **10**-1606, **10**-1617, **12**-586, **12**-604, **14**-133, **14**-320, **15**-63, **15**-285, **16**-455, **16**-863, **16**-880, **16**-992, **16**-2012, **16**-2048, **16**-2051, **17**-523
Kharasch, N. **14**-374, **14**-376, **14**-449, **15**-296, **17**-224, **17**-516, **19**-768, **19**-838, **19**-1575
Kharrat, A. **19**-1516
Khartabil, H.K. **10**-1702
Khatik, G.L. **15**-1441
Khatri, N.A. **16**-316
Khattak, J. **10**-295
Khau, V.V. **16**-2290
Khawaled, K. **10**-723
Khazdooz, L. **11**-198, **11**-455
Khedhair, K.A. **4**-379
Khedkar, V. **15**-325, **15**-366
Kheifets, G.M. **2**-432
Kheifets, V.I. **16**-1553
Khelevin, R.N. **11**-194
Khenkin, A.M. **11**-578, **19**-162
Khiar, N. **4**-50
Khidekel, M.L. **16**-318, **18**-535
Khlebnikov, A.F. **15**-2476
Khmel'nitskaya, E.A. **10**-1570
Khmel'nitskii, L.I. **13**-772
Khodaei, M.M. **11**-441, **11**-454, **16**-208, **16**-1849, **16**-2171, **18**-343, **19**-85
Khodakov, Yu.S. **15**-432
Khodei, M.M. **11**-199
Khodykin, S.V. **12**-153
Khoee, E. **16**-67
Khoee, S. **16**-48, **19**-84
Kholodov, L.E. **2**-376
Khong, A. **2**-406
Khoobi, M. **16**-2176
Khor, T. **16**-1390
Khorana, H.G. **16**-1825
Khorlina, I.M. **19**-1109
Khosropour, A.R. **16**-1778
Khosrowshahi, J.S. **15**-2039
Khotinsky, E. **12**-472
Khouri, F.F. **16**-28
Khriachtchev, L. **4**-309
Khristov, V.Kh. **15**-61
Khrizolitova, M.A. **14**-460
Khuddus, M.A. **19**-625
Khudyakov, I.V. **5**-320, **5**-332, **14**-37
Khundhar, M.H. **12**-489, **12**-491
Khuong, K.S. **15**-2271, **18**-734
Khurana, J.M. **17**-372, **19**-221, **19**-304, **19**-816, **19**-898, **19**-1164, **19**-1275, **19**-1305, **19**-1586
Khuriganova, O.I. **11**-354
Khusid, A.Kh. **16**-234
Khuthier, A. **18**-431
Khutoryanskii, V.A. **12**-34
Ki, S.H. **15**-1742
Kianmehr, E. **16**-1007
Kiany-Burazjani, M. **12**-732, **19**-30
Kiasat, A.R. **10**-843, **10**-981, **16**-64, **16**-65, **19**-954
Kiattansakul, R. **15**-2691
Kice, J.L. **5**-262, **10**-861, **10**-225, **10**-390, **16**-2280, **17**-516
Kidawi, M. **7**-117
Kiddle, J.J. **16**-1313
Kido, Y. **16**-1170
Kidwai, M. **9**-142, **13**-183
Kidwell, H. **4**-82.
Kidwell, R.L. **17**-393
Kiedaisch, W. **15**-2545
Kiefer, E.F. **18**-571
Kiefer, H.R. **17**-408
Kielbasinski, P. **10**-865, **16**-2187, **19**-773, **19**-799, **19**-803
Kiely, A.F. **2**-407, **18**-843
Kiely, D.E. **19**-106
Kienzle, F. **9**-105, **13**-270, **13**-747, **14**-377
Kier, M.J. **15**-2161
Kierse, S. **15**-2507
Kiesewetter, M.K. **2**-268, **2**-319
Kiesgen de Richter, R. **15**-713
Kiesman, W.F. **15**-644
Kiessling, A.J. **16**-1814
Kiessling, L.L. **15**-291
Kiesten, E.I.S. **19**-1058
Kiewel, K. **12**-310
Kiffer, D. **10**-388
Kigasawa, T. **10**-828
Kiggen, W. **3**-124
Kiguchi, T. **15**-1370
Kihara, N. **3**-192, **19**-1564
Kii, S. **16**-628
Kiji, J. **10**-1991, **15**-649, **15**-2406, **19**-950
Kiji, S. **12**-130
Kijima, A. **16**-1698
Kikiya, H. **15**-2638
Kikuchi, H. **19**-703
Kikuchi, K. **15**-153
Kikuchi, M. **15**-642, **15**-1196, **16**-1087
Kikuchi, O. **10**-23
Kikuchi, S.-i. **19**-1541
Kikuchi, T. **13**-805
Kikugawa, Y. **11**-191, **11**-193, **14**-446, **16**-166, **16**-233, **19**-1137, **19**-1571

Kikukawa, K. **13**-811, **14**-406, **14**-408, **14**-410
Kikukawa, T. **14**-314
Kilbourn, M.R. **14**-478
Kilburn, J.D. **15**-1328
Kilby, D.C. **11**-304
Kiliç, H. **2**-274
Killeen, N.M. **19**-533
Killion Jr., R.B. **10**-255
Killough, J.M. **16**-2008
Killpack, M.O. **10**-1701
Kilpatrick, M. **11**-21
Kilway, K.V. **3**-46
Kim, A.I. **14**-95, **15**-919
Kim, A.R. **16**-1611
Kim, B.-K. **15**-174
Kim, B. **16**-906
Kim, B.C. **10**-1141
Kim, B.G. **18**-889
Kim, B.H. **19**-1186, **19**-1204
Kim, B.M. **10**-888, **10**-529, **15**-715, **15**-1394, **15**-1556, **15**-1838, **16**-667, **16**-754, **18**-856
Kim, B.S. **12**-116, **18**-226
Kim, B.T. **10**-1574, **17**-528
Kim, C.-Y. **4**-475
Kim, C.-K. **16**-46
Kim, C. **16**-858
Kim, C.J. **10**-170, **10**-179
Kim, C.K. **10**-22, **10**-56
Kim, C.S. **15**-2351
Kim, C.U. **10**-1174
Kim, D.-H. **13**-242, **13**-555, **18**-889
Kim, D.-S. **18**-963
Kim, D. **6**-31, **15**-631
Kim, D.J. **19**-1020
Kim, D.W. **10**-442, **10**-532, **10**-1114, **10**-1183, **19**-254, **19**-782
Kim, D.Y. **10**-1670, **15**-1063, **16**-2298, **19**-1591
Kim, E.-H. **19**-661
Kim, E.G. **16**-334
Kim, E.J. **19**-1095, **19**-1098
Kim, E.S. **16**-111
Kim, H. **13**-689, **15**-351, **15**-855, **15**-868, **15**-1415
Kim, H.-C. **15**-1161
Kim, H.D. **19**-945
Kim, H.J. **16**-849
Kim, H.-J. **8**-86, **10**-327, **13**-401, **15**-1989, **19**-543
Kim, H.K. **10**-532
Kim, H.R. **12**-191, **19**-945
Kim, H.-S. **10**-532, **16**-355, **17**-434
Kim, H.W. **19**-1190
Kim, H.-Y. **9**-21, **10**-82, **19**-652
Kim, I.-J. **15**-970
Kim, I.C. **10**-82
Kim, I.S. **10**-607, **15**-149, **15**-2018
Kim, J.-G. **10**-1059, **11**-446
Kim, J.-S. **10**-1458, **13**-201
Kim, J.-W. **13**-324
Kim, J.-H. **13**-383
Kim, J.-G. **16**-1865, **19**-1445
Kim, J. **10**-1352, **13**-208, **15**-1803, **16**-800, **16**-1826, **18**-742, **19**-973, **19**-1029
Kim, J.B. **11**-77
Kim, J.C. **16**-1525
Kim, J.D. **15**-2018
Kim, J.E. **3**-128, **19**-1091, **19**-1093
Kim, J.G. **16**-638
Kim, J.H. **11**-331, **15**-2209, **16**-2108, **19**-1530, **19**-1531, **19**-1581, **19**-1591, **19**-1660
Kim, J.I. **13**-467
Kim, J.K. **13**-56
Kim, J.M. **19**-1095, **19**-1098, **19**-1178
Kim, J.N. **16**-111, **16**-366, **17**-432, **17**-434
Kim, J.S. **15**-1562
Kim, J.T. **15**-563
Kim, J.W. **13**-383, **16**-239
Kim, J.Y. **15**-348, **15**-1351, **16**-1640, **19**-945
Kim, K,-Y. **10**-1141
Kim, K.-C. **8**-119
Kim, K.-J. **15**-1589
Kim, K. **3**-195, **12**-206, **12**-545, **12**-730, **15**-678, **16**-1687, **18**-455
Kim, K.M. **10**-641
Kim, K.S. **15**-928, **19**-104, **19**-1310
Kim, M. **4**-514, **10**-1262, **15**-240, **15**-265, **15**-855, **15**-2059, **16**-1912, **18**-351, **18**-821, **18**-877, **18**-889, **19**-1677
Kim, M.H. **10**-1670
Kim, M.-J. **15**-1394, **19**-1151
Kim, M.K. **16**-1640
Kim, M.-S. **13**-334, **19**-884
Kim, N. **10**-1723
Kim, N.D. **10**-56
Kim, S.-J. **5**-352
Kim, S.-I. **10**-758
Kim, S.-Y. **12**-273
Kim, S.-G. **15**-1035
Kim, S.-W. **15**-1550, **15**-1551
Kim, S.-H. **16**-2035, **16**-604, **18**-841, **19**-1638
Kim, S. **2**-459, **4**-129, **4**-150, **10**-176, **10**-1939, **10**-1210, **10**-1938, **10**-1973, **11**-325, **12**-530, **13**-689, **14**-14, **15**-635, **15**-855, **15**-1290, **15**-1489, **16**-239, **16**-563, **16**-1601, **16**-2097, **17**-488, **18**-300, **18**-840, **19**-128, **19**-1315
Kim, S.B. **16**-742
Kim, S.C. **15**-1989, **19**-847, **19**-857, **19**-1006, **19**-1470
Kim, S.H. **10**-434, **10**-471, **10**-472, **10**-1593, **15**-1746, **15**-2037, **16**-111, **16**-2108, **17**-396, **17**-434, **19**-1581, **19**-1660
Kim, S.i. **16**-180
Kim, S.K. **15**-1351
Kim, S.S. **10**-1235, **11**-574, **14**-41, **14**-76, **16**-1070, **16**-1496, **16**-1611, **19**-176, **19**-782
Kim, S.Y. **10**-1235, **14**-76, **16**-1609
Kim, T.-S. **13**-473
Kim, T.H. **10**-1268
Kim, W.-Y. **10**-1910, **10**-1920
Kim, Y.-J. **3**-38, **4**-323, **8**-232
Kim, Y.-M. **13**-627
Kim, Y. **16**-641, **16**-849, **17**-170, **19**-1185, **19**-1213, **19**-1310, **19**-1633
Kim, Y.H. **10**-763, **10**-1224, **12**-191, **12**-206, **12**-730, **14**-397, **16**-173, **16**-548, **16**-841, **16**-1687, **17**-396, **19**-841, **19**-1160, **19**-1388
Kim, Y.K. **15**-354
Kim, Y.M. **13**-325, **15**-1183
Kim, Y.S. **15**-1071, **19**-1091
Kim. H.S. **16**-2298
Kim. J.Y. **18**-351
Kim. T.-J. **10**-1574
Kim., J.K. **15**-2082
Kimball, D.B. **2**-317, **2**-331
Kimel, W. **18**-723
Kimling, H. **4**-495
Kimoto, H. **10**-372
Kimoto, K. **17**-179
Kimura, F. **15**-774
Kimura, H. **16**-1582
Kimura, J. **16**-1285
Kimura, K. **15**-836, **16**-693, **16**-1049, **16**-1062
Kimura, M. **1**-90, **2**-32, **15**-632, **16**-595, **16**-712, **16**-982, **16**-1560, **16**-2140, **16**-2206, **18**-585, **18**-936
Kimura, O. **13**-840
Kimura, S. **18**-203
Kimura, T. **7**-87, **7**-102, **15**-612, **15**-894, **17**-243
Kimura, Y. **3**-114, **10**-695, **10**-737, **13**-261
Kinal, A. **15**-2408
Kinart, W.J. **15**-1003
Kinchin, E. **17**-215, **17**-217
Kinder, R.E. **15**-416
Kinderman, S.S. **18**-834
Kindler, K. **19**-1273
Kindon, N.D. **10**-979, **16**-256
King, A.O. **10**-1463. **17**-195
King, A. **10**-1194
King, A.E. **19**-128
King, B.T. **18**-562
King, F. **15**-1829. **19**-990, **19**-1036
King, G.S.D. **2**-356
King, G.W. **7**-15
King, H.F. **5**-326, **14**-99

King, J.A. **19**-1775
King, J.C. **15**-2575
King, J.F. **4**-229, **10**-18, **10**-306, **16**-2277, **17**-324, **18**-755
King, K. **2**-91, **15**-2278, **16**-2166
King, R.A. **2**-280
King, R.B. **1**-84, **2**-395, **15**-1620
King, R.W. **15**-47, **17**-147, **17**-231, **17**-237, **17**-259
King, S.A. **16**-240
King, S.W. **19**-336
King, T.J. **4**-249
Kingsbury, C.A. **4**-396, **10**-174
Kingsbury, C.L. **15**-1240
Kingsbury, J.S. **18**-847, **18**-892
Kingsland, M. **11**-73
Kingston, H.M. **7**-109, **7**-110
Kingston, J.F. **16**-2148
Kingston, J.V. **10**-1731, **13**-186
Kinner, L. **10**-1393
Kinney, W.A. **15**-2179
Kinoshita, A. **15**-839, **15**-2619, **18**-835
Kinoshita, H. **10**-1509, **10**-1572, **13**-322, **15**-787, **15**-2611, **19**-581
Kinoshita, N. **10**-1535, **10**-1724
Kinoshita, S. **11**-527
Kinoshita, T. **3**-135, **5**-120, **5**-124, **5**-210, **10**-70, **10**-83, **10**-84, **15**-567, **15**-1034, **16**-1326, **19**-1654
Kinoshita, Y. **16**-1962
Kinter, K.S. **15**-1120
Kintner, R.R. **11**-648, **14**-489, **19**-413
Kinzel, T. **13**-494
Kinzelmann, H. **12**-608
Kipke, J. **8**-98
Kipphardt, H. **10**-1768, **15**-1463
Kiprianova, L.A. **10**-590, **19**-1553
Kira, M. **5**-258, **5**-337
Kira, T. **16**-1299
Kirahara, M. **19**-141
Kirai, N. **15**-1276
Kiran, B. **2**-117
Kiran, Y.B. **19**-685
Kirby, A.J. **1**-66, **4**-173, **4**-299, **4**-355, **4**-376, **4**-475, **5**-375, **10**-568, **10**-569, **16**-32, **16**-34, **16**-1653, **16**-1665
Kirby, G.W. **4**-104, **12**-538, **17**-244, **19**-12, **19**-300, **19**-843
Kirby, R.E. **1**-19
Kirchhoefer, P.L. **15**-1093
Kirchhoff, J.H. **13**-532
Kirchner, J.J. **18**-733
Kireev, A.S. **15**-1153
Kirichenko, K. **10**-1084
Kirihara, M. **19**-790
Kirillova, M.V. **19**-460
Kirin, V.N. **10**-791, **15**-10
Kirino, K. **13**-283
Kiripolský, M. **7**-96
Kiritani, R. **13**-122
Kirk, D.N. **4**-277
Kirk, G.G. **15**-1554
Kirk, J.M. **10**-650
Kirkland, T.A. **18**-822
Kirkor, E. **3**-174
Kirkpatrick, D. **10**-1227, **12**-727
Kirkpatrick, E. **19**-688
Kirms, M.A. **2**-350
Kirmse, W. **5**-357, **5**-383, **5**-387, **5**-388, **5**-413, **10**-133, **10**-419, **10**-545, **12**-360, **15**-2470, **15**-2481, **18**-2, **18**-11, **18**-19, **18**-27, **18**-28, **18**-42, **18**-46, **18**-179, **18**-219, **18**-220, **18**-230, **18**-231
Kirn, W.N. **16**-435
Kirpichenko, S.V. **15**-305, **19**-1766
Kirpichenok, M.A. **1**-32
Kirsanov, A.V. **16**-1924
Kirsch, G. **2**-354
Kirsch, J.F. **16**-24
Kirsch, S.F. **18**-744, **18**-747, **19**-188
Kirschberg, T. **14**-87
Kirschleger, B. **12**-650
Kirschner, S. **18**-92
Kirschning, A. **15**-2087, **16**-422
Kirss, R.U. **5**-232
Kirst, H.A. **10**-1353, **19**-1227
Kirste, B. **5**-218
Kirtane, J.G. **10**-525
Kirwan, J.N. **19**-1287, **19**-1395
Kisanga, P. **15**-805, **16**-767
Kisanga, P.B. **16**-1204
Kischel, J. **11**-349
Kise, M. **13**-111
Kise, N. **10**-1831, **19**-1671, **19**-1672
Kiselev, V.D. **15**-2187
Kiselyov, A.S. **14**-387
Kishali, N. **10**-1173
Kishi, I. **19**-1742
Kishi, Y. **4**-122, **4**-124, **4**-125, **16**-856
Kishida, N. **15**-225
Kishikawa, K. **18**-238
Kishikawa, Y. **15**-2600
Kishimoto, S. **16**-695
Kishimoto, Y. **15**-1514
Kishimura, K. **18**-473
KishoreBabu N. **13**-660
Kiso, S. **19**-1596
Kispert, L.D. **2**-232, **5**-294
Kiss, G. **15**-1498
Kiss, J. **9**-13, **18**-258
Kissel, W.J. **19**-431
Kissel, W.S. **15**-643
Kissling, R.M. **16**-1803
Kita, I. **16**-2057
Kita, T. **10**-325
Kita, Y. **10**-573, **10**-875, **10**-1286, **12**-257, **14**-11, **19**-198, **19**-1497, **19**-1758, **19**-1760
Kitagaki, S. **15**-251
Kitagawa, A. **11**-558
Kitagawa, H. **11**-290
Kitagawa, K. **13**-346
Kitagawa, O. **12**-186, **13**-234, **15**-1718
Kitagawa, S. **19**-1742
Kitagawa, T. **4**-476, **5**-65, **5**-88, **5**-124, **5**-210, **10**-315, **10**-138, **10**-317, **18**-625, **18**-680
Kitaguchi, H. **12**-112, **14**-165
Kitahara, S. **18**-268
Kitahara, T. **15**-2322
Kitahonoki, K. **19**-1236
Kitajima, H. **11**-104, **11**-458, **11**-646
Kitamura, M. **4**-153, **10**-1189, **12**-307, **15**-1353, **16**-352, **16**-494, **16**-1058, **19**-1014, **19**-1016
Kitamura, T. **10**-1238, **11**-375, **13**-43, **16**-1677, **18**-885, **19**-1680
Kitani, A. **15**-392
Kitano, T. **18**-386
Kitano, Y. **10**-1013, **11**-325, **15**-1634
Kitao, T. **9**-64, **19**-1761
Kitaoka, S. **9**-135
Kitaoka, Y. **19**-1761
Kitatani, K. **10**-1415
Kitatsuji, C. **15**-590
Kitayama, K. **10**-715
Kitazawa, E. **16**-1174
Kitazume, T. **10**-697, **10**-1641, **18**-254
Kitazume, T. **19**-995
Kitching, W. **4**-342, **4**-353, **5**-96, **5**-109, **8**-69, **12**-14, **12**-36, **12**-37, **12**-46, **12**-502, **15**-182
Kite, G.F. **14**-470
Kito, T. **11**-530
Kittredge, K.W. **5**-129
Kiuchi, H. **15**-532
Kivinen, A. **16**-1613, **16**-1875
Kiwiet, N.J. **15**-2314
Kiyan, N.Z. **10**-328, **16**-2269
Kiyobayashi, T. **2**-362
Kiyooka, S.-i. **19**-684
Kiyooka, S. **16**-1098, **16**-1170
Kiyosawa, Y. **10**-577
Kiyoshige, K. **19**-882
Kiyota, K. **15**-954
Kiyota, M. **10**-1240
Kizaki, H. **13**-694
Kizil, M. **15**-1362
Kizilian, E. **5**-110, **8**-188
Kizirian, M. **18**-52
Kizner, T.A. **13**-116
Klabunde, K.J. **12**-625
Klabunovskii, E.I. **19**-1333
Klages, U. **4**-382
Klahre, G. **16**-1360
Klamann, D. **10**-788, **16**-2287

Klamer, J.C. **2**-68
Klamt, A. **10**-441
Klang, J.A. **14**-463, **19**-421, **19**-1689, **19**-1697
Klankermayer, J. **16**-960
Klapars, A. **13**-189, **13**-236, **13**-237, **13**-240, **13**-265
Klappa, J.J. **16**-255
Klaps, E. **15**-939
Klärner, F.-G. **2**-58
Klärner, F. **17**-303, **18**-573, **18**-596, **18**-597
Klasinc, L. **5**-159
Klauber, D.J. **15**-417
Klaunzer, N. **12**-62
Klaus, S. **11**-521
Klausner, Y.S. **16**-1907
Klawonn, M. **15**-1901
Klebe, J. **15**-2538
Kleijn, H. **15**-981
Kleimann, H. **16**-2262
Klein, A. **11**-139
Klein, D.J. **2**-132
Klein, G. **10**-165, **10**-1906, **16**-1210
Klein, H. **15**-330, **16**-278, **19**-396
Klein, H.S. **1**-52
Klein, J. **10**-1413, **12**-415, **15**-683, **15**-686, **15**-1239, **16**-1076
Klein, P. **7**-84
Klein, R. **12**-441
Klein, W.R. **12**-591
Kleinen, J. **16**-960
Kleiner, C.M. **10**-840
Kleinman, M.H. **5**-218
Kleinpeter, E. **4**-312, **4**-408
Kleinschmidt, R.F. **15**-364
Kleinstück, R. **17**-485
Klem, R. **19**-429
Klemmensen, P. **10**-948
Klender, G.J. **15**-676
Klenke, K. **15**-748
Klepacz, A. **10**-924
Kleschick, W.A. **12**-330
Kless, A. **18**-567
Klessinger, M. **4**-275, **11**-82
Klester, A.M. **18**-119
Klibanov, A.M. **4**-156
Kliewer, M.A. **15**-515
Kliimann, H. **16**-2249
Klima, R.F. **16**-1408
Klima, W. L. **17**-195
Klimisch, R.L. **17**-94
Klimkina, E.V. **16**-2084
Klimo, V. **14**-6, **14**-7
Klimov, E.M. **16**-1779
Klimova, E.I. **16**-1567
Kline, A.D. **4**-133
Kline, M. **5**-412
Kline, M.W. **18**-416
Klinger, F. **18**-515
Klingstedt, T. **10**-1453
Klink, J.R. **11**-616
Klink, J.R. **11**-617
Klitzke, C.F. **13**-577
Klivenyi, P. **5**-222
Klobukowski, M. **15**-12
Kloc, K. **19**-678
Kloetzing, R.J. **10**-1537, **16**-849
Kloosterziel, H. **18**-585, **18**-603
Klopfenstein, C.E. **2**-364
Klopman, G. **5**-31, **10**-345
Klopper, W. **2**-279
Klosa, J. **16**-1917
Klose, J.R. **4**-228
Klose, T.R. **12**-765
Klosin, J. **15**-1613, **15**-1615
Klotz, P. **16**-354
Klug, W. **2**-361
Kluge, H. **17**-478
Kluge, R. **19**-513
Kluger, R. **6**-83, **16**-20, **16**-1877
Klumpp, D.A. **11**-324, **15**-2622
Klumpp, G.W. **6**-9, **6**-23, **8**-149, **9**-1, **10**-345, **10**-430, **10**-739, **12**-613, **15**-44, **15**-2300, **18**-625, **18**-677
Klunder, J.M. **13**-847, **15**-1689, **15**-1971
Klusacek, H. **16**-2262, **18**-677
Klusener, P.A.A. **10**-1698
Klutsch, G. **19**-344
Klyashchitskii, B.A. **4**-164
Klym, A. **8**-64
Klyne, W. **4**-99, **4**-104
Klyuev, M.V. **16**-318
Knapp, F.F. **12**-520
Knapp, S. **15**-1723, **19**-44
Knauer, K.H. **2**-199
Knaup, G.L. **2**-195
Knaus, E.E. **10**-1603, **16**-1904
Knauss, E. **15**-2263
Knausz, D. **16**-264
Kneib-Cordonier, N. **16**-1929
Knettle, B.W. **19**-1132, **19**-1677
Kniel, P. **19**-1518
Knier, B.L. **10**-99
Kniezo, L. **17**-16
Knight, C. **19**-489
Knight, D.W. **10**-727, **15**-402, **18**-630, **18**-729
Knight, G.T. **12**-749
Knight, J.C. **19**-1450
Knight, J.G. **15**-2067
Knight, J.W. **17**-255
Knights, E.F. **18**-470
Knipe, A.C. **10**-431, **10**-636, **16**-1741, **16**-1841, **17**-58
Knist, J. **18**-11, **18**-46
Knobelsdorf, J. **16**-2173
Knobler, C.B. **3**-126, **3**-180
Knoche, H. **18**-810
Knochel, P. **10**-1384, **10**-1403, **10**-1427, **10**-1437, **10**-1446, **10**-1456, **10**-1457, **10**-1463, **10**-1470, **10**-1471, **10**-1477, **10**-1537, **10**-1778, **10**-1780, **12**-602, **13**-133, **13**-211, **13**-233, **13**-335, **13**-345, **13**-350, **13**-795, **15**-387, **15**-717, **15**-953, **15**-983, **15**-1214, **15**-1215, **15**-1996, **16**-470, **16**-473, **16**-571, **16**-665, **16**-849, **16**-925, **16**-2009, **19**-170
Knoeber, M.C. **4**-370
Knölker, H.-J. **15**-2690
Knoll, F. **1**-12
Knöpfel, T.F. **15**-1170
Knopp, M. **18**-739
Knorr, R. **5**-377
Knossow, M. **4**-169, **4**-170
Knowles, D.A. **19**-533, **19**-640
Knowles, J.R. **4**-32, **18**-694
Knowles, W.S. **4**-150, **15**-454, **15**-635, **19**-333
Knox, B.E. **1**-98
Knox, D.E. **10**-120
Knox, G.R. **17**-262, **19**-1412
Knox, L.H. **2**-175, **2**-182, **10**-50, **12**-366, **15**-2541
Knox, S.A.R. **2**-196
Knözinger, H. **17**-178
Knudsen, R.D. **13**-839
Knudson, K.R. **16**-966
Knueppel, D. **16**-560
Knunyants, I.L. **2**-456, **15**-73, **15**-1731, **15**-1755, **16**-43
Knupfer, H. **17**-481
Knutov, V.I. **3**-119
Knutson, D. **6**-40
Knutson, F.J. **10**-415
Knutsson, L. **18**-211
Ko, B.-S. **15**-876, **16**-723
Ko, C. **15**-2563
Ko, E.C.F. **10**-1259, **18**-24
Ko, H.C. **9**-26
Ko, J.J. **19**-1660
Ko, J.S. **19**-1315
Ko, K.H. **13**-500
Ko, M. **19**-415
Ko, S. **15**-1493, **15**-1523
Ko, S.-B. **10**-1024, **15**-79
Ko, S.-L. **15**-1633
Ko, S.Y. **10**-697, **15**-1971
Kobata, M. **16**-1430
Kobayashi, H. **10**-496, **13**-24, **15**-2275, **18**-398, **19**-416
Kobayashi, K. **11**-328, **15**-642, **15**-762, **15**-849, **16**-870, **18**-883
Kobayashi, M. **10**-534, **10**-926, **13**-824, **19**-806
Kobayashi, N. **19**-1021
Kobayashi, S. **8**-204, **8**-247, **10**-267, **10**-289, **10**-290, **10**-298, **10**-692, **10**-916, **10**-958, **10**-974, **10**-975, **10**-1505, **10**-1672, **10**-1707, **11**-375, **11**-438, **11**-440, **11**-482, **11**-585, **13**-192, **15**-443, **15**-1038, **15**-1073, **15**-1087, **15**-1104, **15**-1124, **15**-1131, **15**-1419, **15**-1437, **15**-1805, **15**-1845, **15**-2108,

15-2194, **15**-2327, **16**-355, **16**-359, **16**-402, **16**-623, **16**-738, **16**-751, **16**-770, **16**-772, **16**-841, **16**-905, **16**-912, **16**-947, **16**-952, **16**-953, **16**-962, **16**-972, **16**-974, **16**-983, **16**-1050, **16**-1099, **16**-1133, **16**-1134, **16**-1140, **16**-1149, **16**-1172, **16**-1191, **16**-1536, **16**-1782, **19**-128, **19**-865
Kobayashi, Sh. **16**-913
Kobayashi, T. **5**-89, **10**-834, **10**-2008, **10**-2010, **10**-2012, **12**-363, **12**-728, **13**-646, **13**-711, **15**-1535, **16**-1316, **17**-308
Kobayashi, Y. **4**-122, **4**-124, **4**-125, **10**-543, **10**-1635, **15**-2469, **16**-779, **18**-686
Kobbelgaard, S. **13**-635
Kober, H. **5**-436
Kobierski, M.E. **10**-887
Kobori, K. **19**-1031
Kobori, T. **15**-1738
Kobori, Y. **10**-1387
Koboyashi, K. **3**-156
Köbrich, G. **12**-649, **12**-652, **17**-3, **17**-313
Köbrich, G. **4**-512
Kobrina, L.S. **13**-81, **13**-90, **14**-46, **18**-259
Kobsa, H. **11**-596
Kobyashi, J.-i. **16**-688
Kočevar, M. **11**-232, **16**-1790
Koch Jr, S.D. **14**-185
Koch, A. **4**-408
Koch, D. **18**-849
Koch, E. **5**-68
Koch, G.K. **16**-2156
Koch, H. **5**-252
Koch, H.F. **17**-40
Koch, J. **16**-2233
Koch, J.R. **15**-1864, **15**-1865
Koch, K.R. **18**-451
Koch, M. **13**-88
Koch, R. **15**-1285
Koch, S. **16**-265
Koch, V.R. **14**-123
Koch, W. **2**-349, **10**-146, **10**-198, **10**-199, **10**-213, **10**-219, **10**-221, **15**-141, **15**-2558, **18**-77
Kochetkov, A.N. **15**-393
Kochetkov, K.A. **4**-139, **10**-258
Kochetkov, N.K. **16**-1779
Kochi, J.K. **2**-138, **3**-81, **3**-100, **5**-211, **5**-218, **5**-220, **5**-262, **5**-283, **5**-295, **5**-302, **10**-1111, **10**-1318, **10**-1360, **10**-1401, **10**-1583, **11**-19, **11**-20, **11**-104, **11**-123, **11**-153, **12**-25, **12**-42, **13**-749, **14**-20, **14**-39, **14**-46, **14**-56, **14**-59, **14**-77, **14**-104, **14**-105, **14**-107, **14**-134, **14**-145, **14**-219, **14**-237, **14**-283, **14**-286, **14**-380, **14**-417, **14**-474, **15**-51, **15**-285, **15**-885, **15**-1789, **15**-2209, **15**-2642, **16**-2205, **17**-145, **18**-54, **18**-72, **18**-81, **18**-176, **18**-411, **19**-264, **19**-265, **19**-418, **19**-421, **19**-424, **19**-698
Kochi, T. **13**-451
Kochloefl, K. **19**-889
Kochly, E.D. **5**-58
Kochurina, V.S. **13**-828
Kocián, O. **17**-28
Kocienski, P. **10**-1613
Kociok-Köhn, G. **16**-396
Kociolek, M.G. **15**-2583
Kock, I. **15**-701
Köckritz, A. **16**-1865
Koçoğlu, M. **16**-474
Kočovský, P. **10**-1546, **13**-244, **15**-1886, **16**-773, **16**-775, **16**-776, **16**-778, **16**-1490, **19**-1129, **19**-1156
Kocsis K. **17**-504
Koda, T. **13**-535
Kodama, H. **10**-1449
Kodama, S. **19**-148, **19**-151
Kodama, T. **19**-220, **19**-405
Kodera, M. **16**-1837
Kodoi, K. **15**-1583
Kodomari, M. **11**-343
Kodukulla, K. **15**-2109
Koeberg-Telder, A. **8**-35, **8**-36, **11**-205, **11**-668, **11**-669
Koelliker, V. **15**-1711
Koeng, F.R. **10**-160
Koenig, K.E. **15**-637, **15**-639, **16**-2163
Koenig, M. **15**-1114
Koenigsberger, R.U. **12**-40
Koepp, E. **16**-1266
Koeppl, G.W. **6**-96
Koerner, M. **12**-601
Koga, G. **18**-788
Koga, K. **4**-149, **10**-1707, **10**-1743, **12**-725, **13**-779, **15**-1168, **15**-1171, **15**-2248
Koga, N. **2**-31, **7**-24, **15**-100, **15**-116, **15**-491, **18**-788
Koga, Y. **13**-633, **15**-1535
Kogami, K. **16**-1038
Kogan, G.A. **2**-34, **2**-39
Kogan, V. **19**-1379
Koguchi, S. **19**-995
Kogure, K. **19**-703
Kogure, T. **19**-902
Koh, C.A. **3**-19, **3**-164
Koh, H.Y. **10**-1593, **19**-1185, **19**-1213, **19**-1496
Koh, Y. **15**-962
Koharski, D. **19**-1376
Kohaus, R.L. **16**-63
Kohda, K. **10**-372
Kohl, D.A. **1**-64, **5**-368, **15**-59
Kohler, B. **7**-17
Kohler, B.A.B. **16**-1125
Köhler, F. **2**-345
Köhler, V. **16**-1161
Kohli, T.-P. **5**-104
Kohlmiller, C.K. **19**-349
Kohlpaintner, C. W. **15**-1497
Kohmarch, G. **16**-197
Kohmoto, S. **18**-238
Kohmura, Y. **12**-229, **19**-469
Kohn, H. **16**-1757
Kohnke, F.H. **2**-342
Kohno, S. **19**-1291
Kohnstam, G. **10**-455, **11**-39, **13**-858
Kohra, S. **16**-2068
Koichiro Oshima, K. **10**-1365
Koide, K. **10**-1636, **12**-80, **18**-273, **19**-880
Koike, N. **10**-745
Koike, T. **13**-713, **15**-1253, **16**-769, **16**-1166
Koiyama, Y. **10**-1537
Koizumi, T. **15**-1509
Koizumi, Y. **14**-312
Kojima, M. **15**-2457
Kojima, R. **10**-1012
Kojima, S. **16**-2081
Kojima, T. **19**-282, **13**-352, **16**-964
Kok, D.M. **15**-2444
Kok, G.B. **19**-1606
Kokel, B. **11**-172
Koketsu, J. **18**-426
Koketsu, M. **16**-170
Kokhlova, V.M. **13**-117
Kokil, P.B. **15**-18
Kokin, A.A. **14**-169
Kokin, K. **16**-1362
Kokko, B. **12**-540
Kokko, B.J. **12**-538, **12**-539
Kokotos, G. **16**-1624
Kokubo, K. **15**-1477
Kokubo, M. **15**-1087
Kokubo, T. **15**-1852
Kokumai, R. **15**-2487, **19**-39
Kol, M. **15**-1709
Kolahdoozan, M. **10**-844
Kolano, C. **5**-217
Kolar, L.W. **10**-752
Kolářová, L. **16**-1993
Kolarovi, A. **12**-690
Kolarska, Z. **19**-781, **19**-787
Kolasa, T. **10**-1042
Kolb, H.C. **15**-1793, **15**-1831, **15**-1835, **15**-1835
Kolb, M. **10**-1247
Kolb, V.M. **17**-346
Kolbah, D. **10**-910
Kolbasenko, S.I. **15**-2003
Kolbeck, K.J. **7**-74
Koldobskii, G.I. **18**-318, **18**-320, **18**-334
Kolehmainen, E. **3**-125
Kolesnichenko, G.A. **14**-226
Koleva, G. **11**-226
Koley, D. **15**-277
Kollman, P.A. **2**-219, **3**-3, **4**-370

Kollonitsch, J. **19**-1501
Kołodziejska-Huben, M. **10**-1930
Kolomiets, A.F. **10**-840
Kolomitsyn, I.V. **14**-169
Kolomnikov, I.S. **16**-863
Kolomnikova, G.D. **2**-174
Kolos, W. **1**-4
Kolsaker, P. **19**-362
Kolsaker, P. **2**-489
Kolshorn, H. **4**-492, **4**-493, **15**-2232
Kolsov, A.I. **2**-432
Kolthoff, I.M. **8**-9, **8**-46
Koltun, E.S. **19**-456
Koltunov, K.Yu. **15**-657, **15**-1219
Kolyaskina, Z.N. **15**-1771
Komagawa, S. **16**-1430
Komanduri, V. **16**-930
Komáromi, A. **13**-591
Komarov, I.V. **4**-475, **5**-375
Komarov, N.V. **10**-1928
Komatsu, H. **15**-1504
Komatsu, K. **2**-137, **2**-176, **5**-65, **5**-124, **5**-210, **10**-70, **10**-84, **15**-1057
Komatsu, K.i. **19**-355
Komatsu, M. **10**-648, **10**-1660, **10**-1982, **10**-1996, **15**-1139, **15**-1743, **15**-2069, **15**-2075, **16**-2004, **19**-580, **19**-593
Komatsu, N. **19**-978
Komatsubara, A. **10**-1047
Komatsuzaki, T. **9**-76
Komeyama, K. **15**-392
Komine, N. **4**-203, **15**-156, **15**-924
Komiya, N. **19**-480, **19**-558, **19**-559
Komiya, S. **15**-156
Komiya, Y. **14**-308
Komiyama, M. **3**-183, **11**-56, **16**-1623
Komiyama, S. **16**-1536
Kommandeur, J. **7**-22
Komoto, I. **11**-482, **16**-1140
Komoto, R.G. **10**-1985, **10**-1986
Kompa, K. **11**-178
Komura, K. **10**-1297
Komura, M. **16**-1098
Komuro, Y. **15**-2250
Kon, Y. **19**-681
Konakahara, T. **13**-590, **16**-547, **19**-685, **19**-1448, **19**-1477
Kondaji, G. **11**-459, **12**-129, **16**-619
Kondakov, D.Y. **15**-929
Kondaskar, A. **10**-964, **10**-965, **10**-974
Kondo, H. **15**-468, **15**-2598
Kondo, I. **14**-416
Kondo, J.N. **5**-70
Kondo, K. **10**-1341, **12**-771, **15**-2357, **16**-1965, **19**-387
Kondo, S. **2**-353, **10**-1381, **16**-1896
Kondo, T. **10**-815, **10**-1544, **13**-584, **15**-1583, **15**-1835, **15**-2689
Kondo, Y. **10**-1541, **13**-535, **13**-554, **16**-870
Kondoh, A. **15**-308
Kondolff, I. **10**-1882
Kondratenko, M. **15**-2694
Kondrat'eva, L.A. **16**-541
Kondrat'eva, L.V. **15**-363
Konen, D.A. **14**-170, **16**-1308
Kong, F. **12**-113
Kong, J.-R. **16**-929
Kong, L. **15**-449, **19**-502
Kong, N. **15**-2510
Kong, S. **10**-1695
Kong, W.-L. **19**-1014
Konieczny, M.T. **10**-1206
Konieczny, W. **10**-1206
König, B. **15**-2225
König, E. **19**-1554, **19**-1556
König, J. **18**-572, **18**-588
König, W.A. **4**-178, **13**-507
Königshofen, H. **2**-302
Konishi, H. **2**-228, **16**-953, **19**-950
Konishi, K. **15**-1990
Konishi, M. **10**-1387
Konishi, T. **19**-259
Kono, D.H. **16**-2000
Kono, K. **13**-811, **14**-406, **14**-410, **18**-778
Konoike, T. **19**-820
Konopelski, J.P. **13**-649, **13**-650
Konovalov, A.I. **15**-2170, **15**-2187
Konrad, K.M. **4**-409
Konradi, A.W. **19**-1641, **19**-1642
Konshin, V.V. **10**-1928
Konuma, M. **19**-802
Konwar, D. **16**-58, **17**-467, **18**-297, **19**-222, **19**-240, **19**-1239
Konya, D. **15**-1557, **15**-1572
Koo, B.-S. **19**-661
Koo, I.S. **16**-17, **16**-1614
Koo, S. **12**-116, **19**-778
Kooijman, H. **13**-244, **13**-732, **19**-209
Kooistra, D.A. **16**-161, **19**-1427
Koola, J.J. **14**-261
Koort, E. **8**-86
Kooshki, B. **19**-797
Koovský, P. **18**-391
Kooyman, E.C. **2**-135, **11**-233, **11**-680, **14**-122, **14**-147, **17**-138, **17**-143
Kop, J.M.M. **16**-2156
Kopach, M.E. **10**-887
Kopecky, D.J. **19**-1462
Kopecky, K.R. **5**-354
Kopel, L.C. **13**-586
Kopf, J. **4**-538
Kopf, N.A. **15**-1056
Kopinke, F. **14**-79
Kopka, I.E. **4**-533
Koplick, A.J. **18**-48
Koposov, A.Y. **19**-783
Kopp, F. **10**-1384
Kopp, J. **6**-68
Kopp, R. **10**-265
Koppel, I.A. **8**-176
Koppes, W.M. **16**-2000
Kopping, B. **15**-790
Koptyug, V.A. **11**-13, **11**-92, **11**-644, **18**-6, **18**-30, **18**-35
Koradin, C. **16**-925
Korber, H. **19**-354
Korblova, E. **4**-209
Korcek, S. **14**-241
Korchagina, D.V. **18**-35
Kore, A.R. **19**-313
Koreeda, M. **18**-733, **18**-777, **19**-913
Koreshkov, Yu.D. **15**-2532
Korivi, R.P. **15**-2605
Kormos, B.L. **10**-356
Kormos, C.M. **10**-1988, **13**-102, **13**-503, **13**-674
Korn, S. **15**-863
Korn, T.J. **13**-335, **13**-345
Kornblum, N. **10**-301, **10**-457, **10**-517, **10**-519, **10**-520, **10**-809, **10**-1055, **10**-1552, **10**-1553, **10**-1554, **10**-1555, **10**-1556, **10**-1557, **10**-1689, **12**-352, **13**-777, **16**-97, **19**-615, **19**-616, **19**-618, **19**-1514
Kornegay, R.L. **10**-144
Korneva, L.M. **2**-160.
Kornienko, A. **15**-1153
Korobitsyna, I.K. **10**-420, **18**-226
Korolev, B.A. **8**-234
Korolev, D.N. **13**-497, **13**-557
Koroniak, H. **18**-493, **18**-517
Koroniak, L. **10**-1190
Korostova, S.E. **10**-1597
Korostylev, A.P. **13**-91
Korshunov, S.P. **19**-10
Kort, C.W.F. **11**-201, **11**-204
Korte, S. **4**-488
Korte, W.D. **10**-1393
Korth, H.-G. **1**-96, **1**-110, **14**-38
Korth, H. **5**-256
Kortüm, G. **8**-25
Korytnyk, W. **19**-965
Korytsky, O.L. **10**-1259, **10**-921
Korzeniowski, S.H. **13**-776, **13**-823, **19**-1547
Korzhenevskaya, N.G. **8**-103, **9**-48, **10**-396
Kos, A.J. **10**-146
Kos, N.J. **1**-94
Kosak, J.R. **11**-631
Kosal, A.D. **15**-603
Kosbahn, W. **18**-713
Koseki, A. **16**-1792
Kosel, C. **13**-767
Koser, G.F. **18**-303
Köser, H.G. **2**-259
Koshchii, V.A. **11**-361

Koshiba, N. **11**-325
Koshimoto, K. **16**-401
Koshiro,Y. **19**-1744
Koshoji, G. **15**-392, **15**-765
Koshtaleva, T.M. **18**-334
Kosinska, W. **12**-84
Kosjek, B. **19**-993
Koski, W.S. **5**-215
Koskikallio, E.A. **16**-1801
Koskikallio, J. **10**-373
Koskimies, J.K. **4**-144, **10**-1775, **10**-1812
Koskinen, A.M.P. **12**-219
Kosma, P. **16**-349
Kośnik, W. **15**-1923
Kosower, E.M. **3**-86, **10**-461, **10**-475
Kossmann, S. **5**-434
Kosswig, K. **19**-297
Kost, A.N. **11**-525
Kost, D. **1**-1
Köster, A.M. **2**-6, **2**-101
Köster, F. **16**-879
Koster, G.F. **10**-127
Köster, H. **5**-154
Köster, R. **12**-468, **15**-1255
Kostermans, G.B.M. **2**-67
Kostikov, R.R. **2**-230, **7**-123, **15**-2116, **15**-2476, **15**-2488
Kostova, K. **16**-606
Kostyanovsky, R.G. **4**-37, **4**-40, **4**-43
Kostyk, M.D. **5**-50
Kostyukov, I.N. **14**-24
Kostyukovskii, Ya.L. **12**-733
Kosugi, M. **10**-1327, **10**-1738, **10**-1970
Kosugi, Y. **14**-60, **16**-1727, **16**-1791
Kosynkin, D. **3**-81
Koszelewski, D. **16**-362, **16**-2255
Kotake, H. **10**-1509
Kotani, S. **16**-776
Kotcher, P.G. **13**-35
Kotelevskii, S.I. **2**-168
Kotera, K. **19**-1236
Kotha, S. **10**-1680, **13**-486, **15**-2681, **18**-705
Kotian, K. **16**-2066
Kotian, K.D. **16**-166
Kotke, M. **16**-126
Koto, H. **16**-501
Kotora, M. **12**-723, **10**-1379, **10**-1911, **15**-989, **15**-2634, **16**-776, **18**-824
Kotov, V. **15**-329
Kotrusz, P. **15**-1064, **15**-1443, **16**-673
Kotschy, A. **13**-583
Kotsuki, H. **10**-1225, **13**-352, **15**-1052, **16**-1972
Kotsuma, T. **15**-873
Kotti, S.R.S.S. **15**-370, **15**-1747
Kou, Y. **8**-127, **15**-553
Koubek, E. **13**-845
Kouchi, Y. **19**-1156
Koudelka, J. **1**-38
Kourouli, T. **16**-1027
Kousaka, T. **15**-765
Koutecky, J. **5**-299
Kouwenhoven, A.P. **12**-53
Kovač, B. **4**-249, **5**-265
Kovac, F. **19**-226
Kovačević, M. **4**-169
Kovacic, M.K. **10**-908
Kovacic, P. **4**-518, **4**-519, **10**-1010, **11**-174, **11**-175, **11**-183, **11**-184, **11**-415, **12**-753, **17**-448, **18**-372
Kovacs, C.A. **18**-433, **18**-448
Kovács, G. **15**-345
Kovács, I. **13**-683, **15**-1619
Kovačević, B. **8**-95
Kovalenko, S.V. **5**-386, **8**-103, **13**-274, **18**-522
Kovalev, B.G. **16**-479
Kovasy, R. **16**-1084
Kovelesky, A.C. **10**-1846
Kovrizhnykh, E.A. **5**-155
Kovtonyuk, V.N. **18**-259
Kovtunenko, V.A. **15**-2280
Kowal, J.J. **15**-466
Kowalak, S. **15**-459
Kowalski, C.J. **16**-2105, **16**-2106
Kowalski, M.H. **10**-1461
Kowalski, P. **19**-781, **19**-787
Kowalski, T. **10**-222
Koyama, I. **10**-267
Koyama, K. **15**-1775, **19**-591
Koyanagi, M. **16**-2161
Koyano, M. **16**-605
Koyasu, K. **19**-896
Koyunçu, D. **19**-829
Kozaki, T. **10**-23
Kozerski, L. **15**-1923
Kozhevnikov, I.V. **10**-455, **11**-432, **13**-368
Kozhushko, B.N. **16**-1364
Kozhushkov, S.I. **4**-460, **10**-1683, **12**-780, **18**-87, **18**-562
Koziar, J.C. **7**-7
Koziara, A. **10**-945, **10**-1076, **19**-1263
Kozima, K. **3**-57
Kozima, S. **11**-347
Koziski, K.A. **13**-108
Kozlikovskii, Ya.B. **11**-361
Kozlov, V.A. **11**-674, **13**-253
Kozlowski, J. **10**-1621
Kozlowski, J.A. **10**-1402, **10**-1426, **12**-590, **15**-1150
Kozlowski, M.C. **16**-666, **16**-898, **16**-899, **18**-728
Kozmin, A.S. **10**-791, **10**-790, **15**-10, **15**-1700
Kozmin, S.A. **10**-716, **15**-867, **18**-805
Kozuka, S. **19**-1584
Kraeutler, B. **14**-458
Krafczyk, R. **12**-372
Krafft, M.E. **10**-1534, **15**-1533, **15**-1534, **15**-1547, **15**-1549, **15**-1552, **15**-1559, **15**-1571, **15**-1580, **16**-825, **19**-210, **19**-1341
Krafft, T.E. **14**-465
Kraft, L. **19**-314
Kraft, P. **16**-1110
Kraft, S. **18**-821
Kragl, U. **9**-118
Krahnert, W.-R. **11**-521
Krahulic, K.E. **5**-373
Kraka, E. **4**-418, **4**-436
Krakauer, H. **19**-1
Kramar, J. **12**-417
Kramer, B.D. **15**-2461
Kramer, G.M. **5**-16, **10**-195, **15**-133
Kramer, K.E. **18**-397
Kramer, P.A. **12**-53
Krämer, T. **16**-1263
Krane, J. **3**-111, **4**-342
Kranich, R. **10**-1734
Krapcho, A.P. **12**-685, **12**-337, **15**-2496, **16**-2157, **18**-20
Krapp, A. **1**-120
Krasna, A.I. **15**-483
Krasnokutskaya, E.A. **11**-289, **13**-795, **13**-795
Krass, N. **11**-569
Krattiger, P. **16**-1084
Kratzer, O. **16**-1321
Kraus, G.A. **9**-116, **10**-51, **10**-339, **10**-1352, **10**-1478, **15**-1324, **15**-1491, **15**-2093, **15**-2230, **19**-55, **19**-1444
Kraus, K.W. **16**-997
Kraus, M. **17**-180, **19**-889
Kraus, M.A. **16**-1930
Kraus, W. **19**-1323
Krause, H. **10**-1384
Krause, M.M. **11**-303
Krause, N. **15**-1241, **10**-1499, **10**-1900, **15**-381, **15**-1099, **15**-1143
Krause, P. **10**-163
Krause, R.A. **4**-455
Krause, V. **12**-676
Krauss, I.J. **15**-1612
Kraut, J. **2**-423
Krautscheid, H. **10**-693
Krayushkin, M.M. **11**-318
Krebs, A. **4**-492, **4**-494, **4**-495, **4**-522, **4**-538, **15**-87, **18**-737
Krebs, A.W. **2**-221
Krebs, O. **15**-1029, **18**-522
Krebs, P.J. **14**-27
Kreevoy, M.M. **6**-9, **6**-25, **6**-27, **6**-29, **8**-114, **8**-131, **6**-31, **10**-371, **10**-555, **10**-563, **10**-566, **10**-657, **19**-1465
Kreider, E.M. **13**-862, **13**-865
Kreil, D.J. **18**-611

Kreile, J. **2**-240
Kreimerman, S. **10**-1982, **10**-1996
Kreis, M. **14**-496
Kreiser, W. **19**-937
Kremer, K.A.M. **4**-147
Kremsner, J.M. **7**-123
Krepski, L. **16**-1494
Krepski, L.R. **19**-1691, **19**-1682
Kresge, A.J. **2**-435, **2**-437, **2**-438, **2**-440, **2**-441, **2**-443, **2**-447, **2**-448, **6**-42, **6**-69, **6**-94, **6**-96, **8**-64, **8**-110, **8**-117, **8**-118, **8**-149, **8**-151, **10**-564, **10**-587, **10**-588, **10**-589, **10**-591, **11**-113, **12**-83, **12**-91, **12**-93, **12**-96, **12**-97, **12**-160, **15**-26, **15**-80, **15**-211, **15**-219, **15**-256, **16**-2053
Kresge, A.R. **2**-436
Kresin, V.Z. **7**-47
Krespan, C.G. **15**-2261
Kress, A. **2**-232
Kress, J. **18**-894
Kress, R.B. **4**-194
Kresze, G. **12**-226, **16**-1443, **18**-713
Kretzschmar, G. **17**-155
Kreuder, R. **16**-1363
Kribber, T. **15**-221
Krichevtsova, T.I. **16**-2301
Kricka, L.J. **15**-2445
Kriedelbaugh, D. **19**-779
Krief, A. **10**-800, **10**-853, **10**-1827, **12**-649, **15**-1192, **15**-1849, **16**-702, **17**-205, **18**-134, **18**-245, **19**-547, **19**-1598
Krieg, H. **2**-312
Krieger, C. **2**-337, **3**-33, **4**-76, **8**-99, **8**-198, **8**-199, **8**-202
Krieger, J.K. **11**-77
Krieger, P.E. **15**-258
Krimen, L.I. **16**-2170
Krimer, M.Z. **15**-21
Krimm, H. **11**-387
Krimmer, H.-P. **15**-648
Krimmer, H. **18**-236
Krintel, S.L. **15**-1373
Krische, M.J. **10**-1575, **15**-850, **15**-1486, **15**-1490, **15**-2156, **15**-2381, **16**-713, **16**-714, **16**-741, **16**-749, **16**-929, **16**-930, **16**-946
Krishna Mohan, K.V.V. **11**-285
Krishna, A.D. **11**-217, **19**-992
Krishna, G.R. **15**-2212
Krishna, P.R. **10**-885, **10**-1048, **10**-1197, **15**-1401, **16**-803, **16**-811
Krishna, V.H. **16**-1555
Krishnaiah, M. **10**-840, **11**-286
Krishnamurthy, D. **15**-452, **16**-2012
Krishnamurthy, R. **14**-34
Krishnamurthy, S. **8**-195, **19**-844, **19**-847, **19**-851, **19**-855, **19**-857, **19**-858, **19**-867, **19**-921, **19**-967, **19**-1006, **19**-1279, **19**-1280, **19**-1359, **19**-1380
Krishnamurthy, V. **12**-267, **14**-326
Krishnamurthy, V.V. **5**-87, **16**-1346, **18**-73
Krishnamurti, R. **10**-1198
Krishnaveni, N. **10**-689
Krishnaveni, N.S. **19**-192
Krishtalik, L.I. **15**-572
Kristensen, J. **10**-1736
Kristensen, J.L. **16**-2025
Kristensen, T.E. **15**-1095
Kristián, P. **16**-1868
Kristiansen, P.O. **3**-111
Kritchevsky, J. **15**-63
Krivokapic, A. **4**-406
Kriz Jr., G.S. **6**-80
Krogh-Jespersen, K. **2**-224, **2**-232, **5**-366, **5**-389, **5**-400, **5**-402, **5**-416, **15**-2479
Krogh, E.T. **2**-441
Krogh, J.A. **16**-96
Krois, D. **16**-44
Kromhout, R.A. **3**-12
Krompiec, M. **15**-158
Krompiec, S. **15**-158
Kronenberg, W.J. **4**-318
Kronenburg, C.M.P. **13**-732
Kroner, J. **2**-247
Krongauz, E.S. **19**-547
Kronja, O. **4**-360, **5**-103, **5**-104, **10**-147, **10**-155
Kroon, J. **3**-29, **3**-54
Kropp, P.J. **15**-166, **15**-1872, **18**-569, **18**-919, **18**-922, **19**-737
Kroto, H.W. **2**-392
Krough-Jespersen, K. **18**-93
Krout, M. **8**-92
Kroutil, W. **16**-362, **19**-217, **19**-993
Krow, G. **4**-15, **4**-102
Krow, G.R. **18**-247, **18**-321, **18**-352, **18**-380, **18**-673
Krstulović, A.M. **4**-176
Krubiner, A. **19**-1594
Kruck, P. **19**-315
Krueger, C.A. **16**-1540
Krug, C. **12**-345
Kruger, A.W. **4**-396, **12**-107
Krüger, C. **2**-357
Krüger, C.M. **15**-1961
Krüger, H. **6**-58
Kruger, T.L. **8**-66, **8**-71
Kruizinga, W.H. **10**-719
Kruk, C. **8**-35
Krumpe, K.E. **12**-364
Krumper, J.R. **16**-986
Krupicka, J. **17**-28
Kruppa, G.H. **5**-87
Kruse, C.G. **4**-95, **7**-128
Kruse, C.W. **15**-364
Kruse, L.I. **6**-18, **6**-21, **11**-64
Krusic, P.J. **5**-295
Kryger, L. **10**-8
Krygowski, T.M. **2**-61, **2**-74, **2**-98, **2**-124, **2**-153, **2**-207, **8**-189
Krylov, E.N. **11**-673
Kryshtal, G.V. **15**-1032
Krysiak, J. **16**-2255
Krzemiński, M.P. **19**-971
Kshirsagar, S.W. **19**-616
Ku, A.T. **5**-32
Ku, A.Y. **18**-911
Ku, B. **16**-195
Ku, C.-K. **14**-375
Ku, Y.-Y. **16**-240
Kuang, C. **14**-469, **14**-481, **17**-384
Kuang, K. **10**-124
Kuang, L. **13**-279
Kuang, Y.-Q. **15**-1846
Kuang, Y.-Y. **16**-313, **18**-878
Kuang, Y. **15**-1829
Kuar, K.P. **10**-505
Kubo, A. **4**-202
Kubo, M. **2**-357
Kubo, T. **11**-672, **15**-1907
Kubo, Y. **19**-874
Kubota, A. **11**-256
Kubota, H. **4**-202, **11**-565
Kubota, K. **11**-166, **16**-275, **16**-781
Kubota, N. **15**-660
Kubota, S. **5**-298, **15**-995
Kubota, Y. **13**-678, **13**-679
Kubu, M. **16**-1165
Kucejko, R.J. **15**-768
Kucerovy, A. **12**-598
Kuchar, E.J. **15**-1652
Kucher, R.V. **15**-1878
Kuchitsu, K. **1**-79, **4**-329
Kuck, D. **4**-455
Kuck, V.J. **2**-260, **5**-365
Kucsman, Á **10**-33
Kuczkowski, R.L. **1**-55, **19**-340, **19**-347, **19**-359, **19**-363, **19**-364, **19**-365, **19**-366, **19**-369
Kudian, A.K. **1**-42
Kudo, K. **13**-677, **16**-1085, **18**-130
Kudo, N. **13**-517
Kudo, T. **11**-329, **15**-587, **15**-588, **19**-1060, **19**-1061, **19**-1062
Kudoh, M. **12**-338
Kudryavtsev, R.V. **18**-948
Kuebrich, J.P. **16**-1584
Kuehne, M.E. **4**-134, **10**-1785, **10**-1792, **15**-2575
Kuenkel, A. **10**-1718
Kuethe, J.T. **9**-112
Kugatova-Shemyakina, G.P. **4**-273
Kuhakarn, C. **19**-267
Kühle, E. **14**-293, **15**-1731
Kuhler, J.L. **16**-416
Kuhlmann, H. **15**-1462, **15**-1487, **16**-722, **16**-1587
Kuhlmann, K.F. **11**-152

Kuhn, A. **5**-439
Kuhn, C. **12**-106
Kühn, F.E. **16**-1436
Kuhn, H.J. **14**-250, **14**-263
Kuhn, S.J. **11**-14, **11**-26, **11**-27, **11**-28, **11**-140, **11**-316, **11**-357, **11**-485, **11**-518, **16**-1996, **16**-1997
Kühnau, D. **10**-992
Kuhnen, F. **14**-475
Kuhnert, N. **7**-119, **15**-992, **15**-1246
Kuil, M. **15**-1609
Kuivila, H.G. **12**-660, **18**-452, **18**-452, **19**-975, **19**-1294
Kuki, A. **10**-1680
Kukolja, S. **10**-1037
Kukreja, G. **19**-1164, **19**-1305
Kukuhara, T. **10**-1103
Kukui, Y. **10**-1991
Kukushkin, V.Yu. **19**-1583
Kulak, A.N. **15**-248
Kulandainathan, M.A. **11**-227
Kulangiappar, K. **11**-227
Kul'bovskaya, N.K. **15**-294
Kulczycki Jr., A. **15**-2535
Kulganek, V.V. **15**-1032
Kulicke, K. J. **5**-185
Kulik, N.I. **10**-40, **10**-437
Kulinkovich, O.G. **10**-1779, **10**-1570, **11**-511
Kulkarni, M.G. **19**-137
Kulkarni, R.S. **18**-395
Kulkarni, S.J. **11**-251, **11**-253, **11**-285, **11**-295
Kulkarni, S.U. **10**-1180, **15**-680, **15**-694, **15**-695, **15**-700, **15**-711, **18**-476, **18**-480
Kulp, S.S. **19**-433
Kumada, M. **10**-712
Kumada, M. **10**-1309, **10**-1317, **10**-1387, **10**-1388, **10**-1389, **10**-1614
Kumadaki, I. **10**-543, **15**-1468, **15**-2469, **18**-686
Kumagai, N. **15**-1034, **15**-1122, **16**-940, **16**-1090, **16**-1216, **16**-1523, **19**-1654
Kumagai, T. **7**-62
Kumamoto, T. **10**-993, **15**-1254
Kumar, D.K. **12**-768
Kumar, A. **10**-670, **13**-19, **13**-115, **15**-1439, **15**-1900, **15**-2210, **15**-2227, **16**-800, **18**-371, **19**-103
Kumar, A.R. **16**-1865
Kumar, A.V. **13**-151, **19**-787
Kumar, B.A. **16**-2283
Kumar, C.V. **14**-436, **15**-2464
Kumar, D. **14**-94, **18**-527, **19**-28
Kumar, E.V. **16**-574
Kumar, G. **12**-742
Kumar, G.A. **3**-45
Kumar, G.D.K. **10**-1004
Kumar, G.M. **10**-1656, **10**-1009, **11**-192, **16**-1563
Kumar, H.M.S. **10**-894, **16**-295, **16**-980, **16**-1235, **18**-328, **18**-642, **18**-699
Kumar, J.S.D. **15**-1391, **19**-1208
Kumar, K.A. **16**-1879, **16**-1937
Kumar, K.S.R. **15**-194
Kumar, K.V. **16**-1087
Kumar, M. **10**-1241
Kumar, M.P. **10**-1618, **18**-153, **16**-1858, **19**-1100
Kumar, N. S. **4**-165
Kumar, N.V. **4**-142
Kumar, P. **10**-1134
Kumar, P. **15**-300, **19**-77, **19**-158
Kumar, R. **9**-109, **14**-399, **15**-1441, **16**-122
Kumar, R.K. **15**-1811
Kumar, S. **16**-567, **16**-568
Kumar, S.P. **11**-459
Kumar, V. **11**-397, **16**-194, **16**-568
Kumar, V.A. **16**-7
Kumar, V.N. **16**-330
Kumaragurubaran, N. **12**-156, **16**-364, **16**-826
Kumaran, G. **17**-156
Kumaran, R.S. **19**-1037
Kumareswaran, R. **16**-1722, **19**-583
Kumata, Y. **4**-12
Kumbar, S.M. **15**-368
Kume, A. **11**-686, **11**-694
Kümin, A. **12**-35
Kumli, K.F. **16**-1356
Kümmerlin, M. **4**-399
Kumobayashi, H. **14**-268, **19**-1016
Kumps, L. **16**-1295
Kunai, A. **10**-1192, **10**-1888, **14**-223, **14**-227, **19**-611
Kunda, S.A. **12**-521
Kündig, E.P. **15**-2144, **15**-2694
Kundu, A. **16**-1432
Kundu, D. **16**-1865
Kundu, K. **15**-1485
Kundu, M.K. **16**-795, **19**-1036
Kundu, N.G. **10**-1912, **13**-418, **16**-2041
Kunerth, D.C. **10**-717
Kunesch, E. **12**-685
Kunesch, N. **10**-1601
Kung, D.W. **10**-1766
Kung, L.-R. **15**-1178
Küng, W. **18**-51
Kunii, H. **15**-123
Kunimitsu, K. **9**-135
Kunin, A.J. **12**-778
Kuninobu, Y. **10**-1908, **15**-408, **16**-2137
Kunisada, H. **10**-1381
Kunishima, M. **10**-872, **16**-1938, **18**-778, **19**-1561
Kunitake, K. **12**-575
Kuniyasu, H. **10**-1362, **10**-1388, **12**-791, **14**-414, **15**-304, **15**-313, **15**-321
Kunshenko, B.V. **16**-442
Kuntz, K.W. **16**-1540
Kunwar, A.C. **15**-2462, **16**-1555
Kunz, H. **15**-1217, **16**-2262
Kunz, K. **13**-125
Kunz, R.K. **16**-1479
Kunzer, A. **12**-317
Künzer, H. **15**-2265
Kuo, C.-W. **15**-1445, **16**-303
Kuo, H. **12**-523
Kuo, Y. **16**-2155
Kuok, M. **4**-304
Kupczyk-Subotkowska, L. **18**-693
Kuperman, J. **8**-89
Kurahashi, T. **13**-449
Kuranov, G.L. **7**-123
Kurashima, F. **19**-665
Kurata, K. **19**-1525
Kurchan, A.N. **10**-836
Kurek, J.T. **15**-183, **15**-263
Kureshy, R.I. **15**-1979
Kuribayashi, M. **16**-1166
Kurihara, A. **16**-342
Kurihara, H. **14**-457, **15**-2192
Kurihara, K. **10**-1373
Kurihara, M. **12**-328, **16**-133, **16**-1136
Kurihara, T. **13**-824, **16**-1494
Kurimoto, M. **10**-1960
Kurita, J. **16**-2040
Kurita, K. **16**-1871
Kurita, T. **14**-356
Kurita, Y. **4**-78, **16**-967
Kuriyama, M. **13**-495, **15**-1204, **16**-759, **16**-933
Kurland, R.J. **5**-92
Kuroboshi, M. **10**-1276, **13**-308, **15**-1669, **16**-695
Kuroda, J. **13**-452
Kuroda, K. **15**-2357
Kuroda, M. **13**-323
Kuroda, S. **2**-332, **2**-333, **2**-335, **2**-359
Kuroda, T. **16**-1172, **16**-693
Kuroda, Y. **3**-84, **3**-183, **11**-672
Kuroiwa, T. **19**-993
Kurokawa, T. **15**-563
Kuroki, T. **10**-851
Kuroki, Y. **16**-779
Kurono, N. **12**-661, **13**-460, **16**-1506
Kurosa, M. **16**-630
Kurosawa, H. **12**-791, **15**-859
Kurosawa, K. **11**-515, **15**-2359
Kurosawa, S. **15**-175
Kurosu, M. **10**-881
Kuroyanagi, M. **19**-974
Kurozumi, S. **12**-258, **14**-401
Kurreck, H. **5**-218
Kurreck, H. **7**-6

Kursanov, D.N. **2**-177, **10**-1454, **15**-499, **15**-501, **15**-750, **15**-2532, **16**-162, **19**-1341
Kürshner, U. **2**-357
Kurt, R. **15**-2224
Kurth, M.J. **10**-1676, **14**-346, **17**-265, **19**-1022
Kurth, T. L. **2**-244
Kürti, L. **15**-1981
Kurts, A.L. **10**-509, **10**-515, **10**-520, **10**-798, **10**-1163
Kurtz, K.C.M. **10**-1051
Kurukulasuriya, R. **16**-1740
Kurumizawa, S. **15**-1718
Kurushima, H. **15**-1281
Kurusu, T. **16**-2279
Kurusu, Y. **10**-942, **16**-464, **16**-590, **16**-612, **16**-642
Kurz, J.L. **8**-120, **10**-530
Kurzawa, J. **17**-49
Kurzer, F. **16**-2187
Kusabayashi, S. **10**-234, **10**-1394, **15**-2115
Kusaka, C. **19**-1561
Kusaki, I. **16**-1723
Kusakin, M.S. **16**-1967
Kusama, H. **11**-330, **15**-954, **15**-2116, **15**-560
Kusano, K. **13**-684
Kusche, A. **18**-784
Kushino, Y. **10**-1995
Kusmic, D. **12**-623
Kustanovich, Z. **4**-175
Kusuda, K. **19**-1339, **19**-1398
Kusui, K. **19**-1077
Kusumoto, H. **3**-66
Kutateladze, A.G. **10**-836, **15**-1294, **15**-2003, **16**-2208
Kutchan, T.M. **18**-606
Kutepow, N.V. **15**-2586
Kutsuwa, E. **12**-457
Kutyrev, A.A. **15**-40
Kutzelnigg, W. **2**-13
Kuwabara, K. **19**-239
Kuwabara, S. **15**-856
Kuwabara, T. **14**-268, **19**-559
Kuwabe, S.-i. **13**-132
Kuwahara, A. **13**-220
Kuwajima, I. **15**-999, **10**-1431, **10**-1675, **10**-1757, **15**-1139, **15**-1139, **16**-483, **16**-699, **16**-1061, **16**-1228, **19**-507
Kuwamura, T. **10**-290
Kuwano, R. **10**-1541, **13**-186, **13**-531, **15**-560, **15**-563, **18**-725
Kuwata, K.T. **15**-994
Kuwjima, I. **13**-655
Kuzmanova, R.B. **9**-23
Kuz'min, V.A. **5**-320, **5**-332, **7**-9
Kuznetsov, D.V. **7**-123, **14**-148
Kuznetsov, L.L. **12**-744
Kuznetsov, M.A. **5**-427
Kuznetsova, T.S. **10**-1683
Kvaran, A. **4**-384
Kveseth, K. **4**-295
Kvícala, J. **10**-1104
Kvick, A. **1**-83.
Kwa, T.L. **10**-1288
Kwak, J. **18**-888
Kwak, J.M. **16**-1496
Kwak, K.H. **10**-1086
Kwak, Y. **19**-112
Kwan, L.C.H. **15**-2252
Kwan, T. **4**-179
Kwart, H. **2**-91, **6**-49, **6**-66, **12**-176, **14**-103, **15**-581, **15**-1875, **15**-2278, **16**-1568, **16**-2166, **17**-15, **17**-33, **17**-76, **17**-78, **17**-495, **18**-752, **18**-753, **18**-795, **18**-799, **19**-94
Kwart, L.D. **14**-103
Kwast, A. **13**-756
Kwiatkowski, D. **16**-638
Kwiatkowski, G.T. **16**-1375
Kwiatkowski, P. **16**-624
Kwok, F.C. **2**-458
Kwok, W.K. **17**-60
Kwon, D.W. **10**-763, **10**-1224, **16**-548
Kwon, H.B. **10**-1461
Kwon, H.S. **13**-334
Kwon, K.M. **3**-128
Kwon, M.S. **10**-1723, **16**-239
Kwon, O. **15**-1418, **16**-1357, **17**-318
Kwon, O.O. **19**-1095, **19**-1098, **19**-1178
Kwon, S. **10**-1766
Kwon, T.W. **15**-1183, **16**-1326
Kwong, C.K.-W. **15**-154
Kwong, F.-Y. **13**-198, **13**-249, **13**-291, **13**-495, **13**-516, **13**-661, **15**-1539
Kwong, H.-L. **15**-1832, **15**-1835, **15**-1843, **15**-2068, **19**-468
Kyba, E.P. **5**-438
Kyler, K.S. **10**-1695, **14**-429, **19**-1402
Kyoda, M. **15**-1453
Kyong, J.B. **10**-70
Kyriakou, G. **13**-613
Kyrtopoulos, S.A. **12**-736
Kyung, S. **16**-655, **16**-657
Kyung, S.H. **16**-608
Kyushin, S. **5**-258

La Belle, B.E. **19**-864
La Chapelle, E. **11**-258
la Cour, T.V. **15**-775
La Londe, R.T. **14**-459
La Rochelle, L.K. **16**-681
La Rosa, C. **10**-1041
La, B. **19**-1008
Laali, K. **8**-26, **10**-421, **12**-357, **18**-35
Laali, K.K. **2**-70, **11**-23, **11**-123, **11**-133, **15**-1641, **19**-465
Laan, J.A.M. **11**-361, **19**-50, **19**-337
Laane, J. **4**-365
Laane, R.W.P.M. **15**-1911
Laarhoven, W.H. **4**-70, **4**-72, **18**-506, **18**-547, **18**-549, **18**-552
Laba, V.I. **15**-294
Labadie, J. **16**-335, **16**-1857
Labadie, J.W. **16**-2032
Labadie, S.S. **10**-1969, **16**-1061, **16**-2308, **18**-146
Labar, D. **18**-134
Labastida, V. **4**-340
Labaudiniere, R. **10**-816
L'Abbé, G. **5**-436
Labeish, N.N. **15**-1740
Labelle, M. **16**-1948
Labiad, B. **16**-1827
Labinger, J.A. **19**-15
Labo, A.M. **15**-2051
Labonne, A. **10**-1362, **15**-221
Laboureur, J.L. **18**-134, **18**-245, **18**-245
Labrouillère, M. **10**-1152
Labunskaya, V.I. **18**-535
Lacasse, M.-C. **15**-2560
Lacey, J.R. **16**-163
Lacey, R.N. **16**-1703
Lachance, A. **12**-684
Lachance, H. **16**-750
Lacher, B. **14**-476
Lachhein, S. **15**-92, **15**-1306
Lachkar, A. **8**-101
Lacie, C. **16**-560
Lacourt, A. **15**-1706
Lacroix, D. **10**-853
Lacroix, T. **10**-951
Ladenheim, H. **16**-1689
Ladjama, D. **12**-325
Laemmle, J. **16**-512, **16**-513, **16**-514, **16**-515
Laemmle, J.T. **4**-141, **16**-5
Laera, S. **13**-382
Laferriere, M. **5**-119
Lafferty, W.J. **1**-55
Laffitte, J. **17**-351
Lafont, F. **13**-544
Lafontaine, J.A. **10**-1744
Lafortune, M.C. **18**-744
Laganis, E.D. **2**-167, **15**-1947
Lago, J.M. **16**-1773
Lagow, R.J. **14**-150
Lagowski, J.M. **13**-76, **19**-756, **19**-1526
Lahav, M. **4**-104, **4**-195
Lahiri, K. **13**-486, **15**-2681
Lahmann, M. **10**-1189
Lahoti, R.J. **11**-242, **13**-592
Lahousse, F. **15**-2388, **15**-2432, **17**-361
Lahrache, H. **15**-970
Lahti, M.O. **10**-567
Lahti, P.M. **5**-307
Lai, C. **16**-1695

Lai, C.W. **13**-249
Lai, G.-Q. **4**-155, **16**-165
Lai, G. **16**-1208, **18**-749
Lai, H. **16**-675
Lai, J.T. **16**-241
Lai, K.W. **15**-868
Lai, R.-Y. **19**-388
Lai, Y. **12**-610, **12**-631
Lai, Y.-C. **13**-495
Lai, Y. **2**-140, **10**-1577, **19**-1683
Lai, Y.H. **2**-308
Lai, Z. **6**-92, **10**-445
Laicher, F. **10**-1528
Laidig, K. **15**-144
Laidig, K.E. **4**-288, **8**-210, **10**-213
Laidlaw, G.M. **4**-529
Laidler, K.J. **1**-101, **6**-8, **6**-53
Lail, M. **15**-965
Laila, A.H. **12**-39
Laine, R.M. **15**-462, **19**-282
Laing, M. **1**-93
Laity, J.L. **2**-107
Lajis, N. Hj. **16**-505
LaJohn, L.A. **5**-127
Lajunen, M. **10**-191, **10**-652
Lake, J.F. **15**-798
Lakhdar, S. **10**-399
Lakhvich, F.A. **19**-1424
Lakminarayana, B. **19**-1256
Lakouraj, M. **16**-1721
Lakouraj. M.M. **10**-923, **16**-211, **16**-1735, **19**-776
Lakritz, J. **18**-311
Lakshimaiah, G. **10**-1283
Lakshmi, A.B. **15**-2462
Lakshmi, B. **3**-41
Lakshminarayana, V. **16**-1685
Lal, G.S. **12**-463
Lal, J. **18**-882
Lalancette, J.M. **12**-684
Lalic, G. **10**-1645, **15**-1280
Lalitha, A. **16**-2179
Lalitha, P. **19**-791
Lallemand, J.Y. **10**-1801
Laloi-Diard, M. **10**-386
Laloi, M. **10**-388
LaLonde, R.L. **15**-416
LaLonde, R.T. **4**-265, **16**-1979
Lam, B. **10**-204
Lam, C.H. **14**-443
Lam, C.S.-L. **15**-154
Lam, H. **10**-714
Lam, H.W. **15**-1341
Lam, J.N. **12**-427
Lam, K.H. **15**-1997
Lam, L.K.M. **10**-66
Lam, L.K.M. **10**-296
Lam, P.Y.S. **13**-239
Lam, Y. **15**-622
Lamarque, L. **15**-1039, **15**-2091
Lamartine, R. **3**-130
Lamaty, F. **13**-397, **13**-611, **16**-955, **19**-760
Lamaty, G. **10**-568, **16**-188, **19**-923, **19**-998
Lamb, J.D. **3**-110
Lamb, J.T. **10**-151
Lambert, A. **18**-385
Lambert, C. **8**-123
Lambert, D. **19**-1773
Lambert, D.M. **19**-1768
Lambert, G.J. **14**-421
Lambert, J.B. **1**-94, **2**-231, **2**-423, **2**-426, **4**-34, **4**-362, **4**-366, **4**-367, **5**-29, **5**-57, **5**-362, **10**-124, **10**-154, **10**-160, **15**-140, **15**-2493, **15**-2538
Lambert, R.M. **13**-613, **15**-452
Lamberti,V. **16**-1762
Lambrechts, H.J.A. **11**-202
Lambrechts, H.J.A. **8**-36
Lamei, W. **10**-709
Lamidey, A.-M. **10**-995
Lamm, B. **10**-1677
Lammer, O. **17**-420
Lammert, S.R. **10**-1037
Lammertsma, K. **2**-475, **2**-478, **5**-2, **11**-206
Lamoreaux, M.J. **15**-1993
Lamothe, S. **10**-1685
Lamoureux, C. **19**-1211
Lampe, J. **12**-330
Lampman, G.M. **4**-456, **10**-1302
Lamrani, M. **16**-607
Lämsä, M. **3**-179
Lamson, D.W. **10**-1396, **19**-1721
Lamy-Pitara, E. **15**-447
Lan, J.-B. **13**-222
Lan, J. **13**-129
Lan, P. **16**-1899
Lana, J.C.A. **16**-1888
Lanari, S. **19**-1254
Lancaster, N.L. **11**-131
Lancelot, C.J. **10**-66, **10**-171, **10**-175, **10**-177, **10**-296
Lancelot, L.A. **10**-166
Land, D.P. **19**-17
Landa, A. **15**-1106
Landais, Y. **10**-866
Landau, R.L. **5**-228
Landau, R.N. **15**-460
Landell, R.G.M. **13**-36
Lander Jr., S.W. **15**-2105
Landesberg, J.M. **3**-97
Landesman, H. **10**-1791
Landgrebe, J.A. **12**-17
Landgrebe, K. **15**-2093
Landini, D. **10**-321, **10**-368, **10**-484, **10**-487, **10**-994, **10**-1033, **10**-1126, **10**-1182, **15**-172, **17**-373, **18**-344, **19**-105, **19**-1241
Landis, C.A. **15**-2621, **18**-525
Landis, C.R. **15**-1613, **15**-1615
Landis, M.E. **15**-2366, **15**-2467
Landis, P.S. **18**-934, **18**-938
Landmesser, N.G. **18**-249
Lando, V.R. **13**-308, **13**-539
Landon, S.J. **16**-1364
Landor, P.D. **17**-386
Landor, S.R. **4**-67, **15**-107, **15**-110, **15**-1678, **15**-1963, **15**-2256, **15**-2389, **15**-2495, **17**-386
Landré, P.D. **15**-988
Landry, S.R. **15**-1377
Landwehr, M. **19**-500
Lane, B.S. **13**-517, **15**-1883
Lane, C.F. **12**-513, **15**-670, **16**-339, **19**-851, **19**-858, **19**-967, **19**-1138
Lane, G.C. **4**-126
Lane, J.F. **18**-294
Laneman, S. **13**-245
Lang-Anderson, M.M.S. **15**-913
Lang, D. **15**-2184, **15**-2289
Lang, E.S. **19**-1405
Lang, F. **10**-638
Lang, J. **15**-648
Lang, K. **19**-830
Láng, K.L. **10**-406
Lang, R.W. **12**-142
Langa, F. **7**-118, **15**-2203, **18**-917
Lange, B.C. **5**-134, **5**-198, **5**-199, **10**-360, **10**-515
Lange, D.A. **19**-1027
Lange, G. **5**-158
Lange, G.L. **19**-374
Lange, H. **4**-258, **4**-511, **18**-668
Lange, J.H.M. **7**-128
Lange, P.P. **11**-658, **16**-1893
Lange, U.E.W. **19**-1119
Langemann, K. **18**-849, **18**-876
Langensee, P. **2**-282
Langer, F. **15**-1214
Langer, P. **16**-1161
Langer, V. **4**-55
Langhals, E. **10**-1705, **15**-2128
Langhals, H. **10**-459, **10**-1705
Langille, J.D. **16**-277
Langille, N.F. **10**-583
Langkopf, E. **18**-612
Langle, S. **10**-1883
Langler, R.F. **2**-211, **15**-2305, **19**-1588
Langlois, B.R. **11**-512
Langshaw, J. **14**-115
Langstrom, B. **9**-115
Lankin, D.C. **19**-258
Lanneau, G.F. **19**-1083, **19**-1091
Lanni, E.L. **18**-368
Lannou, M.-I. **16**-2103, **19**-1629
Lansbury, P.T. **5**-443, **18**-355, **18**-445, **19**-914
Lansinger, J.M. **16**-437
Lansky, A. **16**-1936
Lanter, J.C. **18**-129
Lantos, D. **19**-126
Lanz, K. **2**-183
Lanz, M. **19**-1483, **19**-1484
Lanzalunga, O. **14**-15, **18**-55
Lapachev, V.V. **2**-476

Lapekas, S.P. **16**-1916
Lapenue, M. **10**-1940
Lapeva, T. **18**-835
Lapidus, A.L. **10**-1994, **15**-1494, **16**-863
Lapierre, A.J.B. **13**-435, **15**-1342
Lapin, Yu.A. **15**-2003
Lapkin, A.A. **16**-116
Laporterie, A. **7**-120, **11**-218, **16**-2142, **19**-1300
Lapouyade, R. **10**-1940
Lappert, M.F. **12**-471, **12**-490, **16**-1586, **18**-896
Lapworth, A. **16**-1520, **16**-1585
Lara, R.G. **15**-314
Laramay, S. **10**-339
Larchar, A.W. **16**-185
Larchevêque, M. **10**-1623, **16**-2282, **17**-451, **19**-506
Lardelli, G. **16**-1762
Lardicci, L. **15**-378, **16**-2016, **17**-380, **19**-1105
Large, R. **14**-319
Large, S.E. **10**-1536
Larhed, M. **7**-123, **7**-125, **7**-126, **10**-781, **11**-544, **11**-545, **12**-272, **12**-273, **12**-298, **13**-219, **13**-382, **13**-397, **13**-408, **13**-409, **13**-416, **13**-422, **13**-671, **13**-683, **16**-453, **16**-1952
Larichev, V. **16**-1748
Larichev, V.S. **16**-1518
Larionov, O.V. **12**-780
Larkin, D.R. **19**-675
Larksarp, C. **16**-168
Larkworthy, L.F. **13**-781
Larmanjat, B. **16**-1460
Laroche, C. **10**-1916, **15**-912, **15**-2673
LaRochelle, L.K. **16**-675
Larock, R.C. **10**-246, **10**-604, **10**-671, **10**-717, **10**-982, **10**-990, **10**-1095, **10**-1116, **10**-1119, **10**-1289, **10**-1304, **10**-1332, **10**-1333, **10**-1364, **10**-1406, **10**-1598, **10**-1626, **10**-1639, **10**-1665, **10**-1681, **10**-1684, **10**-1695, **10**-1696, **10**-1697, **10**-1713, **10**-1763, **10**-1775, **10**-1803, **10**-1807, **10**-1845, **10**-1974, **11**-224, **11**-416, **11**-431, **11**-467, **11**-485, **11**-566, **11**-583, **11**-662, **12**-56, **12**-110, **12**-180, **12**-244, **12**-321, **12**-336, **12**-498, **12**-505, **12**-506, **12**-556, **12**-559, **12**-567, **12**-587, **12**-683, **12**-724, **13**-257, **13**-280, **13**-319, **13**-368, **13**-375, **13**-428, **13**-433, **13**-467, **13**-480, **13**-587, **13**-681, **13**-693, **13**-743, **14**-144, **14**-230, **14**-270, **14**-273, **14**-411, **14**-426, **14**-427, **14**-431, **14**-442, **14**-472, **15**-164, **15**-182, **15**-186, **15**-201, **15**-239, **15**-261, **15**-266, **15**-273, **15**-274, **15**-282, **15**-373, **15**-383, **15**-414, **15**-468, **15**-538, **15**-592, **15**-608, **15**-640, **15**-674, **15**-959, **15**-977, **15**-990, **15**-1124, **15**-1136, **15**-1139, **15**-1160, **15**-1165, **15**-1283, **15**-1287, **15**-1526, **15**-1636, **15**-1680, **15**-1699, **15**-1708, **15**-1710, **15**-1789, **15**-1868, **15**-2007, **15**-2169, **15**-2371, **15**-2470, **15**-2481, **15**-2482, **15**-2586, **15**-2587, **15**-2618, **15**-2624, **15**-2625, **15**-2626, **16**-99, **16**-106, **16**-141, **16**-323, **16**-432, **16**-471, **16**-481, **16**-556, **16**-904, **16**-1009, **16**-1112, **16**-1124, **16**-1245, **16**-1289, **16**-1311, **16**-1337, **16**-1342, **16**-1438, **16**-1545, **16**-1575, **16**-1622, **16**-1682, **16**-1724, **16**-1737, **16**-1760, **16**-1784, **16**-1810, **16**-1824, **16**-1914, **16**-1937, **16**-1964, **16**-1989, **16**-1994, **16**-2028, **16**-2056, **16**-2117, **16**-2216, **17**-159, **17**-203, **17**-211, **17**-240, **17**-296, **17**-302, **17**-314, **17**-332, **17**-374, **17**-395, **17**-429, **17**-474, **17**-477, **18**-140, **18**-160, **18**-222, **18**-378, **18**-477, **18**-488, **18**-633, **18**-776, **19**-25, **19**-40, **19**-55, **19**-63, **19**-78, **19**-303, **19**-308, **19**-374, **19**-432, **19**-564, **19**-614, **19**-634, **19**-644, **19**-646, **19**-664, **19**-669, **19**-688, **19**-860, **19**-878, **19**-919, **19**-1010, **19**-1052, **19**-1066, **19**-1083, **19**-1091, **19**-1107, **19**-1161, **19**-1174, **19**-1191, **19**-1225, **19**-1247, **19**-1277, **19**-1287, **19**-1336, **19**-1350, **19**-1361, **19**-1372, **19**-1374, **19**-1420, **19**-1461, **19**-1472, **19**-1545, **19**-1563, **19**-1628, **19**-1684, **19**-1700, **19**-1743
Larouche, D. **15**-932
Larrahondo, J. **17**-494
Larrégaray, P. **6**-47
Larrosa, I. **19**-600
Larsen, A.S. **9**-123
Larsen, D.S. **15**-74, **15**-1734
Larsen, D.T. **17**-98
Larsen, D.W. **15**-58
Larsen, J. **15**-949, **19**-281
Larsen, J.W. **5**-96, **10**-96, **10**-461, **10**-475, **11**-114
Larsen, R.D. **15**-466
Larsen, S. **19**-504
Larson, E.G. **5**-362
Larson, G.L. **6**-19, **10**-1750, **14**-190
Larson, H.O. **10**-1055, **12**-213, **19**-616, **19**-741
Larson, J.K. **16**-2150
Larson, K.D. **19**-275
Larsson, E.M. **14**-274
Lasemi, Z. **10**-1135
Lash, T.D. **3**-139
Lashley, J.C. **19**-455
Laskar, D.D. **10**-868, **16**-201, **16**-922, **16**-977, **16**-1309, **16**-2110
Laskar, S. **16**-1865
Laskovics, F.M. **16**-42
Lasne, M.-C. **16**-430, **16**-1876, **16**-2016
Lasne, M. **2**-468, **15**-2278
Lasne, M.C. **16**-238
Laso, A. **16**-1213
Laso, N.M. **15**-1451
Lasperas, M. **16**-516
Lassaletta, J.-M. **19**-292
Lassaletta, J.M. **5**-372
Last, L.A. **18**-541
Lastomirsky, R.R. **18**-397
Laszlo, P. **1**-36, **8**-161, **11**-358, **15**-1917, **16**-1930, **18**-192
Lathan, W.A. **1**-55
Lathioor, E.C. **7**-40
Latif, N. **17**-227
Latourette, H.K. **11**-469
Lattanzi, A. **15**-232, **15**-1883, **16**-815
Lattes, A. **10**-1060, **15**-325, **15**-329, **16**-1066
Latxague, L. **13**-82
Latypov, S.K. **4**-110, **4**-112
Latypova, F.M. **10**-1454
Lau, C.D.H. **4**-421, **4**-425, **4**-440
Lau, C.J. **4**-196
Lau, C.P. **13**-198, **13**-495, **13**-516, **16**-577
Lau, K.-C. **19**-723
Lau, K.C.Y. **12**-264, **17**-330
Lau, T.-C. **15**-1809, **19**-492
Lau, W. **13**-749
Lau, Y.K. **8**-239, **8**-240
Lau. C.-P. **13**-291
Laube, T. **2**-424, **5**-8, **5**-87, **5**-134, **5**-201, **10**-145, **16**-6
Laue, P. **12**-503
Lauens, M. **10**-1615
Lauenstein, O. **14**-163, **14**-169
Lauer, R.F. **12**-254, **17**-293
Lauer, W. **12**-676
Lauer, W.M. **18**-759
Laufer, A.H. **5**-355
Laugal, J.A. **15**-582
Lauransan, J. **3**-19
Laureillard, J. **10**-93
Laurence, C. **1**-54, **3**-19, **8**-101, **8**-102, **8**-104, **8**-105, **8**-106, **8**-107, **10**-461
Laurent, A. **12**-226, **18**-33
Laurent, A. **19**-1236
Laurent, I. **18**-821
Laurent, P. **10**-1965
Laurent, R. **7**-120
Laurenzo, K.S. **13**-765

Lauria, E. **15**-243
Laurie, V.W. **1**-41, **1**-55, **4**-486, **8**-250
Lauru, S. **11**-216
Lautens, M. **10**-1638, **13**-288, **13**-302, **13**-414, **13**-549, **13**-666, **15**-972, **17**-235, **18**-863, **19**-1366
Lauterbach, T. **13**-613
Laval, G. **12**-687
Lavandera, I. **16**-362, **19**-217, **19**-993
Lavenot, L. **13**-310
Lavieri, F.P. **18**-919
Lavigne, A. **19**-271
LaVilla, J.A. **5**-416
Lavis, J.M. **12**-266
Lavis, J.M. **13**-454
Lavrov, V.I. **10**-680, **15**-255
Law, K.-L. **16**-326, **16**-327
Lawesson, S.-O. **16**-224
Lawesson, S. **10**-948, **12**-461, **16**-216, **16**-217, **16**-224, **16**-1920, **18**-752
Lawler, M.J. **10**-1543, **16**-776
Lawler, R.G. **5**-228, **5**-229, **5**-231, **5**-232, **10**-1401, **10**-1395, **12**-657, **16**-191
Lawlor, D.A. **5**-82
Lawrence, J.P. **18**-807
Lawrence, K.E. **12**-640
Lawrence, L.M. **12**-635
Lawrence, N.J. **10**-1501, **16**-1405
Lawrence, R.M. **4**-186, **16**-412
Lawrence, S.E. **19**-800
Lawrie, C.J. **15**-2641
Lawrynowicz, W. **15**-2486
Laws, A.P. **11**-115
Lawson, A.J. **11**-159
Lawson, D.D. **2**-151
Lawson, E.C. **19**-922
Lawson, K.R. **3**-85
Lawson, R.C. **5**-222
Lawton, M. **10**-687, **10**-974
Laxman, E. **10**-581, **10**-1204
Laxman, N. **10**-1172
Laxmi, Y.R.S. **19**-868
Laye, P.G. **4**-243
Layek, S. **14**-482
Laynez, J. **8**-138, **8**-144
Lazar, L. **2**-486, **2**-487
Lazár, M. **14**-6, **14**-7
Lazareva, M.I. **19**-592
Lazaridis, N.V. **12**-168
Lazaris, A.Ya. **16**-119
Lazarus, M. **19**-477
Lazdins, I. **10**-72
Lazny, R. **16**-75, **16**-1074
Le Berre, A. **15**-361
Le Bideau, F. **16**-487
Le Bigot, Y. **16**-1384
Le Blanc, R. **13**-178
Le Borgne, J.F. **17**-451
Le Bras, G. **15**-214
Le Bras, J. **15**-450
Le Bris, A. **16**-319
Le Carpentier, J. **5**-64, **5**-75, **11**-480
Le Corre, M. **19**-1468, **19**-1493
Le Deit, H. **19**-1493
Le Drian, C. **13**-494, **13**-509, **13**-565, **18**-37
Le Fave, G.M. **10**-541
Le Fevre, R.J.W. **3**-104, **4**-292
Le Gall, T. **16**-1447
Le Gendre, P. **16**-575, **19**-981
Le Gras, J. **15**-2548
Le Grognec, E. **11**-258
Le Guen, J. **11**-53
Le Hénaff, P. **16**-38
Le Hyaric, M. **18**-928
Le Maistre, J.W. **17**-447
Le Marquand, P. **16**-1437
Le Maux, P. **15**-2525
Le Merrer, Y. **16**-1102
Le Moigne, F. **5**-224
le Noble, W.J. **6**-57, **9**-87, **10**-91, **10**-507, **10**-519, **10**-521, **10**-546, **15**-120, **15**-2208, **17**-71, **19**-1012
Le Perchec, P. **15**-991, **18**-720
Le Questel, J.-Y. **8**-101
Le Roux, C. **11**-438
Le Roux, E. **18**-873
Lê, L.T. **12**-421
Le, V.T. **10**-578
Le, Z.-G. **10**-900, **10**-1550, **16**-1884
Le, Z. **19**-242
Lea, L. **10**-1506
Leach, A.G. **15**-994, **15**-1029, **15**-1305, **16**-1848, **18**-605, **18**-638
Leach, D.R. **14**-431
Leach III, F.E. **2**-220
Leadbeater, N.E. **7**-118, **7**-126, **7**-127, **9**-138, **13**-267, **13**-288, **13**-674, **13**-506, **10**-1988, **13**-102, **13**-294, **13**-309, **13**-397, **13**-503, **13**-506, **13**-506, **13**-560, **13**-596
Leadbeater, N.W. **13**-278
Leader, H. **15**-525, **16**-2289
Leahy, D.K. **10**-622, **10**-1544
Leahy, J.W. **16**-791, **16**-800, **16**-813, **10**-1744
Leake, W.W. **13**-636
Leal, J.M. **8**-131
Leal, S. **13**-379
Leandri, E. **11**-244
Leão, R.A.C. **15**-2520
Leardini, R. **5**-331, **18**-73, **19**-1258
Learn, K. **19**-1363, **19**-1397, **19**-1471
Learn, K.S. **16**-462
Leathers, T. **19**-688
Leaver, D. **2**-348
Leavey, T. **13**-673
Lebedev, B.L. **15**-746
Lebedev, M.Y. **16**-2172
Lebel, H. **15**-2056, **16**-1435, **16**-1435, **18**-307
LeBel, N.A. **15**-55, **15**-127, **17**-3, **17**-250, **17**-260
Leber, P.A. **18**-508, **18**-594, **18**-619
Leber, W. **18**-679
Leblanc, J.C. **19**-1083
LeBlanc, R. **18**-645
Leblanc, Y. **15**-401
LeBlond, C. **15**-460
LeBras, J. **19**-467
Lebreton, C. **16**-916
Lebreton, J. **16**-687
Lebrilla, C.B. **15**-478
Lebrun, M.-E. **16**-1437
Leca, D. **15**-2623
Lecadet, D. **16**-1466
Lecce, L. **15**-126
Lecea, B. **15**-2119, **15**-2239, **16**-852
Lechevallier, A. **10**-571
Lechtken, P. **7**-44
LeClair, G. **15**-2203
Leclerc, E. **10**-873
Lécolier, S. **16**-430
Lecomte, F. **13**-336
Lecomte, J.-P. **7**-80
Lecomte, L. **10**-605
Lecomte, V. **16**-487
Leconte, M. **18**-807, **18**-842
Lecourt, T. **12**-331
Lectard, S. **15**-2056
Lectka, T. **3**-67, **3**-68, **12**-49, **12**-125, **12**-175, **15**-2249, **15**-2386, **16**-2226, **16**-2228, **16**-2229, **16**-2230, **17**-322
Lectka, T. **19**-1682
L'Ecuyer, P. **13**-846
Led, J.J. **3**-83
Ledaal, T. **17**-523
Lededev, B.A. **12**-745
Lederer, M. **15**-1707
Ledlie, D.B. **15**-1148, **18**-52
Lednicer, D. **16**-86
Ledon, H. **12**-220
Ledon, H.J. **15**-1917
Ledwith, A. **15**-2445, **17**-496
Lee-Ruff, E. **8**-23, **10**-312, **10**-317, **17**-511
Lee Jr., C.T. **9**-104
Lee, A.-L. **15**-157, **15**-1804
Lee, A. **16**-1845
Lee, A.F. **13**-493
Lee, A.S.-Y. **16**-1001, **16**-1746
Lee, A.S. **15**-1083
Lee, B.S. **15**-1847
Lee, B.-S. **10**-22, **10**-60
Lee, B. **17**-524
Lee, B.C. **10**-330
Lee, C.-L.K. **16**-895
Lee, B.M. **19**-1186

Lee, C.-H. **13**-307
Lee, C.-S. **15**-2068, **19**-558
Lee, C.-W. **19**-1313
Lee, C. **13**-732, **15**-415, **15**-868, **15**-868, **15**-1227, **19**-108
Lee, C.B. **16**-151, **16**-159
Lee, C.C. **2**-158, **10**-169, **10**-223, **10**-223, **11**-384, **15**-138, **18**-2, **18**-22, **18**-24, **18**-26
Lee, C.G. **16**-366
Lee, C.K.Y. **15**-2126
Lee, C.S. **10**-1699, **14**-76
Lee, C.W. **18**-817, **18**-826, **18**-860, **18**-872
Lee, D.-H. **13**-494, **15**-2243
Lee, D.-M. **15**-876
Lee, D.-S. **15**-1210, **19**-1043
Lee, D.-Y. **13**-217
Lee, D. **13**-202, **15**-780, **15**-1030, **16**-352, **18**-735, **18**-877, **18**-889, **18**-890
Lee, D.C. **15**-849, **17**-447
Lee, D.G. **8**-34, **8**-43, **19**-42, **19**-64, **19**-95, **19**-104, **19**-108, **19**-117, **19**-122, **19**-375, **19**-377, **19**-389, **19**-394, **19**-401, **19**-411, **19**-434, **19**-556, **19**-579, **19**-645, **19**-668, **19**-708, **19**-808
Lee, D.F. **10**-818
Lee, D.R. **15**-1093
Lee, D.S. **19**-1190
Lee, E. **15**-1351, **15**-1489
Lee, E.H. **10**-852, **16**-1987
Lee, E.K.C. **7**-48
Lee, F.-Y. **16**-303
Lee, F.L. **4**-523
Lee, G. **4**-512
Lee, G.A. **19**-636
Lee, G.H. **15**-2521, **17**-528, **19**-945
Lee, G.K. **19**-751
Lee, G.M. **15**-1774
Lee, H.-W. **13**-201, **15**-1539
Lee, H.-Y. **15**-505
Lee, H.-C. **16**-1074, **16**-1075
Lee, H.-S. **16**-1511
Lee, H.-Y. **18**-889
Lee, H. **8**-170, **13**-348, **16**-599, **16**-1854, **16**-1912, **19**-554, **19**-1542
Lee, H.B. **10**-1141
Lee, H.D. **18**-480
Lee, H.G. **16**-667
Lee, H.J. **19**-1286
Lee, H.K. **17**-528
Lee, H.M. **13**-708
Lee, H.S. **16**-111, **19**-1178
Lee, H.T. **19**-1058
Lee, H.W. **5**-334, **9**-21, **10**-60, **10**-82, **10**-82, **10**-320, **16**-1959, **16**-2273
Lee, H.Y. **10**-607, **19**-1388
Lee, I.-M. **13**-494
Lee, I. **6**-28, **6**-29, **9**-21, **10**-22, **10**-56, **10**-60, **10**-82, **10**-320, **10**-330, **15**-148, **16**-1615, **16**-2273
Lee, I.H. **6**-31
Lee, I.S. **16**-841, **19**-1160
Lee, J.-H. **12**-305
Lee, J.-y. **13**-710
Lee, J.-Y. **16**-1959
Lee, J. **2**-472, **10**-530, **12**-759, **15**-2059, **18**-253, **19**-1342
Lee, J.B. **16**-1990, **18**-406, **19**-1292
Lee, J.C. **10**-606, **10**-718, **10**-1136, **12**-121, **12**-134, **19**-133, **19**-203, **19**-321, **19**-438, **19**-530, **19**-531, **19**-549, **19**-1178
Lee, J.G. **10**-1086, **14**-398, **17**-16, **19**-709, **19**-1185
Lee, J.I. **10**-718, **16**-2077, **16**-2097
Lee, J.K. **3**-3, **16**-1511, **18**-634
Lee, J.M. **18**-888
Lee, J.S. **19**-128
Lee, J.T. **10**-1631
Lee, J.Y. **3**-194, **10**-1939, **19**-203
Lee, K.-S. **11**-168
Lee, K.-J. **16**-1852, **19**-661
Lee, K. **10**-763, **10**-1489, **10**-1546, **15**-855, **15**-954, **15**-958, **15**-1161, **15**-1248, **16**-2298, **19**-1089
Lee, K.C. **19**-1204
Lee, K.J. **15**-1989
Lee, K.W. **19**-1093
Lee, K.Y. **16**-366, **19**-254
Lee, L. **15**-70
Lee, L.C. **15**-1675
Lee, M. **13**-689
Lee, M.C. **19**-1190
Lee, M.W. **6**-66
Lee, N.H. **19**-558, **19**-1204
Lee, N.R. **16**-2077
Lee, O.-Y. **16**-326, **16**-327
Lee, P.G. **15**-2554
Lee, P.H. **10**-1489, **10**-1546, **13**-689, **15**-351, **15**-855, **15**-954, **15**-958, **15**-1161, **15**-1248, **16**-563, **18**-253
Lee, P.S. **15**-155
Lee, R.E. **5**-133
Lee, S.-H. **13**-202, **13**-555
Lee, S.-M. **13**-150
Lee, S.-W. **13**-334, **13**-556
Lee, S.-G. **15**-1529, **16**-1640
Lee, S.-J. **16**-650
Lee, S.-W. **16**-731
Lee, S.-Y. **15**-2695
Lee, S. **10**-1343, **11**-392, **13**-683, **13**-689, **15**-855, **15**-1290, **18**-766
Lee, S.B. **13**-146, **15**-240, **15**-265
Lee, S.D. **15**-206
Lee, S.E. **19**-1178
Lee, S.H. **10**-607, **15**-521, **19**-966, **19**-1308, **19**-1313, **19**-1722
Lee, S.I. **15**-1529, **15**-1550, **15**-1551, **15**-1558, **16**-1173
Lee, S.J. **10**-1235, **15**-1410, **16**-2108, **19**-203, **19**-1660
Lee, S.L. **19**-1457
Lee, S.P. **16**-1924
Lee, S.S. **15**-1551
Lee, S.W. **13**-689, **16**-226
Lee, S.Y. **2**-459, **17**-364
Lee, T. **12**-530
Lee, T.J. **2**-67
Lee, T.S. **19**-79
Lee, T.W. **15**-2196
Lee, T.W.S. **8**-56
Lee, V. **12**-283
Lee, W.-M. **10**-618
Lee, W.-D. **16**-823
Lee, W.-C. **18**-307
Lee, W.-S. **19**-468
Lee, W. **10**-1835, **15**-2536, **16**-1129, **19**-326
Lee, W.G. **17**-60
Lee, W.K. **10**-1334, **12**-659, **16**-985
Lee, W.S. **16**-1864
Lee, W.Y. **3**-154
Lee, Y.-S. **13**-150, **13**-383, **19**-1190
Lee, Y. **10**-1371, **10**-1450, **19**-1265
Lee, Y.C. **19**-321
Lee, Y.R. **18**-226
Lee, Y.S. **10**-60, **18**-888
Lee, Y.-T. **13**-333
Lee, Y.T. **12**-52
Lee. K. **16**-563
Leebrick, J.R. **12**-481
Leeds, J.P. **19**-1227
Leeke, G.A. **15**-2126
Leeming, S.W. **13**-276
Leenson, I.A. **15**-179
Leermakers, P.A. **5**-354, **17**-527
Lees, W.A. **3**-44
Lefebvre, C. **10**-431
Lefebvre, D. **8**-207
Lefebvre, F. **18**-842
Lefebvre, G. **16**-319
Lefeuvre, M. **16**-1822
Lefeuvre, S. **7**-120
Leffek, K.T. **6**-77, **6**-81, **8**-114, **10**-1259, **13**-630, **17**-49
Leffingwell, J.C. **19**-26
Leffler, J.E. **6**-49
LeFlohic, A. **18**-833
Lefort, L. **15**-1278, **18**-873
Lefour, J. **2**-6, **2**-44
Lefrancois, J.-M. **10**-641
LeGall, E. **16**-399
LeGall, T. **15**-736
Legan, E. **10**-390, **16**-2280
Legars, P. **10**-605
Legault, C. **16**-899
Legault, C.Y. **15**-2699

Leggett, T.L. **5**-368, **15**-59
Leginus, J.M. **15**-2105
LeGoff, E. **2**-197, **15**-2552
Legon, A.C. **3**-30, **3**-42, **4**-390, **4**-393
Legrand, M. **4**-277
Legrand, O. **19**-1021
Legros, J. **10**-1508, **16**-896
LeGuyader, F. **15**-892
Lehd, M. **15**-2291
Lehmann, C.W. **16**-960, **19**-1113
Lehmann, U. **13**-458
Lehmkuhl, H. **5**-170, **15**-898
Lehn, J.-M. **3**-121
Lehn, J. **4**-252
Lehn, J.M. **3**-106, **3**-124, **3**-160, **4**-34, **4**-37, **4**-251, **4**-253
Lehner, H. **16**-44
Lehnert, E.K. **15**-2578
Lehnert, W. **16**-1248
Lehr, R.E. **15**-2303
Lehr, G.F. **10**-1401
Lehr, R.E. **15**-2307, **15**-2308, **15**-2389, **15**-2390, **17**-357, **18**-174, **18**-512, **18**-513
Lei, A. **10**-1469, **10**-1904, **10**-1905, **10**-1992, **13**-453, **13**-491, **13**-648, **13**-665, **14**-343, **14**-413, **19**-1017
Lei, C.-J. **10**-1924
Lei, L. **16**-1085
Lei, M. **19**-175
Lei, X. **10**-1443
Lei, Z.-G. **11**-243
Leigh, D.A. **3**-206
Leigh, G. **18**-807
Leigh, W.J. **7**-40, **7**-58, **18**-510, **18**-516
Leighton, J.L. **15**-1204, **15**-1612, **15**-2113, **16**-781, **16**-954
Leighton, T.G. **7**-73
Leijonmarck, H. **11**-339
Lein, G.M. **3**-148
Leinhard, G.E. **16**-22
Leino, R. **19**-836
Leis, J.R. **12**-203, **12**-734
Leiserowitz, L. **4**-104, **4**-195
Leisten, J.A. **10**-552
Leister, M.C. **4**-402
Leitch, S.K. **10**-974
Leitereg, T.J. **4**-140
Leitner, A. **10**-1467, **15**-949
Leitner, W. **9**-106, **16**-960, **18**-849, **19**-1014
Leito, I. **8**-86
Leitus, G. **19**-658, **19**-1075
Leivers, M. **18**-538
Lejon, T. **16**-351
Lekhok, K.C. **16**-1236
LeLagadec, R. **10**-1330
Leleti, R.R. **18**-267
Lem, G. **15**-2448
LeMahieu, R. **19**-1434
Lemaire-Audoire, S. **19**-1600
Lemaire, J. **19**-675
Lemaire, M. **4**-63, **10**-941, **10**-1075, **11**-261, **12**-354, **13**-310, **15**-892, **16**-1889, **18**-143
LeMaire, S.J. **15**-1631
Lemaître, F. **13**-442
Lemal, D.M. **2**-167, **4**-456, **15**-1947, **17**-354, **18**-528
Lemay, G. **16**-510, **16**-994
Lemek, T. **13**-756
LeMénez, P. **10**-1601
Lemenovskii, D.A. **15**-1641
Lemière, G.L. **4**-18
Lemière, G.L.F. **13**-190, **13**-204
Lemieux, R.U. **4**-376, **4**-379, **15**-1811, **19**-386
Lemin, A.J. **19**-66
Lemini, C. **18**-241
Lemor, A. **10**-1075
Lemoucheux, L. **16**-430, **16**-1876, **16**-2016
Lempert, K. **16**-1769
Lena, J.I.C. **19**-309
Lenardão, E.J. **15**-314, **15**-322
Lenden, P. **7**-115
Lendzian, F. **7**-20
Lengel, R.K. **5**-353
Lenges, C.P. **15**-1481
Lengyel, I. **10**-1054
Lenmartz, H.-W. **5**-304
Lennartz, H. **10**-188, **15**-2442, **18**-625
Lenoir, D. **1**-46, **10**-190, **15**-1641, **15**-1651, **19**-128, **19**-1683
Lentz, C.M. **10**-1443, **15**-1166
Lenz, F. **15**-88
Lenz, G. **16**-2205
Lenz, P.A. **10**-565
Lenz, R. **19**-119. **19**-120
Leo, A. **9**-20. **9**-63
Leo, G.C. **15**-2686
Leogane, O. **18**-307
Léon, H. **16**-916
Leonard, J.E. **4**-239, **10**-360
Leonard, N.J. **19**-41
Leonard, N.M. **16**-143
Leonard, N.M. **16**-783, **18**-139
Leonarduzzi, G.D. **15**-189
Leone-Bay, A. **13**-260
Leone, R.E. **18**-9
Léonel, É. **13**-311, **15**-2484
Leong, A.Y.W. **10**-1777
Leonori, D. **13**-187
Leonov, A.A. **16**-1364
Leonov, A.P. **15**-835
Leonova, T.V. **16**-1967
Leopold, A. **13**-776
Leopold, D.G. **5**-353
Leou, S.-P. **15**-545
LePage, T.J. **2**-44, **5**-292
Lepeska, B. **15**-32
Lepetit, C. **2**-344
Lepley, A.R. **5**-228, **10**-1395, **10**-1828, **13**-847, **18**-411, **18**-418, **18**-419
Lepley, R.L. **5**-229
Lepoint, T. **7**-86
LePoire, D.M. **10**-784
Lepore, S.D. **10**-625
LeQuestel, J.-Y. **8**-104
Lerchner, A.M. **15**-1105
Lerebours, R. **13**-587
Leriverend, P. **18**-589
Lerman, O. **15**-1709
Lerner, L.R. **19**-702
Lerner, R.A. **15**-1109
Leroi, G.E. **4**-285, **13**-51
LeRoux, C. **10**-1152
Leroux, Y. **16**-482
Leroy, B. **10**-575
Leroy, M. **3**-141
Leroyer, L. **2**-344
Lerum, R.V. **15**-1226
Lesage, D. **15**-1572
Leseul, J. **16**-1958
Leshina, T.V. **10**-1395
Lesieur, D. **19**-1768
Lesko, P.M. **4**-516
Lesovoy, D.E. **16**-1518
Lessard, J. **15**-1740
Lessène, G. **12**-332
Lester Jr., W.A. **7**-17, **7**-47
Leszczynski, J. **12**-85, **17**-211
LeTadic-Biadatti, M.-H. **5**-326
Letavic, M.A. **13**-683
Lete, E. **16**-2078
Letendre, L.J. **10**-1643
Lethbridge, A. **19**-704
Letort, M. **19**-675
LeTourneau, M.E. **12**-196
Letsinger, R.L. **13**-301, **17**-188, **19**-1210
Lettan II, R.B. **16**-1192
Leuck, D.J. **16**-339
Leung, C.W. **16**-659
Leung, D. **18**-538
Leung, K.P. **16**-1551
Leung, M.-k. **4**-84
Leung, M.-K. **12**-483
Leung, S.-W. **15**-2280
Leung, S.S.-H. **10**-232, **10**-244
Leung, S.S.-W. **16**-454
Leuschner, G. **14**-318
Leusink, A.J. **18**-356
Leussing, D.L. **16**-140
Lev, D.A. **15**-222
Lévai, A. **12**-332, **15**-1912
Levand, O. **19**-616
Levart, M. **15**-1917
Levene, R. **10**-1413
Leveque, J.-M. **7**-87
Lever Jr., O.W. **10**-1775, **12**-432, **15**-1465, **16**-1259
Leveson, L.L. **10**-550
Levi, G.I. **1**-101
Levi, N. **7**-54

Levillain, J. **9**-137
Levin, C.C. **4**-77
Levin, D. **16**-632, **16**-912
Levin, P.P. **5**-320
Levin, R.D. **8**-240
Levin, R.H. **13**-39
Levina, A. **19**-471
Levine, R. **12**-708, **13**-636
Levine, R.A. **4**-402
Levine, S.G. **19**-1005
Levisky, J.A. **11**-184
Levit, A.F. **13**-834, **19**-734, **19**-1553
Levitin, I.Ya. **12**-13
Levitt, B.W. **13**-764
Levitt, L.S. **1**-49. **13**-764
Levitt, T.E. **16**-1925
Levitz, M. **10**-15
Levkovskaya, G.G. **15**-1739
Levy, A.B. **10**-1881, **12**-525, **15**-20, **15**-1767
Levy, A.J. **15**-45, **15**-46
Levy, D.E. **6**-1
Levy, G.C. **8**-30
Levy, H. **18**-629
Levy, J.F. **10**-79
Levy, L.M. **11**-663
Lew, G. **18**-481
Lewandowska, E. **15**-1032
Lewarchik, R.J. **13**-837
Lewars, E.G. **15**-1946
Lewars, Y. **18**-232
Lewin, A.H. **11**-516, **13**-475
Lewin, A.H. **3**-15
Lewis, D.E. **6**-70, **6**-76
Lewis, D.F.V. **2**-17
Lewis, E.J. **15**-2555
Lewis, E.S. **6**-29, **6**-66, **6**-69, **8**-156, **8**-177, **9**-16, **9**-35, **10**-100, **10**-114, **10**-224, **10**-225, **13**-31, **13**-35
Lewis, F.D. **15**-2457, **18**-309
Lewis, G.N. **10**-6
Lewis, G.R. **3**-221
Lewis, H.B. **14**-376
Lewis, H.L. **5**-156
Lewis, I.C. **9**-47, **9**-50, **9**-52, **9**-54
Lewis, J.C. **11**-417, **16**-306
Lewis, J.D. **19**-861
Lewis, J.W. **19**-1509
Lewis, K.D. **18**-522
Lewis, M. **5**-69, **13**-29
Lewis, M.D. **15**-1871
Lewis, N.G. **16**-2288
Lewis, N.J. **13**-104
Lewis, R. **16**-470
Lewis, R.G. **18**-98
Lewis, R.J. **11**-143
Lewis, R.S. **7**-48
Lewis, S.N. **18**-76, **18**-379
Lewis, T. **18**-836
Lewis, T.A. **15**-1098
Lex, J. **2**-310, **2**-312, **2**-324, **2**-357, **2**-361
Ley, S.V. **2**-283, **10**-579, **10**-613, **12**-171, **12**-253, **13**-506, **15**-157, **15**-443, **15**-1081, **15**-1804, **15**-1867, **15**-2523, **16**-1292, **16**-1644, **16**-1848, **16**-1938, **19**-10, **19**-51, **19**-103, **19**-117, **19**-119, **19**-120, **19**-121, **19**-869
Leybach, H. **10**-1054
Leydet, A. **18**-221
Leykajarakul, J. **11**-303
Leyrer, U. **4**-38
Leyva, A. **15**-203
Leyva, E. **5**-440
Leznoff, C.C. **16**-1935, **16**-1936
Lherbet, C. **16**-1364
L'Hermine, G. **15**-112
L'Heureux, A. **7**-128
Lhoste, P. **10**-826, **15**-2520
Li, A.-H. **16**-1386
Li, B.-J. **10**-701, **13**-517, **16**-408
Li, B.-Z. **19**-956
Li, B. **11**-264, **13**-720, **19**-1261
Li, C.-J. **3**-8, **3**-9, **9**-98, **10**-1681, **10**-1922, **10**-1923, **11**-426, **12**-339, **13**-308, **13**-330, **14**-296, **14**-370, **15**-1231, **15**-753, **15**-950, **15**-1224, **15**-1252, **15**-1492, **15**-2097, **15**-375, **15**-788, **16**-409, **16**-1140, **16**-1564, **16**-268, **16**-269, **16**-271, **16**-475, **16**-476, **16**-559, **16**-559, **16**-578, **16**-596, **16**-923, **16**-926
Li, C.-Q. **16**-793, **16**-955
Li, C.-Y. **16**-1597
Li, C.-J. **19**-1643
Li, C. **10**-13, **14**-186, **15**-1347, **16**-1862, **18**-773, **19**-163, **19**-1014, **19**-1143, **19**-1145, **10**-1630, **16**-644, **16**-915
Li, C.S. **13**-266
Li, D-R. **19**-83
Li, D.-P. **10**-932
Li, D. **14**-344, **16**-59, **16**-134, **16**-489, **16**-1371
Li, F. **4**-155, **4**-415, **10**-765, **11**-241
Li, G. **13**-232, **15**-370, **15**-1742, **15**-1746, **15**-1747, **15**-2020, **15**-2037, **15**-2061, **16**-787, **16**-814, **16**-820, **16**-821, **16**-958, **16**-1025, **16**-1085, **19**-1149
Li, G.-l. **16**-612, **16**-613
Li, G.-Q. **19**-1025
Li, G.S. **19**-1474, **19**-1488
Li, G.Y. **15**-2024
Li, H. **10**-855, **10**-977, **11**-314, **11**-472, **12**-256, **13**-385, **13**-588, **15**-1052, **15**-1059, **15**-1106, **15**-2252, **15**-2579, **16**-546, **16**-675, **16**-697, **16**-710, **16**-815, **16**-1084, **16**-1219, **19**-128, **19**-1055
Li, J.-H. **10**-1732, **12**-267, **12**-284, **13**-494, **13**-498, **13**-502, **13**-525, **13**-588, **13**-591, **13**-497, **14**-357, **15**-945, **15**-2596
Li, J.-L. **13**-497
Li, J.-T. **16**-573, **16**-1233, **19**-1626, **19**-1627, **19**-1636
Li, J. **10**-538, **10**-1067, **10**-1916, **10**-2000, **12**-531, **13**-453, **14**-335, **14**-344, **15**-465, **15**-1515, **15**-1520, **15**-2648, **15**-2686, **16**-343, **16**-631, **16**-910, **16**-1084, **16**-1428, **16**-1862, **19**-647, **19**-650, **19**-1087, **19**-1304
Li, J.C. **4**-486
Li, J.P. **17**-131
Li, J.-W. **13**-134, **15**-1417, **15**-1424
Li, K. **15**-1174, **15**-1200, **15**-2562, **15**-2564, **19**-913
Li, L.-H. **16**-583
Li, L.-J. **16**-1233
Li, L.-S. **16**-1100
Li, L.-Z. **18**-185, **18**-242
Li, L. **4**-155, **10**-1232, **11**-694, **15**-287, **15**-619, **15**-1424, **16**-1582, **18**-136, **19**-68, **19**-1101
Li, M. **13**-288, **16**-151
Li, N.-S. **15**-730
Li, P. **10**-540, **10**-1992, **13**-385, **13**-494, **13**-588, **13**-600, **13**-613, **13**-616, **16**-1343, **16**-2043, **19**-1582
Li, P.T. **12**-628
Li, Q. **3**-43, **10**-1469, **16**-1496
Li, R.-x. **19**-1014
Li, R. **7**-24, **10**-573, **10**-701, **15**-1737, **15**-2171, **16**-1085
Li, S.-J. **19**-572
Li, S.J. **10**-1335
Li, S. **10**-569, **10**-1829, **13**-386, **15**-646, **16**-854, **6**-1823
Li, T.-S. **16**-1233, **19**-1626, **19**-1627, **19**-1636
Li, T. **15**-461, **19**-1640
Li, W.-S. **16**-1942
Li, W.-K. **19**-723
Li, W. **10**-538, **10**-1904, **13**-168, **19**-32, **19**-1014, **19**-1142
Li, X.-Q. **15**-1903
Li, X. **5**-261, **9**-128, **11**-123, **13**-166, **13**-381, **15**-167, **15**-449, **15**-619, **15**-1210, **15**-1218, **15**-1761, **15**-2330, **16**-670, **16**-893, **16**-1728, **16**-1838, **18**-606, **19**-83, **19**-529, **19**-990, **19**-1014, **19**-1034, **19**-1036, **19**-1044
Li, W.-R. **11**-403, **16**-561, **16**-1141
Li, X.-j. **19**-1014
Li, Y. **1**-45, **10**-727, **10**-1143, **12**-433, **13**-148, **13**-166, **13**-205,

13-206, **13**-450, **13**-514, **15**-367, **15**-2026, **15**-2280, **15**-2293, **15**-2509, **16**-1084, **16**-1502, **16**-1503, **16**-1512, **16**-2256
Li, Y.-C. **19**-1430
Li, Y.-L. **15**-2556
Li, Y.-M. **15**-643, **15**-1204
Li, Y.-Y. **13**-148, **19**-956
Li, Y.-Z. **13**-517
Li, Z.-C. **15**-553
Li, Z.-B. **16**-670
Li, Z. **1**-108, **10**-1011, **10**-1175, **10**-1658, **10**-1922, **10**-1923, **11**-277, **12**-242, **12**-373, **13**-100, **13**-279, **13**-421, **14**-75, **15**-1576, **15**-1902, **15**-2076, **15**-2660, **16**-53, **16**-268, **16**-269, **16**-409, **16**-429, **16**-1138, **16**-2083, **19**-235, **19**-491, **19**-539, **19**-540, **19**-541, **19**-542, **10**-499
Lian, H. **15**-597
Lian, J.-J. **15**-2617
Liang, B. **13**-584, **13**-665, **13**-697, **15**-1522
Liang, C.D. **4**-175
Liang, F. **15**-2183
Liang, G. **2**-191, **5**-52, **5**-87, **5**-94, **10**-52, **10**-181, **11**-16, **15**-2114
Liang, K.S.Y. **14**-369
Liang, L. **15**-1202, **15**-1204
Liang, X. **13**-196, **19**-171, **19**-174, **12**-546
Liang, Y.-m. **10**-1520
Liang, Y.-M. **15**-1055, **19**-1025
Liang, Y. **12**-267, **12**-284, **14**-357, **15**-2697, **19**-1014, **19**-1149, **19**-1259
Liang, Z. **16**-1085, **18**-830
Liao, C. **7**-32
Liao, H.-Y. **15**-283
Liao, J. **15**-619, **15**-908
Liao, M.-c. **10**-1520
Liao, Q. **16**-2066
Liao, W.-W. **15**-1200, **16**-1084, **16**-1461, **16**-1481
Liao, W. **16**-324, **16**-1073
Liao, X. **11**-265, **13**-296, **13**-366
Liao, Y.-L. **12**-483
Liao, Y. **5**-307, **13**-599, **16**-129, **16**-1462
Liard, A. **16**-534
Lias, S.G. **8**-240
Liaskopoulos, T. **17**-438
Libbey, W.J. **18**-39
Liberman, J. **8**-89
Líbero, F.M. **15**-297
Libertini, E. **19**-1687
Liblikas, I. **10**-1053
Libman, J. **16**-160
Lichtenthaler, F.W. **16**-1200
Lichtin, N.N. **10**-352
Lichtor, P.A. **13**-206
Licini, G. **19**-299
Lick, C. **10**-773
Liddon, A.J.P.S. **16**-1490
Lide Jr., D.R. **1**-40, **1**-81, **4**-285
Lide, D.R. **5**-278, **14**-183
Lide, Jr., D.R. **1**-63, **1**-91, **1**-92
Lidström, P. **7**-110, **7**-125
Liebeskind, L.S. **11**-472, **12**-261, **13**-158, **13**-292, **13**-623, **16**-2090, **16**-2091, **16**-2096, **19**-1220
Liebl, M. **18**-849
Liebman, J.F. **1**-87, **2**-42, **2**-54, **2**-162, **2**-229, **2**-362, **2**-388, **4**-418, **4**-427, **4**-444, **4**-483, **5**-348, **8**-240, **18**-114, **18**-683
Liebscher, J. **10**-1487, **15**-1400
Liedhegener, A. **16**-2296
Liégault, B. **16**-1084
Lien, A.P. **11**-637
Lienard, P. **16**-1075
Lienhard, G.E. **12**-95
Liesen, P.J. **13**-467
Liew, C.C. **18**-347
Lifson, S. **4**-182
liger, F. **13**-95
Liggero, S.H. **18**-120
Light, J. **19**-1296
Lightfoot, A.P. **12**-480
Lightner, D.A. **3**-70, **4**-91
Lightner, S.A. **4**-61
Ligthart, G.B.W.L. **19**-209
Liguori, L. **14**-159, **19**-320, **19**-325
Lii, J.-H. **4**-416
Lijnen, E. **2**-268
Likhar, P.R. **10**-937, **10**-1618, **13**-494
Likhomanova, T.I. **15**-1667
Likhotvovik, I.R. **5**-391
Lilburn, J. **13**-128
Liler, M. **8**-12, **8**-31, **8**-136, **15**-181
Liljefors, T. **4**-345, **4**-526
Lilla, G. **17**-99
Lillington, M. **2**-98
Lillocci, C. **10**-408
Lim, C.J. **14**-14, **15**-1290, **18**-840
Lim, D. **16**-788, **16**-1927
Lim, E.C. **7**-24
Lim, G. **17**-78
Lim, H.J. **19**-1633
Lim, J. **15**-1351, **15**-2671
Lim, K.-H. **10**-1920
Lim, M. **16**-350, **19**-676
Lim, S.-E. **13**-573
Lim, S. **15**-930
Lim, S.C. **12**-191
Lim, S.T. **10**-1114
Lim, Y.-K. **11**-168
Lim, Y. **16**-723, **16**-731
Lim, Y.Y. **16**-2250
Lima, C.F. **12**-706
Lima, E.L.S. **16**-1898
Limberger, J.B. **16**-598
Limburg, D.C. **16**-1642
Limmert, M.E. **10**-1309
Limmert, M.E. **13**-338
Lin, B.-N. **10**-1309
Lin, B. **13**-698
Lin, C.-C. **12**-483, **13**-495
Lin, C.-K. **19**-189
Lin, C. **15**-1444
Lin, D.K. **19**-693
Lin, F.L. **19**-1259
Lin, G.-Q. **16**-945, **19**-1670, **19**-1674
Lin, H.-C. **15**-1364
Lin, H. **4**-91, **10**-1685, **16**-462
Lin, H.C. **10**-614, **11**-30, **11**-96, **11**-147, **11**-481, **12**-215
Lin, J.-M. **12**-333
Lin, J. **3**-26, **10**-1629, **15**-741
Lin, J.J. **15**-527
Lin, K.-W. **16**-1422
Lin, L.-S. **16**-1001
Lin, L. **4**-155
Lin, L.S. **13**-290
Lin, M.-Y. **15**-2631
Lin, M.-J. **16**-562
Lin, M. **16**-1066
Lin, N. **5**-397
Lin, P.-S. **15**-802, **15**-927, **15**-1069, **15**-1216
Lin, P. **15**-1959
Lin, Q. **19**-1014
Lin, R. **5**-266
Lin, S.-I. **10**-1351
Lin, S.-W. **19**-332
Lin, S. **15**-1270, **19**-1101
Lin, S.H. **7**-22
Lin, W.-W. **15**-1220
Lin, W. **19**-1014, **19**-1018, **19**-1255
Lin, X.-F. **15**-297
Lin, X. **15**-1378
Lin, Y.-S. **10**-471, **16**-794
Lin, Y.-L. **18**-561, **18**-706
Lin, Y. **10**-202, **13**-386, **14**-195, **15**-2283
Lin, Z.-P. **19**-1627, **19**-1636
Linck, C.F. **19**-234
Linclau, B. **10**-1175, **16**-1752, **16**-1753
Lincoln, D.N. **5**-48
Lincoln, S.F. **3**-196
Linda, P. **2**-471, **11**-497
Lindbeck, A.C. **12**-595
Lindberg, T. **19**-62
Lindeman, S.V. **3**-81, **15**-2209
Lindemann, P. **13**-587
Linden, A. **2**-403, **11**-326, **15**-1269, **15**-2119
Lindén, A.A. **19**-794
Linden, S. **12**-58
Lindenschmidt, A. **13**-587
Linder, C. **11**-658, **11**-663, **16**-162
Linder, L. **18**-568
Linder, M.R. **16**-2241
Linder, S.M. **12**-695
Linderman, J.J. **18**-960
Linderman, R.J. **15**-1139

Lindert, A. **10**-1699, **12**-184, **16**-2135, **19**-818
Lindh, J. **12**-282
Lindhardt, A.T. **10**-1309
Lindlar, H. **15**-461, **15**-462
Lindner, D.L. **15**-492
Lindner, E. **5**-61, **18**-893
Lindner, H.J. **2**-193, **2**-195, **2**-250, **5**-150
Lindsay Smith, J.R. **11**-262, **14**-172, **14**-227
Lindsay, C.I. **10**-1295, **15**-1347
Lindsay, C.M. **12**-425
Lindsay, D.A. **18**-82
Lindsay, D.M. **15**-1548, **15**-1554, **19**-120, **19**-1021
Lindsay, H.A. **18**-731
Lindsey, A.S. **11**-529
Lindsley, C.W. **12**-323
Lindstrom, M.J. **14**-209
Lindström, U.M. **9**-90, **9**-97, **10**-963, **15**-1066
Lindy, L.B. **10**-1825
Lineberger, W.C. **5**-139, **5**-284, **5**-338, **5**-353, **17**-35
Linehan, J.C. **19**-484
Linevsky, M.J. **1**-98
Ling, H.-Y. **16**-895
Ling, Y.-C. **16**-146
Lingaiah, B.V. **16**-627
Lingaiah, N. **17**-442
Linghu, X. **16**-1594
Linker, T. **15**-1987
Lin'kova, M.G. **15**-1731
Linn, W.J. **15**-2175
Linnett, J.W. **2**-2
Linschitz, H. **7**-37
Linstead, R.P. **16**-419
Linstrumelle, G. **10**-1355, **13**-778, **15**-879
Linti, G. **5**-189
Linton, E.C. **18**-728
Lion, C. **10**-1441, **10**-1443, **10**-1864, **14**-476, **16**-2017, **16**-2157
Liotta, C. **3**-107, **10**-484, **10**-485, **10**-492, **10**-493, **10**-628, **10**-720, **10**-1106, **10**-1708, **10**-1932, **15**-2485, **16**-1281
Liotta, C.L. **10**-1756, **15**-651, **16**-30
Liotta, D. **10**-800, **10**-849, **12**-251, **16**-519, **16**-1069, **17**-293
Liotta, D.C. **5**-126, part**2**-6, **10**-849, **12**-250, **18**-779, **19**-10
Liotta, R. **19**-396
Liou, L.R. **10**-1702
Lipari, V.R. **16**-551
Lipinska, T. **18**-762
Lipinski, C.A. **10**-1354
Lipinsky, E.S. **15**-2454
Lipnick, R.L. **4**-394, **4**-395
Lipp, H.I. **10**-895
Lippard, S.J. **15**-1975
Lippens, G. **12**-106
Lipshutz, B.H. **10**-1402, **10**-1403, **10**-1406, **10**-1412, **10**-1421, **10**-1426, **10**-1428, **10**-1429, **10**-1440, **10**-1448, **10**-1621, **10**-1806, **12**-323, **12**-590, **12**-600, **12**-601, **12**-788, **13**-129, **13**-210, **13**-212, **13**-244, **13**-494, **13**-495, **13**-561, **13**-603, **15**-624, **15**-630, **15**-742, **15**-768, **15**-1140, **15**-1145, **15**-1149, **15**-1150, **15**-1162, **15**-1460, **15**-2360, **16**-683, **16**-1109, **18**-861, **19**-128, **19**-505, **19**-1038, **19**-1154
Lipshutz, B.L. **13**-594
Lipsky, S.D. **16**-532
Liptak, M.D. **8**-185, **8**-191
Lipton, M.A. **16**-1756
Lipton, M.F. **17**-277
Liras, S. **10**-339
Liras, S. **15**-2230
Lis, L. **2**-31, **4**-434
Lis, T. **3**-16
Liskey, C.W. **13**-296
Lisle, J.B. **1**-55
Lissel, M. **10**-486, **10**-1751, **10**-1815
Lissi, E.A. **7**-51
List, B. **10**-1787, **10**-1800, **11**-409, **15**-616, **15**-617, **15**-1080, **15**-1921, **16**-358, **16**-363, **16**-364, **16**-394, **16**-1108, **16**-1110, **16**-1429, **16**-1543, **16**-2258
List, B. **19**-1044
Listemann, M.L. **18**-884
Lister-James, J. **14**-153
Liston, T.V. **12**-436
Littell, R. **19**-46
Littke, A.F. **12**-278, **13**-371
Little, D. M. **14**-97
Little, D.A. **2**-282
Little, E.L. **15**-326
Little, J. **12**-740
Little, K. **10**-1025
Little, R.D. **10**-1412, **16**-839, **18**-623
Little, W.T. **16**-1267
Littler, J.S. part 2-5, **11**-589, **11**-581, **19**-5, **19**-98, **19**-101, **19**-102
Litvinenko, L.M. **13**-91, **16**-2301
Litvinenko, M. **16**-2286
Litvinov, V.P. **16**-1477
Litwinienko, G. **19**-961
Liu, A.-X. **10**-1067
Liu, B.-S. **12**-333
Liu, B.-K. **15**-297
Liu, B. **10**-198, **10**-199, **10**-213, **10**-660, **12**-389, **13**-314, **15**-141, **16**-893, **17**-189, **18**-304, **19**-1073
Liu, B.Y. **10**-611
Liu, C.-W. **16**-794
Liu, C. **13**-648, **15**-416, **15**-855, **19**-229
Liu, C.M. **16**-1055
Liu, C.Z. **2**-400
Liu, D. **10**-716, **10**-1522, **15**-439, **15**-2068, **15**-2252, **19**-1158
Liu, F. **13**-470, **15**-1922, **19**-830
Liu, G.-B. **10**-537, **15**-551
Liu, G.-H. **16**-664
Liu, G. **15**-419, **16**-747, **19**-715
Liu, H. **5**-194, **10**-1024, **11**-362, **13**-218, **15**-1732, **15**-2326, **16**-400, **16**-1924, **19**-1182, **19**-1304
Liu, H.-J. **10**-1567, **15**-1178, **16**-1184, **16**-1115, **19**-871
Liu, H.J. **18**-250
Liu, J. **10**-1309, **10**-1469, **11**-694, **13**-244, **13**-386, **13**-665, **15**-1747, **15**-1880, **16**-202, **16**-489, **16**-651, **16**-893, **16**-1084, **16**-1761, **19**-1034, **19**-1640
Liu, J.H.-C. **15**-868
Liu, J.-M. **10**-932
Liu, J.S. **5**-48, **5**-49
Liu, J.-T. **13**-841, **15**-1220, **15**-1440, **15**-1444, **15**-1445
Liu, J.-P. **16**-79
Liu, J.-X. **19**-1429
Liu, J.-Y. **15**-1220
Liu, K.-T. **10**-288, **10**-304, **10**-471
Liu, K. **6**-84, **10**-468, **15**-117, **15**-118, **18**-920
Liu, K.T. **10**-291
Liu, L. **1**-115, **1**-117, **10**-1067, **13**-236, **13**-313, **13**-421, **13**-496, **13**-497, **13**-500, **14**-84, **14**-88, **15**-1346, **15**-1347, **16**-545, **16**-666, **16**-670, **18**-548, **19**-163, **19**-196, **19**-1017
Liu, L.F. **3**-219, **4**-493
Liu, L.K. **17**-324
Liu, L.-P. **18**-169, **18**-170
Liu, M. **4**-368, **15**-2251, **16**-743, **16**-944, **19**-686
Liu, M.M. **15**-2409
Liu, M.T.H. **5**-312, **5**-395, **5**-414, **5**-416, **12**-368, **18**-89
Liu, P. **15**-1491, **15**-1802, **15**-1891, **15**-2699, **16**-1485
Liu, P.C. **8**-146
Liu, P.N. **19**-1036
Liu, Q.-Y. **15**-607
Liu, Q. **10**-1080, **14**-347, **15**-1485, **16**-202, **19**-645
Liu, R.-S. **15**-1945, **15**-2616, **15**-2617, **15**-2631, **17**-189, **18**-153, **18**-581
Liu, R. **19**-171, **19**-174, **19**-720
Liu, R.S.H. **14**-375, **15**-2261, **15**-2449

Liu, S. **3**-222, **10**-34, **10**-1031, **11**-376, **11**-377, **13**-205, **15**-1055, **15**-1260, **16**-549, **16**-1220, **19**-800, **19**-1014
Liu, S.H. **13**-594
Liu, S.-M. **19**-1626
Liu, S.-T. **10**-1309, **19**-388
Liu, T.-Y. **16**-408
Liu, T. **14**-501, **15**-465
Liu, W.-Z. **1**-109
Liu, W.-B. **4**-155
Liu, W.-J. **10**-1732, **12**-267, **13**-498, **13**-525
Liu, W.-y. **19**-887
Liu, W. **10**-1780, **13**-100, **13**-453, **14**-413, **15**-2262, **18**-90
Liu, X.-Y. **10**-1522, **16**-751
Liu, X.-G. **19**-981
Liu, X. **4**-155, **5**-57, **15**-215, **15**-643, **15**-895, **15**-896, **15**-1024, **15**-1059, **16**-649, **16**-1084, **16**-1496, **16**-1497, **16**-1529, **19**-1087
Liu, Y.-i. **3**-138
Liu, Y.-K. **10**-701, **18**-185, **18**-242
Liu, Y. **10**-935, **10**-1911, **13**-285, **13**-630, **14**-444, **15**-846, **15**-1921, **15**-2252, **16**-324, **16**-637, **16**-1201, **16**-1605, **16**-1719
Liu, Z.-M. **15**-1906
Liu, Z.-Q. **19**-224
Liu, Z. **10**-725, **10**-1150, **13**-319, **13**-398, **13**-410, **15**-347, **15**-1339, **16**-429, **16**-1605, **16**-2027, **16**-2047, **19**-204
Liu, X. **13**-785
Liua, Z. **16**-2041
Livant, P. **15**-2579
Livendahl, M. **13**-613
Livett, M.K. **2**-465
Livinghouse, T. **15**-348, **15**-351, **15**-354, **15**-808, **15**-855, **15**-1545, **16**-1491, **18**-835
Livingston, A.G. **13**-387
Livingston, R.C. **14**-328, **15**-404
Livingstone, D. **3**-75
Liz, L. **2**-217
Lizarzaburu, M.E. **10**-669
Lizzani-Cuvelier, L. **16**-225
Llagostera, K.B. **2**-112
Lledós, A. **10**-879, **15**-345, **15**-493, **16**-667
Llera, J.-M. **19**-292
Llewellyn, G. **10**-409, **10**-435, **10**-461, **10**-466, **16**-1706
Llewellyn, J.A. **6**-77
Llopis-Mestre, V. **11**-131
Llorca-Baragaño, M.A. **15**-2500
Llorente V.R. **15**-1552
Lloyd-Williams, P. **13**-517
Lloyd-Jones, G.C. **15**-2040, **15**-735, **16**-559, **16**-911
Lloyd, D. **2**-96, **2**-99, **2**-149
Lloyd, D.J. **17**-81, **17**-102
Lloyd, J.R. **5**-21
Lloyd, R.V. **14**-55
Lloyd, W.G. **14**-237
Lo Galbo, F. **16**-680
Lo, C.-Y. **15**-1945, **17**-189
Lo, H.-C. **16**-1074
Lo, M.M.-C. **12**-383
Lo, W.F. **13**-162
Loader, C.E. **11**-72
Loan, L.D. **19**-357
Loar, M.K. **12**-289
Lobkovsky, E. **10**-1769, **15**-2379
Lobkovsky, E.B. **10**-1633
Lobo, A.M. **4**-103, **15**-2063, **15**-2072
Locatelli, F. **5**-413, **19**-37
Locatelli, M. **10**-616, **10**-972, **15**-1106
Locati, L. **15**-1967
Locher, C. **11**-410, **16**-726
Lock, C.J.L. **5**-50
Lock, S. **16**-589
Lockley, W.J.S. **11**-119
Lockyer Jr, G.D. **14**-10
Lodder, G. **5**-78, **12**-507, **18**-915, **5**-66
Loe, Ø. **12**-394
Loening, K. **4**-101
Loening, K.L. **5**-6, **6**-53
Loeppky, R.N. **12**-740
Loeschorn, C.A. **18**-248
Loewen, M.J. **2**-451
Löffler, F. **15**-2507
Löfstedt, J. **15**-875
Loft, M.S. **10**-1535
Loftfield, R.B. **18**-208
Logan, T.J. **18**-279
Loghmani-Khouzani, H. **12**-139
Loh, T.-P. **13**-405, **15**-331, **15**-338, **15**-1023, **15**-1126, **15**-1185, **15**-1222, **15**-1383, **15**-1922, **16**-391, **16**-560, **16**-561, **16**-562, **16**-565, **16**-586, **16**-590, **16**-614, **16**-637, **16**-639, **16**-734, **16**-895, **16**-1159, **16**-1048, **16**-1141, **16**-1151, **16**-1156, **16**-1508, **16**-1527
Lohray, B.B. **4**-201, **10**-1074, **15**-1790, **15**-1811, **15**-1828
Lohri, B. **4**-144
Loim, L.M. **16**-162
Loim, N.M. **15**-499
Loiseau, A.-M. **16**-225
Lok, C.M. **19**-1182
Lok, M. **19**-185
Loken, H.Y. **12**-657
Lokhande, P.D. **16**-1632
Lokot, I.P. **19**-1424
Loktev, A.S. **15**-549
Lomas, D. **15**-2374
Lomas, J.S. **5**-293, **12**-694, **12**-699, **16**-507, **17**-162
Lombardi, P.J. **15**-2113, **16**-781
Lombardo, D.A. **12**-73
Lombardo, L. **16**-485
Lombardo, M. **16**-1084
Lomölder, R. **17**-514
Loncar, M. **11**-157
Loncharich, R.J. **15**-998, **15**-2291, **16**-1381
Long, D.A. **11**-412
Long, F.A. **11**-113, **16**-1667
Long, J. **15**-2562, **15**-2564, **16**-408
Long, J.A. **2**-475
Long, M.A. **11**-120, **11**-121, **11**-122
Long, Q. **10**-797, **16**-260
Long, R.A.J. **14**-48, **14**-368
Longenecker, H.E. **16**-1991
Longford, D. **10**-1461
Longmire, J.M. **19**-54
Longo Jr., L.S. **19**-568, **19**-582
Longone, D.T. **12**-462
Longshaw, A.I. **15**-2276
Longstaff, P.A. **2**-46
Longstaff, S.C. **15**-1339
Longuet-Higgins, H.C. **2**-115, **18**-511
Lönnqvist, J.-E. **19**-836
Lonsdale, K. **1**-58
Loo, D. **12**-540
Look, G.C. **16**-130
Loones, K.T.J. **13**-190, **13**-196
Loop, C.K. **12**-425
Loos, C. **15**-350
Loos, R. **10**-375, **16**-1369
Loosen, K. **18**-27
Lopata, A. **15**-52
Lopes, C.C. **15**-1198
Lopes, E.C.S. **16**-796
Lopes, R.S.C. **15**-1198
Lopez-Perez, A. **10**-1309
Lopez-Rodriguez, G. **19**-1506
López-Alvarado, P. **10**-1039
López-Pérez, A. **10**-1364
López-Mardomingo, C. **13**-698
López-Cantarero, J. **15**-1049
López-Carrillo, V. **15**-2375
López-López, J.A. **15**-2098
López-Serrano, J. **15**-493
López, C. **2**-488
López, C.J. **15**-1802
López, F. **10**-1544, **15**-1181, **15**-1185, **15**-2667, **16**-466, **18**-869
López, I. **15**-2193
López, J.C. **15**-1319
Lopez, L. **10**-1611, **15**-2369, **18**-124
López, L.A. **15**-2133, **15**-2654, **18**-276
Lopez, M. **19**-1030
López, M.C. **16**-831
López, P. **15**-2248
López, R. **13**-141
Lopez, R.C.G. **16**-215
Lopez, R.M. **19**-1382, **19**-1385

López, S. **15**-2269
Lopez, S.S. **18**-272
Lopez, V.O. **9**-47, **9**-55
Lopez, X. **2**-451, **16**-852, **16**-1679
Lopp, M. **19**-501
Lopusinski, A. **19**-765
Lorance, E. **8**-108
Lorand, J.P. **3**-100, **4**-11, **13**-27, **18**-428
Lorca, M. **16**-630
Lord, R.C. **4**-391
Loren, S. **15**-2249, **15**-2251
Lorenc, Lj. **14**-233
Lorentz-Petersen, L.L.R. **10**-880
Lorenz, O. **19**-357
Lorenzi, P. **15**-1660
Lorenzo, A. **10**-1252
Lorenzo, E. **16**-860
Lorenzo, F.M. **12**-737
Lorenzo, S. **3**-221
Loreta, M.A. **15**-2049
Lorimer, J.P. **7**-86
Lorne, R. **18**-785
Lorte, A. **10**-1889
Losensky, H. **3**-159
Loska, R. **15**-1338
Lossing, F.P. **2**-262, **5**-77, **5**-278, **10**-197
Lothrop, W.C. **13**-477
Lotoski, J.A. **10**-1338
Lötsch, G. **14**-388
Lotsch, W. **5**-243
Lotz, M. **10**-1537
Lou, B. **10**-855, **15**-693
Lou, F.-W. **15**-297
Lou, J.-D. **19**-68, **19**-69
Lou, J.D. **19**-109
Lou, S. **16**-398, **16**-737
Loubinoux, B. **10**-949
Loudon, A.G. **17**-249
Loudon, G.M. **18**-302
Loudon, J.D. **13**-89, **14**-218
Lough, A.J. **10**-1892, **16**-762
Lough, W.J. **4**-176
Louie, J. **15**-254, **15**-2636, **15**-2682, **18**-819
Loupy, A. **7**-110, **10**-499, **10**-723, **10**-1106, **10**-1108, **10**-1932, **11**-447, **12**-120, **13**-119, **15**-970, **15**-1114, **16**-351, **16**-801, **16**-1646, **16**-1827, **16**-1900, **17**-118, **17**-309, **18**-350, **18**-762, **18**-851, **19**-1000
Lourak, M. **13**-479
Lourenço, A. **15**-185
Lourenço, T. **19**-793
Louvet, A. **10**-1283
Louw, R. **11**-680, **17**-138, **17**-143
Lovas, F.J. **1**-55, **19**-349, **19**-370
Lovato, G. **16**-1682
Love, B.E. **16**-242
Love, J.A. **15**-309, **15**-2671, **15**-2676, **18**-612, **18**-891
Love, M.E. **10**-530
Lovel, C.G. **15**-1627
Lovely, C.J. **12**-376, **13**-236
Lovering, E.G. **1**-101
Lovey, A.J. **16**-2157
Low, C.M.R. **3**-46, **3**-85
Low, K.-H. **13**-604
Lowe, G. **4**-31, **4**-32
Lowe, J.P. **4**-287, **17**-94
Lowe, K.L. **5**-306
Lowe, P.A. **2**-92
Lowe, S.R. **19**-1658
Lowell, S. **10**-319
Lower, A. **15**-768, **19**-1038
Lower, S.K. **7**-26
Lowery, M.K. **18**-372
Lowery, T.A. **15**-2161
Lown, J.W. **15**-2151, **15**-2152
Lowry, T.H. **2**-8, **2**-420, **5**-26, **16**-46
Loy, R.N. **15**-382
Lozanova, A.V. **15**-2205
Lozinskii, M.O. **10**-1090, **10**-1664, **12**-201
Lu, C.-D. **18**-644
Lu, C. **15**-1440, **15**-1445
Lu, C.V. **11**-239
Lu, G. **13**-564, **16**-396, **16**-670
Lu, J.-F. **16**-603
Lu, J.-M. **18**-170
Lü, J.-W. **19**-1683
Lu, J. **13**-405, **15**-1023, **15**-1922, **16**-590, **16**-590, **16**-637, **16**-639, **19**-32
Lu, K. **13**-697, **15**-1163
Lu, L. **16**-313, **16**-915, **18**-878
Lu, M. **19**-163
Lu, P. **10**-960, **18**-123
Lu, S. **8**-111, **12**-775, **16**-1198, **16**-1968, **19**-1026, **19**-1024
Lü, S.-F. **19**-1021
Lu, S.-M. **12**-782, **15**-562, **16**-2247, **19**-1014
Lu, S.-P. **16**-1415
Lu, T.-J. **19**-189
Lu, T. **15**-2494, **15**-2563
Lu, W. **16**-918, **16**-919
Lu, W.-J. **15**-646
Lu, X. **10**-1548, **15**-1029, **15**-1270, **15**-1402, **15**-1921, **15**-2119, **15**-2252, **16**-747, **16**-750, **16**-1006, **17**-177, **19**-763
Lu, X.-R. **3**-128
Lu, Y.-Q. **10**-1681, **16**-559
Lu, Y.-Y. **16**-1895
Lu, Y.-F. **18**-519
Lu, Y. **4**-198, **10**-1207, **13**-168, **13**-515, **15**-1041, **16**-1085, **19**-652
Lu, Z. **10**-1223, **13**-207, **13**-538, **16**-989
Luan, X. **15**-1269
Luanay, D. **10**-1935
Luanphaisarnnont, T. **16**-703, **19**-1649
Luart, D. **13**-336
Lübben, D. **15**-1830
Lubell, W.D. **16**-2079
Lubin-Germain, N. **15**-2217, **16**-564
Lubin, N. **15**-2333
Lubineau, A. **15**-1075, **15**-2333
Lubitz, W. **5**-218, **7**-20
Luborsky, F.E. **11**-21
Lucarini, M. **1**-110, **5**-331, **14**-8, **14**-32, **14**-33
Lucarini, S. **10**-975
Lucas, G.B. **18**-394
Lucas, H. **19**-1594
Lucas, H.J. **10**-116
Lucchetti, J. **15**-1192
Lucchini, V. **8**-11, **15**-21, **15**-1994, **15**-2180
Lucci, E.M. **16**-848
Lucero, C.G. **10**-1503
Luche, J. **10**-504, **10**-1219, **10**-1504, **12**-638, **13**-108, **15**-1213, **16**-472, **19**-1641
Luche, J.-L. **7**-88, **7**-95, **7**-104, **10**-499, **11**-236, **15**-187, **15**-1212, **16**-861, **16**-1011
Luche, M. **16**-383
Lucherini, A. **18**-882
Luchinat, C. **4**-213
Lucht, B.L. **5**-204, **8**-221, **8**-222, **8**-223, **16**-1022
Lucien, J. **10**-807
Luckenbach, R. appendixa-22, appendixa-23
Lucon, M. **1**-54, **10**-461
Luderer, M.R. **16**-465
Lüdke, G. **16**-2253, **16**-2262
Lüdtke, D.S. **16**-598, **16**-746
Ludwieg, A. **10**-1691
Ludwig, M. **13**-423
Ludwig, R. **9**-118
Ludwig, U. **18**-416
Lue, P. **16**-260
Luef, W. **4**-536
Luengo, J.I. **18**-733
Lüers, S. **15**-833
Luft, J.A.R. **15**-2112
Luft, R. **9**-75
Luftmann, H. **14**-175
Lugad, A.G. **19**-1203
Luger, P. **4**-392, **18**-674
Luh, T. **2**-378, **14**-442, **14**-443, **19**-1563
Luh, T.-Y. **10**-1347
Lührs, K. **19**-1273
Lui, B. **12**-155
Lui, C.Y. **10**-200, **18**-108
Luibrand, R.T. **19**-906
Luis, A.L. **15**-2381, **16**-714
Luis, S.V. **13**-50, **16**-667
Luisi, R. **13**-731
Luka, G.Ya. **13**-818
Lukacs, Z. **19**-474, **19**-476
Lukanich, J.M. **13**-654

Lukas, J. **5**-19, **5**-30, **5**-32, **12**-53
Lukashev, N.V. **15**-797
Lukasiewicz, M. **15**-1904, **19**-648
Luke, G.P. **14**-429
Luke, M.O. **12**-55, **15**-494, **15**-495
Lukehart, C.M. **2**-185
Lukevics, E. **10**-796
Lukin, O. **3**-208
Lukins, P.B. **2**-156
Luknitskii, F.I. **16**-41, **17**-323
Luk'yanenko, N.G. **10**-501
Luk'yanets, E.A. **19**-814
Lulinski, P. **11**-284
Lum, R.C. **17**-126
Lumb, J.T. **12**-713
Lumbierres, M. **15**-1044
Luna, D. **15**-482, **15**-593
Lunazzi, L. **4**-56, **4**-57, **4**-62, **4**-90, **4**-303, **4**-325, **4**-327, **4**-436
Lund, H. **10**-102, **10**-103, **14**-150, **14**-456, **19**-926, **19**-1219, **19**-1666
Lund, T. **10**-102, **10**-103, **14**-483
Lundberg, S. **16**-1817
Lundeen, A.J. **17**-163
Lundgren, S. **16**-1496
Lundin, P.M. **13**-653
Lundstedt, T. **19**-1768
Luneau, D. **5**-305
Lunetta, S.E. **15**-2555
Lungwitz, R. **9**-119
Lüning, U. **5**-11, **14**-212, **15**-2507
Lunn, G. **19**-10, **19**-1223
Luo, F.-T. **15**-941, **15**-1633, **16**-107
Luo, F. **13**-592, **13**-698, **14**-415, **15**-503
Luo, H. **15**-453, **19**-224
Luo, J.-M. **16**-469
Luo, J. **15**-1522
Luo, M. **11**-189, **16**-650
Luo, S.-P. **9**-137, **15**-1055
Luo, S.-W. **16**-400
Luo, S. **15**-1055, **16**-786, **16**-794, **16**-800, **16**-1084
Luo, X. **19**-1304
Luo, X.M. **15**-1976
Luo, Y. **13**-121
Luçon, M. **8**-106, **8**-107
Luong-Thi, N. **16**-2005
Lupes, M.E. **16**-1584
Luque, F.J. **3**-81, **3**-82, **3**-85
Lusch, M.J. **6**-18, **6**-22, **15**-1159
Lush, R.K. **15**-1341
Lusinchi, X. **18**-157
Lusk, D.I. **12**-650
Lustgarten, R.K. **10**-144
Lusztyk, E. **19**-1084
Lusztyk, J. **5**-296, **5**-330, **5**-414, **14**-82, **14**-89, **14**-136, **14**-139, **14**-142, **14**-180, **15**-1304, **15**-1313, **18**-78, **19**-1084
Lusztyk, J.L. **18**-82
Lutete, L.M. **15**-365, **15**-370
Lüthi, H.P. **2**-279, **3**-77
Luthra, N.P. **6**-13
Lutomski, K.A. **10**-1856
Luts, S. **8**-126
Lutskii, A.E. **3**-49
Lutter, H. **16**-1586
Lüttke, W. **1**-86
Lutz, B. **3**-40
Lutz, C. **15**-1214
Lutz, F. **16**-766
Lutz, G. **15**-2210
Lutz, H.J. **17**-408
Lutz, M. **13**-732
Lutz, R.P. **18**-655, **18**-717
Lux, R. **19**-1268
Luz, Z. **4**-395, **18**-656
Luzung, M.R. **15**-867, **15**-2389
Luzzio, F.A. **16**-1200, **19**-81, **19**-753, **19**-1189
Lv, C. **16**-1498
Lwowski, W. **5**-427, **5**-435, **5**-437, **5**-443, **10**-1081, **12**-235, **12**-240, **15**-2079, **18**-292, **18**-309
Ly, K.S. **13**-683
Ly, T. **8**-92
Ly, T.W. **16**-1115
Lyapkalo, I.M. **17**-197
Lyashchuk, S.N. **8**-103
Lyerla, J.R. **11**-17
Lyga, J.W. **13**-793
Lygo, B. **10**-639, **10**-1651, **15**-1912, **15**-1914, **15**-1915, **15**-1960
Lyle, G.G. **4**-13
Lyle, R.E. **4**-13
Lynch, G.J. **15**-183
Lynch, J. **15**-2158
Lynch, K.M. **4**-452
Lynch, P.P. **19**-1509
Lynch, S.M. **15**-2182
Lynch, T.-Y. **5**-259
Lynch, T. **5**-258
Lynch, T.J. **19**-1739
Lynch, V. **15**-197
Lynch, V.M. **8**-187
Lynn, D.M. **18**-822
Lyons, A. **7**-44
Lysén, M. **16**-2025
Lysenko, V.P. **16**-1471
Lyster, M.A. **10**-1199
Lythgoe, D.J. **19**-1113
Lyubimov, S.E. **10**-882
Lyushin, M.M. **11**-414

Ma, B. **18**-307
Ma, C. **16**-776
Ma, D. **10**-1029, **11**-222, **13**-100, **13**-125, **13**-205, **13**-620, **16**-2076, **19**-561
Ma, F.-F. **16**-1433
Ma, H.-r. **13**-524
Ma, H. **19**-242
Ma, J.-A. **12**-141, **15**-2045, **16**-1523
Ma, J. **5**-301, **10**-1295, **18**-510
Ma, J.C. **3**-81
Ma, L. **19**-180
Ma, M. **18**-773
Ma, S. **10**-1346, **12**-302, **13**-517, **15**-107, **15**-249, **15**-286, **15**-287, **15**-411, **15**-452, **15**-870, **15**-1587, **18**-830, **19**-1366
Ma, V. **16**-1828
Ma, Y.-C. **19**-68
Ma, Y.-x. **19**-887
Ma, Y. **5**-423, **11**-452, **13**-651, **16**-776, **17**-306
Ma, Z. **11**-264, **15**-2146, **15**-2147
Maag, H. **16**-382, **16**-384
Maag, R. **2**-403
Maahs, G. **2**-382
Maas, G. **4**-500, **5**-392, **10**-420, **12**-219, **13**-778, **15**-795, **15**-2505, **17**-284, **17**-496, **18**-223, **18**-531, **19**-290
Maas, L.W. **19**-402
Maas, M. **13**-738, **14**-378
Maass, G. **3**-150
Mabbett, I. **10**-685, **18**-147
Mabille, C. **14**-255
Mabrouk, P.A. **9**-107
Mabry, T.J. **15**-1866
Mabuchi, T. **10**-1831
MacAlpine, G.A. **17**-423
Macaulay, J.B. **15**-2243
Macaulay, S.R. **12**-76
Maccarone, E. **16**-2273
Macchia, B. **10**-600
Macchia, F. **10**-600, **10**-683, **10**-837, **10**-996, **10**-997, **10**-1219, **10**-1647, **10**-1891
Macchitella, D. **19**-172
Macciantelli, D. **4**-62, **4**-303, **10**-1278
MacClellan, A.L. **1**-39
Maccoll, A. **5**-278, **17**-3, **17**-128, **17**-135, **17**-136, **17**-150
Macdonald, D. **18**-642, **18**-645
MacDonald, D.J. **2**-379
Macdonald, G.J. **12**-334
MacDonald, I.D. **2**-439
Macdonald, T.L. **12**-598, **15**-2578
MacDougall, K.N. **19**-1129, **19**-1156
MacFarlane, D.R. **9**-140
MacGarvey, U. **5**-222
MacGee, D.I. **17**-362
MacGibbon, A.K.H. **17**-69
Mach, M.H. **11**-234, **11**-684
Machácek, J. **19**-888
Machajewski, T.D. **10**-1746
Macheleid, J. **10**-421, **10**-427
Machida, H. **17**-373
Machida, Y. **10**-771
Machiguchi, T. **2**-239
Machii, D. **7**-98
Machioka, K. **15**-1014, **15**-1015
Machrouhi, F. **13**-625

Maciá, B. **16**-849
Maciejewski, G. **10**-1206, **19**-1533
Maciejewski, G. **19**-1534
Macielag, M. **18**-919
MacIntyre, D.W. **9**-52
Mack, A.G. **13**-476
Mack, H.-G. **4**-305
Mack, J. **10**-25
Mack, J.P.G. **12**-60
Mack, T.L. **13**-503
Mackay, G.I. **8**-254, **10**-355
Mackenzie, K. **10**-226, **12**-57, **17**-502, **18**-953, **18**-956
Mackenzie, P.B. **16**-1077
Mackie, I.D. **4**-409
Mackie, R.K. **10**-1159, **17**-339
Mackiernan, J. **15**-135
Macklen, E.D. **8**-24, **8**-255
Macklin, T.K. **13**-730
Mackor, E.L. **11**-5
MacLachlan, M. J. **3**-200
Maclaren, J.A. **19**-768
MacLean, C. **2**-67, **11**-5
Macleod, L.C. **19**-1435
Maclin, K.M. **16**-486
MacMillan, D.W.C. **11**-345, **11**-392, **12**-123, **12**-146, **13**-550, **15**-615, **15**-615, **15**-1402, **15**-2236, **16**-358, **16**-1081, **16**-1154, **16**-1479
MacMillar, S. **10**-1930
Macnaughtan, M.L. **18**-880
MacNeil, S.L. **10**-1348
MacNicol, D.D. **3**-106, **3**-110, **3**-124, **3**-147, **3**-162, **3**-163, **3**-166, **3**-170, **3**-172, **3**-175, **3**-176, **3**-183, **3**-185, **3**-186, **3**-222, **4**-169
MacNulty, B.J. **17**-37, **17**-124, **17**-127
Macoas, E.M.S. **4**-309
Macomber, D.W. **2**-185
Macomber, R. **10**-150
Macor, J.E. **11**-249
MacPhee, J.A. **9**-74, **16**-2021
MacPherson, D.T. **15**-2159
Macquarrie, D.J. **18**-385, **19**-602
MacQuarrie, R.A. **8**-66
MacWeeny, R.M. **1**-2
Madan, C. **11**-192
Madan, P. **4**-186
Madaule-Aubry, F. **10**-446
Madavi, C. **16**-1555
Maddaluno, J. **5**-187, **8**-215
Madder, R.D. **4**-475
Maddess, M.L. **10**-1638, **18**-863
Maddocks, P.J. **18**-461
Madec, D. **13**-160
Mader, M.M. **19**-1276
Madesclaire, M. **19**-773, **19**-1583
Madhav, M. **12**-122
Madhavan, S. **19**-1052
Madhavendra, S.S. **13**-509
Madhavi, M. **12**-116
Madhi, S. **16**-357
Madhsudhan, P. **16**-1744
Madhuri, Ch. **16**-782
Madhusaw, R.J. **15**-2631
Madhusudhan, P. **15**-609, **16**-294, **17**-444
Madine, J.W. **15**-853
Madjdabadi, F.A. **11**-412
Madni, M. **5**-423
Madrakian, E. **11**-134
Madras, G. **9**-109
Madrigal, D. **10**-906
Madrikian, E. **12**-732
Madroñero, R. **16**-2170
Madsen, J.Ø. **19**-993
Madsen, R. **10**-880, **10**-1044, **14**-496, **18**-889
Madura, J.D. **8**-227
Madyar, V.R. **11**-130, **11**-590, **16**-114
Maeda, H. **3**-31, **14**-26, **16**-2014
Maeda, K. **10**-1273
Maeda, N. **12**-511
Maeda, T. **11**-327
Maeda, Y. **19**-215
Maegawa, T. **11**-694, **12**-263, **13**-589, **14**-356, **19**-499, **19**-1355, **19**-1356
Maekawa, H. **10**-630, **11**-576, **12**-528, **15**-1452, **15**-1453, **19**-1656
Maekawa, N. **2**-176, **15**-1334
Mäeorg, U. **15**-577
Maercker, A. **5**-178, **12**-597, **16**-1311, **17**-184
Maerker, C. **2**-116, **5**-81
Maerschalk, C. **7**-86
Maerten, E. **13**-696
Maes, B.U.W. **13**-190, **13**-196, **13**-204
Maesano, M.G. **15**-292
Maestro, M.A. **15**-1557
Maezaki, N. **15**-1193
Maffioli, S.I. **17**-471
Maftouh, M. **19**-1234
Magano, J. **10**-681, **19**-1058
Magdassi, S. **10**-489
Magdesieva, T.V. **12**-43
Magdolen, P. **7**-97, **13**-182
Magee, M.P. **19**-1147
Mager, S. **2**-485, **4**-79, **4**-375
Mägerlein, W. **10**-1734, **13**-288, **13**-676
Magers, D.H. **4**-435.
Mageswaran, R. **3**-158
Mageswaran, S. **3**-158, **18**-417
Maggi, R. **11**-416, **11**-430, **15**-1930, **16**-212, **16**-1202, **19**-466
Maggini, M. **4**-541
Magid, R.M. **10**-231, **10**-240, **10**-1164, **10**-1315
Magin, A. **15**-2586
Magloire, V.P. **4**-186
Magna, L. **8**-126
Magnane, R. **17**-205
Magnera, T.F. **10**-286, **10**-447
Magnier, E. **5**-110, **8**-188
Magnotta, F.A. **16**-2301
Magnus, P. **15**-191, **15**-197, **15**-627, **15**-1541, **15**-1569, **16**-1289, **16**-1296
Magnus, P.D. **10**-1824, **16**-2175, **17**-412
Magnuso, R.H. **12**-13
Magomedev, N.A. **15**-1094
Magoon, E.F. **18**-64
Magro, A.A.N. **19**-1473
Maguire, A.R. **15**-1655, **19**-800
Maguire, J.A. **19**-56
Magyar, E.S. **10**-154
Mah, Y.J. **16**-1611
Mahadevan, R. **2**-308
Mahadevan, V. **10**-1632
Mahaffy, P.G. **19**-234
Mahajan, A.N. **19**-1181
Mahajan, D. **16**-1081, **16**-1085
Mahajan, M.P. **15**-2345
Mahajan, S. **15**-1847
Mahajan, U.S. **17**-470
Mahajan, Y.R. **12**-128
Mahale, G.D. **17**-435
Mahalingam, A.K. **16**-1778, **19**-1609
Mahanty, J.S. **13**-418
Maharvi, G.M. **10**-1142
Mahata, P.K. **18**-257
Mahatthananchai, J. **18**-709
Mahboubghah, N. **16**-70
Mahdavi, H. **10**-981, **10**-1233, **19**-885
Mahdavinia, G.H. **19**-36
Mahé, R. **15**-281
Mahender, G. **15**-1212, **16**-1629, **16**-1636
Mahender, I. **16**-1750
Mahendran, M. **5**-50
Maher, D.J. **16**-805
Maher, J.P. **18**-953
Mahesh, M. **17**-208
Maheswari, C.U. **16**-315
Mahía, J. **15**-1557
Mahindroo, V.K. **18**-487
Mahiou, B. **15**-102
Mahmud, H. **13**-236
Mahon, M.F. **10**-1535
Mahoney, B.D. **16**-551
Mahoney, J.M. **15**-2055
Mahoney, W.S. **16**-1121
Mahrwald, R. **10**-916, **16**-1015, **16**-1018, **16**-1045, **16**-1052, **16**-1060, **16**-1060, **16**-1083
Mahuteau-Betzer, F. **13**-343
Mahuteau, J. **15**-1406
Mai, K. **16**-1524
Mai, W. **13**-495
Mai, W.P. **15**-210

Maia, A. **10**-368, **10**-487, **10**-1693, **18**-344
Maia, A.M. **10**-321
Maia, M.P. **16**-850
Maier, A. **15**-795
Maier, A.H. **11**-474
Maier, A.J. **11**-50
Maier, G. **2**-183, **2**-233, **2**-238, **2**-245, **4**-458, **4**-522, **17**-512, **18**-503, **18**-531, **18**-683, **18**-689
Maier, W.F. **4**-513, **15**-462, **15**-478, **15**-486, **15**-488, **15**-489, **15**-536, **19**-1081
Maier, M.E. **18**-814, **18**-835
Maietti, S. **15**-1953
Maifeld, S.V. **15**-780, **18**-889
Maikap, G.C. **19**-816
Maillard, B. **10**-769, **19**-1084
Maillard, D. **19**-1752
Mailleux, I. **10**-628
Maimind, V.I. **2**-177, **18**-945, **18**-948
Main, C.A. **16**-1428
Mainolfi, N. **15**-1539
Mains, H.E. **14**-283
Maio, W.A. **10**-1937
Maiolo, F. **13**-145
Maione, A.M. **19**-135
Maiti, D. **13**-129
Maiti, G. **12**-665
Maiti, N.C. **3**-48
Maiti, S. **10**-1046, **16**-1711, **16**-1714, **16**-1863
Maiti, S.N. **15**-162, **19**-1251, **19**-1624
Maitlis, P.M. **2**-252, **15**-2586
Maitra, K. **2**-405
Maitra, U. **10**-658, **11**-685
Maitro, G. **13**-160
Maiuolo, L. **10**-1189, **16**-92, **16**-1723
Maiz, J. **16**-852
Maizell, R.E. appendixa-1
Majchrzak, M.W. **15**-2120
Majdoub, M. **10**-723
Majee, A. **16**-348
Majee, A. **16**-1865
Majerski, Z. **2**-470, **10**-212, **18**-29, **18**-120, **18**-233
Majetich, G. **7**-106, **7**-109, **11**-247, **11**-376, **11**-377, **15**-1247, **15**-1889, **19**-1365
Majewski, M. **8**-211, **10**-1704, **16**-1071, **16**-1074
Majhi, A. **15**-1212
Maji, B. **11**-322
Maji, M.S. **11**-423, **13**-593
Majima, K. **15**-869
Majima, T. **5**-308
Majo, V.J. **15**-809
Majumdar, K.C. **15**-1343, **15**-1373, **18**-703, **18**-744, **18**-754
Majumdar, K.K. **16**-686
Majumdar, S.P. **18**-250
Mak, A.N.S. **11**-654
Mak, C.-K. **19**-492
Mak, S. **13**-126
Mak, T.C.W. **2**-270, **3**-162
Mak, X.Y. **15**-376
Makamura, T. **13**-461
Makani, S. **11**-266
Makara, G.M. **16**-1899
Makarova, L.G. **12**-453, **12**-505, **12**-577, **12**-587, **13**-807
Makhija, R.C. **19**-604
Makhova, I.V. **12**-711
Maki, A.G. **1**-55
Maki, B.E. **19**-687
Maki, T. **5**-263, **12**-268, **16**-2133, **18**-299, **19**-984, **19**-1078
Maki, Y. **10**-1433
Makida, Y. **10**-1884
Makino, K. **7**-71, **19**-504
Makino, S. **16**-942
Makioka, Y. **19**-1680
Makisumi, Y. **18**-753
Makone, S.S. **16**-55
Makosza, M. **10**-484, **10**-489, **10**-911, **10**-1101, **10**-1666, **10**-1708, **13**-755, **13**-756, **13**-757, **13**-758, **13**-759, **13**-95, **15**-1123, **16**-1457, **19**-1712
Makowski, B.T. **16**-218
Makrlík, E. **3**-146
Maksić, Z. **4**-437
Maksić, Z.B. **2**-88, **2**-349, **2**-383, **4**-423, **4**-424, **8**-93, **8**-95, **8**-133, **11**-82, **15**-607
Maksimovic, L. **16**-616
Maksimovic, Z. **14**-233
Maksyutin, Yu.K. **3**-86
Makwana, V.D. **19**-232
Mal, D. **10**-867, **10**-718
Malacria, M. **10**-1342, **15**-877, **15**-1319, **15**-1368, **15**-2164, **15**-2588, **15**-2612, **15**-2623, **18**-582
Malai Haniti S.A. **10**-933
Malakhov, V. **10**-1456
Malament, D.S. **15**-2535
Malan, C. **10**-1506
Malana, M.A. **16**-1692
Malanga, C. **16**-2016, **17**-380, **19**-1105
Malarski, Z. **3**-16
Malasare, M.G. **16**-584
Malashock, D.S. **10**-602
Malcolm, S.C. **12**-393
Malda, H. **10**-1447
Maldonado, L. **15**-1467
Malecki, A. **10**-968
Maleczka Jr., R.E. **12**-266, **13**-107, **13**-454, **13**-629, **18**-438, **18**-440, **19**-1089
Malek, F. **14**-495, **19**-1394
Málek, J. **15**-1472, **19**-10, **19**-850, **19**-1004, **19**-1177, **19**-1491
Maleki, M. **10**-317
Malerich, J.P. **4**-322, **15**-1056, **18**-500
Malesci, I. **10**-691
Malfroot, T. **10**-1258
Malhotra, N. **2**-129
Malhotra, R. **10**-672, **10**-1200, **10**-1247, **11**-123, **11**-152, **12**-209, **19**-98
Malhotra, S.V. **9**-127, **11**-397, **15**-1207, **19**-1027
Mali, R.S. **12**-409, **12**-429
Mali, S.I. **11**-274
Malik, H.T. **19**-993
Malik, P. **19**-127, **19**-680
Malik, S.S. **11**-124
Malini, U.U.R. **11**-227
Malinowski, M. **19**-1687, **19**-1689, **19**-1699
Malkin, Yu.N. **7**-9
Malkov, A.V. **10**-1546, **15**-1886, **15**-1887, **16**-773, **16**-775, **16**-776, **16**-778, **16**-1490, **18**-391, **19**-1129, **19**-1156
Malladi, R.R. **10**-764, **19**-970
Mallagaray, Á. **15**-2683
Mallakpour, B. **16**-80
Mallakpour, S.E. **16**-66, **16**-67, **16**-80, **19**-84, **19**-87, **19**-244, **19**-247, **19**-883
Mallan, J.M. **12**-409, **15**-581
Mallart, S. **12**-537
Mallat, T. **19**-128
Mallion, R.B. **2**-8, **2**-106
Mallison, P.R. **18**-465
Mallory, C.W. **2**-339, **18**-547
Mallory, F.B. **2**-339, **18**-547
Malmberg, H. **10**-1426
Malmvik, A. **19**-1002, **19**-1003
Malnar, I. **10**-155
Malone, G.R. **10**-1846, **10**-1848
Malone, Y.M. **13**-436
Maloney, D.J. **19**-892
Maloney, J.R. **13**-754
Malpass, D.B. **16**-485
Malpass, J.R. **16**-2238, **18**-371, **18**-673
Malpezzi, L. **4**-39
Malsch, K. **4**-458
Malsch, K.D. **2**-243
Malta, L.F.B. **13**-379, **13**-497
Malte, A. **16**-2010
Maltese, F. **15**-1482, **19**-1698
Maltsev, A. **5**-439
Maltsev, A.K. **5**-238, **5**-349, **15**-2537
Malvaldi, M. **9**-120
Malvestiti, I. **16**-847
Malykhin, E.V. **14**-226
Malyshev, D.A. **15**-1887, **16**-808
Mamaev, V.P. **2**-476, **9**-20
Ma'Mani, L. **16**-1515
Mamdani, H.T. **18**-635
Mamedova, Yu.G. **5**-268

Mamposo, T. **16**-1249
Mampreian, D.M. **15**-1170, **15**-1208
Mamuzic, R.I. **14**-233
Man, T.-O. **4**-84
Manabe, K. **10**-974, **13**-347, **15**-1038, **15**-1073, **16**-402, **16**-623, **16**-770, **16**-962, **16**-972, **16**-1140, **16**-1172, **16**-1782
Manabe, O. **7**-62, **19**-1557
Manabe, S.v. **11**-329
Manage, A.C. **10**-1560
Manatt, S.L. **2**-142
Manchand, P.S. **10**-1526
Mancini, G. **4**-53, **15**-205
Mancuso, A.J. **19**-154
Mancuso, N.R. **18**-355
Mancuso, R. **12**-770
Mandai, T. **16**-1047
Mandal, A.B. **10**-539
Mandal, A.K. **15**-710
Mandal, B. **11**-319
Mandal, G.C. **14**-482
Mandal, K. **18**-705
Mandal, S.B. **19**-1465
Mandal, S.K. **10**-1512, **19**-211
Mandal, T. **15**-298, **15**-1448, **16**-1220
Mandel, F. **6**-66
Mandel, S.M. **5**-433
Mandelbaum, A. **16**-2003
Mander, L.N. **3**-213, **4**-1, **4**-101, **4**-102, **4**-116, **4**-117, **4**-118, **4**-128, **4**-155, **4**-160, **4**-162, **4**-268, **4**-283, **4**-328, **4**-364, **4**-389, **4**-444, **16**-2147, **18**-775
Mandoli, A. **16**-822
Mandolini, L. **6**-13, **6**-14, **6**-15, **10**-362, **10**-737, **11**-104
Mane, R.B. **11**-252, **16**-1209
Manek, M.B. **14**-93
Manenschijn, A. **5**-233
Manescalchi, F. **19**-377
Mang, J.Y. **16**-2298
Mangelinckx, S. **18**-258
Mangeney, P. **4**-113, **10**-1600, **10**-1612, **15**-1134, **16**-901, **17**-221, **19**-1667
Mangini, A. **2**-94, **4**-48, **5**-126, **5**-127, **5**-128, **10**-800, **15**-21, **16**-1470
Manglik, A.K. **11**-99
Mango, F.D. **15**-2407, **18**-535
Mangoni, L. **17**-205
Mangroo, D. **16**-1776
Manhas, M.S. **7**-109, **10**-1684, **11**-128, **16**-1900
Manickam, G. **19**-1037
Manickam, GF. **10**-1143
Manimaran, T. **10**-1088
Manju, K. **15**-828, **16**-1495
Manjuvani, A. **16**-803
Mankand, N.P. **13**-315
Manley, J.M. **16**-1916
Mann, A. **13**-666, **15**-2335, **16**-354
Mann, D.E. **1**-40, **1**-92
Mann, J. **10**-1099, **15**-2664
Mann, K. **2**-231
Mann, L.W. **15**-2677
Mann, M. **2**-302
Mannen, S. **19**-288
Manner, J.A. **10**-178, **10**-179
Mannhardt, H. **7**-10
Mannina, L. **3**-85
Mannion, M.R. **2**-73, **2**-74, **13**-373
Mannschreck, A. **4**-40, **4**-234, **4**-529
Mannucci, S. **19**-1105
Mano, E. **19**-650
Manoda, T. **10**-1013
Manoharan, M. **2**-117, **2**-340, **4**-350, **4**-356, **5**-386, **15**-1327, **18**-522
Manolikakes, G. **10**-1463, **13**-133, **13**-211
Manor, P.C. **3**-187
Manor, S. **10**-1215
Manoso, A.S. **13**-718
Manoury, E. **15**-1830
Manpadi, M. **15**-1153
Mansfield, K.T. **15**-2413, **15**-2416
Manske, R.H.F. **10**-1035
Mansoor, U.F. **12**-340
Manta, N. **16**-1181
Manthey, J.W. **10**-301
Mantilli, L. **18**-266
Manuilov, A.V. **10**-424
Manyem, S. **14**-45
Manzano, F.L. **14**-200
Manzer, L.E. **13**-668
Manzo, A.M. **16**-848
Manzo, P.G. **7**-100, **13**-67
Manzocchi, A. **19**-89, **19**-425
Mao, C. **18**-534
Mao, J. **16**-546
Maple, S.R. **16**-1033
Mapp, A.K. **18**-751
Maquestiau, A. **4**-507
Mar, E.K. **10**-1623
Maradyn, D.J. **15**-2458
Maragni, P. **11**-216
Marais, D.J. **2**-36
Maran, U. **2**-462
Marans, N.S. **12**-455
Marao, I. **15**-2123
Maraval, V. **2**-344
Marazzi, A. **17**-471
Marcaccioli, S. **2**-62
Marcantoni, E. **10**-616, **10**-870, **10**-1125, **10**-1189, **11**-483, **15**-1065, **15**-1182, **15**-1388, **15**-1397, **16**-606, **16**-610, **16**-1229, **16**-124, **16**-1723, **17**-164, **19**-969, **19**-1254
Marcantonio, K.M. **13**-285
Marcelli, T. **15**-230, **16**-1220
March, J. **11**-188, **12**-663, **12**-714
March, S. **15**-1204
Marchand-Brynaert, J. **15**-2186, **15**-2233, **15**-2422
Marchand, A.P. **4**-462, **5**-371, **15**-2303, **15**-2307, **15**-2308, **15**-2389, **15**-2390, **15**-2470, **17**-172, **17**-174, **17**-357, **18**-174, **18**-512, **18**-513, **18**-900
Marchese, G. **10**-1331, **10**-1903, **16**-2015, **16**-2020, **17**-14
Marchesini, A. **2**-159
Marchetti, F. **5**-339
Marchi-Delapierre, C. **15**-1949
Marchi, C. **15**-1044
Marchot, E.C. **5**-209
Marchueta, I. **15**-2588
Marciniak, B. **7**-37, **7**-38
Marcinow, Z. **2**-403, **2**-404
Marco-Contelles, J. **15**-1320, **15**-877
Marco, J.A. **16**-1039
Marco, M. **7**-126, **7**-127, **13**-596
Marcotullio, M.C. **12**-757, **15**-1758, **19**-1698
Marcoux, D. **13**-250
Marcoux, J.-F. **13**-416, **19**-1135
Marcuccio, S.M. **13**-320
Marcum, J.D. **5**-333
Marcus, A.P. **15**-1083
Marcus, J. **16**-1500
Marcus, N.L. **18**-927
Marcus, R.A. **6**-30, **8**-151
Marcus, Y. **10**-64
Marcuzzi, F. **15**-35
Marczewski, J.M. **15**-314
Marder, T.B. **10**-1469, **12**-588, **15**-731
Marecot, P. **15**-447
Mareda, J. **10**-14
Marek, I. **10**-641, **10**-1471, **10**-1600, **10**-1612, **12**-362, **12**-412, **15**-528, **15**-915, **15**-1602
Marelli, C. **16**-943
Marets, J. **15**-1239
Marfat, A. **15**-979
Margaretha, P. **7**-1
Margarita, R. **19**-199, **19**-1747
Margerison, D. **6**-59, **6**-60
Margeta, R. **16**-2193
Margolin, Z. **6**-84, **6**-85, **8**-58
Margraf, D. **5**-66
Margrave, J.L. **5**-370, **14**-150
Margues, A. **19**-788
Margulis, M.A. **7**-74
Margulis, T.N. **4**-391
Maria Colacino, F. **19**-760
Maria, P.-C. **8**-97
Maria, P. **3**-20, **8**-22
Mariampillai, B. **13**-288, **13**-414
Marianelli, R.S. **16**-1552
Mariani, A. **19**-1129, **19**-1156
Mariano, P.S. **7**-31, **7**-48, **15**-1399, **18**-908
Marianucci, E. **16**-243

Marié, J.-C. **10**-1342, **16**-1610
Mariet, N. **15**-2373
Marigo, M. **12**-123, **12**-124, **12**-156, **15**-1409, **15**-1439, **15**-1954
Marin, M. **19**-788
Marinas, J.M. **13**-643, **15**-188, **15**-482, **15**-593, **19**-1736
Marinelli, F. **15**-245, **15**-2633, **16**-146
Marinescu, L. **16**-1982
Marinescu, L.G. **16**-1982
Marinez, E.R. **11**-210
Marini, F. **10**-694
Marino-González, A. **19**-167
Marino, G. **2**-165, **10**-45, **11**-71, **11**-85, **11**-86, **11**-497
Marino, J.P. **11**-550, **19**-1763
Marion, N. **15**-203, **16**-112, **18**-269
Marioni, F. **15**-14, **15**-22
Maris, A. **3**-17
Marisco, W.E. **15**-518
Mariz, R. **15**-1269
Mark, H.W. **10**-154
Markby, R. **15**-1496
Markert, M. **16**-1020
Markezich, R.L. **19**-891
Markgraf, J.H. **19**-574, **19**-575
Markham, J. **15**-848
Markham, J.P. **15**-867, **18**-165
Markides, K.E. **9**-115
Markiewicz, M.K. **3**-118
Markina, N.A. **13**-587
Märkl, R. **10**-269
Marko, D.E. **4**-362
Marko, I. **15**-1830, **15**-1840, **15**-1841
Markó, I.E. **10**-575, **14**-216, **14**-294, **15**-349, **15**-784, **15**-1254, **15**-1393, **15**-1655, **15**-1656, **16**-659, **16**-812, **16**-1723, **16**-2038, **16**-1295
Markó, L. **15**-1618, **15**-1619, **15**-1620
Markopoulos, G. **1**-74
Markov, J. **15**-880
Markov, P. **10**-858
Marković, D. **8**-136
Markovski, L.N. **1**-12, **16**-1999
Marks, T.J. **15**-238, **15**-311, **15**-312, **15**-344, **15**-353, **15**-353, **15**-734, **15**-2024, **15**-2025, **15**-2026, **15**-2027, **15**-2028, **19**-689
Marktscheffel, F. **19**-315, **19**-1358
Markwell, R.E. **14**-153
Markworth, C.J. **13**-586
Marle, I. **4**-180
Marlier, J.F. **16**-20, **16**-1695
Maroni, R. **10**-273, **15**-1772
Marotta, E. **15**-230
Marples, B.A. **15**-1942
Marquais, S. **10**-1483, **10**-1446
Marquarding, D. **16**-2249, **16**-2253, **16**-2262, **17**-481
Marque, S. **13**-119, **15**-333
Marques, F.de.A. **16**-701
Marques, M.M.B. **16**-392
Marquet, A. **5**-145, **16**-383
Marquet, J. **13**-8, **13**-69, **13**-71, **13**-173
Marquez, R. **15**-1321
Marquez, V.E. **19**-1464
Marquié, J. **11**-218, **16**-2142, **19**-1300
Marquis, E.T. **4**-504
Marradi, M. **19**-752
Marriott, S. **9**-49, **9**-52, **9**-55
Marrot, J. **16**-1460
Marsaioli, A.J. **18**-692
Marsch, M. **5**-143
Marschner, C. **10**-1771
Marsella, J.A. **10**-944
Marsh, F.D. **12**-240
Marshall, C. **4**-103
Marshall, D.R. **11**-490
Marshall, J.A. **4**-489, **4**-491, **10**-1640, **10**-1642, **15**-260, **15**-1018, **15**-1206, **16**-612, **16**-684, **18**-784, **19**-1179
Marshall, J.L. **4**-273, **19**-19, **19**-1303
Marshall, P.A. **15**-683
Marshall, P.J. **16**-31
Marshall, R.L. **16**-616
Marshall, W.J. **12**-372
Marshall, W.S. **18**-356
Marsi, M. **17**-194
Marsman, B. **15**-1911
Marson, C.M. **10**-416, **10**-1693, **15**-399, **16**-426, **16**-426
Marstokk, K. **3**-60
Marston, C.R. **15**-258
Martel, J.P. **16**-1447
Martell, A.E. **12**-67, **15**-201, **15**-2661
Martell, A.E. **19**-698
Martelli, G. **15**-2380
Marten, D.F. **10**-1505
Martens, D. **2**-285
Martens, T. **16**-399
Marth, C.F. **16**-1345, **16**-1348
Marti, M.J. **10**-1060
Martín-Matute, B. **13**-549
Martin D. **15**-1181
Martin, A. **12**-259, **16**-1865, **16**-2035
Martin, B. **12**-667, **16**-1885
Martin, C.G. **11**-368
Martin, D. **10**-439, **16**-2186
Martin, G.J. **11**-496
Martin, H.-D. **18**-679
Martin, H. **15**-2411, **18**-684
Martin, H.J. **16**-394
Martin, I. **17**-137
Martin, J. **16**-1304
Martin, J.C. **5**-245, **12**-425, **14**-134, **14**-207, **14**-208, **15**-2396, **16**-2237, **19**-190
Martín, J.D. **18**-841
Martin, J.S. **3**-58
Martin, K. **5**-196
Martin, M.M. **4**-478, **18**-50, **18**-74
Martin, M.T. **16**-1891
Martin, N.J.A. **15**-616, **15**-617
Martin, P. **15**-1775, **15**-2384
Martin, P.S. **15**-1399
Martin, R. **10**-1383, **11**-587, **14**-422, **15**-869, **16**-872, **16**-2057
Martin, R.A. **19**-1710
Martin, R.B. **6**-35, **16**-87, **16**-288, **16**-1661
Martin, R.H. **4**-70, **4**-71, **4**-72, **4**-193, **15**-2015
Martín, S.E. **19**-125
Martin, S.F. **10**-534, **10**-1774, **10**-1841, **15**-2318, **16**-379, **16**-1252, **16**-1327, **18**-823
Martin, S.J. **15**-2083
Martín, V.S. **19**-393, **19**-579
Martin, W.B. **16**-365
Martin, W.P. **12**-334
Martina, S.L.X. **15**-1269
Martinek, T.A. **2**-486
Martinelli, G. **16**-1380
Martinelli, J.R. **13**-494
Martinelli, M.J. **16**-2290
Martinez, A.G. **10**-269, **10**-1435, **10**-1488, **11**-498, **16**-2174
Martinez, F.N. **5**-327, **14**-83, **14**-143
Martinez, G. **17**-421
Martínez, I. **16**-1414, **16**-1416
Martinez, II, E. **15**-1375
Martinez, J. **13**-397, **13**-611, **15**-701, **16**-955, **19**-760
Martínez, J.R. **11**-366
Martínez, P. **15**-791
Martínez, R. **10**-748, **10**-1721, **13**-381, **15**-1279, **16**-1526
Martinez, R.I. **19**-373
Martinez, R.L. **16**-1899
Martínez, S. **15**-2654
Martinho Simões, J.A. **1**-121
Martinon, S. **15**-2444
Martinović, S. **16**-1566
Martins, J.,E,D, **19**-1014
Martins, M.A.P. **9**-129
Martins, T.L.C. **12**-304, **15**-217, **15**-290
Martinu, T. **5**-394
Marto, S.J.L. **15**-2072
Marton, D. **16**-571
Márton, J. **11**-11
Martorell, G. **12**-410, **13**-244
Marty, W. **4**-213
Martynov, A.V. **15**-296
Martynow, J. **19**-359
Martz, J.T. **10**-1258

Marukado, R. **19**-996
Maruo, M. **15**-1446
Maruoka, H. **16**-654
Maruoka, K. **10**-665, **10**-741, **10**-1709, **12**-126, **12**-135, **12**-377, **12**-390, **12**-550, **15**-738, **15**-999, **15**-1042, **15**-1432, **15**-1433, **15**-2141, **15**-2148, **15**-2570, **16**-397, **16**-628, **16**-1128, **16**-1528, **16**-1596, **16**-1799, **16**-1949, **17**-280, **18**-141, **18**-159, **18**-366, **18**-367, **18**-738, **19**-143, **19**-918, **19**-948, **19**-978, **19**-1235, **19**-1750
Marusawa, H. **14**-124
Marutani, Y. **16**-680
Maruyama, K. **10**-1326, **10**-1448, **10**-1586, **11**-470, **14**-436, **15**-2467, **16**-460, **16**-520, **16**-522, **16**-617, **16**-1062, **19**-252, **19**-609
Maruyama, T. **14**-53, **16**-1094, **16**-1098, **16**-1490, **16**-1492
Maruyama, Y. **11**-342, **18**-198
Marvel, C.S. **4**-14
Marvell, E.N. **11**-670, **15**-461, **17**-491, **18**-174, **18**-506, **18**-532, **18**-632, **18**-758, **18**-759
Marx, A. **16**-652
Marx, J.N. **15**-178, **18**-34
Marx, K.H. **10**-1535
Marx, R. **5**-248
Maryanoff, B. **19**-1721
Maryanoff, B.E. **4**-27, **15**-2628, **15**-2635, **15**-2686, **16**-1311, **16**-1350, **16**-1355, **16**-1381, **16**-1384, **16**-1385, **19**-922, **19**-1316
Maryanoff, C.A. **4**-27, **16**-340, **16**-1069, **19**-1283, **19**-1316
Marzabadi, C. H. **4**-361
Marzi, M. **16**-1843
Marzin, C. **2**-471
Marzinzik, A. **18**-764
Marzorati, E. **17**-471
Marzorati, L. **19**-1759
Mas, R.H. **4**-442
Masada, H. **10**-614, **10**-615, **10**-619
Masaki, M. **2**-477
Masaki, Y. **10**-676, **10**-872, **19**-220, **19**-405
Masala, S. **19**-649
Masamichi, T. **7**-14
Masamune, H. **15**-1971
Masamune, S. **1**-13, **2**-233, **2**-239, **2**-245, **2**-275, **2**-278, **4**-136, **4**-152, **15**-715, **16**-754, **16**-1030, **16**-1079, **16**-1097, **16**-1373, **18**-899, **18**-902, **19**-1281
Masaya, K. **15**-999
Mascal, M. **2**-408, **3**-137, **5**-99
Mascareñas, J.L. **15**-2667, **18**-869
Masci, B. **3**-135
Masdeu, A.M. **12**-786
Mase, N. **12**-148, **15**-1056, **16**-1085
Maseras, F. **4**-50, **13**-445
Mashima, H. **13**-344
Mashima, K. **10**-929, **19**-1042
Mashyanov, M.N. **15**-179
Masias, A. **10**-520
Masilamani, D. **19**-1316
Maskell, R.K. **16**-1586
Maskill, H. **6**-33, **8**-87, **8**-171, **10**-426, **16**-2270
Maskornick, M.J. **16**-191
Maslak, P. **12**-236
Maslin, D.N. **19**-1099
Masllorens, J. **13**-432, **13**-498
Maslov, S.A. **19**-675
Maslowsky Jr., E. **12**-1
Mason, D. **10**-489
Mason, H.J. **11**-249
Mason, R. **2**-287, **2**-293, **3**-89
Mason, S.F. **4**-128
Mason, T.J. **7**-70, **7**-86, **7**-99
Masour, T.S. **10**-538
Massa, A. **15**-1971, **16**-773, **16**-775, **16**-776
Massa, W. **12**-30, **15**-95
Massaccesi, M. **11**-483, **15**-1397, **16**-610, **16**-1229, **16**-1242, **16**-1723
Massanet, G.M. **14**-200, **15**-2098, **15**-284, **15**-1851
Massat, A. **4**-307
Masselot, D. **12**-374, **13**-441
Massey, A.G. **12**-603
Masson, G. **15**-1078, **16**-812, **16**-959
Massy-Westropp, R.A. **10**-1598
Massy, D.J.R. **16**-377
Masterman, S. **10**-6, **10**-17, **16**-1667, **17**-109
Masters, A.P. **17**-394
Mastrorilli, E. **15**-37, **16**-436
Masuda, H. **15**-1686, **19**-1716
Masuda, S. **1**-32
Masuda, Y. **10**-1287, **12**-476, **12**-574, **13**-698, **13**-701, **13**-719, **15**-1282
Masui, A. **3**-177
Masui, M. **19**-495
Masui, R. **15**-1106
Masumi, N. **13**-684
Masuno, M.N. **15**-499
Masure, D. **11**-229, **15**-2295
Masuyama, A. **15**-1926
Masuyama, Y. **10**-942, **16**-464, **16**-590, **16**-612, **16**-642
Mata, J. **19**-952
Mata, P. **4**-103
Matacz, Z. **10**-1666
Mataka, S. **10**-537
Matallana, A. **4**-396
Matano, Y. **10**-1272, **19**-127
Matasa, C. **12**-210
Matassa, V.G. **12**-35
Mateescu, G.D. **5**-87, **11**-15, **11**-16
Mateo, C. **15**-2620
Mateo, S. **6**-69
Mateus, C.R. **16**-796
Matheson, A.F. **6**-81
Mathew T.S. **19**-137
Mathew, K.K. **4**-143
Mathew, L. **14**-89
Mathew, S.P. **15**-1957, **16**-1892
Mathew, T. **4**-468, **11**-154, **11**-221, **11**-241
Mathews, C.J. **19**-640
Mathey, F. **10**-1537
Mathias, J.P. **2**-342
Mathies, A.K. **16**-890
Mathieu, B. **8**-205, **11**-356, **15**-2187, **15**-2195
Mathre, D.J. **18**-329
Mathur, N.K. **16**-1930
Mathur, S.N. **10**-490
Mathvink, R.J. **15**-1469
Mathy, A. **18**-192
Matias, P. **18**-674
Matic, R. **14**-235
Matice, J.J. **11**-593
Matier, W.L. **13**-863
Matin, S.B. **19**-1115
Matínez, R. **4**-374
Matinopoulos-Scordou, A.E. **13**-630
Matlack, G.M. **19**-815
Matos, C.R. **15**-2383
Matos, K. **16**-756
Matos, M.R.P.N. **10**-1285
Matovic, R. **10**-1645
Mátrai, J. **18**-618
Matshshita, Y. **15**-199
Matsson, O. **10**-4, **10**-879, **10**-1930, **12**-64, **17**-41
Matsu, J.-i. **11**-438
Matsuba, N. **5**-271, **5**-272
Matsubara, E. **10**-1466
Matsubara, H. **14**-25, **15**-1365, **15**-1372, **19**-1065
Matsubara, K. **13**-633, **19**-1078
Matsubara, R. **19**-128
Matsubara, S. **10**-1466
Matsubara, S. **13**-457, **15**-975, **15**-1297, **15**-1358, **15**-1389, **16**-602, **16**-804, **16**-841, **16**-1430, **16**-1431, **17**-312, **19**-208, **19**-1640
Matsubara, Y. **11**-576, **15**-2089
Matsubra, S. **16**-1425
Matsuda, A. **16**-1331, **18**-523
Matsuda, H. **12**-327, **12**-792, **16**-1836, **17**-312, **19**-1127
Matsuda, I. **10**-1543, **15**-1125, **15**-1588, **15**-1593, **16**-1183
Matsuda, K. **5**-304, **19**-60
Matsuda, S. **14**-416

Matsuda, T. **11**-538, **13**-811, **14**-406, **14**-408, **14**-410, **15**-225, **19**-963, **19**-994, **19**-995, **19**-996
Matsuda, Y. **2**-348
Matsugi, M. **12**-257, **14**-11, **18**-821
Matsuhashi, H. **10**-1269, **10**-1276, **15**-1933
Matsui, H. **16**-24
Matsui, K. **16**-955
Matsui, T. **9**-26, **15**-198, **15**-199, **16**-841
Matsukawa, M. **17**-207
Matsukawa, S. **10**-1660, **16**-611, **16**-1157, **16**-1170, **19**-1650
Matsukawa, Y. **15**-940
Matsuki, K. **19**-1458
Matsukida, H. **15**-1333
Matsumasa, K. **15**-1477
Matsumoto, A. **5**-291
Matsumoto, H. **3**-131, **10**-544, **13**-481
Matsumoto, K. **6**-57, **9**-85, **9**-86, **10**-506, **10**-1466, **12**-257, **15**-1886, **15**-1984, **15**-2348, **16**-1062, **16**-1199, **16**-1218, **16**-1525, **16**-1940, **16**-1944, **16**-2132, **19**-800, **19**-1758
Matsumoto, M. **2**-333, **2**-335, **4**-220, **10**-1267, **15**-2357, **19**-416
Matsumoto, N. **16**-1143, **16**-1181
Matsumoto, S. **15**-370
Matsumoto, T. **10**-534, **13**-55, **16**-806, **16**-1587
Matsumoto, Y. **10**-715, **15**-1185, **16**-771
Matsumura, A. **15**-962
Matsumura, R. **10**-695
Matsumura, S. **19**-215, **19**-1328
Matsumura, T. **15**-2528
Matsumura, Y. **5**-263, **18**-299, **18**-367, **19**-142, **19**-984, **19**-1156
Matsumura, Y. **19**-1546
Matsunaga, M. **10**-782, **19**-800
Matsunaga, N. **1**-97, **2**-42, **5**-253, **5**-282
Matsunaga, S. **10**-713
Matsunaga, S. **15**-406, **15**-1034, **15**-1071, **15**-1382, **15**-1405, **16**-396, **16**-411, **16**-940, **16**-1090, **16**-1326, **16**-1449, **16**-1480, **19**-327, **19**-1654
Matsunaka, K. **19**-546
Matsuo, H. **16**-1098
Matsuo, J.-i. **10**-1707, **11**-290, **11**-438
Matsuo, K. **12**-754
Matsuo, T. **16**-1170
Matsuoka, H. **10**-1466, **19**-1640
Matsuoka, K. **19**-982
Matsuoka, K. **19**-1050
Matsuoka, M. **19**-950
Matsuoka, T. **13**-352, **15**-995
Matsushima, Y. **10**-1544
Matsushita, M. **5**-298, **11**-418
Matsushita, N. **10**-1816
Matsushita, T. **10**-289, **15**-1720
Matsushita, Y. **15**-198
Matsuura, A. **2**-137
Matsuura, H. **16**-640
Matsuura, T. **15**-2360, **18**-940, **19**-275
Matsuura, Y. **4**-347, **13**-451, **13**-565, **15**-386
Matsuya, T. **14**-26
Matsuya, Y. **18**-496, **18**-497
Matsuyama, H. **11**-260
Matsuyama, K. **5**-312, **10**-1761, **16**-524
Matsuyama, Y. **10**-1541
Matsuza, S. **15**-1139
Matsuzaki, S. **10**-762
Matsuzawa, S. **16**-699
Matsuzono, M. **13**-741
Matt, C. **10**-1972
Matt, D. **3**-189
Matt, J.W. **18**-77
Mattalia, J.-M. **16**-527
Mattay, J. **4**-94, **14**-87
Matte, D. **12**-761
Mattern, R.-H. **17**-157
Mattes, H. **10**-1209
Mattes, K. **13**-51
Mattes, S.L. **15**-2462
Matteson, D.S. **10**-1876, **10**-1878, **12**-482, **12**-494, **15**-671, **15**-697, **15**-1798, **16**-1459, **18**-451, **18**-467
Matteucci, M. **19**-775
Matthews, G.J. **15**-1766
Matthews, I.R. **10**-1619
Matthews, P.S.C. **1**-2
Matthews, R.T. **5**-222
Matthews, W.S. **5**-112, **17**-346
Matthey, G. **11**-517
Mattson, A.E. **15**-1056, **15**-1455, **15**-1487, **16**-722
Mattson, R.J. **16**-339
Matturo, M.G. **4**-540
Matty, L. **19**-1135
Matui, C. **10**-1192
Matula, T. J. **7**-79
Matusamy, S. **12**-382, **15**-864
Matusch, R. **2**-197, **17**-512
Matuszewski, B. **17**-515
Matveev, A.A. **10**-215, **10**-456
Matveeva, E.D. **10**-1163
Matveeva, M.K. **13**-807
Matvienko, V.N. **10**-278
Matxain, J.M. **2**-451
Matyusha, A.A. **11**-361
Matz, J.R. **14**-454, **14**-455
Matzger, A.J. **2**-317, **18**-522
Matzner, E. **15**-2313
Mauder, H. **16**-2209
Mauduit, M. **15**-1181, **16**-645, **18**-821, **18**-848
Maughan, P.J. **11**-606
Mauksch, M. **2**-370, **2**-373
Mauleón, P. **15**-1273, **15**-2389, **18**-275
Maulide, N. **15**-404, **18**-166
Maulitz, A.H. **2**-87
Maumy, M. **11**-573, **19**-271
Maunders, B.M. **18**-873
Maurel, R. **10**-807
Maurer, S. **13**-100
Mauret, P. **15**-2646
Maurin, J. **8**-189
Maury, O. **18**-873
Mautner, B. **19**-217
Mauzé, B. **16**-1679
Maverick, A. **10**-422
Maverick, E. **2**-299
Mävers, U. **16**-1323
Mavis, M.E. **16**-1592
Mavropoulos, I. **15**-267
Maw, G. **12**-480
Maw, G.A. **17**-111, **17**-112, **17**-127
Mawson, S.D. **12**-203
Maxton, P.M. **3**-77
Maxwel, J.I. **8**-56
Maxwell, A.C. **10**-1044
Maxwell, C.R. **10**-1619
Maxwell, R.J. **14**-170, **18**-47
May, E.J. **15**-2529
May, E.L. **11**-407
May, G.L. **14**-371
May, H. **10**-661
May, J.A. **17**-282
May, L.M. **19**-75
May, P.J. **9**-15
May, S.A. **11**-339
Maya, V. **16**-1085
Mayadunne, R.T.A. **15**-1350
Mayahi, M.F. **14**-122, **16**-1957
Mayasundari, A. **13**-377
Maye, J.P. **15**-814
Mayer, A. **19**-1776
Mayer, E. **11**-371
Mayer, J. **2**-300, **9**-107
Mayer, J.M. **14**-31, **19**-440
Mayer, M. **10**-1495
Mayer, P. **16**-665
Mayer, R. **16**-2, **16**-184, **16**-1833, **19**-1433, **19**-1768, **19**-1778
Mayer, S.F. **10**-727
Mayer, U. **14**-284
Mayers, D.A. **18**-127
Maynard, G.D. **12**-698
Maynes, G.G. **15**-143
Mayo, F.R. **14**-36, **14**-237, **15**-63, **15**-171
Mayo, P. **18**-162
Mayon, P. **15**-1320
Mayoral, E.P. **18**-607
Mayoral, J.A. **15**-2238, **15**-2244, **15**-2248, **15**-2524, **16**-682

Mayr, H. **5**-74, **5**-104, **10**-12, **10**-32, **10**-39, **10**-48, **10**-298, **10**-375, **10**-393, **10**-394, **10**-395, **10**-396, **10**-397, **10**-398, **10**-399, **10**-400, **10**-401, **10**-402, **10**-438, **10**-1463, **10**-1784, **11**-225, **11**-346, **13**-95, **15**-2, **15**-30, **15**-749, **15**-1769, **15**-1770, **15**-2095, **15**-2149, **15**-2422, **16**-1065, **16**-1369, **16**-1489
Mazet, C. **18**-266
Mazhar-Ul-Haque. **16**-1354
Mazid, M. **15**-1167
Mazidi, M.R. **16**-68
Mazik, M. **3**-71
Mazloumi, Gh. **16**-1860
Mazuela, J. **15**-452
Mazume, T. **16**-1835
Mazur, R.H. **10**-206
Mazur, S. **2**-262
Mazur, U. **19**-366
Mazur, Y. **10**-761, **10**-789, **16**-160, **16**-1831, **19**-435, **19**-743
Mazzacani, A. **15**-1930, **16**-212, **16**-1202, **19**-466
Mazzanti, A. **4**-56, **4**-57, **4**-90, **4**-325, **4**-327, **4**-436, **15**-1106
Mazzeo, C. **18**-124
Mazzola Jr., R.D. **15**-1530
Mazzone, L. **10**-1377
McAdoo, D.J. **18**-570
McAlister, D.R. **15**-2644
McAlister, J.A. **16**-1706
McAllister, M.A. **3**-3, **3**-45, **4**-230, **16**-2236
McAllister, T.L. **12**-298
McArthur, D. **19**-1021
McBee, E.T. **11**-224
McBee, E.T. **14**-78
McBride, J. **5**-243
McBride, J.M. **2**-260, **4**-193, **18**-57
McCabe, J.F. **3**-75
McCague, R. **2**-295, **2**-298
McCall, J.M. **18**-909
McCall, M.J. **18**-32
McCann, D.M. **4**-115
McCann, S. **18**-704
McCapra, F. **9**-15
McCarney, C.C. **17**-394
McCarrick, M.A. **15**-2315
McCarroll, A.J. **15**-1310
McCarry, B.E. **15**-820, **19**-891
McCarthy Jr., J.R. **18**-44
McCarthy, D.G. **6**-51, **17**-480
McCarthy, J.R. **10**-925, **12**-196, **13**-558, **16**-339
McCarthy, K.E. **10**-1426
McCarty, C.G. **4**-227, **17**-453, **18**-335, **18**-934
McCasland, G.E. **4**-19
McCaulay, D.A. **11**-637
McCauley, M.D. **19**-1436
McCay, P.B. **5**-273
McCleland, C.W. **11**-290, **15**-1663
McClellan, A.L. **1**-37, **3**-36
McClelland, R.A. **5**-12, **5**-428, **8**-130, **9**-67, **10**-47, **10**-346, **10**-561, **13**-859, **16**-25, **16**-29
McCloskey, C.J. **19**-1692
McCloskey, P.J. **11**-692
McClung, R.E.D. **15**-12
McClure, C.K. **15**-1827, **15**-2177
McClure, C.K. **16**-1814
McClure, J.D. **18**-396
McClure, M. **18**-161
McCluskey, A. **10**-974, **11**-402, **16**-635
McCluskey, C. **10**-670
McCombie, S.W. **10**-1351, **16**-2310
McCombs, D.A. **15**-580
McConaghy Jr., J.S. **5**-435
McConvey, I.F. **13**-392
McConvey, I.F. **13**-501
McCormick, J.R.D. **16**-1339
McCormick, M.M. **15**-2636
McCortney, B.A. **10**-114
McCown, J.D. **10**-411
McCoy, L.L. **3**-46, **14**-202, **14**-205
McCubbin, Q.J. **15**-1616
McCulla, R.D. **13**-428, **16**-1439, **17**-287
McCullagh, J.V. **15**-1485, **15**-2619
McCullough, J.J. **15**-114, **15**-2679
McCullough, K.J. **4**-89
McCullough, L.G. **18**-884
McDaid, P. **15**-1447, **16**-1732
McDaniel, A.L. **10**-920
McDaniel, C.W. **3**-106, **4**-182
McDaniel, D.H. **3**-61, **8**-25, **8**-47, **8**-83, **9**-33
McDermott, M. **10**-493, **19**-828
McDermott, P.J. **14**-465
McDonagh, P.M. **4**-382
McDonald, D.Q. **15**-124
McDonald, F.E. **15**-231, **15**-246, **15**-353, **18**-641
McDonald, J.H. **4**-144
McDonald, K. **12**-407
McDonald, R. **4**-75
McDonald, R.L. **8**-140
McDonald, R.N. **18**-260
McDonald, S.R. **10**-467
McDonough, C.S. **18**-736
McDougal, P.G. **4**-214, **15**-2003
McDougall, A.O. **16**-39
McDougall, P.J. **16**-1196
McElvain, S.M. **10**-678
McElvany, S.W. **2**-393
McEnroe, F.J. **16**-532
McEwen, A.B. **4**-250, **15**-462
McEwen, I. **3**-63, **17**-53, **17**-139, **17**-198
McEwen, W.E. **16**-1346, **16**-1356, **18**-593
McFarland, C. **18**-731
McFarlane, F.E. **10**-175, **16**-2005
McGaffin, G. **18**-608, **18**-625
McGahan, T.J. **10**-722
McGahey, L.F. **12**-14
McGarraghy, M. **12**-87, **12**-446
McGarrigle, E.M. **15**-1983, **15**-1986, **16**-1450, **19**-767
McGarrity, J.F. **10**-423, **10**-657, **19**-349
McGarrity, M.J. **10**-18
McGarry, D.G. **16**-878
McGarvey, B.R. **15**-445
McGarvey, G. **12**-648
McGarvey, G.J. **12**-598
McGee Jr., H.A. **15**-2494
McGee, L.R. **16**-1046
McGee, M.J. **19**-433
McGee, T.W. **15**-1665
McGeoch, G.D. **19**-1156
McGhie, J.F. **19**-1390, **19**-1391
McGill, C.K. **13**-761
McGill, P. **15**-1889
McGillivray, G. **13**-109
McGirk, R.H. **10**-57
McGlinchey, M.J. **2**-386, **12**-625
McGoff, D. **8**-85
McGouran, J.F. **15**-1932
McGrail, P.T. **10**-1295, **15**-1347
McGrath, B.P. **14**-210
McGrath, D.V. **15**-1835
McGrath, M.J. **12**-440
McGreer, D.E. **17**-504
McGregor, S.D. **17**-354
McGuchan, D.C. **13**-745
McGuiness, J.A. **14**-181
McGuire, M.A. **16**-2221, **16**-2122
McGuire, M.J. **18**-669
McGuirk, P.R. **15**-979
McHenry, B.M. **14**-454
McInnis, C.E. **18**-262, **18**-263
McInnis, E.L. **18**-499
McIntosh, A.I. **15**-452
McIntosh, C.L. **2**-238, **13**-51
McIntosh, M.C. **4**-127, **18**-731
McIntyre, J.S. **5**-16
McIsaac Jr., J.E. **10**-392
McIver Jr., R.T. **2**-414, **8**-240, **8**-248, **8**-252, **8**-253, **12**-694, **16**-1673, **19**-17
McIver, E.G. **10**-618
McKean, D.R. **10**-1107, **12**-326, **17**-194
McKee, B.H. **10**-1461
McKeer, L.C. **11**-262
McKelvey Jr., J.M. **11**-304
McKelvey, D.R. **1**-3, **6**-94
McKelvey, R.D. **14**-115, **18**-913
McKelvie, N. **16**-1317
McKendrick, J.J. **3**-163
McKendry, S. **15**-2096
McKennis, J.S. **18**-675
McKennon, M.J. **13**-870, **19**-1063
McKenzie, A. **15**-7
McKenzie, C.J. **16**-110
McKenzie, J.R. **15**-1139
McKeown, E. **14**-256

McKervey, M.A. **4**-51, **4**-478, **10**-595, **12**-367, **12**-392, **12**-721, **15**-2497, **18**-50, **18**-114, **19**-1757
McKie, J.A. **16**-483
McKiernan, G.J. **16**-1428
McKillop, A. **11**-235, **11**-412, **13**-109, **13**-110, **13**-270, **13**-297, **13**-747, **14**-377, **14**-412, **14**-414, **16**-1483, **16**-1710, **16**-1930, **16**-2120, **16**-2159, **19**-88, **19**-391, **19**-435, **19**-748, **19**-829
McKinley, N.F. **10**-1591
McKinnell, R.M. **11**-136, **19**-124
McKinney, R.J. **15**-1625
McKinnis, B.R. **16**-443
McKinnon, D.M. **3**-60
McKittrick, B.A. **10**-528
McKnight, C. **18**-70
McKoon, E. **15**-651
McKusick, B.C. **15**-74, **10**-1936, **15**-2399, **15**-2490, **16**-185
McLachlan, A.D. **2**-422
McLafferty, F.J. **2**-42
McLafferty, F.W. **14**-185
McLane, R.C. **16**-975
McLauchlan, K.A. **5**-230
McLaughlin, E.C. **19**-570
McLaughlin, M. **13**-536, **15**-1548
McLaughlin, M.L. **6**-29
McLaughlin, T.G. **19**-694
McLay, G.W. **16**-1710
McLeish, M.J. **19**-1556
McLennan, D.J. **6**-76, **10**-89, **17**-39, **17**-40, **17**-65, **17**-72, **17**-78
McLeod Jr., W.D. **16**-997
McLeod, D. **16**-1371
McLeod, M.C. **10**-639
McLeod, M.D. **15**-2016
McLLee, I. **10**-320
McMahon, R.J. **5**-418, **18**-236
McMahon, T.B. **10**-13
McManus, S. **10**-113, **10**-451
McManus, S.P. **5**-1, **5**-427, **10**-70, **10**-131, **10**-324, **10**-345, **10**-463, **12**-360, **13**-39, **14**-2, **16**-174
McMasters, D. **2**-362
McMillan, F.H. **19**-1775
McMillan, W.D. **2**-77
McMillen, D.F. **5**-278
McMillen, D.W. **15**-1638
McMorran, D.A. **15**-1484
McMullan, R.K. **1**-83, **18**-674
McMurdie, N. **10**-341
McMurry, J. **10**-1245
McMurry, J.E. **3**-67, **3**-68, **4**-255, **10**-432, **10**-1419, **10**-1432, **10**-1579, **10**-1961, **12**-49, **12**-265, **16**-1113, **17**-333, **17**-404, **19**-1659, **19**-1682, **19**-1683, **19**-1687, **19**-1691, **19**-1693
McMurry, M.E. **8**-180
McNabb, S.B. **16**-1606
McNally, S.J. **15**-1033, **15**-1481
McNamara III, W.B. **7**-74, **7**-76
McNamara, C.A. **15**-1829
McNaught, A.D. **5**-6, **6**-53
McNeil, A.J. **10**-1702
McNeill, E. **13**-707
McNeill, K. **16**-255
McNesby, J.R. **5**-407, **12**-401
McNulty, J. **7**-101, **16**-1371, **16**-1748
McOsker, C.C. **19**-1288
McPake, C.B. **10**-640, **16**-103
McParland, M. **18**-302
McPhee, D.J. **19**-1516
McQuade, D.T. **16**-792
McQuilkin, R.M. **2**-329, **2**-334
McQuillin, F.J. **15**-445
McRiner, A.J. **15**-568
McRowe, A.W. **18**-100
McShane Jr., H.F. **16**-2189
McShane, C.M. **2**-214
McSweeney, J.V. **13**-752
McTigue, P. **8**-45
McTigue. P.T. **8**-41
McWilliams, J.C. **19**-1142
Mdleleni, M.M. **7**-74
Meah, M.Y. **10**-682
Meakin, P.Z. **15**-492
Mealy, M.J. **18**-437
Meanwell, N.A. **11**-460
Mebane, R.C. **15**-1714, **16**-304, **19**-1297
Mecca, T.G. **10**-236
Mechiorre, P. **10**-972
Mečiarová. M. **9**-130, **13**-182, **15**-1443, **19**-557
Meckler, H. **16**-416
Medda, A.K. **16**-1511
Médebielle, M. **13**-57, **16**-717
Medeiros, M.E. **13**-379
Medeiros, M.R. **14**-19, **19**-1387
Medel, R. **15**-303
Medici, A. **15**-1953
Medici, A. **19**-223, **19**-842
Medina, J.R. **15**-688
Medina, M.A. **5**-148, **5**-190
Medina, R. **13**-35
Medina, S. **15**-2683
Mee, S.P.H. **12**-283
Meehan, G.V. **18**-587
Meek, A.G. **10**-216
Meek, J.S. **17**-12
Meel, M.J. **11**-351
Meerbeek, T.G. **18**-356
Meerdink, J.E. **10**-1030
Meerwein, H. **10**-767, **12**-360, **18**-14
Meetsma, A. **15**-1795
Megarity, E.D. **7**-58
Meghani, P. **16**-775
Meguro, M. **10**-1003, **10**-1625, **15**-377
Mehdi, H. **19**-126
Mehdinejad, H. **13**-235
Meher N.K. **5**-99
Mehler, G. **15**-638
Mehler, K. **5**-170
Mehltretter, G. **11**-543
Mehltretter, G.M. **19**-231
Mehrdad, M. **10**-968
Mehrotra, A. **10**-832
Mehrotra, A.K. **15**-2391, **16**-147, **16**-1626
Mehrsheikh-Mohammadi, M.E. **10**-322
Mehta, A.S. **17**-249
Mehta, G. **16**-7, **16**-8
Mehta, S. **10**-1270, **19**-816
Mei, X. **13**-205
Mei, Y. **10**-855, **12**-114, **16**-157, **16**-1084, **19**-302
Mečiarová, M. **7**-96, **7**-97
Meidar, D. **10**-1216, **11**-678, **15**-202
Meidine, M.F. **10**-1049
Meienhofer, J. **16**-1909, **16**-1929, **16**-2262
Meier, G.B. **19**-1520
Meier, G.P. **16**-1353
Meier, H. **2**-72, **4**-492, **4**-493, **12**-676, **15**-2232, **18**-219
Meier, M. **18**-435
Meier, M.S. **2**-407
Meier, T. **10**-1525, **10**-1528
Meiere, S.H. **15**-2260
Meignein, C. **16**-709
Meijer, A. **11**-291, **15**-2214
Meijer, E.W. **7**-65, **11**-508, **12**-779
Meijer, J. **10**-245, **12**-525, **15**-981
Meijer, R.H. **19**-209
Meijide, F. **12**-737
Meinecke, A. **10**-1617
Meinema, H.A. **15**-550
Meinhold, P. **15**-1907
Meintzer, C.P. **14**-177
Meinwald, J. **4**-241, **4**-456, **12**-243, **15**-1751, **17**-272, **18**-146, **18**-678
Meinwald, Y.C. **4**-81, **4**-456, **15**-1751
Meisenheimer, J. **13**-7
Meisinger, R.H. **2**-283
Meislich, H. **10**-238
Meister, A. **16**-2266
Meister, H. **17**-253
Meisters, A. **10**-1582, **15**-1217, **16**-654, **16**-2088
Meixner, A. **2**-480
Méjica, C. **15**-2527
Mejuto, J.C. **3**-184
Meketa, M.L. **12**-128
Mekhalfia, A. **14**-216, **14**-294
Mekhtiev, S.D. **11**-414
Mekhtieva, V.Z. **15**-264
Mekley, N. **5**-424
Melamed, D.B. **12**-733
Melamed, M. **12**-472

Melamed, U. **5**-142
Melander, C. **15**-1887
Melander, L. **6**-66, **11**-7
Melandri, S. **3**-17
Melby, L.R. **3**-102
Melchiorre, P. **10**-616, **11**-314, **15**-1106, **16**-1513
Mele, G. **18**-124
Melega, W.P. **2**-191
Meléndez, H.J. **19**-1158
Melera, A. **2**-301
Meleson, K. **15**-2112
Meli, A. **15**-278, **15**-2645
Melikyan, G.G. **15**-1783
Melikyan, V.R. **16**-1545
Mella, M. **11**-314
Mello, R. **18**-387, **19**-70, **19**-479, **19**-777
Mellon, M.G. appendixa-1
Melloni, A. **10**-1544
Melloni, G. **10**-273, **11**-381, **15**-35, **15**-80, **15**-83, **15**-1772, **19**-1519
Mellor, D.P. **4**-8
Mellor, J.H. **14**-287
Mellor, J.M. **4**-249, **15**-2004, **15**-2085, **19**-423
Melman, A. **16**-1772
Melnyk, O. **12**-106
Melpolder, J.B. **2**-50
Melville, M.G. **11**-509
Melvin Jr., L.S. **2**-94, **16**-1441, **16**-1470
Melzer, B. **11**-663
Memarian, H.R. **19**-30, **19**-31
Ménage, S. **15**-1949
Menapace, H.R. **18**-806
Ménard, F. **16**-261
Menashe, N. **15**-213
Mencarelli, P. **4**-53, **5**-252
Menche, D. **16**-343, **16**-576
Menche, G. **16**-343
Mende, U. **2**-238
Mendenhall, G.D. **14**-254, **19**-275
Mendes, L.V.P. **13**-591
Mendes, S.R. **15**-297
Méndez-Andino, J. **18**-827
Méndez, F. **8**-173
Méndez, M. **10**-1548, **15**-812, **15**-853
Mendonca, J.de S. **19**-1070
Mendoza, J.S. **19**-1215
Menegheli, P. **11**-524
Menéndez, J.C. **10**-1039, **15**-2334
Menendez, M. **16**-115
Meneses, L. **11**-436
Meneses, R. **15**-597, **19**-912
Meneyrol, J. **19**-1234
Menezes, P.H. **10**-851, **15**-943, **15**-1436
Meng, F. **13**-206
Meng, G. **19**-1605
Meng, J.-q. **15**-553
Meng, Q. **12**-96, **12**-97, **15**-307
Meng, T. **16**-572
Meng, X.-J. **19**-1008
Meng, Z. **13**-43
Menge, W.M.P.B. **16**-1305
Mengel, W. **16**-1282
Mengenhauser, J.V. **16**-2190
Menger, F.M. **3**-149, **4**-456, **6**-13, **10**-189, **16**-30, **16**-1698, **19**-108
Mengler, H. **16**-2164
Menichetti, S. **15**-1738
Mennen, S. **15**-1487, **16**-722
Menon, B. **5**-117, **5**-137, **8**-72, **8**-73
Menon, B.C. **12**-669
Menon, R.S. **16**-871
Menoret, G. **18**-141
Mentzel, M. **19**-1117
Menyailo, A.T. **19**-331
Menzel, K. **12**-308
Menzer, S. **3**-194
Meot-Ner, M. **3**-3, **5**-27, **8**-207, **8**-240
Meot-Ner (Mautner), M. **3**-5
Méou, A. **15**-1039, **15**-2091
Meracz, I. **15**-2226
Merbouh, N. **19**-186
Merced, F.G. **19**-1158, **19**-1234
Mercero, J.M. **16**-1679
Mercier, F. **10**-1537
Mereddy, A.R. **12**-508, **13**-576
Meredith, C.C. **2**-150
Merényi, R. **5**-256, **5**-258, **15**-2388, **15**-2432, **15**-2584, **17**-361, **18**-671, **18**-672, **19**-1772
Merer, A.J. **7**-16
Meresz, O. **16**-1551
Mereyala, H.B., **16**-1788
Mergelsberg, I. **14**-497
Merger, F. **16**-1761
Merinero, J.A.V. **19**-325
Merino, E. **15**-163
Merino, G. **2**-9
Merino, P. **16**-979
Merk, W. **18**-535, **18**-536
Merkel, A. **10**-363
Merkert, J. **15**-1399
Merkley, J.H. **15**-888
Merkushev, E.B. **11**-281, **12**-551, **13**-269, **19**-719
Merle, D. **16**-2261
Merlic, C.A. **10**-1558, **15**-2475
Merlin, A. **12**-761
Mermerian, A.H. **16**-2128
Mero, C.L. **15**-1298
Merola, J.S. **4**-442
Mérour, J.-Y. **19**-1605
Merrer, D.C. **18**-89
Merrifield, J.H. **10**-1969
Merrifield, R.B. **16**-1928, **16**-1929, **16**-1931, **16**-1932
Merrigan, S.R. **15**-2280
Merrill, R.E. **10**-1337
Merritt, A. **10**-1935
Merritt, A.T. **16**-325
Merritt, E.A. **16**-117
Merritt, J.E. **15**-937
Merritt, M.V. **10**-770
Merstetter, P. **5**-335, **5**-341
Mert, O. **16**-218
Mertes, K.B. **3**-160
Mertes, M.P. **3**-160
Mertins, K. **11**-349
Mesaros, E. **4**-79
Meshcheryakov, A.P. **14**-316
Meshram, H.M. **11**-396, **16**-1717, **16**-1859, **19**-774, **19**-1205, **19**-1580
Mesic, M. **10**-133
Meske-Schüller, J. **4**-505
Meskens, F.A.J. **16**-120, **16**-128
Mesnard, D. **10**-1604, **10**-1898, **17**-154
Messe, O. **10**-1757
Messeguer, A. **19**-371
Messer, L.A. **19**-442
Messinger, J. **16**-422
Messmer, G.G. **13**-11
Mestdagh, H. **10**-2006
Mester, L. **16**-280
Mestre, V.L. **15**-2225
Mestres, R. **18**-336, **19**-817
Mészáros, L. **16**-2112
Meta, C.T. **19**-880
Metcalf, B.W. **2**-329, **2**-358
Metelitsa, D.I. **14**-218
Metesich, M.A. **12**-679
Meth-Cohn, O. **5**-427, **11**-493
Metoki, K. **15**-2220
Metsger, L. **19**-584
Metts, L. **7**-58
Metz, M.V. **15**-353, **15**-2027, **15**-2028
Metz, P. **18**-742
Metz, W.A. **15**-2506
Metzger, A. **10**-1456, **10**-1463
Metzger, J. **13**-822, **13**-830
Metzger, J.O. **15**-748, **15**-1285
Metzner, P. **16**-4, **16**-231, **16**-1451
Meul, T. **2**-351
Meuldijk, J. **19**-209
Meunier, B. **18**-377
Meunier, P. **13**-590
Meunier, S. **16**-1937
Meurer, E.C. **16**-1412
Meurer, K.P. **4**-70
Meurling, P. **16**-182
Mevius, K. **10**-933
Meybodi, F.A. **18**-343
Meyer, A.Y. **9**-68, **9**-72
Meyer, C. **16**-766, **16**-2075, **18**-349, **18**-833
Meyer, C.J. **14**-223
Meyer, D.T. **2**-399
Meyer, E. **16**-1905
Meyer, E.A. **3**-78
Meyer, F. **16**-896
Meyer, F.E. **12**-285, **13**-439

Meyer, F.J. **5**-158
Meyer, G. **13**-155, **13**-484
Meyer, G.R. **15**-32, **15**-606
Meyer, J. **19**-1259
Meyer, J.W. **11**-598
Meyer, K.H. **2**-464, **18**-270, **19**-1435
Meyer, M.D. **19**-442
Meyer, M.P. **15**-994, **19**-149
Meyer, M.W. **11**-643, **11**-645
Meyer, N. **10**-1844
Meyer, O. **15**-1070
Meyer, R.G. **18**-905
Meyer, S.D. **19**-192
Meyer, W.L. **4**-402
Meyers, A.I. **4**-149, **4**-175, **10**-1768, **10**-1836, **10**-1837, **10**-1846, **10**-1848, **10**-1849, **10**-1851, **10**-1852, **10**-1853, **10**-1854, **10**-1855, **10**-1856, **10**-1857, **12**-349, **12**-429, **13**-469, **13**-485, **13**-724, **14**-471, **19**-1063
Meyers, C. **13**-190
Meyers, C.Y. **14**-449, **15**-296, **17**-224, **17**-346, **17**-516, **19**-768, **19**-1575
Meyerson, S. **13**-831, **18**-21, **18**-23, **18**-25, **18**-26
Meynhardt, B. **15**-2507
Meystre, C. **19**-1005
Mhehe, G.L **19**-871
Mi, A.-Q. **15**-1272, **16**-1082, **16**-1084
Mi, A. **19**-1255
Mi, X. **15**-1055, **16**-786, **16**-794
Miani, F. **17**-269
Miano, J.D. **7**-28
Miao, C.-X. **19**-179
Miao, G. **10**-1404, **10**-1438, **13**-506, **15**-1240
Miao, H. **15**-245
Miao, M. **16**-544
Miao, Q. **16**-589, **16**-612
Mibae, J. **19**-1717
Micalizio, G.C. **15**-843
Micetich, R.G. **19**-1624
Micha-Screttas, M. **14**-452, **18**-201
Michael, A. **15**-8, **17**-14
Michael, F.E. **15**-415
Michael, P. **16**-1344
Michael, U. **16**-2085
Michaelis, D.J. **15**-2017
Michaels, R.J. **10**-1668
Michaelsen, H. **18**-608
Michaely, W.J. **10**-1984
Michailenko, I.E. **17**-155
Michalczyk, M.J. **1**-13, **1**-14
Michalik, D. **10**-933
Michaud, G. **10**-1893, **13**-816
Michaut, M. **15**-806
Michaux, J. **15**-333
Michejda, C.J. **15**-1640
Michel, P. **16**-1344
Michelet, V. **15**-242, **15**-972, **15**-1008
Michelot, D. **18**-785
Michels, H.P. **2**-328
Michibata, T. **19**-1077
Michl, J. **1**-12, **1**-13, **1**-14, **2**-243, **3**-174, **4**-453, **4**-490, **4**-518, **4**-519, **7**-1, **18**-494, **18**-562
Michno, D.M. **18**-499
Michrowska, A. **18**-832
Mickelson, E.T. **19**-731
Miclo, Y. **19**-1565
Micskei, K. **12**-332
Middlemiss, D. **15**-1554, **15**-2096
Middleton, W.J. **10**-1139
Midland, M.M. **12**-458, **12**-515, **10**-1872, **10**-1881, **12**-466, **12**-470, **12**-515, **14**-16, **16**-539, **18**-484, **18**-486, **19**-1009, **19**-1011, **19**-1045
Midorikawa, H. **10**-1810
Miekka, R.G. **17**-44
Mielert, A. **15**-2184, **15**-1106
Mielniczak, G. **19**-765
Mierop, A.J.C. **15**-44
Mieszała, A. **14**-101
Mieusset, J.-L. **5**-393, **17**-391
Mifsud, M. **16**-395
Miftakhov, M.S. **14**-428
Migdal, C.A. **17**-77
Miginiac, L. **10**-1604, **10**-1898, **12**-33, **15**-1135, **17**-154
Miginiac, P. **15**-43, **15**-1156
Migita, T. **10**-1327, **10**-1738, **10**-1970
Migliorese, K.G. **15**-1698
Mignani, G. **4**-63, **12**-703, **15**-767
Mignani, S. **15**-2155
Mignard, M. **15**-1917
Mignini, E. **16**-827
Mignogna, A. **16**-849
Mignonac, S. **13**-665
Mihailovic, M.Lj. **14**-229, **14**-233, **14**-234, **14**-235, **19**-6
Mihalic, Z. **10**-155
Mihanparast, S. **13**-614
Mihara, J. **15**-1985, **19**-461
Mihara, M. **10**-648, **15**-1519, **16**-1424
Mihelich, E.D. **4**-175, **10**-1853, **10**-1854
Mihovilovic, M.D. **10**-1339, **18**-389
Miiller, D.E. **19**-19
Mijlhoff, F.C. **4**-329
Mijs, W.J. **19**-10
Mikaelyan, R.G. **5**-349
Mikami, K. **4**-64, **13**-244, **15**-857, **15**-1025, **16**-716, **16**-728, **16**-1170, **16**-1574, **18**-776, **18**-784, **19**-1367
Mikami, M. **3**-77
Mikami, S. **15**-1358
Mikawa, H. **15**-2401
Mikhael, I. **10**-1522
Mikhail, G. **15**-2445
Mikhail, G.K. **18**-245
Mikhailov, B.M. **1**-80, **2**-39, **10**-1879
Mikhailov, I.E. **18**-574
Mikhaleshvili, I.L. **15**-50
Miki, K. **3**-177, **15**-236, **16**-1965
Miki, T. **16**-1058, **16**-1922
Miko ajczyk, M. **4**-48
Mikol, G.J. **19**-1734, **19**-1765
Mikolajczyk, M. **10**-865, **15**-1296, **16**-2187, **19**-773, **19**-799, **19**-803, **19**-1583
Milakofsky, L. **10**-461
Milan, A. **10**-602
Milan, D.S. **16**-2297
Milanesi, S. **13**-832
Milano, D. **15**-2004
Milaszewski, R.F. **10**-237
Milburn, R.M. **15**-84
Milburn, R.R. **16**-676
Milcoveanu, A.B. **7**-99
Mile, B. **5**-212, **19**-367
Milenkov, B. **12**-702
Miles J.H. **11**-650
Miles, B. **16**-1066
Miles, D.E. **3**-34
Miles, M.L. **16**-2153
Miles, T.J. **10**-1619, **17**-367
Miles, W. **14**-103
Milesi, L. **17**-373
Milet, A. **15**-1540, **15**-1572, **15**-1573
Milewski, C. **19**-1721
Milgram, B.C. **15**-1031, **16**-2061
Milhailovic, M.Lj. **14**-229
Militzer, H.-C. **15**-1961, **19**-231
Militzer, H. **10**-1690, **10**-1691
Miljanić, O.S. **4**-54
Mill, T. **14**-73
Millar, I.T. **13**-798
Millar, R.W. **3**-168, **10**-792
Millard, A.A. **10**-1737
Millbanks, C. **15**-1329
Millen, D.J. **3**-30, **11**-150
Miller Jr., W.T. **14**-185, **15**-75
Miller, A.H. **12**-462
Miller, A.R. **12**-89
Miller, A.W. **12**-793
Miller, B. **18**-194
Miller, B.W. **4**-249
Miller, C.P. **17**-440
Miller, D. **16**-530
Miller, D.A. **4**-321
Miller, D.B. **10**-1837
Miller, D.D. **19**-1693
Miller, D.J. **17**-68
Miller, D.O. **2**-74, **2**-309
Miller, E.B. **13**-31
Miller, E.H. **12**-481
Miller, F.A. **4**-391
Miller, G. **15**-1148

Miller, G.I. **15**-1307
Miller, I.J. **5**-51
Miller, J. **8**-259, **10**-328, **10**-1059, **13**-4, **13**-30, **13**-73, **13**-74, **13**-86, **13**-92, **15**-423, **15**-1757, **16**-1439, **16**-2269
Miller, J.A. **10**-1076, **10**-1096, **13**-581, **15**-1660, **15**-2520
Miller, J.J. **16**-691, **18**-76
Miller, J.M. **10**-721, **13**-167, **13**-263
Miller, J.S. **1**-15, **8**-248, **12**-694
Miller, K.D. **11**-29
Miller, K.M. **16**-703, **16**-711
Miller, L.L. **18**-593
Miller, L.S. **18**-679
Miller, M. **10**-602
Miller, M.J. **10**-1042, **10**-1551
Miller, N.A. **15**-1233
Miller, N.C. **12**-677
Miller, R.B. **12**-648, **15**-888
Miller, R.C. **16**-894
Miller, R.D. **12**-326, **17**-194
Miller, R.F. **12**-223
Miller, R.J. **5**-229
Miller, R.L. **14**-423, **18**-877
Miller, S.A. **19**-651
Miller, S.I. **1**-119, **10**-302, **15**-80, **15**-2297, **17**-60
Miller, S.J. **16**-722, **15**-1416, **15**-1487, **15**-2249, **16**-815, **16**-818, **18**-841, **18**-874
Miller, S.P. **7**-126, **18**-738, **19**-1733
Milligan, B. **10**-857, **10**-862
Milligan, D.E. **5**-290
Mills, A.J. **19**-1034
Mills, A.M. **19**-209
Mills, N.S. **2**-112, **2**-366
Mills, O.S. **2**-181
Mills, S.G. **2**-462
Mills, W.H. **2**-84, **11**-80
Milne, D.J. **17**-220
Milne, G.M. **10**-1165, **10**-1328
Milnes, K.K. **5**-254
Milstein, D. **10**-927, **10**-1967, **13**-455, **15**-1497, **19**-658, **19**-1075
Milstein, S.R. **18**-376
Mil'tsov, S.A. **14**-80, **14**-177
Mil'vitskaya, E.M. **18**-650
Mimero, P. **10**-1191
Mimoun, H. **15**-1917, **19**-705
Mimun, A. **2**-313
Mimura, H. **10**-1312
Minachev, Kh.M. **15**-432
Minakata, S. **10**-648, **10**-1660, **10**-1982, **15**-1743, **15**-2069, **15**-2075, **19**-580
Minami, I. **10**-1520, **10**-1734, **17**-329, **19**-53
Minami, K. **14**-295
Minami, S. **18**-322
Minami, T. **10**-1189, **12**-329, **15**-343, **15**-1061
Minami, Y. **19**-581
Minamide, N. **11**-104
Minari, M. **13**-530
Minas da Piedade, M. E. **2**-362
Minasyan, T.T. **19**-374
Minasz, R.J. **10**-346
Minato, H. **13**-824
Minato, T. **15**-2187
Mincione, E. **19**-968
Minegishi, S. **10**-32, **10**-298
Minehan, T., **13**-458, **13**-690
Mineur, C. **15**-2216
Mingardi, A. **15**-1177
Mingos, D M.P. **7**-109, **7**-112, **10**-502
Minière, S. **12**-281
Minieri, P.P. **16**-2170
Minisci, F. **11**-180, **11**-182, **11**-262, **14**-111, **14**-140, **14**-159, **14**-168, **14**-172, **14**-174, **14**-378, **14**-379, **14**-382, **14**-383, **14**-384, **14**-385, **14**-389, **15**-51, **19**-100, **19**-167, **19**-320, **19**-489, **19**-578, **19**-1040
Mink, D. **16**-1212
Minkin, V.I. **2**-234, **2**-316, **2**-431, **3**-49, **4**-447, **5**-348, **18**-574, **18**-953, **18**-953
Minnaard, A.J. **15**-414, **15**-643, **15**-1181, **15**-1185, **15**-1208, **15**-1269, **15**-1278, **16**-466, **16**-746, **16**-849
Minniear, A.B. **19**-861
Minns, R.A. **15**-2419, **15**-2431
Mino, T. **10**-1522, **13**-496, **16**-1793
Minoshima, T. **14**-401
Minoshima, Y. **5**-312
Minot, C. **1**-51
Minozzi, M. **19**-1258
Minsky, A. **2**-326, **2**-327
Mintcheva, I. **4**-318
Minter, D.E. **19**-889
Minton, M. **4**-273
Mintz, M.J. **14**-215
Minyaev, R.M. **4**-447, **18**-574
Minzoni, M. **4**-56, **4**-325
Mio, M.J. **13**-586
Miocque, M. **11**-546, **16**-98, **16**-177, **16**-418
Mioskowski, C. **10**-873, **10**-1161, **10**-1277, **10**-1972, **12**-328, **13**-304, **15**-257, **15**-736, **15**-767, **15**-1688, **15**-2112, **16**-1241, **16**-1432, **16**-1447, **16**-1892, **16**-1937, **17**-212, **17**-475
Miotti, U. **19**-1755
Miqueu, K. **5**-360
Mir, M. **13**-71
Miranda, E.I. **10**-806
Miranda, M.A. **16**-2203
Mirbach, M.F. **15**-1617
Miré, M.-A. **16**-916
Mirjalili, B.B.F. **10**-664, **11**-198
Mirkhani, V. **10**-688, **15**-1981, **15**-1999
Mirkind, L.A. **14**-460
Mironov, V.A. **18**-560, **18**-592
Mirrington, R.N. **10**-825
Mirskova, A.N. **2**-476, **10**-276, **15**-296, **15**-1739
Mirza-Aghayan, M. **15**-1114, **19**-72
Mirza, A.R. **13**-395, **13**-396
Mirzaei, F. **15**-396
Mirzael, M. **14**-340
Misaki, T. **12**-328, **16**-1745, **16**-2132
Misawa, H. **19**-629
Misawa, H. **6**-86
Misbach, P. **15**-829
Miscione, G.P. **15**-2559
Miser, J.R. **13**-788
Mishima, H. **17**-165
Mishima, M. **5**-334, **8**-87, **19**-984, **10**-31, **10**-182, **10**-183, **10**-289, **10**-290
Mishra, A. **5**-435
Mishra, B.K. **7**-35, **19**-73, **19**-289, **19**-832
Mishra, R.K. **13**-546
Mishra, S. **3**-123
Mishriky, N. **17**-227
Misiti, D. **4**-62, **19**-1494
Mislow, K. **2**-276, **3**-213, **4**-1, **4**-20, **4**-34, **4**-35, **4**-90, **4**-207, **4**-210, **4**-212, **4**-256, **4**-259, **4**-525, **4**-526, **5**-242, **15**-62
Misokowski, C. **13**-723
Mison, P. **12**-226, **19**-1236
Misra, S.C. **19**-1390
Mißfeldt, M. **8**-94
Mistry, J. **14**-381
Misumi, A. **10**-1741
Misumi, O. **19**-993
Misumi, S. **2**-325
Misumi, Y. **16**-1218
Mita, N. **10**-1341
Mita, S. **11**-577
Mita, T. **10**-708, **15**-1635, **15**-2324
Mitamura, S. **11**-438, **11**-440, **16**-1650
Mitani, M. **15**-1775, **19**-591
Mitchel, A.R. **11**-177
Mitchell, A.L. **15**-1155
Mitchell, C. **19**-869
Mitchell, D. **19**-726
Mitchell, D.J. **4**-378, **10**-387
Mitchell, D.K. **3**-210, **3**-211
Mitchell, H.L. **12**-634
Mitchell, J.C. **14**-265
Mitchell, L.H. **13**-874
Mitchell, M.B. **14**-381
Mitchell, M.J. **2**-233
Mitchell, R.D. **2**-259

Mitchell, R.H. **2**-304, **2**-308, **2**-364, **16**-2072, **17**-361
Mitchell, T.A. **12**-464
Mitin, A.V. **13**-644
Mitka, K. **19**-781, **19**-787
Mito, S. **15**-1054
Mitoma, Y. **19**-1425
Mitra, A. **18**-506
Mitra, A.K. **16**-81
Mitra, J. **3**-33
Mitra, S. **13**-494
Mitsch, R.A. **15**-2533
Mitsky, J. **8**-243
Mitsuboshi, T. **15**-969
Mitsuda, N. **19**-1524
Mitsudera, H. **15**-1435
Mitsudo, K. **10**-1343, **15**-1542
Mitsudo, K. **15**-2590
Mitsudo, T.-a. **10**-1544, **10**-815, **15**-1583, **15**-2689
Mitsudo, T. **10**-1987, **15**-280, **19**-1103, **19**-1748
Mitsuhashi, K. **12**-449
Mitsuhashi, T. **18**-404, **18**-750
Mitsui, K. **10**-235, **10**-1630, **16**-916, **16**-1565
Mitsui, S. **15**-427, **19**-1347, **19**-1348
Mitsumori, S. **16**-395, **16**-1081
Mitsunobu, O. **10**-644, **10**-726, **10**-1042, **17**-490
Mitsuya, H. **15**-962
Mitten, J.V. **15**-902
Mitton, C.G. **6**-95
Mitzel, T.M. **16**-555
Miura, K. **15**-230, **15**-398, **15**-626, **15**-778, **15**-814, **16**-1126, **16**-1127, **19**-1290
Miura, M. **10**-1995, **10**-1596, **13**-329, **15**-845, **15**-1477, **15**-1953, **15**-2596
Miura, T. **10**-1013, **15**-858, **15**-954, **16**-1008, **19**-143, **19**-1541, **19**-1750
Miura, Y. **5**-271, **5**-272, **10**-915
Miwa, K. **6**-63
Miwa, M. **13**-678, **13**-679
Miwa, Y. **15**-410
Miwata, H. **4**-200
Miyabe, H. **15**-1340, **16**-971, **16**-1603, **16**-1604, **19**-1139
Miyabo, A. **5**-124, **5**-210
Miyachi, H. **15**-643
Miyadera, H. **18**-404
Miyafuji, A. **15**-1982, **19**-545
Miyagawa, N. **14**-386
Miyagi, Y. **10**-1620
Miyaguchi, N. **19**-1602
Miyahara, I. **1**-72
Miyahara, T. **19**-1640
Miyahara, Y. **8**-203
Miyai, T. **19**-1340
Miyake, A. **15**-468
Miyake, H. **10**-813, **15**-2230, **16**-199
Miyake, N. **15**-2275
Miyake, Y. **12**-424, **13**-551, **15**-643, **15**-783
Miyamoto, H. **4**-171, **16**-538, **16**-1118
Miyamoto, I. **2**-324
Miyamoto, K. **10**-817, **19**-533
Miyamoto, M. **19**-581
Miyamoto, S. **13**-192
Miyamoto, T. **15**-861, **16**-666, **16**-671
Miyamoto, Y. **10**-929
Miyamura, H. **19**-128
Miyamura, K. **15**-815
Miyano, M. **11**-398
Miyano, N. **16**-519, **16**-528
Miyano, S. **4**-180, **15**-1229, **16**-1336
Miyanohana, Y. **15**-874
Miyasaka, M. **13**-568, **14**-360
Miyasaka, T. **2**-304
Miyashi, T. **15**-153, **15**-2310
Miyashita, A. **15**-2409, **18**-141
Miyashita, H. **15**-643
Miyashita, M. **10**-1627, **10**-1949, **12**-252, **15**-1052, **15**-1125, **19**-864
Miyata, A. **19**-214
Miyata, M. **3**-177, **4**-184
Miyata, N. **16**-1136
Miyata, Y. **10**-328
Miyaura, N. **10**-1876, **10**-1877, **10**-1878, **12**-475, **12**-566, **13**-486, **13**-487, **13**-490, **13**-694, **15**-735, **15**-1070, **15**-1232, **15**-1256, **15**-1271, **16**-742, **16**-941, **18**-484
Miyazaki, M. **14**-360, **16**-342
Miyazaki, S. **16**-1836
Miyazaki, T. **2**-39, **18**-367, **19**-1235
Miyazaki, Y. **3**-134, **19**-128
Miyazawa, A. **10**-886
Miyazawa, E. **11**-191
Miyoshi, H. **15**-1856
Miyoshi, K. **13**-465, **13**-686
Miyoshi, N. **12**-252, **16**-589, **16**-593, **16**-784
Miyoshi, T. **11**-343
Mizhiritskii, M.D. **12**-321
Mizobe, Y. **19**-1233
Mizoguchi, T. **13**-779
Mizokami, T. **13**-790
Mizoroki, T. **13**-370
Mizugaki, T. **15**-1953
Mizuguchi, Y. **12**-728
Mizuhara, T. **16**-1938
Mizumura, M. **16**-1695
Mizuno, A. **11**-330
Mizuno, H. **11**-427
Mizuno, K. **3**-31, **3**-192, **5**-303
Mizuno, M. **10**-938, **16**-1372
Mizuno, N. **11**-418, **15**-2136, **16**-239, **19**-128, **19**-270
Mizuno, S. **16**-779
Mizuno, T. **11**-576, **13**-570, **16**-688, **16**-1425, **16**-1430
Mizuno, U. **19**-1640
Mizuno, Y. **16**-1492
Mizusaki, T. **19**-1355, **19**-1356
Mizushima, E. **10**-1267, **15**-369
Mizushima, K. **10**-1987
Mizushima, Y. **15**-926
Mizuta, M. **16**-1835
Mizuta, T. **13**-465, **16**-326
Mizutani, H. **12**-338
Mizutani, T. **16**-130
Mladenova, M. **10**-1801
Mlinarić-Majerski, K. **16**-2193
Mlochowski, J. **19**-678
Mloston, G. **15**-2128, **16**-1467
Mlynarski, J. **16**-1152, **16**-1153
Mndzhoyan, O.L. **16**-372, **16**-373
Mo, F. **11**-241
Mo, H. **4**-133
Mo, J. **13**-403, **13**-406, **13**-410
Mo, W. **19**-168
Mo, Y. **2**-38, **4**-286, **4**-291, **5**-33, **8**-209, **15**-683
Mo, Y.K. **5**-62, **10**-129, **10**-413, **11**-15, **12**-356, **14**-188, **15**-73, **18**-797
Mo, Y.M. **5**-52
Mobbs, D.B. **19**-291
Mobbs, R.H. **15**-71, **15**-253
Moberg, C. **7**-123, **7**-125, **10**-683, **16**-1496
Mobinikhaledi, A. **19**-1617
Mobley, T.A. **15**-1214
Mocella, C.J. **15**-2262
Mochalin, V.B. **2**-201
Mochalina, E.P. **15**-73
Möchel, T. **13**-386
Mochida, I. **19**-1182
Mochida, K. **16**-1051, **19**-1460
Mochizuki, K. **15**-1813
Mochizuki, M. **16**-695
Mock-Knoblauch, C. **15**-1980
Mock, W.L. **3**-222, **15**-513, **17**-354, **17**-355, **17**-357, **18**-249
Modak, J. **9**-109
Modarelli, D.A. **5**-377
Modarresi-Alam, A.R. **4**-312
Modec, B. **15**-1697
Modena, G. **10**-252, **10**-273, **15**-21, **15**-35, **15**-36, **15**-80, **15**-83, **15**-1772, **15**-2180, **17**-14, **19**-428, **19**-769, **19**-809, **19**-810, **19**-826, **19**-1755
Modi, D.P. **18**-326, **19**-54
Modro, A. **15**-88
Moebius, D.C. **18**-845
Moeini, L. **7**-95
Moeller, K.D. **15**-414
Moelwyn-Hughes, E.A. **10**-617

Moffatt, J.G. **19**-165, **19**-614, **19**-626
Moffett, K.K. **10**-916
Mogali, S. **10**-323, **19**-911
Moggi, L. **7**-13
Moghadam, M. **15**-1981
Moghaddam, F.M. **11**-605, **12**-79, **15**-1392, **18**-353, **19**-1134
Mohacsi, E. **16**-1779
Mohadjerani, M. **13**-123, **13**-235
Mohajer, D. **19**-796
Mohajerani, B. **19**-249
Mohamed, M. **18**-734
Mohamed, N.M. **16**-442
Mohamed, R.H. **19**-378
Mohamed, S.K. **11**-173
Mohammadi, M. **15**-1392
Mohammadpoor-Baltork, I. **10**-664, **10**-688, **11**-287, **16**-1778, **16**-1849, **16**-286, **16**-68, **19**-30, **19**-322
Mohan, G.H. **16**-2284, **19**-1362
Mohan, J.M. **15**-2047
Mohan, L. **19**-742
Mohan, R.S. **9**-126, **16**-137, **10**-576, **16**-63, **16**-143, **16**-154, **16**-163, **16**-164, **16**-783, **16**-1778, **18**-139, **18**-144, **19**-139
Mohanakrishnan, A.K. **12**-132
Mohanazadeh, F. **10**-873, **10**-1120
Mohanazadeh, F. **16**-1988
Mohanraj, S. **10**-1432
Mohanty, P.K. **16**-764
Mohaptra, S. **10**-1452
Mohile, S.S. **11**-211, **11**-400
Mohler, D.L. **2**-87
Mohr, F. **15**-2067
Mohr, J.T. **10**-1520
Mohri, S.-i. **15**-1626
Mohrig, J.R. **10**-422, **15**-47, **15**-436, **19**-234
Moilliet, J.S. **11**-312
Moineau, J. **13**-389
Moinet, C. **19**-1211
Moisak, I.E. **10**-1112
Moisan, L. **15**-600
Moïse, C. **16**-575, **19**-981, **19**-1083, **19**-1647
Moiseenkov, A.M. **15**-2205, **19**-71
Moiseikina, N.F. **11**-525
Mojé, S. **16**-2010
Mojica, C. **19**-986
Mojtahedi, M.M. **19**-236, **19**-1673, **19**-1726
Mokbel, L. **7**-121
Mokhtar, R. **14**-478
Mokhtari, B. **16**-1900
Mokhtari, M. **13**-6
Mokrosz, J.L. **16**-1980
Mokrushin, V.S. **16**-1521
Molander, G.A. **10**-1366, **10**-1537, **10**-1895, **10**-1896, **10**-1897, **11**-549, **12**-297, **12**-493, **12**-495, **13**-360, **13**-462, **13**-463, **13**-464, **13**-486, **13**-570, **13**-572, **13**-573, **13**-575, **13**-625, **15**-362, **15**-766, **15**-772, **15**-807, **15**-1004, **15**-1262, **15**-1331, **15**-2320, **15**-2573, **16**-483, **16**-841, **19**-118, **19**-864, **19**-1507
Molard, Y. **3**-130
Molchanov, A.P. **2**-230, **15**-2116, **15**-2476, **15**-2488
Mole, T. **10**-1582, **12**-587, **15**-1217, **16**-654, **16**-2088
Molina, G.A. **19**-1551
Molina, P. **10**-1252, **16**-427
Molinari, F. **19**-223, **19**-993
Molinari, H. **15**-1959
Molinaro, C. **15**-2571, **16**-703
Molins, E. **2**-488
Molinski, T.F. **15**-499
Molitor, E. **16**-109
Moll, G. **16**-1090
Moll, J.F. **2**-277
Mollarazi, E. **19**-241
Molle, G. **16**-471, **16**-507
Møllendal, H. **3**-60
Möller, F. **17**-304, **17**-305
Möllerstedt, H. **2**-204
Molnár, Á. **13**-384, **13**-385, **17**-176, **18**-125
Moloney, M.G. **10**-1493
Moloyama, Y. **16**-646
Molter, K.E. **5**-209, **10**-59
Molvinger, K. **19**-1030
Molz, T. **4**-492
Momany, F.A. **1**-63
Momeni, A.R. **10**-1120, **16**-1988, **19**-31
Momeni, M.R. **5**-372
Momiyama, N. **12**-208
Monack, L.C. **13**-78
Monagle, J.J. **16**-2188, **16**-2189, **16**-2190, **19**-615
Monahan, R. **10**-849
Monasterios, J.R. **4**-296
Mondal, E. **10**-582, **10**-584, **16**-212, **16**-634
Mondal, M.A.S. **16**-1806
Mondal, P. **2**-343, **13**-509, **18**-339, **15**-1430
Mondière, R. **16**-799
Mondon, M. **10**-1442
Moneitro, A.L. **13**-539
Monestel, R. **15**-709
Monflier, E. **10**-951, **15**-1497
Mongelli, N. **10**-875
Mongin, F. **10**-1405, **13**-350
Monguchi, Y. **11**-694, **12**-263, **13**-589, **14**-356, **19**-499, **19**-1356
Monkovic, I. **19**-639
Monnereau, C. **11**-300
Monnier, F. **13**-129, **13**-611
Monnier, M. **18**-234
Monopoli, A. **9**-132, **13**-382, **13**-500
Monroe, B.M. **7**-33, **15**-2363
Monson, R.S. **17**-162, **17**-463
Montagnon, T. **15**-2258
Montaña, A.M. **7**-103
Montanari, F. **4**-48, **5**-266, **10**-484, **10**-487, **10**-1126, **10**-1182, **19**-105, **19**-673
Montañez, R.L. **8**-108
Montanucci, M. **13**-142, **13**-113, **13**-142
Montaudon, E. **10**-769
Montavecchi, P.C. **15**-2080
Montavon, G. **11**-258
Montchamp, J.-L. **10**-922, **15**-389, **15**-390, **15**-421
Monte, A. **10**-1465
Monteiro, A.L. **10**-1883, **13**-308
Monteith, M. **15**-1592
Montermini, F. **14**-17
Montero, C. **18**-757
Montero, J.-L. **18**-221
Montes, L. **10**-1728
Monteux, D. **16**-351
Montgomery, F.C. **18**-310
Montgomery, I. **14**-23, **15**-1225, **15**-1225, **15**-2693, **16**-706, **16**-719, **16**-725, **16**-1561
Montgomery, L.K. **5**-295, **10**-202, **18**-77, **18**-81
Monti, C. **16**-943
Monti, L. **15**-126
Montierth, J.M. **14**-346
Montillier, J.P. **12**-500
Montingelli, F. **13**-500
Montoro, R. **14**-161
Montserrat, J.M. **13**-18
Montury, M. **15**-547
Moodie, R.B. **1**-35, **11**-34, **11**-44, **11**-54, **11**-58, **11**-59, **11**-97, **11**-99, **11**-100, **11**-123, **11**-143, **11**-155, **11**-158, **18**-362, **19**-98
Moody, C.J. **2**-295, **2**-298, **10**-1187, **15**-585, **15**-586, **18**-691, **18**-765, **19**-1231
Moody, E.M. **4**-405, **4**-407
Moody, H.M. **19**-1463
Mooiweer, H.H. **10**-1436
Moon, C.J. **15**-1989
Moon, J. **13**-683
Moon, K.S. **11**-446
Moon, S. **15**-131, **16**-1645
Moon, S.J. **19**-964
Moonga, B.S. **11**-647
Moore, C. **12**-697
Moore, D.E. **7**-52
Moore, D.R. **15**-77
Moore, G.G. **10**-722
Moore, G.J. **12**-645
Moore, G.R. **19**-693
Moore, H.W. **15**-2436
Moore, J.A. **16**-1670
Moore, J.C. **19**-993

Moore, J.S. **8**-234, **13**-797, **17**-450, **18**-821, **18**-883
Moore, J.W. **6**-9, **6**-59
Moore, K. **10**-221
Moore, L.R. **13**-526
Moore, M.L. **16**-351
Moore, P.R. **15**-1816
Moore, P.T. **4**-232, **17**-250
Moore, R.E. **19**-1723
Moore, W.M. **7**-25
Moore, W.R. **4**-232, **4**-508, **15**-2428, **17**-250
Moorehead, A.W. **2**-221
Moorman, A.E. **19**-742
Moors, R.G. **17**-56
Moorthy, J.N. **7**-35, **16**-100, **19**-205
Moosmayer, A. **5**-246
Mootoo, D.R. **10**-568
Moquist, P.N. **16**-737, **16**-751
Moradi, W.A. **13**-365
Morai, S. **15**-873
Morales-Morales, D. **13**-150
Morales, N.M. **4**-230
Morales, O. **17**-359, **17**-360
Moran, D. **2**-220, **2**-473, **5**-358, **15**-2270
Moran, J. **15**-1291
Moran, M. **15**-2047
Moran, P.J.S. **15**-659, **16**-816
Moran, W.J. **15**-2162, **19**-1375
Morand, P. **19**-1455
Morandi, J.R. **15**-495
Morandini, F. **10**-1588
Morao, I. **15**-2119, **15**-2304
Moravski, A. **12**-289
Morchat, R. **17**-507, **17**-509
Mordas, D.M. **15**-1127
Mordini, A. **10**-1523, **12**-417, **15**-1141, **17**-213
More O'Ferrall, R.A. **5**-72, **5**-82, **6**-72, **6**-94, **6**-96, **8**-141, **8**-142, **10**-420, **12**-96, **17**-3, **17**-8
More, S.V. **10**-611
Moreau, B. **15**-804
Moreau, C. **10**-568
Moreau, E. **16**-899
Moreau, J.J.E. **4**-27
Moreau, N. **15**-589
Moreau, X. **16**-1150, **16**-1763
Morehead, Jr., A.T. **15**-1485
Moreira, A.P.D. **16**-850
Moreira, D.N. **9**-129
Morel, D. **12**-703
Morel, Y. **13**-82
Moreland, Jr., W.T. **1**-43
Morelli, C. **16**-1765, **16**-2224
Moreno-Dorado, F.J. **14**-200
Moreno-Mañas, M. **13**-372, **13**-432, **13**-542, **13**-544, **15**-1044, **15**-1070
Moreno-Dorado, F.J. **15**-284, **15**-1851, **15**-2098
Moreno, A. **15**-2203
Moreno, I. **15**-2099
Morera, E. **10**-1990, **19**-1352
Moretó, J.M. **10**-619, **10**-1906, **15**-1038
Moretti, I. **4**-39, **16**-2246
Moretti, R. **12**-601
Moretto, A.F. **15**-2635, **15**-2686
Morey, J. **19**-245
Morey, J.V. **11**-301
Morgan, B.S. **16**-666
Morgan, C.R. **19**-1737
Morgan, D.H. **14**-237
Morgan, J.B. **7**-126, **15**-1854
Morgan, J.P. **18**-870
Morgan, M.M. **19**-359
Morgan, T.D.B. **11**-622
Mori, A. **10**-1269, **10**-1913, **10**-1914, **10**-1947, **12**-299, **12**-329, **13**-380, **13**-584, **13**-697, **13**-713, **13**-715, **13**-719, **14**-358, **15**-623, **15**-1253, **16**-769, **16**-1650, **19**-1323, **19**-1355, **19**-1356
Mori, C. **16**-359
Mori, H. **18**-500
Mori, I. **10**-1602
Mori, K. **4**-108, **4**-137, **13**-370, **19**-1634
Mori, M. **10**-1531, **10**-1999, **15**-806, **15**-836, **15**-839, **15**-1509, **15**-2593, **15**-2639, **15**-2683, **16**-705, **16**-1560, **18**-835, **18**-885, **18**-885, **18**-962
Mori, N. **15**-2591, **15**-2599, **16**-315, **16**-841, **19**-659
Mori, S. **10**-1407, **10**-1408, **10**-1706, **12**-541, **13**-589, **13**-677, **19**-1557
Mori, T. **10**-1680, **13**-768, **15**-786, **19**-1053, **19**-1094
Mori, Y. **14**-423, **15**-1038, **15**-1073, **16**-1578, **16**-2102, **17**-315
Moriarty, R. **19**-821
Moriarty, R.M. **4**-390, **10**-54, **12**-753, **15**-1735, **15**-1855, **15**-2039, **18**-534, **19**-198, **19**-392, **19**-493, **19**-494, **19**-521, **19**-823, **16**-2237, **16**-2239
Moriel, P. **10**-934, **17**-271
Morigaki, M. **2**-357
Morihashi, K. **10**-23, **15**-1832, **15**-1843
Morimoto, C. **13**-721
Morimoto, H. **16**-396
Morimoto, I. **15**-2590
Morimoto, T. **3**-135, **15**-523, **15**-813, **15**-1568, **15**-2275
Morin, C. **12**-479
Morin, F.G. **4**-168
Morinelli, T.A. **19**-1520
Morini, G. **14**-140
Morioka, M. **16**-593
Morisaki, D. **16**-1938
Morisaki, Y. **10**-815
Morita, H. **15**-2349
Morita, J. **10**-1752
Morita, K. **19**-144
Morita, M. **10**-1574, **12**-791, **15**-204, **15**-2210
Morita, N. **2**-225, **5**-45, **5**-46, **12**-131, **15**-381
Morita, R. **15**-1435
Morita, T. **11**-646, **19**-1346
Moritani, I. **10**-946, **13**-367, **15**-2400
Moritz, K.L. **11**-67
Moriuchi-Kawakami, T. **19**-1127
Moriwaki, M. **11**-440, **11**-585
Moriya, T. **19**-1448
Moriyama, A. **3**-142
Moriyama, K. **9**-12
Moriyasu, M. **2**-442, **2**-464
Moriyoshi, T. **18**-149
Morizawa, Y. **10**-1328
Morizur, J. **14**-430
Morken, J.P. **7**-126
Morken, J.P. **15**-740, **15**-1260, **15**-1854, **15**-2387, **16**-1560, **17**-191, **18**-738, **19**-1733
Morkovnik, A.S. **11**-105
Moro, M. **15**-1229, **16**-931
Morokuma, K. **7**-24, **10**-215, **10**-1407, **10**-1408, **15**-116, **15**-491, **16**-1955
Moroz, A.A. **13**-125
Morra, N.A. **19**-1447
Morreale, A. **15**-2044, **15**-2050
Morrell, C.E. **10**-254
Morrill, C. **18**-264, **18**-870
Morrill, T.C. **4**-216
Morris Jr., P.E. **19**-106
Morris, A.R. **10**-506
Morris, A.R. **9**-85
Morris, D.G. **1**-54, **2**-92, **8**-107, **10**-105, **12**-259
Morris, D.J. **19**-989
Morris, G.A. **13**-518
Morris, G.F. **17**-9
Morris, G.M. **19**-367
Morris, J. **12**-588, **17**-217
Morris, J.J. **3**-19
Morris, K.P. **8**-26, **14**-227
Morris, R.H. **15**-1102
Morrison, A. **15**-1786
Morrison, A.J. **15**-1548
Morrison, D.J. **12**-329
Morrison, D.W. **16**-1117
Morrison, G.A. **4**-270, **4**-272, **4**-363
Morrison, G.F. **10**-1880
Morrison, H. **18**-370
Morrison, H.A. **7**-57
Morrison, J.D. **4**-13, **4**-27, **4**-29, **4**-46, **4**-48, **4**-137, **4**-139, **4**-140, **4**-144, **4**-149, **4**-150, **4**-153, **4**-156, **4**-210, **4**-215, **4**-216, **4**-218, **4**-219, **4**-221, **4**-222

Morrison, J.D. (*Continued*) **10**-1389, **10**-1742, **10**-1767, **10**-1799, **10**-1856, **12**-67, **15**-637, **15**-639, **15**-709, **15**-818, **15**-1168, **15**-1613, **15**-1710, **15**-1874, **15**-1969, **15**-1974, **15**-1976, **16**-494, **16**-530, **16**-1058, **18**-662, **19**-1009
Morrison, J.J. **17**-268
Morrison, M.A. **15**-113
Morrison, R.T. **13**-821
Morriss, F.V. **12**-772
Mörschel, P. **15**-2242
Morse, B.K. **18**-15
Morse, C.S. **11**-62
Morten, D.H. **10**-92
Mortensen, J.Z. **18**-752
Mortier, J. **13**-729
Mortimer, C.T. **1**-103
Mörtl, M. **16**-264
Morton, D. **7**-48
Morton, H.E. **10**-632
Morton, R.C. **16**-1776
Mortreux, A. **13**-695, **13**-696, **15**-640, **15**-834, **15**-1497, **15**-1574, **18**-884
Morzycki, J.W. **12**-253, **19**-51
Mosconi, E. **17**-57
Moseley, J.D. **7**-115
Moser, W.H. **18**-957, **18**-965
Moses, L.M. **15**-886
Mosettig, E. **15**-463
Mosher, H.S. **4**-107, **4**-139, **4**-520, **5**-165, **10**-284, **10**-1117, **16**-530, **18**-17, **18**-98
Mosher, M.D. **15**-537
Mosher, M.W. **14**-279
Mosher, W.A. **15**-1237
Moskal, J. **16**-1257, **16**-1338
Moskalenko, M. **16**-1285
Moskalenko, M.A. **16**-1518
Moskau, D. **5**-155, **18**-679
Moskva, V.V. **15**-40
Mosquera, J. **10**-918
Moss, J.C. **15**-2420
Moss, R.A. **2**-224, **5**-348, **5**-366, **5**-389, **5**-395, **5**-396, **5**-397, **5**-400, **5**-402, **5**-416, **5**-421, **5**-423, **5**-441, **10**-388, **10**-1093, **12**-361, **15**-2476, **15**-2478, **15**-2479, **15**-2483, **15**-2486, **15**-2534, **15**-2539, **18**-89, **18**-90, **18**-93
Moss, R.E. **4**-250
Moss, S. **18**-562
Moss, T.A. **10**-1655
Mossé, S. **7**-124
Mosset, P. **16**-916, **18**-265
Mossman, C.J. **18**-324
Mossoba, M.M. **7**-71
Mostafavi, M. **10**-1148
Mostafavipoor, Z. **19**-296
Mota Nelson, C.E. **15**-810
Motallebi, S. **15**-12
Motell, E.L. **6**-71, **14**-182
Motevalli, S. **16**-1759
Motherwell, W.B. **10**-1220, **12**-253, **13**-651, **19**-51, **19**-421, **19**-1237, **19**-1522
Motie, R.E. **16**-1617, **16**-1856
Motlagh, A.R. **10**-923
Motoda, D. **15**-763
Motohashi, S. **18**-203
Motoi, M. **4**-182
Motoo, S. **19**-198
Motorina, I. **15**-1810
Motoyama, Y. **16**-645, **19**-1182, **19**-1476, **19**-1479
Motoyoshi, H. **19**-1513
Motoyoshiya, J. **16**-1362
Mott, R.C. **12**-165, **14**-275
Motta, A.R. **18**-855
Motti, E. **13**-530
Motyka, L. **18**-506
Mou, C.-Y. **10**-1309
Moughamir, K. **10**-2006
Mouk, R.W. **18**-205
Moule, D.C. **7**-17
Moulin, D. **15**-1203, **19**-766
Moulines, J. **10**-995
Moulton, W.N. **19**-960
Mouri, M. **16**-1094, **16**-1490
Mouriño, A. **15**-1212
Mourning, M.C. **10**-175, **17**-25
Moussa, Z. **15**-252
Moutet, J. **19**-926
Moutou, J.-L. **16**-876
Moutrille, C. **14**-310
Mouvier, G. **15**-69
Movahedi, Z. **10**-683
Movassagh, B. **10**-923, **16**-211, **16**-293, **16**-305, **16**-1721, **16**-1735
Movassaghi, M. **10**-1634, **12**-554
Mowat, R. **11**-267
Mowery, M.E. **13**-716
Moyano, A. **7**-95, **15**-1557, **15**-2421, **15**-2588, **17**-422
Moyer Jr., C.E. **11**-683
Moyeux, A. **10**-1366
Moynihan, H.A. **6**-51
Mozdzen, E.C. **12**-693, **19**-1474, **19**-1490
Mozingo, R. **15**-463
Mozuraitis, R. **10**-1053
Mraz, T.J. **19**-876
Mridha, N.K. **13**-204
Mrowiec-Bialon, J. **15**-158
Mu, L. **10**-434
Mu, R. **8**-228, **10**-1702
Mu, X.-d. **15**-553
Mu, Y. **5**-272
Mucci, A. **8**-236
Muchowski, J.M. **13**-787, **16**-1817
Muci, A.R. **12**-484, **15**-733, **15**-773, **15**-1978
MuCullough, K.J. **15**-2115
Mudryk, B. **13**-758
Muedas, C.A. **14**-325
Mueller-Westerhoff, U.T. **16**-2062
Mueller, A.M. **15**-1318
Mueller, M.E. **5**-259
Mueller, P.H. **15**-2120
Mueller, R.A. **15**-2575
Mueller, W.A. **9**-95
Mueller, W.H. **15**-21
Muenter, J.S. **1**-41, **8**-250
Mues, C. **18**-742
Muetterties, E.L. **15**-474, **15**-551, **19**-16
Muezelaar, G.J. **10**-1506
Mügge, K. **18**-574
Mugnaini, V. **14**-8
Mugnoli, A. **2**-313, **17**-60
Mühlthau, F. **11**-336
Muhsin, M. **17**-71
Muhuhi, J.M. **13**-320
Muir, D.M. **17**-101, **17**-102
Mujika, J.I. **2**-451, **16**-1679
Mujsce, A.M. **10**-1400
Mukai, C. **15**-251, **15**-1562, **16**-61
Mukai, T. **18**-585
Mukaide, K. **15**-1859
Mukaiyama, T. **10**-1505, **10**-1598, **10**-1616, **10**-1818, **11**-290, **12**-354, **15**-306, **15**-1124, **15**-1131, **15**-1991, **16**-144, **16**-232, **16**-389, **16**-1037, **16**-1054, **16**-1061, **16**-1099, **16**-1101, **16**-1125, **16**-1148, **16**-1174, **16**-1175, **16**-1765, **16**-1825, **16**-1839, **16**-1913, **16**-1992, **16**-2054, **18**-124, **19**-49, **19**-519, **19**-840, **19**-1109, **19**-1311, **19**-1640, **19**-1675
Mukerjee, A.K. **15**-2386, **16**-2216
Mukhametshin, F.M. **10**-1834, **19**-1272
Mukherjee, C. **16**-103, **16**-1851
Mukherjee, D. **19**-924
Mukherjee, S. **10**-1787
Mukherjee, S.B. **16**-795
Mukherjee, S.K. **19**-96
Mukhopadhyay, K. **15**-1499
Mukhopadhyay, P.P. **15**-1343, **15**-1373
Mukhopadhyay, T. **18**-931
Mukkanti, K. **11**-686
Mukouyama, M. **19**-996
Mulder, J.A. **10**-1051
Mulder, P. **1**-110, **2**-26
Muldoon, J. **19**-207
Muldowney, M.P. **15**-2067, **19**-1020
Mulhausen, H.A. **10**-392
MülHiroya, K. **15**-370
Mulholland, D.L. **2**-383
Mulholland, K.R. **18**-429, **18**-430
Mullane, M. **16**-32
Mullay, J. **1**-28, **1**-32
Mülle, P. **15**-2235
Mullen, A. **15**-1494, **15**-1606

Mullen, C.A. **15**-824
Mullen, D.G. **16**-1929
Müllen, K. **2**-282, **2**-300, **2**-302, **2**-310, **2**-334, **2**-336, **2**-351, **2**-364, **15**-76, **18**-674
Müller, B. **18**-389
Muller, B.L. **12**-695
Müller, C. **15**-350, **15**-1625
Müller, E. **5**-246, **10**-957, **14**-293, **15**-2505, **15**-2545, **15**-2545, **18**-244
Müller, E.P. **10**-1073
Müller, G. **4**-254, **10**-1532
Müller, H.R. **15**-508
Müller, J. **5**-53, **5**-150, **10**-551
Müller, K. **2**-72, **18**-656
Muller, L.L. **15**-2043
Muller, L.L. **16**-1463, **16**-2197, **16**-2205, **16**-2216
Muller, M. **12**-357, **12**-637, **15**-2507, **16**-1590, **19**-514
Muller, N. **2**-427, **13**-288
Müller, P. **4**-488, **10**-14, **10**-415, **10**-1648, **10**-1953, **12**-245, **15**-1648, **15**-2047, **15**-2066, **16**-1669, **19**-63, **19**-92, **19**-276, **19**-1332, **19**-1360
Müller, R.K. **17**-426
Müller, S. **4**-522
Müller, T. **5**-8, **5**-66
Müller, T.E. **15**-324
Müller, T.J.J. **15**-931, **16**-2042
Müller, U. **2**-176
Müller, W. **5**-304, **10**-1089, **19**-441
Müller, W.M. **3**-117, **3**-159, **4**-253
Müllhofer, G. **17**-63
Mullie, F. **7**-86
Mulligan, P.J. **18**-204
Mulliken, R.S. **2**-427, **3**-86, **3**-87, **3**-105, **7**-16
Mullin, A. **10**-282
Mullins, R.J. **15**-1233
Mulvaney, A.W. **19**-1500, **19**-1603
Mulvey, R.E. **13**-726, **13**-733
Mulzer, J. **16**-1043, **17**-409, **17**-418, **17**-420, **17**-422
Mulzer, M. **16**-1020
Munakata, R. **15**-2267
Munbunjong, W. **10**-852
Munch, H. **10**-1092
Munchausen, L.L. **15**-2120
Mundy, B.P. **16**-1112, **16**-1766, **19**-699, **19**-1117, **19**-1382, **19**-1627
Munechika, T. **10**-220
Muneer, M. **7**-66
Munekata, T. **17**-325
Mungall, W.S. **4**-200, **15**-1841
Muñiz, K. **15**-2021, **15**-2033, **15**-2038, **19**-1014, **19**-1017
Munjal, R.C. **2**-224
Munn, N.M. **2**-81
Munot, Y.S. **16**-1754
Muñoz-Muñiz, O. **16**-681, **16**-1130
Muñoz, L. **12**-219, **13**-517
Muñoz, M.P. **15**-853
Munro-Leighton, C. **15**-1382
Munro, M.H.G. **15**-614
Munslow, I. **15**-449
Munslow, I.J. **15**-1929
Münsterer, H. **12**-226
Muntean, L. **2**-485
Munyemana, F. **10**-1150
Münzel, N. **2**-240
Mura, L.A. **10**-1861
Murabayashi, A. **18**-753
Muraglia, E. **15**-1780
Murahashi, S.-I. **15**-1802, **16**-981, **19**-480, **19**-558, **19**-559, **19**-1602
Murahashi, S. **2**-251, **10**-946, **10**-1065, **10**-1341, **10**-1356, **10**-1941, **12**-787, **14**-268, **14**-269, **14**-436, **14**-494, **16**-423, **19**-278, **19**-282, **19**-870
Murahashi, T. **10**-1063
Murai, A. **10**-1420
Murai, K. **15**-1720
Murai, S. **11**-329, **11**-424, **11**-490, **12**-252, **12**-558, **13**-563, **13**-688, **15**-758, **15**-793, **15**-813, **15**-960, **15**-1590, **15**-2690, **19**-53, **19**-725, **19**-1492
Murai, T. **10**-1644, **15**-774, **16**-1182, **16**-1301
Murakami, H. **10**-1189, **16**-2265
Murakami, K. **15**-904
Murakami, M. **10**-1598, **10**-1918, **15**-858, **15**-1527, **16**-1008, **16**-1148, **16**-1168, **16**-2264, **18**-725, **19**-214
Murakami, N. **15**-1435
Murakami, S. **16**-784
Murakami, Y. **15**-911, **15**-1486
Murakami, Y. **16**-1965
Murakata, M. **10**-1743
Murakawa, K. **12**-756
Muraki, M. **19**-1109
Muraki, T. **10**-738
Muraki,T. **13**-503
Muralha, V.S.F. **1**-103
Murali, R. **15**-22258
Muralidhar, B. **19**-1100
Muralidharan, D. **15**-2316
Muralimohan, K. **13**-632
Muramatsu, I. **16**-1730
Muramatsu, K. **16**-1507
Muramatsu, Y. **15**-1704, **16**-467
Muranaka, Y. **5**-272
Murao, S. **19**-1021
Muraoka, K. **10**-1394
Muraoka, M. **16**-214
Muraoka, T. **10**-1543, **10**-1544
Murari, M.P. **10**-1684
Murarka, S. **13**-593
Murata, I. **2**-147, **7**-23
Murata, K. **12**-257, **15**-1052, **15**-1072, **19**-1301
Murata, M. **10**-1287, **12**-475, **12**-476, **13**-698, **13**-701, **13**-719
Murata, N. **10**-573
Murata, S. **15**-2006, **16**-1148
Murata, Y. **8**-184, **18**-779
Murati, M.P. **10**-1581
Muratov, N.N. **16**-442
Murawski, D. **18**-925
Murayama, D.R. **2**-251
Murchie, M.P. **3**-118
Murcko, M.A. **4**-290
Murga, J. **16**-1039
Murguly, E. **4**-75
Murhashi, S.-I. **18**-390
Muri, D. **15**-2112
Murov, S. **16**-2207
Murphy, A. **15**-1873
Murphy, D.K. **10**-528
Murphy, D.L. **11**-241
Murphy, F. **16**-1295
Murphy, J.A. **11**-368, **11**-697, **15**-1362, **16**-1334, **17**-208, **19**-1565
Murphy, J.M. **11**-265
Murphy, M. **10**-1408, **10**-1410, **15**-1154
Murphy, M.D. **15**-1144
Murphy, P.J. **10**-1560, **16**-1402, **17**-220
Murphy, R.B. **11**-649
Murphy, T.J. **15**-2416
Murphy, W.S. **12**-544, **10**-1667
Murr, B.L. **15**-2370
Murray, C.B. **10**-640
Murray, C.D. **13**-833
Murray, C.J. **8**-155
Murray, K.J. **15**-517
Murray, K.K. **5**-353
Murray, N.G. **14**-480
Murray, R.E. **12**-573
Murray, R.W. **10**-1016, **14**-250, **14**-251, **14**-252, **14**-263, **15**-1889, **15**-1924, **15**-2360, **15**-2361, **15**-2362, **15**-2364, **15**-2366, **19**-10, **19**-347, **19**-357, **19**-358, **19**-359, **19**-360, **19**-361, **19**-363, **19**-481, **19**-735, **19**-742
Murray, W.V. **18**-852
Murrell, J.N. **1**-2
Murry, J.A. **13**-673, **15**-2249, **16**-998
Murthy, Ch.V.S.R. **10**-1009, **16**-1563
Murthy, R.S. **16**-1408
Murty, M.S.R. **10**-707, **10**-885, **10**-1003, **10**-1069
Murugesan, V. **19**-86
Murzin, D.Yu. **8**-83
Musaev, D.G. **16**-1955
Musavi, S.M. **5**-372
Musch, P.W. **2**-90
Muscio Jr., O.J. **13**-22

Musco, A. **4**-88
Musharraf, M.A. **19**-1088
Musio, B. **13**-731
Musker, W.K. **2**-95, **17**-248, **19**-41, **19**-827
Musser, M.T. **10**-301
Musso, H. **4**-179, **4**-465, **4**-467, **18**-677, **19**-1554, **19**-1556
Musson, A. **11**-135
Mustanir. **10**-31
Musumarra, G. **2**-101, **10**-89, **10**-416
Mutai, K. **6**-14
Mutch, A. **18**-842
Mutele, I. **13**-523
Muth, A. **13**-420
Muth, C.L. **19**-1490
Muthard, J.L. **2**-388
Muthukrishnan, S. **10**-25, **16**-1408
Muthukumaran, A **11**-227
Muto, T. **15**-813
Mutter, L. **17**-151
Mutter, M. **16**-1930
Mutter, M.S. **16**-1355, **16**-1385
Mutti, S. **4**-113
Mutule, I. **10**-1464
Muzart, J. **10**-1569, **15**-450, **19**-48, **19**-211, **19**-467, **19**-471, **19**-564, **19**-565, **19**-699
Myers, A.G. **10**-1766, **12**-79, **13**-373, **13**-446, **19**-1462
Myers, B.J. **15**-2677
Myers, J.D. **17**-366
Myers, M. **15**-1187, **16**-1478
Myers, M.C. **15**-1031
Myers, M.M. **15**-899
Myers, R.J. **1**-88
Myhre, P.C. **5**-21, **5**-80, **10**-196, **10**-214, **10**-548, **11**-11, **11**-60, **11**-62, **15**-99
Myint, Y.Y. **15**-1685
Myles, D.C. **10**-762
Mynett, D.M. **16**-1644
Myoung, Y.C. **15**-831
Myrseth, V. **11**-47
Myshenkova, T.N. **10**-1975
Mysík, P. **10**-1104

Na, S. **15**-411
Na, Y. **15**-1493, **15**-1523
Naab, P. **15**-5, **15**-35
Naae, D.G. **15**-17
Naasz, R. **16**-822
Nabana, T. **19**-532
Nabeya, A. **10**-1846
Nacci, A. **9**-132, **13**-382, **13**-500
Nace, H.R. **17**-129, **17**-237, **19**-615
Nachod, F.C. **1**-18, **1**-95, **4**-273, **8**-25, **8**-47
Nachtigall, G.W. **10**-76
Nachtsheim, B.J. **10**-1718
Nadal, B. **10**-1175
Nadal, M.L. **10**-1906
Nadeau, C. **10**-2001
Nadeau, E. **10**-974, **16**-962
Nadein, O.N. **11**-548
Nadelson, J. **16**-2006
Nadi, S. **14**-169
Nadir, U.K. **10**-1007, **10**-1652
Nadkarni, D. **19**-986
Nadler, E.B. **2**-449, **2**-453
Naef, R. **16**-495
Naegele, W. **15**-111
Naeimi, H. **10**-1229
Naemura, K. **4**-68, **4**-489, **4**-491, **4**-514
Näf, F. **10**-1760
Nafti, A. **12**-226
Nagahara, K. **10**-1996, **15**-1355, **18**-141
Nagahara, T. **17**-166
Nagai, T. **12**-238
Nagai, K. **10**-1327
Nagai, K. **15**-1204, **16**-900, **16**-933
Nagai, M. **5**-124, **5**-210
Nagai, T. **5**-243, **14**-137, **16**-2277, **17**-324
Nagai, Y. **10**-544, **15**-2093, **15**-2595, **19**-10
Nagaiah, K. **16**-60, **16**-330, **16**-1234, **17**-433
Nagaki, A. **15**-2347
Nagaku, M. **10**-729
Naganawa, Y. **12**-377
Nagano, H. **15**-595, **15**-633
Nagano, T. **10**-916, **10**-1382
Nagano, Y. **16**-1818, **16**-1959
Nagao, K. **18**-787
Nagao, S. **14**-201
Nagao, Y. **4**-139, **4**-347, **16**-192
Nagaoka, Y. **16**-1873
Nagarajan, K. **12**-91
Nagarajan, M. **16**-1778
Nagareda, K. **16**-528, **16**-1346
Nagarkatti, J.P. **19**-312
Nagasawa, K. **16**-1709
Nagasawa, M. **19**-1171
Nagasawa, T. **11**-538
Nagase, H. **12**-338
Nagase, R. **16**-2132
Nagase, S. **10**-215, **10**-1394, **16**-1346
Nagashima, H. **15**-1137, **15**-1774, **19**-1078, **19**-1182, **19**-1476, **19**-1479
Nagashima, T. **13**-515
Nagata, H. **15**-856
Nagata, J. **15**-2401
Nagata, K. **16**-342
Nagata, M. **13**-698, **13**-701
Nagata, R. **19**-59
Nagata, S. **15**-384
Nagata, T. **14**-231, **14**-236
Nagata, W. **11**-391, **15**-1623, **15**-1630
Nagata, Y. **19**-1474
Nagatomo, H. **18**-385
Nagayama, S. **15**-1805, **16**-905, **16**-983, **16**-1134, **16**-1172, **16**-1172, **16**-1172
Nagel, C.J. **15**-1937
Nagel, M. **18**-613, **19**-550
Nagendrappa, G. **15**-1997
Nageswar, Y.V.D. **10**-689, **10**-707, **19**-192, **19**-251
Nagino, C. **10**-729
Nagira, K. **14**-408, **14**-410
Nagle, A.S. **10**-889, **10**-891, **16**-1976, **17**-236
Nagorny, P. **16**-1838
Nagorski, R.W. **12**-99, **15**-1650
Nagraba, K. **15**-2364
Nagubandi, S. **11**-401
Naguib, Y.M.A. **14**-211
Nagumo, S. **15**-1481
Nagura, T. **11**-347
Nagy, J.B. **16**-1958
Nagy, O.B. **16**-1958
Nahabedian, K.V. **11**-650
Nahm, M.R. **15**-1076
Nahm, S. **16**-2074, **16**-2080, **19**-1117
Nahm, S.H. **15**-997
Nahmany, M. **16**-1772
Naicker, K.P. **10**-1062, **13**-467, **15**-1815, **16**-1945
Naidenov, S.V. **11**-30
Naidu, A.B. **13**-124
Naidu, B.N. **15**-1412
Naik, N.H. **10**-611
Naik, R. **16**-1815
Naik, R.G. **15**-719
Naik, S. **10**-1156, **16**-1878
Naik, S.N. **13**-810
Naik, Y.A. **10**-539
Nailor, K.E. **15**-1374
Naimi-Jamal, M.R. **10**-1650, **14**-340
Nair, D. **13**-387
Nair, J.J. **16**-1748
Nair, K.B. **15**-1784
Nair, L.G. **15**-1729, **15**-1757, **19**-707
Nair, R.V. **16**-1647
Nair, V. **15**-1658, **15**-1729, **15**-1757, **16**-871, **19**-707
Nairn, M.R. **15**-1818
Naito, H. **15**-2042
Naito, T. **7**-45, **15**-1370, **15**-2445, **16**-971, **16**-1603, **16**-1604, **16**-1606, **16**-2205, **19**-1139
Najafi, P. **4**-312
Najem, T.S. **16**-1676
Nájera, C. **5**-186, **13**-388, **13**-494, **13**-582, **15**-1045, **15**-2114, **16**-1084, **16**-1897
Najime, R. **10**-995
Nakabayashi, T. **19**-1139
Nakada, M. **15**-2528, **16**-601
Nakadaira, Y. **4**-539, **5**-258
Nakae, Y. **16**-1723

Nakagaki. R. **6**-14
Nakagawa, H. **10**-621
Nakagawa, K. **14**-295, **15**-1370, **19**-398
Nakagawa, M. **2**-300, **2**-314, **2**-330, **2**-357, **4**-68, **4**-492, **14**-194, **14**-330, **15**-1027, **16**-937, **19**-800
Nakagawa, S. **15**-1509, **16**-1742
Nakagawa, T. **3**-84, **12**-755, **15**-230, **15**-398, **16**-1127
Nakagawa, Y. **15**-2136
Nakahara, M. **3**-7
Nakahara, S. **4**-514
Nakahara, Y. **15**-1670
Nakahigashi, J. **15**-1646
Nakai, K. **10**-249
Nakai, M. **18**-287, **19**-1596
Nakai, S. part 2-6, **18**-367
Nakai, T. **1**-72, **4**-203, **15**-924, **16**-1259, **16**-1574, **18**-776, **18**-778, **18**-779, **18**-784
Nakai, Y. **3**-51, **16**-1085
Nakajima, K. **10**-1911, **11**-664, **15**-838, **15**-843, **15**-846, **16**-2111
Nakajima, M. **15**-1277, **16**-776, **18**-248
Nakajima, N. **10**-1743, **14**-494, **17**-469, **19**-1141
Nakajima, R. **15**-854
Nakajima, S.-I. **18**-142
Nakajima, S. **18**-154
Nakajima, T. **2**-215, **11**-381, **16**-1167
Nakajo, M. **15**-1953
Nakajo, T. **19**-1740
Nakama, T. **15**-199
Nakamaye, K.L. **12**-19
Nakamichi, N. **19**-20
Nakamoto, K. **10**-434, **10**-471
Nakamura, A. **3**-89, **10**-815, **15**-1720, **15**-2539, **16**-448
Nakamura, E. **7**-98, **10**-1409, **10**-1407, **10**-1408, **10**-1413, **10**-1431, **10**-1445, **10**-1535, **10**-1757, **10**-1770, **13**-344, **13**-655, **15**-946, **15**-948, **15**-1136, **15**-1139, **15**-1152, **15**-1204, **15**-2163, **16**-275, **16**-699, **16**-1061, **19**-507
Nakamura, H. **5**-334, **10**-290, **10**-1625, **15**-224, **15**-1411, **16**-905, **16**-950
Nakamura, I. **15**-177, **15**-926, **15**-971
Nakamura, K. **11**-186, **11**-538, **16**-511, **16**-905, **16**-950, **19**-994, **19**-996
Nakamura, K. **4**-186
Nakamura, M. **2**-332, **10**-1770, **13**-554, **15**-844, **15**-946, **15**-948, **15**-2352
Nakamura, N. **2**-245, **9**-12, **13**-868
Nakamura, R. **13**-679, **19**-1497
Nakamura, S. **10**-782, **15**-768, **15**-776, **15**-779, **15**-822, **16**-1537, **19**-800, **19**-974
Nakamura, T. **3**-153, **8**-217, **13**-322, **13**-465, **15**-1358, **15**-1360, **15**-1370, **15**-1778, **15**-1779, **16**-1149, **16**-2031
Nakamura, Y. **2**-75, **10**-1102, **10**-1103, **11**-214, **15**-836, **16**-908
Nakanishi, H. **18**-674
Nakanishi, K. **4**-118
Nakanishi, S. **10**-1579
Nakano, A. **15**-388
Nakano, H. **10**-1537
Nakano, K. **13**-220, **15**-2252, **16**-1058
Nakano, M. **12**-234, **13**-850, **16**-1098, **16**-1913
Nakano, N. **15**-2250, **19**-943
Nakano, S. **15**-123
Nakano, T. **10**-544, **15**-2093, **16**-1836, **19**-138
Nakano, Y. **15**-2592, **16**-1518
Nakao, J. **15**-936
Nakao, R. **11**-695
Nakao, S. **15**-2352
Nakao, T. **2**-76
Nakao, Y. **13**-705, **16**-199
Nakaoka, K. **15**-2603
Nakashima, D. **10**-593, **15**-2189
Nakashima, H. **16**-622, **16**-645
Nakashima, K. **19**-60
Nakashima, T. **10**-327, **19**-681
Nakata, D. **19**-1561
Nakata, K. **10**-289, **10**-290, **15**-1985
Nakata, M. **19**-613
Nakata, T. **16**-1770, **17**-243, **19**-1049
Nakata, Y. **5**-359
Nakatani, H. **15**-1501
Nakato, T. **19**-1602
Nakatsugawa, M. **16**-680
Nakatsuji, M. **5**-272
Nakatsuji, S. **2**-357, **19**-60
Nakatsuji, Y. **3**-153
Nakatsuka, T. **19**-49
Nakatsuka, Y. **16**-622, **16**-771, **16**-1049
Nakayama, H. **7**-62
Nakayama, J. **15**-2000, **17**-368, **17**-373, **19**-819, **19**-1548
Nakayama, M. **5**-377, **15**-199, **15**-1775, **16**-1778
Nakayasu, T. **11**-347
Nakazaki, A. **16**-1149
Nakazaki, M. **2**-76, **4**-21, **4**-82, **4**-489, **4**-491, **4**-514
Nakazawa, M. **18**-238
Nakazawa, T. **7**-23, **14**-416
Nakazono, Y. **13**-686
Nakazumi, H. **9**-64
Nakhshunov, V.S. **15**-432
Nakmura, H. **17**-390
Nakoji, M. **10**-1527
Nakova, E.P. **19**-1777
Nalbandyan, A.B. **19**-675
Nalepa, C.J. **17**-508
Nam, G.S. **16**-2108
Nam, H. **13**-51
Nam, M.H. **19**-1313
Nam, W. **19**-443
Nam. G.S. **19**-1581
Namane, C. **19**-1234
Namanworth, E. **5**-17, **10**-404
Namavari, M. **10**-1115
Namba, M. **19**-1139
Namboodiri, V. **13**-598
Namboodiri, V.V. **10**-635
Nambu, H. **10**-1869, **10**-1860, **10**-1863, **10**-1864, **10**-1868, **12**-257, **15**-426
Nambu, M. **15**-2251
Namiki, H. **12**-338
Namy, J.-L. **16**-570, **16**-2103, **18**-141, **19**-950, **19**-1629
Namy, J. **16**-2113
Nan, Y. **15**-245
Nanda, P. **11**-447, **19**-601
Nandakumar, M.V. **10**-693, **13**-243
Nandi, P. **19**-1607
Nandi, S. **1**-29
Nandy, S.K. **16**-1558
Nangia, A. **16**-1379, **16**-1828
Nanjundaswamy, H.M. S. **16**-279
Nanke, T. **10**-1971
Nanni, D. **15**-1351, **18**-73, **18**-327, **19**-1258
Nano, G. **16**-1975
Naot, T. **19**-278
Naota, T. **14**-268, **14**-269, **14**-494, **15**-510, **16**-423, **19**-559, **19**-1602
Napier, S. **13**-320
Napolitano, E. **16**-436, **17**-192
Naqvi, S.M. **18**-606
Nara, S. **11**-193
Nara, S.J. **11**-592, **16**-1230
Narang, C.K. **16**-1930
Narang, S.C. **10**-785, **10**-1200, **10**-1247, **11**-123, **12**-209
Narasaka, K. **10**-1818, **15**-1125, **15**-1479, **15**-1535, **15**-1798, **15**-2249, **16**-1125
Narashimhan, S. **19**-1052, **19**-1056
Narasimhan, C.S. **19**-930
Narasimhan, M.S. **12**-409
Narasimhan, N.S. **12**-429
Narasimhan, S. **19**-1068, **19**-1162
Narasimhulu, C.P. **10**-1068
Naravane, A. **13**-417, **13**-576
Narayan, K.V. **18**-270
Narayan, R.S. **19**-382
Narayan, S. **13**-305
Narayana Kumar, G.G.K.S. **16**-1555.

Narayana, A. **15**-1677
Narayana, C. **12**-555, **15**-690, **18**-468, **19**-1579
Narayanan, B. **15**-452
Narayanan, B.A. **16**-443
Narayanan, K.V. **10**-247
Narayanan, R. **16**-1116
Nardello, V. **14**-255
Nardi, M. **10**-974, **16**-136
Nardi, M. **16**-1723
Narender Reddy, A.V. **19**-1624, **19**-1251
Narender, M. **10**-707, **19**-251
Narender, N. **11**-251, **11**-253, **11**-285, **11**-295
Narender, R. **15**-1662, **16**-2283, **17**-442
Narin, S.Yu. **14**-221
Narisada, M. **11**-690
Narita, K. **10**-1964, **15**-1457
Narita, N. **14**-47, **14**-124
Narita, S. **16**-1362
Narkunan, K. **15**-1138, **16**-146
Narsaiah, A.V. **9**-133, **13**-174, **15**-1385, **16**-60, **16**-330, **16**-574, **16**-1231, **16**-1234, **17**-443
Narsihmulu, C. **10**-866
Narsihmulu, Ch. **10**-703, **13**-390, **15**-430, **15**-464, **16**-802, **16**-819
Narsireddy, M. **15**-405
Narula, A.P.S. **15**-462
Narusawa, H. **16**-646
Naruse, Y. **18**-501
Naruta, Y. **11**-470, **16**-617, **19**-252, **19**-609
Nascimento, M.de G. **16**-1738
Nascimento, S.C.C. **15**-2063
Nash, E.G. **17**-458
Nash, J.J. **13**-53, **17**-242
Nashi, T. **10**-1229
Nasibov, S.S. **4**-43
Nasielski, J. **10**-1309
Nasipuri, D. **15**-573
Naskar, D. **14**-467, **16**-2245
Naskar, S. **10**-909, **15**-620
Naso, F. **10**-1377, **10**-1331, **16**-2020, **17**-14
Nasreen, A. **14**-228, **16**-73
Nassetta, M. **11**-633
Nassimbeni, L.R. **3**-178
Nata, A. **16**-188
Natale, N.R. **16**-339, **19**-1138, **19**-1438
Natarajan, R. **10**-561, **10**-562
Natero, R. **5**-222
Nathan III, E.C. **2**-227
Nathan, W.S. **2**-411, **10**-330
Näther, C. **15**-2507
Natsume, H. **10**-1274
Natt, F. **11**-491
Natta, G. **4**-1
Nattier, B.A. **16**-143, **19**-139
Naudet, M. **14**-203
Näumann, F. **16**-1103
Naumann, R. **2**-38
Naumov, Yu.A. **11**-525
Nauta, W.T. **11**-635
Navangul, H.V. **2**-122
Navarre, L. **15**-1279
Navarrini, V. **11**-182
Navarro-Vázquez, A. **18**-664
Navarro, A. **10**-974
Navarro, M. **13**-311
Navarro, O. **13**-540
Naven, R.T. **3**-137
Nawa, S. **11**-343
Nayak, M.K. **16**-1633
Nayak, S.K. **10**-1211, **15**-1210, **19**-1681
Naylor, M. **18**-400
Nayyar, N.K. **14**-119
Nazaré, M. **13**-587
Nazareno, M.A. **10**-108
Nazari, E. **11**-454
Nazarov, I.N. **15**-1082
Nazarova, N.E. **11**-171
Nazer, B. **19**-1093
Nazran, A.S. **5**-369, **14**-64
Ndakala, A.J. **16**-1414
Ndibwami, A. **16**-32
Ndubaku, C.O. **19**-1649
Neale, R.S. **15**-1739, **18**-927
Neamati-Mazreah, N. **10**-463
Neary, A.P. **11**-115
Nebenzahl, L. **8**-17, **8**-60
Neber, P.W. **18**-285
Nebois, P. **7**-95
Necas, D. **12**-723
Nechvatal, A. **14**-191, **18**-68
Neckers, D.C. **2**-343, **17**-2, **17**-527, **19**-1662, **19**-1664
Necsoiu, I. **19**-607
Nédélec, J.-Y. **10**-1485, **10**-1956, **10**-1963, **13**-311, **13**-355, **15**-1235, **16**-715
Nédélec, Y.-Y. **15**-2484
Nedugov, A.N. **10**-830
Née, G. **10**-516
Neelamkavil, S. **19**-152
Neeland, E.G. **4**-404
Neelima, B. **11**-223, **15**-1398
Neeman, M. **10**-655
Neeraja, V. **15**-2071
Neese, F. **5**-434
Nefedov, B.K. **16**-1829
Nefedov, O.M. **5**-238, **5**-349, **5**-399, **15**-2537, **16**-1477
Negashima, S. **19**-1425
Negele, S. **19**-591
Negishi, E. **10**-1463, **10**-1337, **10**-1379, **10**-1451, **10**-1463, **10**-1738, **10**-1862, **10**-1909, **12**-1, **12**-306, **12**-501, **12**-603, **12**-646, **12**-649, **13**-432, **13**-617, **15**-677, **15**-718, **15**-719, **15**-720, **15**-737, **15**-739, **15**-740, **15**-814, **15**-929, **15**-986, **15**-1180, **15**-1257, **17**-195, **18**-451, **18**-454, **18**-456, **18**-457, **18**-472, **18**-480, **18**-481, **18**-482
Negoro, N. **16**-1628, **17**-377
Negoro, T. **15**-1666
Négrel, J.-C. **16**-527
Negri, J.J. **15**-522
Negri, J.T. **12**-426
Négri, S. **10**-1993
Neh, H. **15**-652, **15**-1128
Nehru, K. **19**-176, **19**-782
Neibecker, D. **15**-1503
Neidigh, K.A. **16**-331, **19**-1121
Neidle, S. **4**-100
Neidlein, R. **4**-488, **18**-680
Neier, R. **18**-734
Neilands, O. **3**-103
Neilson, D.G. **16**-177
Neiman, L.A. **2**-177
Neiman, M.B. **5**-268
Neitzel, M.L. **18**-256
Nekhoroshev, M.V. **16**-1712
Nelke, J.M. **19**-1700, **19**-1710
Nell, P.G. **16**-460
Nelson-Reed, K.T. **12**-290
Nelson, B.W. **14**-43
Nelson, D.J. **12**-513, **12**-514, **15**-90, **15**-509, **15**-689, **15**-1737, **15**-1792, **15**-2171
Nelson, D.P. **3**-113
Nelson, D.W. **15**-1835
Nelson, E.C. **16**-1322
Nelson, E.D. **13**-25
Nelson, G.C. **18**-163
Nelson, J.V. **16**-1058
Nelson, K.L. **11**-55, **11**-195
Nelson, N.T. **17**-145
Nelson, P. **16**-1925
Nelson, P.G. **1**-3
Nelson, R.B. **11**-691
Nelson, S.F. **5**-262, **5**-347, **15**-1744, **15**-2367, **15**-2368
Nelson, S.G. **15**-2344, **16**-2200, **18**-711
Nelson, T.D. **13**-485
Nelson, W.M. **15**-2370
Nemec, S. **13**-285
Nemeth, L. **19**-951
Nemo, T.E. **19**-444
Nemoto, H. **10**-249, **10**-1625, **18**-496, **18**-497, **19**-141, **19**-475, **19**-982, **19**-1050
Nemoto, T. **15**-1883, **15**-1918, **16**-806
Nendel, M. **15**-2256, **18**-567
Nenitzescu, C.D. **11**-415, **12**-311, **15**-1781, **19**-8, **19**-603, **19**-607
Neplyuev, V.M. **10**-1664, **12**-200
Nepveux, F.J. **7**-126
Neri, O. **17**-205
Neri, P. **3**-128, **3**-133, **3**-144, **4**-69, **4**-95, **4**-167
Neri, V. **15**-1895
Nerz-Stormes, M. **16**-1068
Nesakumar, J.E. **18**-137

Nesloney, C.L. **15**-741
Nesmayanov, N.A. **16**-1353
Nesmeyanov, A.N. **10**-258, **16**-1471
Nestrick, T.J. **15**-506
Neth, J.M. **4**-355
Netherton, M.R. **13**-532
Nething, M. **15**-709
Netscher, T. **16**-2278
Neuberger, K.R. **7**-58
Neubert, L. **10**-927
Neudörfl, J.-M. **16**-815, **19**-1027
Neuenschwander, K. **19**-1444
Neugebauer, F.A. **5**-246, **5**-342, **5**-346
Neumann, A. **6**-89
Neumann, B. **2**-361, **5**-182, **10**-1751
Neumann, C. **15**-2536
Neumann, E. **15**-449
Neumann, F.W. **13**-97
Neumann, G. **2**-310
Neumann, H. **10**-643, **10**-927, **11**-521, **12**-769, **13**-98
Neumann, H.M. **16**-512, **16**-513, **16**-514, **16**-515, **16**-1005
Neumann, P. **2**-66
Neumann, R. **11**-510, **11**-578, **15**-1883, **19**-162, **19**-167
Neumann, R.A. **16**-1351
Neumann, W.P. **5**-248, **5**-249, **16**-1012, **16**-2305, **19**-1294
Neumeister, J. **19**-337
Neumüller, O. **14**-257
Neunhoeffer, H. **16**-300
Neunhoeffer, O. **13**-180
Neurath, H. **16**-1929
Neureiter, N.P. **17**-225
Neuville, L. **13**-700
Nevado, C. **15**-853
Nevalainen, V. **16**-1028, **19**-1752
Nevar, N.M. **10**-1779
Nevill, S. M. **5**-328
Neville, A.G. **5**-336
Nevitt, T.D. **15**-32
Newbold, B.T. **19**-287, **19**-1266, **19**-1527, **19**-1613
Newcomb, M. **3**-122, **5**-326, **5**-327, **5**-328, **5**-330, **10**-106, **10**-106, **10**-1799, **10**-1855, **14**-53, **14**-83, **14**-84, **14**-85, **14**-91, **14**-93, **14**-100, **14**-143, **15**-1313, **15**-1314, **15**-1375, **15**-1380, **18**-75, **18**-649, **9**-1324
Newcomb, M.E. **12**-623
Newcomb, R.C. **16**-1694
Newcombe, N.J. **15**-1816
Newham, J. **15**-663
Newirth, T.L. **12**-563
Newkirk, D.D. **14**-141
Newkome, G.R. **16**-282, **16**-2121
Newlands, S.F. **15**-16
Newman Jr, R.C. **14**-10
Newman, A. **16**-1066
Newman, C. **15**-1002, **15**-1019
Newman, D.A. **12**-22
Newman, H. **15**-169, **16**-536
Newman, M.S. **5**-63, **5**-75, **6**-46, **11**-66, **14**-40, **16**-435, **16**-439, **16**-1739, **16**-2054, **17**-103, **18**-12, **18**-31
Newman, P.A. **9**-27
Newsom, I. **8**-99, **8**-202
Newton Jr., R.J. **15**-517, **15**-687
Newton, B.N. **10**-1555
Newton, C.G. **19**-1113
Newton, C.G. **2**-376
Newton, M.D. **4**-451
Newton, R.F. **7**-48
Newton, T.A. **15**-99
Newton, T.W. **16**-1282
Ney, J.E. **15**-346, **19**-279
Nezu, J. **19**-1524
Nezu, T. **15**-1626
Ng, C. **19**-692
Ng, J.S. **12**-601
Ng, K.D. **13**-342
Ng, K.M. **11**-81
Ng, L.-Y. **19**-468
Ng, L. **15**-87
Ng, S.-S. **15**-2156, **15**-803, **16**-694, **16**-704, **16**-707
Ng, S.M. **15**-2403
Ng, W.W. **15**-94
Ngai, M.-Y. **16**-946
Ngidi, E.L. **18**-866
Ngo, D. **16**-1916
Ngo, H.L. **19**-1014, **19**-1018
Ngoviwatchai, P. **14**-52
Nguefack, J.-F. **10**-1912
Nguên, NV. **16**-1056
N'Guessan, T.Y. **18**-234
Nguyen, H.N. **15**-338
Nguyen, K.P.P. **13**-729
Nguyen, M.T. **18**-335, **18**-360, **18**-618
Nguyen, N. **18**-510
Nguyen, N.V. **17**-318
Nguyen, R.V. **15**-2097
Nguyen, S.B.T. **15**-2073, **15**-2520
Nguyen, S.C. **10**-1702
Nguyen, S.L. **10**-1426
Nguyen, S.T. **10**-1627, **12**-793, **13**-518, **16**-597, **19**-952, **19**-957
Nguyen, T.-H. **13**-729
Nguyen, T.T. **10**-1405
Nguyen. S.T. **19**-143
Ni, B. **18**-830
Ni, M. **16**-545, **16**-666
Ni, Y. **15**-2693, **16**-358
Ni, Z. **14**-442, **19**-1563
Niat, M. **13**-71
Nibbering, N.M.M. **16**-29
Nicaise, O. J.-C. **19**-1141
Nicaise, O. **16**-970
Nicasio, M.C. **12**-375, **19**-535
Niccolai, G.P. **5**-413, **19**-37
Nice, L.E. **15**-1163
Nicholas, A.M. de P. **5**-277
Nicholas, K.M. **12**-228, **15**-337, **15**-360, **15**-2019, **19**-1651
Nicholls, B. **3**-96
Nicholls, D. **18**-400
Nichols, J.M. **15**-2057
Nichols, M.A. **5**-180, **8**-230, **16**-1041
Nickel, W. **4**-538
Nickell, E.C. **19**-356
Nickisch, K. **15**-652, **15**-1128
Nickle, J.H. **19**-94
Nickon, A. **3**-186, **10**-192, **10**-202, **14**-250, **15**-2356, **17**-283, **18**-31, **18**-88, **18**-932, **19**-1264, **19**-1502
Niclas, H. **10**-439
Niclause, M. **19**-675
Nicolaides, N. **19**-95
Nicolaou, K.C. **10**-771, **10**-1734, **15**-2258, **16**-878, **18**-820, **19**-599
Nicolas, E.C. **12**-102
Nicolet, P. **3**-19, **10**-461
Nicoletti, M. **16**-358, **16**-363
Nicoletti, R. **10**-928, **10**-954
Nicolopoulou, M. **14**-48, **14**-368
Nicoud, J.F. **4**-159
Nidy, E.G. **10**-770
Nie, J. **16**-1523, **16**-1991
Nieddu, G. **12**-760
Niederer, P. **13**-789
Niedermaier, J. **15**-2225
Niedermann, H. **15**-2232
Nieger, M. **2**-328, **15**-2021, **15**-2033
Nieh, T. **17**-331
Niel, G. **16**-736
Niele, F.G.M. **15**-1497
Nielsen, A. **5**-268
Nielsen, A.T. **10**-1552, **16**-1017, **17**-119, **19**-747, **19**-1515
Nielsen, J.K. **19**-993
Nielsen, K.E. **2**-57
Nielsen, M. **15**-1409
Nielsen, M.B. **12**-532
Nielsen, M.F. **14**-31
Nielsen, R.B. **15**-842
Nielsen, R.J. **19**-128, **19**-701
Nielsen, S.A. **3**-110
Niemczyk, M. **7**-48
Niemeier, O. **16**-1592
Niemeyer, H.M. **8**-66, **8**-76, **8**-81
Nieminen, V. **8**-83
Nienhuis, D.M. **19**-234
Nier, A.O. **4**-262
Nierengarten, J.-F. **3**-210, **3**-218
Nierengarten, S.-F. **3**-217
Nierlich, M. **3**-144
Niess, B. **15**-1049
Niestroj, M. **16**-1012
Niesz, K. **13**-683
Niethammer, K. **15**-2263

Nieto-Oberhuber, C. **15**-2269, **16**-1562
Nieto, N. **15**-1929
Nieuwenhuizen, W.F. **15**-577
Nieuwenhuyzen, M. **9**-119, **18**-721
Nigam, A. **10**-1399
Niggemann, M. **11**-351
Nigh, W.G. **14**-329, **14**-351, **14**-414, **19**-672
Nigmatullin, N.G. **16**-1546, **16**-1549
Nigst, T.A. **10**-398
Nii, S. **10**-1267
Niikura, S. **15**-1196
Niimi, T. **15**-2145
Niimi, Y. **15**-1556
Niizuma, S. **16**-1331
Nikalje, M.D. **15**-1768, **19**-730
Nikam, K. **10**-1229
Nikat, S.M. **19**-1422
Nikbaghat, K. **16**-286
Nikeryasova, S.V. **11**-525
Nikiforov, G.A. **2**-467, **2**-469
Nikishin, G.I. **4**-373, **12**-153, **12**-711, **14**-24, **14**-489, **16**-135, **19**-420, **19**-592, **19**-1666
Nikitin, K.V. **13**-670
Nikitin, V.I. **16**-541
Nikitin, Yu.E. **16**-377
Nikitina, T.V. **2**-185
Niknam, K. **10**-1229, **19**-322
Nikoforov, A. **16**-176
Nikolaev, V. **5**-398
Nikolaev, V.A. **16**-2146
Nikolai, J. **12**-395
Nikolenko, L.N. **16**-434
Nikolić, S. **2**-118
Nikonova, L.A. **13**-865
Nikoofar, K. **16**-1849
Nikrad, P.V. **19**-1203
Nilsson, A. **10**-99, **15**-526, **16**-262, **16**-263
Nilsson, M. **2**-432, **2**-467, **10**-1426, **11**-657
Nilsson, P. **7**-125, **12**-282, **13**-397, **13**-409, **13**-422, **16**-453
Nimitz, J.S. **16**-1764
Nimlos, M.R. **5**-286
Ning, Z. **15**-1721
Ninomiya, I. **7**-45, **15**-1370, **15**-2445, **16**-2205
Ninomiya, S. **10**-372
Niphakis, M.J. **13**-578
Nir, M. **10**-486
Nir, Z. **18**-881
Nirei, S. **13**-698
Nisar, M. **17**-329
Nisato, N. **13**-479
Nischwitz, A.K. **10**-812
Nishi, S. **14**-484
Nishi, T. **10**-267
Nishibayashi, Y. **10**-819, **11**-332, **15**-643, **15**-865, **19**-956, **19**-1233
Nishibuchi, T. **10**-1579
Nishida, A. **14**-194, **15**-1027, **15**-2322, **16**-937
Nishida, K. **15**-1990, **19**-151
Nishida, M. **15**-2593, **15**-2639
Nishida, N. **15**-1384
Nishida, S. **4**-442, **10**-1300, **15**-2400, **15**-2470
Nishida, T. **15**-1982, **18**-427
Nishida, Y. **12**-116, **19**-482
Nishide, K. **10**-824, **19**-148
Nishigaki, Y. **18**-940
Nishiguchi, G. **18**-623
Nishiguchi, I. **11**-576, **12**-528, **15**-1452, **15**-1453, **15**-2089, **16**-1424, **19**-1656
Nishiguchi, T. **16**-1797, **19**-78
Nishihama, S. **16**-1424
Nishihara, H. **13**-698
Nishihara, Y. **10**-1456, **10**-1913, **10**-1914, **12**-299, **13**-380, **13**-568, **13**-715, **14**-358, **14**-360, **15**-623, **15**-623, **15**-988, **16**-2022
Nishii, Y. **12**-328
Nishikata, T. **13**-494, **15**-1232
Nishikawa, T. **15**-935, **15**-942
Nishikori, H. **15**-1981, **15**-2074
Nishikubo, T. **10**-1240
Nishimae, S. **16**-576
Nishimori, N. **15**-962, **15**-963
Nishimoto, K. **10**-289
Nishimoto, M. **15**-995
Nishimoto, Y. **10**-1592, **10**-1594, **10**-1726
Nishimura, A. **16**-971
Nishimura, J. **2**-75
Nishimura, K. **12**-787, **15**-1449
Nishimura, M. **15**-2069, **15**-2075
Nishimura, N. **18**-632
Nishimura, S. **15**-557
Nishimura, T. **12**-140, **15**-1223, **15**-1275, **16**-899, **16**-2143, **19**-215
Nishimura, Y. **12**-424
Nishina, N. **15**-340
Nishinaga, A. **19**-275
Nishinaga, T. **2**-137, **2**-176
Nishinaka, E. **15**-323
Nishino, F. **15**-236
Nishino, H. **11**-515, **15**-2359
Nishino, K. **16**-356
Nishino, M. **16**-612
Nishino, T. **10**-851, **10**-1294, **13**-43
Nishio, K. **16**-772
Nishio, M. **15**-1686, **16**-784
Nishio, T. **10**-808
Nishioka, T. **9**-78
Nishitani, K. **10**-1203
Nishitani, S. **13**-597
Nishiuchi, M. **7**-60
Nishiura, M. **15**-861
Nishiwaki, N. **15**-2112, **16**-966
Nishiwaki, Y. **12**-216, **12**-217
Nishiyama, H. **15**-762, **15**-2518, **13**-496, **15**-642, **15**-856, **15**-2594, **15**-2610, **16**-645, **16**-646, **16**-1087, **16**-1183, **19**-981, **19**-1037
Nishiyama, K. **16**-307, **19**-1386, **19**-1396
Nishiyama, T. **10**-630, **10**-1297
Nishiyama, Y. **10**-838, **10**-851, **10**-854, **10**-1294, **13**-43, **13**-682, **15**-1686, **15**-2503, **16**-626
Nishizawa, H. **16**-1972
Nishizawa, K. **8**-240
Nishizawa, M. **11**-329, **15**-872, **15**-1578, **15**-2595, **16**-1634
Nishizuka, A. **15**-2046
Nitabaru, T. **16**-1216
Nitsche, R. **2**-312
Nitta, A. **15**-650
Nitta, M. **15**-358
Nittala, S.S. **15**-2358
Nitzschke, M. **16**-184, **19**-1433
Niu, J., **2**-382
Niu, Y.-N. **15**-1055, **19**-1025
Niu, Y. **7**-50
Nivard, R.J.F. **16**-219
Nivsarkar, M. **10**-859
Niwa, H. **10**-1195
Niwa, J. **1**-36
Niwa, M. **11**-350, **16**-1791
Niwa, S. **16**-462, **16**-1247
Niwa, Y. **16**-912
Niwayama, S. **16**-1648, **18**-493
Nixdorf, M. **4**-458
Nixon, I.G. **2**-84, **11**-80
Niyazymbetov, M.E. **5**-387
Niyomura, O. **15**-2100
Nizar, M. **19**-863
Nizzi, K.E. **13**-53
Njardarson, J.T. **18**-262, **18**-263
Njera, C. **13**-462
No, K. **3**-128
No, Z. **19**-945
Noack, K. **15**-487
Noall, W.I. **15**-1682
Nobe, Y. **15**-897
Noble, D.R. **11**-155, **11**-158
Nobre, S.M. **10**-1883
Nobrega, J.A. **12**-152
Nobuoka, K. **9**-135
Nobutomo, M. **19**-1077
Nocanda, X.W. **16**-828
Noda, K. **15**-1978
Noda, T. **16**-1071
Nodari, N. **4**-462
Node, M. **10**-824, **19**-148, **19**-151
Noe, E.A. **4**-403, **4**-405, **4**-407, **4**-334, **4**-407, **4**-443
Noe, M.C. **15**-1802, **15**-1835
Noels, A.F. **10**-659, **15**-1776, **15**-2142, **15**-2501
Nogami, T. **15**-2401
Nogi, T. **11**-532, **11**-533

Nógrádi, M. **4**-1, **4**-139, **4**-150, **4**-160, **10**-1742, **10**-1799, **15**-635, **16**-494, **16**-1058, **19**-1009, **19**-1049
Noguchi, S. **16**-580
Noguchi, T. **19**-790
Noguchi, Y. **13**-392, **19**-865
Nogueira, C.W. **15**-943, **15**-1436
Noh, K. **15**-855
Noheda, P. **15**-1478
Nohira, H. **18**-141
Noirot, M.D. **12**-778
Noji, S. **19**-480, **19**-558
Nojima, M. **10**-234, **10**-1146, **10**-1249, **10**-1394, **15**-167, **15**-1671, **15**-1756, **15**-1926, **15**-2115, **16**-444, **16**-1992, **16**-1995, **16**-2214, **18**-803
Nokami, J. **16**-640, **16**-1047
Nokami, T. **10**-1343
Nokkeo, S. **16**-2119
Nolan, G.S. **8**-251
Nolan, S.P. **13**-195, **13**-328, **13**-540, **13**-708, **15**-203, **15**-860, **16**-112, **16**-1789, **16**-1803, **18**-269, **18**-821, **19**-981
Nolen, R.L. **10**-1846, **10**-1854
Nolin, K.A. **19**-1144
Noll, B.C. **12**-108
Noll, K. **16**-371, **18**-507
Noller, H. **17**-180, **17**-319
Nolley Jr., J.P. **13**-438, **13**-466
Nolte, R.J.M. **16**-1887
Noltes, J.G. **12**-584, **18**-356
Nome, F. **12**-706
Nomoto, A. **15**-384
Nomoto, T. **2**-330
Nomura, H. **10**-289, **19**-127
Nomura, I. **16**-61
Nomura, K. **19**-60
Nomura, M. **10**-1995, **13**-329, **15**-1477, **15**-2596, **15**-2689
Nomura, N. **10**-1519, **10**-1562, **15**-837
Nomura, R. **12**-792, **13**-591, **16**-1836
Nonappa. **10**-658
Nonhebel, D.C. **5**-211, **14**-2, **14**-46, **14**-81, **15**-51, **18**-54
Nonogawa, M. **13**-750
Noori, G.F.M. **11**-562
Norberto, F. **12**-743
Norcross, R.D. **15**-2249
Nordahl, Å. **15**-2223
Nordeen, C. **16**-1837
Nordlander, J.E. **10**-172, **10**-1049, **15**-64
Nordstrøm, L.U. **10**-1044
Noreen, A.L. **10**-76
Norikate, Y. **10**-1325
Norinder, J. **16**-466
Norinder, U. **2**-336, **2**-357
Norisue, Y. **10**-822
Norman, A.L. **16**-898
Norman, O.L. **13**-869
Norman, R.O.C. **5**-218, **6**-56, **14**-172, **19**-704
Norman, S.J. **16**-1614
Normant, H. **10**-440, **12**-649, **17**-451, **19**-506, **19**-813
Normant, J.-F. **10**-641, **10**-1313, **10**-1600, **10**-1605, **10**-1610, **10**-1612, **10**-1624, **12**-524, **13**-659, **15**-914, **15**-915, **15**-977, **15**-979, **15**-984, **15**-985, **15**-1134, **15**-1215, **16**-368
Norouzi, H. **10**-845
Norrby, P.-O. **13**-438, **14**-355, **14**-496, **15**-1790, **15**-1835, **15**-1981, **15**-906, **16**-549, **16**-669, **16**-678
Norris, A.R. **13**-4
Norris, R.K. **13**-57
Norris, W.P. **19**-747
Norsikian, S. **15**-914, **15**-915
Norsikian, S.L.M. **10**-1279
Nortey, S.O. **16**-1385
North, M. **12**-350, **16**-873, **16**-1284, **16**-1285, **16**-1496, **16**-1518, **16**-1531
Northrop, B.H. **18**-619
Northrop, B.N. **3**-220
Northrop, J.H. **18**-122
Northrup, A.B. **16**-1081
Norton, H.M. **16**-1660
Norton, J.R. **3**-89, **10**-1318, **10**-1402, **10**-1983, **13**-425, **14**-485, **15**-433, **15**-1317, **15**-1597, **15**-1599, **15**-2642, **18**-893, **19**-1147
Norton, K.J. **4**-324
Norton, S.H. **5**-14
Nose, K. **16**-912
Nose, M. **11**-141
Nosek, J. **10**-1290
Noson, K. **15**-768, **19**-1038
Notario, R. **5**-88
Noto, R. **15**-229
Notz, W. **16**-961, **16**-1080
Noureldin, N.A. **19**-108, **19**-645
Nouri, D.H. **18**-164
Nourse, J.G. **4**-131
Novack, A.R. **18**-632
Novak, I. **1**-22, **5**-265
Novak, M. **5**-441
Novák, Z. **13**-583, **13**-591
Novi, M. **8**-183
Novi, M. **17**-60, **10**-1834
Novikov, S.S. **15**-1750, **15**-2176, **16**-2164, **19**-1180, **19**-1272
Novikov, Y.Y. **16**-492
Novoa, J.J. **1**-15
Novoselov, E.F. **18**-354
Nowak, K. **13**-762
Nowak, P. **10**-1704, **16**-1074
Nowicka-Scheibe, J. **3**-16
Nowlan III, D.T. **15**-2143
Nowlan, V.J. **15**-28
Nowotny, H. **4**-178, **4**-180
Nowrouzi, N. **10**-1951
Noyce, D.S. **12**-679, **15**-190, **5**-220
Noyd, D.A. **10**-100
Noyori, R. **4**-153, **4**-200, **10**-1264, **10**-1752, **12**-274, **12**-307, **15**-645, **15**-2168, **15**-2664, **16**-494, **16**-1058, **16**-1148, **18**-151, **18**-398, **19**-677, **19**-1014, **19**-1015, **19**-1016, **19**-1017, **19**-1301, **19**-1307
Nozaki, H. **5**-377, **10**-834, **10**-1328, **10**-1415, **10**-1821, **15**-1197, **16**-130, **16**-502, **16**-690, **16**-693, **16**-1114, **17**-416, **18**-786, **19**-134
Nozaki, K. **10**-1602, **11**-527, **11**-537, **11**-543, **13**-220, **14**-17, **15**-1614, **16**-1039, **19**-1031, **19**-1395
Nozawa, S. **12**-515
Nozawa, Y. **2**-333, **2**-335
Noziri, M. **15**-288
Nozoe, T. **2**-180
Nsanzumuhire, C. **5**-224
Nsenda, T. **11**-543
Nubbemeyer, U **18**-690, **18**-663, **18**-727
Nüchter, M. **7**-123
Nudelman, N.S. **12**-561, **13**-18, **13**-687, **16**-864
Nuding, G. **14**-456
Nugent, B.M. **15**-1374, **16**-965
Nugent, S.T. **10**-1412
Nugent, T.C. **16**-324, **16**-360
Nugent, W.A. **12**-42, **15**-596, **15**-849, **19**-299
Nugiel, D.A. **2**-452, **2**-453, **4**-527
Nuhrich, A. **10**-995
Nukada, T. **4**-281
Numata, T. **19**-1583, **19**-1762, **19**-1762, **19**-1765
Nun, P. **19**-760
Nunami, K. **4**-202
Nuñez, M.T. **19**-393
Nuñez, O. **16**-32
Nunn, M.J. **10**-1096
Nurgatin, V.V. **13**-72
Nuridzhanyan, K.A. **10**-1090
Nurmi, T.T. **12**-656, **15**-916
Nury, P. **10**-1648
Nuss, J.M. **15**-2680
Nussbaumer, T. **10**-681
Nussim, M. **6**-82, **16**-2207
Nutaitis, C.F. **15**-526, **16**-330, **19**-899, **19**-908, **19**-1335
Nuteberg, D. **7**-126
Nuzzo, R.G. **12**-636
Nwaukwa, S. **18**-370
Nwaukwa, S.O. **19**-655
Nyangulu, J.M. **15**-1732
Nyberg, K. **14**-290
Nyburg, S.C. **15**-94
Nyce, J.L. **17**-15

Nyman, C.J. **14**-486
Nyns, C. **17**-361
Nyulászi, L. **2**-42

O'Brien, P. **6**-37
O'Shea, P.D. **19**-1142
Oae, S. **5**-126, **10**-385, **10**-495, **10**-800, **12**-752, **13**-87, **13**-111, **13**-122, **14**-397, **16**-2, **16**-2279, **17**-141, **18**-287, **18**-942, **18**-944, **19**-773, **19**-841, **19**-1578, **19**-1583, **19**-1583, **19**-1584, **19**-1596, **19**-1761, **19**-1762, **19**-1765, **19**-1768
Oakes, R.S. **15**-2220
Oakley, J.E. **10**-409
Oare, D.A. **15**-1060, **15**-1062, **15**-1097, **15**-1115
Oba, M. **16**-307, **19**-1386, **19**-1396
Obara, S. **15**-2250
Obara, Y. **10**-1970
Obayashi, R. **15**-2008
Obenius, U. **19**-1002, **19**-1003
Ober, M.H. **13**-709
Oberhammer, H. **2**-450, **4**-305, **4**-384
Oberli, M.A. **19**-550
Oberlinner, A. **14**-9
Obeshchalova, N.V. **15**-826
Obika, S. **15**-962, **15**-963
Obora, Y. **10**-1574, **18**-341, **19**-48
Obraztsov, P.A. **15**-181, **17**-178
Obrecht, R. **17**-482
O'Brien, C. **11**-116
O'Brien, C.J. **10**-1309, **10**-1469
O'Brien, D.F. **5**-108
O'Brien, D.H. **5**-137, **8**-10, **10**-404, **10**-552
O'Brien, E.M. **16**-2100
O'Brien, J.L. **19**-336
O'Brien, M.J. **10**-1676
O'Brien, P. **8**-225, **10**-1280, **12**-440
O'Brien, S.C. **2**-392
Obushak, N.D. **13**-818
Ocafrain, M. **10**-1963
Ocampo, R. **16**-830
Occhiato, E.G. **10**-1875, **12**-295, **15**-1084, **16**-680
Ochal, Z. **10**-911
Ochiai, H. **10**-1968, **16**-869, **16**-2031
Ochiai, K. **15**-1704
Ochiai, M. **4**-347, **5**-78, **10**-817, **10**-872, **12**-496, **15**-2003, **19**-534
Ochiai, O. **15**-1718
Ochiai, Yy. **19**-141
Ochterski, J. **4**-333
O'Connell, E. **18**-428
O'Connor, C. **16**-1693
O'Connor, C.J. **16**-1705
O'Connor, C.T. **19**-767
O'Connor, G.L. **17**-129
O'Connor, S. **11**-72, **13**-738
Oda, A. **15**-903
Oda, K. **15**-1990
Oda, M. **2**-228, **2**-368, **12**-688, **13**-479, **15**-2544, **18**-505
Oda, N. **15**-1334
Oda, R. **11**-552
Oda, T. **15**-774
Oda, Y. **19**-559
Odaira, Y. **2**-69
Odashima, K. **11**-438, **15**-643, **15**-2591, **15**-2598
Odedra, A. **15**-1945, **15**-2616, **15**-2617, **18**-581
Odell, L.R. **10**-974
Odenkirk, W. **16**-1557
Oderaotoshi, Y. **10**-1660, **15**-1743, **15**-2069
Odinokov, V.N. **19**-331
Ödman, P. **4**-188
Odobel, F. **11**-300
Odom, A.L. **10**-936, **15**-367
O'Donnell, M.J. **13**-651, **15**-2389, **15**-2390
O'Donoghue, A.C. **12**-97
Oeckler, O. **2**-374
Oediger, H. **17**-304, **17**-305
Oehme, G. **15**-2632
Oepen, G. **4**-280
Oertle, K. **16**-1764
Oeser, T. **4**-448
Oestreich, M. **13**-424, **15**-799
Offerhaus, R. **5**-304
Offermann, K. **17**-481
Offermanns, H. **19**-1769
Ofial, A.R. **10**-12, **10**-375, **10**-398, **10**-399, **10**-1784, **12**-351, **15**-2
Ofori-Okai, G. **12**-425
Ofstead, E.A. **18**-807, **18**-809, **18**-881, **18**-894
Ogasawara, K. **15**-1976, **19**-1371, **19**-1467, **19**-1599
Ogasawara, M. **15**-782, **15**-1199, **15**-1263, **15**-1281, **15**-2027, **16**-1096
Ogata, Y. **11**-305, **11**-413, **11**-513, **11**-588, **11**-630, **11**-664, **12**-177, **12**-178, **12**-209, **12**-748, **15**-1948, **16**-1519, **18**-405, **19**-311, **19**-758, **19**-1717, **19**-1742
Ogawa, A. **3**-192, **10**-1971, **13**-684, **15**-304, **15**-321, **15**-323, **15**-384, **15**-1519, **15**-2008, **19**-977, **19**-1564, **19**-1574
Ogawa, C. **10**-692, **15**-1437, **16**-952, **16**-953
Ogawa, H. **2**-324, **2**-357, **10**-656, **10**-931, **12**-575
Ogawa, K. **4**-476, **13**-203, **19**-100
Ogawa, M. **14**-443, **15**-1955, **19**-138
Ogawa, S. **10**-495, **13**-87
Ogawa, T. **10**-1098
Ogg Jr., R.A. **4**-429
Ogi, K. **18**-233
Ogibin, Y.N. **12**-153
Ogibin, Yu.N. **19**-420
Ogino, H. **3**-204
Ogino, T. **15**-1797, **15**-1813
Ogino, Y. **15**-1830
Ogiyama, H. **10**-1275
Ogle, C.A. **5**-105, **10**-1410, **10**-1408, **15**-1144, **15**-1154, **15**-1396
Ogle, J.W. **19**-651
Ogliaruso, M.A. **2**-184, **16**-1760, **16**-1824, **17**-429, **18**-591
Ogo, T. **11**-490
Ogoshi, H. **2**-228
Ogoshi, S. **15**-859
Ogston, A.G. **4**-262
Oguchi, T. **15**-1955
Oguchi, W. **16**-1167
Oguma, T. **15**-1984
Oguni, N. **4**-200, **10**-1620, **10**-1943
Ogura, J. **15**-209
Ogura, K. **3**-203, **10**-1809, **12**-189, **12**-729, **15**-57, **19**-1585
Oguro, D. **16**-843
Oguro, K. **12**-562
Oh, C.H. **13**-626, **15**-878, **15**-928, **15**-974
Oh, C.R. **10**-986
Oh, D.Y. **16**-195
Oh, J.-H. **16**-1927
Oh, L.M. **16**-167
Oh, S.H. **16**-1190
Oh, T. **15**-2226, **15**-2316
Oh, Y.J. **10**-330
Oh, Y.S. **10**-718, **16**-776
O'Hagan, D. **3**-14
Ohanessian, G. **2**-6, **2**-44
Ohannesian, L. **11**-263, **11**-485, **12**-164, **19**-1427
O'Hara, F. **15**-1077
Ohara, M. **4**-179
Ohara, N. **16**-1085
O'Hara, R.K. **2**-203
Ohara, S. **16**-1778, **16**-1915
Ohashi, H. **10**-838
Ohashi, S. **11**-536
Ohashi, Y. **11**-538, **15**-1542
Ohata, S. **15**-1468
Ohe, K. **13**-323, **15**-236, **19**-1716
Ohe, T. **13**-323, **15**-1230
Óhegyi, G. **9**-13
Ohga, T. **19**-1021
Ohga,Y. **10**-315
Ohigashi, N. **15**-1130
Ohira, M. **10**-1381
Ohira, S. **5**-377
Ohishi, H. **15**-1193
Ohishi, M. **16**-1587
Ohishi, T. **13**-352
Ohkata, K. **10**-165, **16**-1285
Ohkatsu, J. **14**-9

Ohkawa, K. **10**-544
Ohki, H. **16**-571
Ohki, M. **16**-859
Ohkubo, H. **19**-806
Ohkubo, T. **16**-1727, **16**-1506, **19**-1014, **19**-1016, **19**-1017, **19**-1301
Ohkuma, T. **4**-200
Ohlberg, D.A.A. **17**-55
Ohlmann, D.M. **16**-1893
Ohlmeyer, M.J. **15**-692, **15**-731
Ohloff, G. **14**-251, **14**-257, **15**-2361, **17**-424, **19**-305
Ohlsson, L. **12**-63
Ohme, R. **4**-40
Ohmiya, H. **10**-1363, **10**-1378, **10**-1884, **13**-465, **15**-394, **15**-904, **17**-308
Ohmori, H. **16**-2014, **19**-1072
Ohmori, K. **19**-1260
Ohmura, T. **10**-1544
Ohnesorge, M. **15**-2637
Ohno, A. **4**-186, **11**-186, **16**-2, **19**-1322
Ohno, H. **9**-128, **10**-794, **10**-1635, **10**-1947, **15**-410, **15**-815, **16**-1393
Ohno, K. **14**-485, **14**-486, **14**-492, **14**-498, **17**-329, **19**-1042
Ohno, M. **10**-1358, **16**-1624
Ohno, T. **15**-1452, **15**-1453
Ohno, Y. **16**-1336
Ohsaku, M. **7**-24
Ohsawa, A. **16**-342
Ohsawa, K. **13**-286
Ohsawa, N. **18**-496, **18**-497
Ohsawa, T. **12**-728, **19**-1317, **19**-1524
Ohshima, M. **19**-49
Ohshima, T. **10**-929, **15**-1071, **15**-1883, **15**-1918, **15**-1919, **16**-552
Ohshima, Y. **3**-15, **19**-580
Ohshiro, Y. **10**-1281, **14**-213, **15**-1580, **15**-1597, **19**-580, **19**-1291
Ohshita, J. **10**-1192
Ohshma, T. **16**-1090
Ohsugi, S.-i. **19**-148, **19**-151
Ohsumi, M. **15**-560
Ohta, A. **16**-838
Ohta, B.K. **8**-89, **15**-23
Ohta, C. **15**-1981
Ohta, H. **14**-308
Ohta, K. **4**-179, **10**-975
Ohta, M. **2**-376, **2**-477, **14**-121, **15**-251, **15**-1692, **17**-413
Ohta, S. **19**-1034
Ohta, T. **11**-187, **13**-198, **16**-745, **19**-1016, **19**-1077
Ohtaka, A. **13**-591
Ohtaka, S. **19**-1634
Ohtake, Y. **12**-390
Ohtani, S. **15**-1347
Ohto, M. **19**-59
Ohtsuka, Y. **15**-612, **17**-163, **19**-896
Ohtsuki, N. **15**-2324
Ohwada, A. **11**-193
Ohwada, T. **4**-510, **11**-504, **15**-776, **15**-779
Ohya-Nishiguchi, H. **5**-218
Ohya, S. **10**-1971, **19**-1574
Ohyabu, Y. **11**-420, **11**-421
Ohyama, H. **16**-1047
Ohyama, T. **11**-94
Ôi, S. **4**-180, **15**-532, **15**-1050, **15**-1229, **15**-1250, **16**-931
Oiarbide, M. **11**-326, **13**-141, **15**-1106, **15**-1407, **16**-1213
Oike, M. **16**-1582
Oisaki, K. **15**-2328, **16**-737, **16**-1150
Oisaki, M. **16**-942
Oishi, A. **16**-2240
Oishi, M. **17**-280
Oishi, T. **12**-728, **15**-1836, **15**-1839, **16**-1393, **17**-163, **19**-1049, **19**-1317, **19**-1524
Oishi, Y. **10**-619
Ojanperä, I. **10**-833
Ojha, N.D. **4**-443
Ojima, I. **4**-150, **15**-453, **15**-635, **15**-1208, **15**-1613, **15**-1942, **15**-2619, **15**-2695, **19**-824, **19**-902
Ojima, J. **2**-332, **2**-333, **2**-335, **2**-353, **2**-359
Oka, M.-a. **15**-859
Oka, M. **6**-45, **14**-11, **18**-191
Oka, S. **11**-186
Okabe, H. **7**-47
Okachi, T. **16**-733
Okada, A. **10**-1529
Okada, H. **14**-223
Okada, I. **10**-944
Okada, K. **3**-171, **11**-391, **12**-688, **15**-890
Okada, M. **10**-851
Okada, M. **10**-1294, **14**-484, **16**-908, **16**-1058, **16**-1149
Okada, S. **10**-405, **16**-1105, **16**-1326, **19**-1654
Okada, Y. **10**-1660
Okahara, M. **3**-153
Okajima, M. **10**-1830
Okajima, S. **15**-230
Okajima, T. **16**-2143
Okamoto, H. **10**-2011, **15**-343
Okamoto, J. **16**-2014
Okamoto, K. **2**-178, **5**-124, **5**-210, **10**-40, **10**-70, **10**-82, **10**-83, **10**-84, **10**-317, **10**-325, **11**-330, **15**-443, **15**-1269, **18**-680
Okamoto, M. **13**-568, **14**-360, **15**-1175
Okamoto, S. **15**-808
Okamoto, T. **11**-187, **12**-118, **12**-140, **12**-154, **13**-866, **16**-1486, **16**-1940, **16**-1944, **19**-1072
Okamoto, Y. **2**-76, **3**-211, **4**-90, **9**-20, **19**-1346
Okandeji, B.O. **16**-2263
Okano, K. **10**-1206
Okano, M. **4**-480, **11**-413, **11**-134, **13**-748, **15**-1661, **15**-1733, **15**-1852, **15**-1856, **15**-1858
Okano, N. **16**-1157
Okano, T. **10**-1991, **15**-649, **19**-950
Okarma, P.J. **4**-540
Okawara, M. **19**-709, **19**-1378
Okazaki, Y. **18**-426
Okazaki, H. **15**-1197, **15**-1661
Okazaki, N. **11**-608
Okazaki, R. **16**-222
Okazaki, T. **4**-476, **5**-88, **10**-138, **11**-23, **15**-1641
Okazoe, T. **16**-1425
Okazoe, T. **16**-1425
Okello, M,. **9**-125, **9**-131, **13**-402
Okeyo, S. **11**-258
Okhlobystin, O.Yu. **16**-1712
Öki, M. **3**-51, **4**-54, **4**-60, **4**-233, **4**-236, **4**-271, **4**-273, **4**-282, **4**-337, **4**-400, **4**-528, **4**-530, **6**-62, **9**-12, **12**-359
Okimoto, M. **12**-181, **16**-1541
Okimoto, Y. **15**-204
Okino, T. **10**-1527
Okino, T. **15**-1053
Okita, N. **19**-993
Okitsu, T, **10**-573
Okopie, R.A. **13**-554
Okovytyy, S. **17**-211
Okrasinski, S.J. **15**-456
Oksdath-Mansilla, G. **16**-210
Oku, A. **12**-408, **15**-922, **16**-1165
Oku, K.-i. **10**-695
Oku, M. **2**-283, **12**-77, **15**-1953
Okubo, K. **12**-688
Okubo, M. **12**-754
Okubo, Y. **13**-244
Okuda, F. **10**-926, **13**-283
Okuda, K. **13**-872
Okuda, T. **19**-593
Okude, Y. **16**-690
Okuhara, K. **16**-530
Okukado, N. **10**-1451, **10**-1463
Okulova, V.F. **4**-148
Okuma, K. **14**-308
Okumoto, H. **14**-401, **16**-144, **16**-2242, **17**-165
Okumura, A. **11**-608
Okumura, K. **11**-350
Okuno, H. **18**-237
Okuno, M. **13**-861
Okuno, T. **19**-1014
Okura, I. **15**-830
Okuro, K. **15**-1582, **15**-1594

Okutani, M. **17**-315
Okuyama, K. **10**-1206
Okuyama, K. **19**-148
Okuyama, S. **12**-790
Okuyama, T. **5**-66, **5**-78, **10**-594, **12**-507, **15**-108, **15**-1730
Olagbemiro, T.O. **16**-1696
Olah, G.A. **2**-174, **2**-191, **2**-231, **2**-385, **2**-419, **4**-458, **5**-2, **5**-5, **5**-7, **5**-14, **5**-15, **5**-16, **5**-17, **5**-18, **5**-19, **5**-22, **5**-23, **5**-25, **5**-30, **5**-31, **5**-32, **5**-34, **5**-36, **5**-37, **5**-39, **5**-40, **5**-41, **5**-47, **5**-48, **5**-52, **5**-54, **5**-56, **5**-59, **5**-61, **5**-62, **5**-64, **5**-69, **5**-79, **5**-80, **5**-83, **5**-87, **5**-89, **5**-91, **5**-94, **5**-95, **5**-100, **8**-10, **8**-18, **10**-14, **10**-49, **10**-52, **10**-127, **10**-129, **10**-131, **10**-132, **10**-142, **10**-144, **10**-152, **10**-166, **10**-179, **10**-180, **10**-181, **10**-185, **10**-186, **10**-194, **10**-195, **10**-200, **10**-201, **10**-204, **10**-205, **10**-210, **10**-214, **10**-218, **10**-404, **10**-410, **10**-413, **10**-421, **10**-425, **10**-552, **10**-559, **10**-614, **10**-672, **10**-886, **10**-1146, **10**-1196, **10**-1198, **10**-1200, **10**-1216, **10**-1247, **10**-1249, **10**-1250, **10**-1251, **11**-4, **11**-5, **11**-14, **11**-15, **11**-16, **11**-26, **11**-27, **11**-28, **11**-30, **11**-52, **11**-67, **11**-94, **11**-96, **11**-102, **11**-123, **11**-140, **11**-147, **11**-154, **11**-174, **11**-176, **11**-195, **11**-210, **11**-212, **11**-221, **11**-224, **11**-241, **11**-263, **11**-313, **11**-316, **11**-317, **11**-344, **11**-350, **11**-357, **11**-363, **11**-365, **11**-385, **11**-411, **11**-413, **11**-415, **11**-430, **11**-434, **11**-464, **11**-467, **11**-481, **11**-485, **11**-487, **11**-518, **11**-523, **11**-557, **11**-561, **11**-563, **11**-569, **11**-583, **11**-636, **11**-643, **11**-645, **11**-678, **12**-48, **12**-50, **12**-164, **12**-209, **12**-215, **12**-311, **12**-356, **12**-357, **13**-30, **13**-106, **13**-272, **14**-188, **14**-409, **15**-73, **15**-107, **15**-167, **15**-202, **15**-746, **15**-1756, **15**-1761, **15**-1769, **15**-1781, **16**-93, **16**-95, **16**-147, **16**-166, **16**-292, **16**-444, **16**-447, **16**-1346, **16**-1626, **16**-1992, **16**-1995, **16**-1996, **16**-1997, **16**-2066, **16**-2116, **16**-2160, **16**-2170, **17**-173, **17**-454, **18**-7, **18**-9, **18**-45, **18**-48, **18**-73, **18**-104, **18**-105, **18**-108, **18**-114, **18**-118, **18**-354, **18**-408, **18**-797, **19**-8, **19**-62, **19**-631, **19**-751, **19**-1423, **19**-1425, **19**-1427, **19**-1703, **19**-1724
Olah, G.S. **16**-2057
Olah, J.A. **5**-14, **5**-23, **5**-30, **10**-404, **10**-1146, **10**-1249, **11**-94, **11**-523, **11**-678, **12**-356, **15**-167, **15**-1671, **16**-1995, **18**-7
Oldenburg, P.D. **15**-1808
Oldenziel, O.H. **16**-1256
Oldenziel, O.H. **16**-1257, **19**-391
Oldham, J. **19**-600
O'Leary, B. **2**-8
O'Leary, D.J. **4**-348
O'Leary, M.H. **16**-20
Olefirowicz, E. **4**-250
Olejnik, Z. **3**-16
Olekhnovich, L.P. **2**-431, **18**-953
Oliva, A. **15**-2501
Oliveira, G.R. **16**-581, **16**-912
Oliveira, J.S. **16**-598
Olivella, S. **15**-2283, **15**-2588
Oliver A.G. **15**-2250
Oliver, J.P. **5**-152
Oliver, P.A. **15**-1876
Oliver, S.S. **10**-160
Oliver, T.F. **14**-282
Oliver, W.H. **15**-84
Oliverio, M. **10**-974, **16**-136
Olivero, A. **15**-2679
Olivero, S. **19**-1364
Olivi, N. **13**-606
Olivier-Bourbigou, H. **8**-126
Olivieri, A.C. **2**-460
Olivucci, M. **15**-2298, **18**-906
Oller-López, J.L. **5**-321
Öller, M. **17**-257
Ollevier, T. **10**-974, **16**-353, **16**-962, **16**-1138
Ollis, W.D. **2**-376, **18**-417, **18**-420
Ollivier, C. **14**-16, **14**-17, **14**-21, **15**-1286, **15**-1332, **15**-1356, **15**-1357
Ollman, J. **12**-450
Olmos, A. **18**-387, **19**-70
Olmstead, H.D. **10**-1756, **10**-1759, **12**-341, **16**-1042
Olmstead, M.M. **2**-405, **5**-118, **13**-649
Olmstead, W.N. **8**-58, **10**-355, **10**-364
O'Loane, J.K. **4**-4
Olofson, R.A. **10**-1145, **10**-1258, **11**-550, **16**-1355
Olofsson, B. **10**-963
Olofsson, K. **7**-125, **12**-273, **13**-416
Olomucki, M. **10**-1040
Olsen, A.R. **10**-6
Olsen, F.P. **8**-140
Olsen, J.-C. **15**-2316
Olsen, R.K. **10**-1805, **16**-200, **18**-426
Olsen, R.S. **16**-1305
Olson, A.H. **18**-112
Olson, J.M. **15**-136
Olson, L.P. **2**-98, **18**-624, **18**-626
Olson, R.J. **11**-241
Olsson, L. **10**-1610, **19**-1306
Olsson, L.F. **15**-341
Olsson, R. **15**-2277
Olsson, T. **13**-222, **15**-1241
Olsson, V.J. **12**-473
Olszowy, H.A. **4**-353, **12**-14
Oltra, J.E. **5**-321, **15**-1330, **16**-575
Ölund, J. **19**-1317
Ölwegård, M. **17**-53, **17**-153
Omachi, H. **13**-703
O'Mahony, C.P. **15**-1983, **19**-767
O'Mahony, D.J.R. **18**-835
Omar-Amrani, R. **13**-213
Omata, Y. **15**-1435
O'Meara, J.A. **10**-732
Omedes-Pujol, M. **16**-1496
Omkaram, N. **4**-146
Omote, M. **15**-1468
Omoto, K. **15**-1297, **15**-2234
Omoto, M. **19**-1323
Omura, H. **12**-558, **13**-688
Omura, K. **19**-148, **19**-157
Omura, S. **15**-1486
O'Murchu, C. **19**-345
Ona, H. **2**-245
Onagi, H. **3**-196
Onaka, M. **11**-229, **16**-733, **19**-1740
Onami, T. **12**-227, **13**-164
Onan, K.D. **15**-1580
Onda, K. **15**-1998
Ondrus, A.E. **12**-554
Ondruschka, B. **7**-123
O'Neal, H.E. **12**-668, **17**-128
O'Neal, H.R. **15**-2426
O'Neil, I.A. **15**-1414, **17**-483
O'Neill, J. **2**-260
O'Neill, P. **2**-453, **5**-250, **10**-523
Ong, B.S. **15**-1964
Ong, H.H. **11**-407
Ong, S.S. **10**-1207
Oniciu, D.C. **2**-98, **2**-104
Onishi, H. **15**-774
Onishi, T. **19**-629
Onishi, Y. **10**-1153, **19**-1340
Onistschenko, A. **10**-1646
Onitsuka, K. **10**-1544, **15**-1517, **15**-1525, **15**-1585, **15**-1586, **15**-1595
Onitsuka, S. **15**-2359
Ono, A. **19**-1203
Ono, M. **11**-214
Ono, N. **10**-813, **10**-1552, **10**-1557, **15**-2230, **17**-73, **17**-119, **17**-145, **19**-1515, **19**-1518, **19**-1525
Ono, S. **18**-390
Ono, T. **13**-554
Onodera, G. **19**-956
Onoe, A. **15**-1661
Onomura, O. **5**-263, **19**-142, **19**-984, **19**-1156
Onopchenko, A. **19**-406
Onorato, A. **10**-670
Onoue, H. **14**-295, **19**-398

Onozawa, S.-y. **15**-223, **15**-1476, **15**-1785
Onsager, O. **10**-1291, **15**-801
Onuma, Y. **16**-907, **16**-912
Ooi, T. **10**-665, **10**-741, **10**-1709, **15**-999, **15**-1042, **16**-401, **16**-1220, **16**-1528, **16**-1596, **16**-1799, **16**-1949, **18**-141, **19**-143, **19**-1750
Ooka, H. **19**-1017
Ookawa, A. **10**-1034, **19**-1071
Oomkes, P.G. **16**-1258
Ooms, B. **18**-368
Ooms, P.H.J. **16**-219
Oonishi, Y. **15**-209
Oono, K. **19**-148
Oosterbeek, W. **9**-64
Oosterhoff, L.J. **4**-287
Oosterwijk, R. **16**-1257
Oota, O. **16**-1227
Opalka, C.J. **16**-416
Opitz, G. **16**-1468, **16**-2233, **16**-2276, **16**-2277, **17**-324
Oppenheimer, E. **14**-493
Oppenländer, T. **4**-149, **7**-49, **7**-58
Oppolzer, W. **4**-139, **10**-1744, **10**-1745, **12**-607, **15**-898, **15**-991, **15**-993, **15**-2139, **15**-2169, **15**-2185, **15**-2243, **15**-2268, **15**-2451, **16**-1075, **16**-1443
Or, Y.S. **4**-464
Orahovats, A. **17**-16
Orban, J. **12**-325
Orbegozo, T. **19**-217
Orchin, M. **2**-51, **7**-12, **15**-1617, **19**-21
Ordoñez, M. **18**-241
Orena, M. **15**-1710, **19**-89
Orendt, A.M. **2**-243, **15**-1905
Orere, D.M. **16**-77, **16**-1541
Orfanopoulos, M. **14**-260, **14**-262, **14**-263, **14**-266, **19**-226, **19**-1338
Órfão, A.T.G. **16**-240
Organ, M.G. **10**-1309, **10**-1469
Organopoulos, M. **15**-1925
Orioli, P. **16**-1021
Orita, A. **6**-63, **16**-1818
Oritani, T. **18**-328
Orito, K. **19**-59
Oriyama, T. **19**-1311, **19**-1449
Orlandi, S. **16**-927
Orlando, V. **16**-1975
Orlinkov, A. **10**-1977, **14**-160
Orlova, G. **15**-2281
Orlovic, M. **10**-147
Ormiston, R.A. **2**-96
Orozco, M. **3**-81, **3**-82, **3**-85
Orpen, A.G. **1**-55, **1**-68, **2**-33, **4**-248, **4**-258
Orr, B.J. **4**-292
Orr, G. **13**-51
Orr, G.W. **3**-65
Orrling, K.M. **16**-1952
Orsini, F. **16**-718, **16**-848, **16**-1319
Orsini, M. **12**-789, **16**-775
Orsky, A.R. **8**-166
orspool, W.M. **15**-2105
Ortar, G. **10**-1990, **11**-425, **19**-1352
Ortega Schulte, C. M. **5**-270
Ortega, F. **13**-21, **16**-18
Ortega, M. **19**-1679
Ortiz-Marciales, M. **19**-972, **19**-1158, **19**-1234
Ortiz de Montellano, P.R. **14**-97, **14**-98, **18**-59
Ortiz, M. **16**-174
Ortiz, M.J. **18**-607
Ortoleva, E. **2**-350
Ortuño, R.M. **15**-2293, **15**-2454, **15**-2501
Orvedal, A.W. **2**-273
Orzech Jr., C.E. **18**-21, **18**-23
Osa, T. **19**-665
Osakada, K. **15**-1253, **16**-769
Osaku, A. **19**-664
Osamura, Y. **13**-55
Osanai, Y. **12**-686
Osawa, E. **4**-284, **15**-410, **18**-115, **18**-116
Osborn, J.A. **2**-46, **15**-2410, **16**-1426, **18**-894
Osby, J.O. **15**-431, **15**-527
Oscarson, S. **10**-1189
O'Shaughnessy, P. **15**-2070
O'Shaughnessy, P.N. **15**-336
O'Shea, D.F. **10**-1591
O'Shea, J.H. **19**-805
O'Shea, K.E. **15**-2363
O'Shea, P.D. **13**-829
Oshikiri, T. **3**-215
Oshima, K. **10**-872, **10**-1273, **10**-1328, **10**-1363, **10**-1374, **10**-1378, **10**-1466, **10**-1481, **10**-1484, **10**-1486, **10**-1572, **10**-1576, **10**-1626, **10**-1715, **10**-1821, **12**-227, **12**-526, **13**-322, **13**-346, **13**-457, **13**-461, **13**-465, **14**-12, **14**-17, **15**-154, **15**-308, **15**-317, **15**-394, **15**-763, **15**-778, **15**-787, **15**-890, **15**-901, **15**-904, **15**-935, **15**-936, **15**-942, **15**-975, **15**-1261, **15**-1297, **15**-1299, **15**-1344, **15**-1358, **15**-1360, **15**-1778, **15**-1779, **15**-2011, **15**-2012, **15**-2032, **15**-2611, **15**-2638, **16**-466, **16**-576, **16**-602, **16**-739, **16**-869, **16**-1035, **16**-1039, **16**-1425, **16**-1430, **17**-308, **19**-134, **19**-208, **19**-1395, **19**-1640, **19**-1645
Oshima, M. **19**-863
Oshita, J. **10**-1888
Oshita, M. **12**-571
Oshry, L. **12**-682
Oskam, J.H. **18**-818
Oskooie, H.A. **19**-34
Osmialowski, B. **12**-84
Osnabrug, S.J.M. **7**-128
Osowska-Pacewicka, K. **10**-945, **15**-2035, **19**-325, **19**-1263
Oßberger, M. **10**-1457
Ossowska, K. **19**-781
Ostapenko, A.G. **10**-1994
Ostaszewski, R. **16**-2255
Osterath, B. **15**-2021
Ostercamp, D.L. **16**-248
Ostergaard, N. **15**-1804
Osterhout, M.H. **19**-1136
Osterle, C. **4**-119
Ostermann, G. **18**-416, **18**-428
Ostermayer, F. **17**-406
Ostrogovich, G. **16**-2191
Ostrovskii, V.A. **18**-318, **18**-334
Osuka, A. **13**-145, **13**-449, **13**-646, **19**-1517, **19**-1716
O'Sullivan, B. **11**-155, **11**-158
O'Sullivan, M. **18**-791, **18**-792, **18**-793
O'Sullivan, T.P. **16**-691
Osuna, A.M.B. **15**-1610
Oswald, A.A. **15**-111, **15**-296
Oswald, M.C. **16**-143, **18**-139
Oswald, M.F. **16**-1475
Osztrovszky, G. **10**-1044
Ota, K. **11**-531
Otake, H. **15**-1435
Otani, S. **16**-1940, **16**-1944
Otera, J. **6**-63, **10**-742, **10**-762, **10**-834, **15**-1197, **16**-130, **16**-1114, **16**-1486, **16**-1783, **16**-1818, **18**-786, **19**-629
Otey, C.R. **19**-500
Oth, J.F.M. **2**-302, **2**-320, **2**-323, **2**-327, **2**-345, **2**-346, **2**-354, **15**-2468, **15**-2584, **18**-671, **18**-672, **18**-674
Otimoto, K. **16**-602
Otomaru, Y. **15**-1269
Otonnaa, D. **15**-1814
O'Toole, S.E. **16**-1591
Otroshchenko, O.S. **13**-468
Otsubo, K. **19**-864
Otsubo, T. **3**-135
Otsuji, Y. **5**-303, **10**-1579
Otsuka, H. **3**-131, **13**-479
Otsuka, M. **16**-1624
Otsuka, N. **15**-1372
Otsuka, S. **4**-139, **12**-67
Ott, J. **16**-129
Ott, W. **18**-665
Ottavi, L. **17**-57
Ottaway, C. **8**-94
Otte, K.M. **16**-1966
Ottenbrite, R.M. **15**-2190, **15**-2229
Otterbach, A. **4**-465
Otto, C. **15**-2210
Otto, P. **15**-2391, **15**-2426, **15**-2435

Otto, S. **15**-2210, **15**-2211, **15**-2214, **19**-629
Ottolina, G. **19**-801
Ottoni, O. **11**-461, **11**-462
Ottosson, H. **2**-204, **10**-71
Otvos, J.W. **15**-477
Ou, W. **16**-285
Ou, X. **18**-348
Ou, Y. **10**-1630
Ouali, A. **13**-293
Oudenes, J. **16**-1039
Ouellet, S.G. **15**-615
Ouk, S. **10**-605
Oulevey, G. **11**-476
Oullet, S.G. **10**-1638
Oullette, R.J. **15**-182
Ounsworth, J.P. **4**-400
Ourévitch, M. **16**-936
Oussaid, A. **10**-1152
Outram, J.R. **12**-740
Outram, R.J. **15**-320
Ouvry, G. **15**-1300
Ouyang, Y. **16**-202
Ovaska, T.V. **15**-918, **15**-920, **18**-632, **19**-1464
Ovcharenko, V.I. **5**-267, **5**-275
Øverås, A.T. **4**-406
Overberger, C.G. **15**-2565
Overchuk, N.A. **11**-643
Overgaard, J. **10**-1915
Overkleeft, H.S. **5**-78
Overman, J.D. **19**-1620
Overman, L.E. **13**-435, **15**-2229, **18**-655, **18**-655, **18**-743, **18**-747, **19**-1620
Overman, L.F. **18**-744
Overton, K. **19**-277
Owaki, M. **19**-667
Owczarczyk, Z. **13**-759
Owen, D.R. **15**-2523
Owen, N.L. **4**-307
Owen, W.S. **10**-1789
Owens, G.S. **15**-1898
Owens, K.A. **18**-667
Owens, P.H. **8**-66
Owens, P.J. **14**-450, **19**-1576
Owens, T.D. **15**-2250, **16**-934
Owens, W.H. **19**-1102
Owsley, D.C. **19**-1700, **19**-1711
Owston, N.A. **17**-446, **19**-660
Owtischinnkow, J.A. **3**-213
Owton, M.W. **15**-2085
Owton, W.M. **15**-2004
Owuor, P.O. **15**-64
Oxgaard, J. **15**-2197, **15**-2518, **19**-701
Oxley, P.W. **19**-1216
Oya, S. **16**-2243
Oyama, M. **15**-962
Oyama, T. **12**-476
Oyamada, H. **19**-1071
Oyola, Y. **15**-701
Ozaki, A. **13**-370
Ozaki, F. **10**-729
Ozaki, N. **15**-1137
Ozaki, S.-i. **19**-802
Ozaki, S. **16**-1869
Ozaki, Y. **5**-401, **5**-410
Ozanne, N. **16**-1300
Ozarde, P.S. **19**-1181
Ozasa, N. **16**-1142, **16**-1172
Ozawa, F. **10**-1189, **10**-1373, **10**-2008, **10**-2009, **10**-2011, **12**-263, **12**-289, **12**-329, **12**-727, **13**-189, **15**-343
Ozawa, K. **11**-551
Ozawa, M. **10**-1275
Ozawa, S. **14**-224
Ozawa, T. **15**-116
Ozawa, Y. **11**-646
Ozbalik, N. **19**-487, **19**-488, **19**-489
Özdemir, A.D. **15**-1349
Özdemir, I. **13**-595
Özdemïrhan, D. **19**-526
Ozier, I. **1**-42
Ozkan, I. **15**-2408, **18**-661
Özkar, S. **15**-449
Ozores, L. **15**-617
Ozorio, A.A. **10**-1777
Ozretich, T.M. **15**-2428
Öztürk, C. **18**-708
Ozturk, T. **16**-218

Paatz, R. **10**-1977
Pabon, H.J.J. **10**-1699
Pacansky, J. **2**-238, **13**-51
Pace, A. **15**-1873
Pace, E.D. **19**-1245
Pace, R.D.M. **15**-1077
Pace, T.C.S. **7**-35
Pacetti, A. **15**-1084
Pachamuthu, K. **16**-1722
Pacheco, M C. **10**-1179
Pacifici, J.G. **18**-212
Pack, S.K. **15**-362
Packer, J. **8**-37
Packer, J.E. **13**-799
Packschies, L. **4**-424
Paczkowski, M.A. **7**-43
Padakanti, S. **11**-462
Paddon-Row, M.N. **5**-284, **15**-2252, **15**-2270, **15**-2276, **16**-1067, **19**-79
Padias, A.B. **15**-2293
Padmaja, A. **16**-56
Padmakumar, R. **15**-1074, **15**-2084, **16**-795, **19**-901
Padmanabhan, S. **19**-1579
Padmapriya, A.A. **16**-2288
Padmavathi, V. **16**-56
Padmavathy, K. **16**-1004
Padmukumar, R. **11**-442
Padwa, A. **2**-92, **12**-364, **13**-241, **15**-1349, **15**-2105, **15**-2127, **15**-2139, **15**-2151, **15**-2182, **19**-1753
Pae, A.N. **10**-1593
Paetzold, J. **4**-186, **15**-277
Paetzold, P.I. **18**-451
Pagani, G. **2**-159
Pagani, G.A. **5**-122
Pagano, A.S. **15**-1870
Pagano, S. **18**-842
Page, I.D. **10**-433
Page, M.I. **10**-115, **11**-161, **16**-36
Page, P.C.B. **10**-1805, **15**-1167, **15**-1942, **15**-1943, **16**-1484
Page, T.K. **19**-532
Pagenkopf, B.L. **15**-643, **10**-1628, **15**-1545, **15**-1564, **19**-1447
Pagington, J.S. **3**-185
Pagni, R.M. **8**-162, **10**-831, **13**-504, **13**-598, **13**-717, **14**-337, **15**-1675, **15**-2224, **16**-109, **16**-1986
Pagnoni, U.M. **12**-115, **12**-117, **15**-1654, **15**-1732
Pagona, G. **19**-656
Pahadi, N.K. **15**-365
Pai, C.-C. **15**-1600
Pai, C.K. **15**-2218
Pai, G.G. **15**-719
Paiaro, G. **4**-87, **4**-88
Paik, C.H. **19**-1552
Paik, S.-J. **15**-2254
Paike, N. **5**-414
Pain, G.N. **12**-689
Paine, A.J. **13**-228, **17**-500
Painter, M.K. **19**-365
Paira, M. **10**-1512
Paixão, M.W. **14**-361, **14**-364, **16**-666, **16**-677, **16**-746
Paju, A. **19**-501
Pak, C.S. **17**-528
Paknikar, S.K. **10**-525
Pakrashi, S.C. **19**-1465
Pakulski, Z. **4**-120
Pakusch, J. **18**-434
Pal, B. **19**-1411
Pal, M. **10**-1912, **11**-462, **13**-418
Pal, R. **16**-1630
Pal, S. **15**-1945
Palacios, F. **16**-276, **16**-1407
Palacios, J.C. **4**-5, **8**-131, **15**-2187, **15**-2193, **15**-2290
Palacios, S.M. **7**-100, **13**-57, **13**-67, **13**-70
Palais, L. **15**-1173
Palani, N. **13**-838, **18**-602
Palano, D. **16**-1813
Palazzi, C. **18**-392
Palcios, J.C. **4**-312, **4**-315
Pale-Grosdemange, C. **16**-1919
Pale, P. **12**-303, **15**-247, **15**-2101
Palenik, G.J. **13**-11
Paleo, M.R. **5**-195
Palermo, R.E. **15**-1799, **15**-2011
Paleta, O. **10**-1104, **15**-1777
Paley, B.A. **12**-504
Paley, R.S. **10**-1314
Palit, S.K. **10**-521

Palke, W.E. **1**-8
Palkowitz, A.D. **16**-752
Pallan, P.S. **10**-1132
Palma, A. **11**-366
Palma, A.C. **16**-163
Palma, P. **17**-431
Palmelund, A. **14**-496
Palmer, B.W. **18**-404
Palmer, G.J. **18**-525
Palmer, H.B. **1**-98
Palmer, K. **2**-409
Palmer, K.W. **4**-65
Palmer, M.H. **15**-209
Palmer, M.J. **16**-1448
Palmere, R.M. **18**-363
Palmieri, A. **15**-1051, **16**-298, **16**-827
Palmieri, P. **18**-73
Palmisano, G. **13**-284
Palombi, L. **10**-744, **12**-789
Palomero, M.A. **15**-2657
Palomo, C. **10**-1208, **11**-326, **13**-141, **15**-1106, **15**-1407, **16**-308, **16**-351, **16**-555, **16**-831, **16**-1213, **16**-1773
Palovich, M.R. **16**-612
Pálovics, E. **4**-160
Palrisi, M.F. **4**-95
Paluchowska, M.H. **16**-1980
Palumbo, G. **10**-1220, **17**-205
Palumbo, P.S. **17**-352
Palumbo, R. **4**-88
Pan, C. **13**-388, **13**-592, **15**-503
Pan, H.-Q. **15**-1304
Pan, J.-F. **16**-823
Pan, L. **14**-3
Pan, Q. **15**-297
Pan, S.-F. **15**-531, **15**-610
Pan, S.C. **16**-1543, **16**-2258
Pan, W.-B. **15**-545, **16**-1778
Pan, X.-W. **19**-1217
Pan, X. **10**-976, **10**-1029, **19**-238, **19**-1198
Pan, Y. **15**-597, **19**-52, **19**-1017, **19**-1635
Panarina, A.E. **15**-1413
Panaye, A. **9**-74
Panchaud, P. **14**-17
Panda, B. **13**-613
Panda, M. **16**-666
Pandey, A. **15**-1016
Pandey, B. **15**-2201
Pandey, G. **10**-1006, **10**-1283, **15**-1309
Pandey, L.K. **16**-229
Pandey, M.K. **10**-1006, **15**-1016
Pandey, R.K. **15**-300
Pandey, S.K. **10**-1241
Pandhi, S.B. **16**-2223
Pandiarajan, K. **10**-768
Pandiaraju, S. **16**-1210
Pandit, A.B. **17**-479
Pandurangan, K. **10**-658
Pandya, A. **16**-948
Pandya, K. **15**-1056
Pandya, S.U. **16**-978
Panek, E.J. **14**-420
Panek, J.S. **10**-583, **12**-280, **16**-1485
Paneth, P. **10**-4, **10**-1930, **17**-48
Panicker, S.B. **15**-1658, **19**-707
Panja, C. **10**-1673, **11**-154
Pankayatselvan, R. **10**-1253
Panknin, O. **18**-782, **18**-783
Pánková, M. **17**-16, **17**-26, **17**-28, **17**-100, **17**-261
Pankratov, V.A. **16**-2186
Pannala, M. **15**-602
Panne, P. **15**-2504, **15**-2508
Pannell, D.K. **5**-205
Panova, Y.B. **18**-11
Pansare, S.V. **10**-653, **15**-1056
Panshin, S.Y. **4**-483
Panunzi, A. **4**-88
Panunzi, B. **11**-283, **15**-1695
Panunzio, M. **15**-2380
Panyachotipun, C. **10**-200
Panzeri, W. **16**-1532
Paoletti, M. **16**-1229, **16**-1242, **19**-1254
Paolo Ottaviani, P. **3**-17
Paolucci, G. **19**-1115
Papa, P. **12**-788
Papadopoulos, M. **16**-1569, **17**-57
Pape, M. **12**-207
Papeo, G. **10**-733
Papoian, V. **13**-690
Papoula, M.T.B. **13**-651
Papp, A. **13**-385
Pappalardo, J.A. **10**-877, **16**-321, **16**-2065
Pappalardo, S. **3**-144, **4**-95
Pappas, B.C. **15**-2450
Pappas, J.J. **19**-330
Pappas, R.S. **5**-347
Pappas, S.P. **15**-2450
Pappo, R. **15**-1032, **19**-386
Paptchikhine, A. **15**-471
Paquer, D. **16**-1466
Paquet, V. **16**-1435
Paquette, L.A. **2**-191, **2**-192, **2**-264, **2**-266, **2**-283, **2**-384, **2**-385, **2**-388, **4**-89, **4**-91, **4**-196, **4**-463, **5**-89, **10**-165, **10**-239, **10**-1590, **12**-195, **12**-363, **12**-698, **12**-717, **12**-718, **15**-2179, **15**-2240, **15**-2265, **15**-2312, **15**-2363, **15**-2442, **16**-462, **16**-561, **16**-2309, **17**-346, **17**-518, **18**-98, **18**-129, **18**-631, **18**-632, **18**-639, **18**-658, **18**-671, **18**-673, **18**-675, **18**-827, **18**-896, **18**-899, **18**-901, **18**-903, **18**-904, **18**-911, **18**-914, **19**-62
Paquin, J.-F. **10**-1757, **15**-1269
Parac-Vogt, T.N. **11**-125
Paradas, M. **16**-575
Paradine, S.M. **19**-532
Paradisi, C. **10**-73
Paradisi, F. **19**-1044
Paradowska, J. **16**-1152
Parady, T.E. **17**-346
Paragi, G.T. **3**-22
Paras, N.A. **11**-345
Paraskar, A.S. **19**-730
Parcell, R.F. **18**-285
Parchment, O.G. **2**-474
Pardo, C. **10**-1108, **16**-727
Pardo, D.G. **13**-662, **16**-666
Pardo, S.N. **11**-390
Paré, J.R.J. **15**-2203
Paré, P.W. **16**-814, **16**-1044, **19**-555
Parello, J. **18**-157
Parenty, A. **16**-1763
Parfenova, M.N. **10**-501
Parham, W.E. **12**-644, **15**-2472
Parihar, J.A. **11**-124
Parikh, J.R. **19**-156
Parimala, G. **10**-1003
Parini, V.P. **3**-98
Paris, J. **17**-371
Paris, M. **11**-258
Parisel, O. **5**-187
Parish, E.J. **15**-699
Parish, S. **15**-699
Parisi, L.M. **13**-163
Parisi, M.F. **3**-144
Pariza, R. **19**-338
Park, B.-M. **15**-631
Park, B. **10**-112
Park, C. **19**-438
Park, C.H. **3**-154, **4**-251, **13**-318
Park, C.M. **15**-240, **15**-265
Park, C.Y. **15**-1837
Park, E.J. **10**-1670
Park, G.-J. **3**-195
Park, H.-g. **10**-1764, **15**-1404
Park, H. **15**-837
Park, H.-J. **12**-121, **19**-133, **19**-549
Park, H.S. **16**-173, **16**-841, **17**-396, **19**-1160, **19**-1388
Park, I.S. **10**-1723
Park, J.-N. **13**-242
Park, J.-S. **12**-305, **16**-1854
Park, J. **2**-459, **10**-1207, **10**-1723, **15**-1161, **16**-239, **19**-128
Park, J.C. **16**-757
Park, J.H. **10**-1210, **15**-1529, **19**-964
Park, J.K. **15**-1556, **16**-667
Park, J.Y. **10**-1136, **19**-549
Park, K.H. **15**-1535, **16**-1864, **18**-795, **18**-798
Park, K.-M. **3**-195
Park, K.P. **10**-260
Park, K.S. **16**-800
Park, L. **19**-1310
Park, L.Y. **18**-818
Park, M.-k. **10**-1764
Park, M.C. **19**-1590
Park, M.Y. **17**-396

Park, O.-S. **11**-270
Park, R. **16**-906
Park, S.-D. **16**-1927
Park, S. **16**-239, **18**-889, **19**-1324
Park, S.B. **10**-917, **13**-306, **13**-375, **13**-597
Park, S.J. **15**-878, **15**-974
Park, S.W. **15**-1989
Park, S.Z. **12**-223
Park, W. **10**-634, **16**-2143
Park, W.S. **10**-100, **10**-801, **19**-1007
Park, Y.-T. **18**-340
Park, Y.C. **15**-1489
Park, Y.J. **12**-206, **15**-521, **16**-1687
Park, Y.S. **10**-1345, **16**-849, **16**-874, **18**-623, **19**-1313
Párkányi, C. **2**-4
Parker, A.J. **8**-257, **8**-259, **10**-351, **10**-357, **10**-446, **13**-74, **17**-74, **17**-81, **17**-101, **17**-102, **17**-446, **19**-660
Parker, D. **3**-124, **4**-106, **4**-215, **15**-428, **19**-927
Parker, D.A. **10**-1426
Parker, D.G. **15**-553, **18**-408
Parker, J.K. **4**-173, **4**-299
Parker, K.A. **13**-108
Parker, R.J. **3**-32
Parker, S.R. **11**-516
Parker, V.D. **6**-38, **18**-716
Parker, W.L. **15**-2658
Parks, C.R. **19**-357
Parlanti, L. **19**-199, **19**-1747
Parlato, S. **4**-167
Parlman, R.M. **10**-1961, **19**-1512
Parmar, R.R. **16**-103
Parmar, V.S. **11**-397
Parmerter, S.M. **12**-197
Parnas, H.H. **18**-811
Parnes, Z.N. **2**-174, **10**-1454, **15**-499, **15**-501, **15**-750, **16**-162, **16**-763, **19**-1288, **19**-1341
Parola, A. **7**-36, **19**-1663
Parr, J. **15**-458
Parr, J.E. **10**-1825
Parr, R.G. **2**-101, **2**-122, **8**-163, **8**-168, **8**-170, **10**-34, **11**-90
Parrain, J.-L. **10**-1706, **12**-281, **12**-307, **15**-806
Parratt, M.J. **4**-31
Parrinello, M. **18**-347
Parrini, M. **16**-1207
Parris, G. **5**-165, **5**-174, **5**-176
Parris, S. **13**-237
Parrish, C.A. **13**-130, **13**-193
Parrish, D.R. **15**-1117, **16**-1120
Parrish, J.D. **16**-839
Parrish, J.P. **13**-491, **13**-712
Parrot-Lopez, H. **3**-130
Parrott II, R.W. **16**-666
Parrott, M.J. **14**-2, **14**-13, **14**-24
Parrott, S.J. **16**-1573
Parshall, G.W. **11**-120, **16**-1410
Parson, A.F. **12**-115
Parsonage, N.G. **3**-110
Parsons Jr., G.H. **7**-36, **19**-1663
Parsons, A.F. **10**-1295, **14**-23, **15**-1347, **15**-2102, **19**-1608
Parsons, J.A. **15**-512
Parsons, J.L. **15**-436
Parsons, M. **11**-312
Parsons, P.J. **18**-719
Parsy, C.C. **15**-1931
Partch, R. **14**-229
Partington, S.M. **12**-696
Parton, R. **10**-909
Paruch, E. **10**-1619
Parvez, M. **4**-166, **5**-373, **15**-252
Parvin, T. **19**-562
Pârvulescu, L. **15**-2420
Pârvulescu, V.I. **9**-136
Paryzek, Z. **19**-359
Parziale, P.A. **18**-587
Pascal Jr., R.A. **2**-77, **2**-79, **2**-80, **2**-141, **2**-109, **2**-344
Pascal, R. **16**-105
Pascal, R.A. **6**-73
Pascard, C. **3**-218, **4**-253
Paschal, J.W. **16**-1381
Paschalis, P. **15**-192
Paschmann, V. **18**-668
Pascoe, J.D. **18**-959
Pascone, J.M. **10**-297
Pasha, M.A. **10**-1609, **15**-1685, **16**-279, **16**-1815
Pashinnik, V.E. **16**-1999
Pashkovsky, F.S. **19**-1424
Pasi, F. **16**-1084
Pasi, M. **18**-344
Pasquato, L. **15**-2180
Pasquet, M.J. **13**-794
Pasquier, M.L. **4**-213
Pasquini, C. **15**-862
Pasricha, R. **13**-592
Pasta, P. **19**-738, **19**-801
Pasteris, R.J. **18**-920
Pastine, S.J. **10**-1890, **11**-323, **12**-691, **15**-759
Pasto, D.J. **5**-257, **5**-260, **5**-316, **10**-1355, **10**-1356, **10**-1758, **10**-1873, **15**-5, **15**-32, **15**-107, **15**-112, **15**-113, **15**-508, **15**-513, **15**-2429
Pasto, D.J. **18**-502, **18**-568
Pastó, M. **10**-962
Pastor, I.M. **12**-434
Pastor, S.D. **16**-1247
Pastori, N. **16**-121, **16**-1532, **19**-947
Pastukhov, F.V. **16**-2083, **16**-2084
Pastushok, V.N. **10**-501
Pasumansky, L. **13**-184
Patai, S. **1**-9, **1**-48, **1**-77, **1**-80, **2**-41, **2**-378, **3**-3, **3**-11, **3**-53, **3**-55, **3**-56, **3**-89, **3**-99, **3**-101, **4**-27, **4**-33, **4**-48, **4**-67, **4**-227, **4**-270, **4**-277, **4**-363, **4**-492, **5**-126, **5**-152, **5**-267, **5**-311, **5**-312, **5**-334, **5**-336, **5**-436, **7**-49, **7**-54, **7**-68, **8**-50, **8**-53, **8**-68, **8**-171, **8**-177, **8**-190, **8**-194, **8**-235, **8**-240, **9**-31, **9**-32, **10**-127, **10**-226, **10**-305, **10**-403, **10**-406, **10**-414, **10**-420, **10**-421, **10**-454, **10**-492, **10**-536, **10**-551, **10**-603, **10**-617, **10**-662, **10**-677, **10**-773, **10**-776, **10**-802, **10**-810, **10**-863, **10**-874, **10**-877, **10**-899, **10**-1059, **10**-1081, **10**-1090, **10**-1094, **10**-1121, **10**-1180, **10**-1331, **10**-1518, **10**-1552, **10**-1626, **10**-1805, **10**-1898, **10**-1929, **10**-1983, **11**-39, **11**-162, **11**-230, **11**-271, **11**-470, **11**-609, **11**-620, **11**-648, **11**-665, **12**-1, **12**-2, **12**-57, **12**-59, **12**-74, **12**-75, **12**-82, **12**-84, **12**-225, **12**-311, **12**-315, **12**-320, **12**-409, **12**-415, **12**-448, **12**-455,**12**-456, **12**-497, **12**-505, **12**-533, **12**-579, **12**-594, **12**-604, **12**-611, **12**-623, **12**-668, **12**-733, **13**-39, **13**-54, **13**-57, **13**-96, **13**-139, **13**-769, **13**-772, **13**-773, **13**-774, **13**-775, **13**-776, **13**-778, **13**-780, **14**-145, **14**-218, **14**-240, **14**-251, **14**-268, **14**-329, **14**-330, **14**-390, **14**-438, **14**-485, **14**-489, **15**-1, **15**-38, **15**-39, **15**-40, **15**-76, **15**-78, **15**-80, **15**-293, **15**-301, **15**-423, **15**-461, **15**-500, **15**-591, **15**-722, **15**-744, **15**-801, **15**-884, **15**-977, **15**-991, **15**-1494, **15**-1597, **15**-1623, **15**-1643, **15**-1652, **15**-1757, **15**-1952, **15**-2105, **15**-2118, **15**-2253, **15**-2358, **15**-2361, **15**-2366, **15**-2444, **15**-2448, **15**-2470, **15**-2586, **16**-2, **16**-3, **16**-16, **16**-82, **16**-120, **16**-177, **16**-200, **16**-240, **16**-258, **16**-259, **16**-288, **16**-418, **16**-451, **16**-455, **16**-863, **16**-880, **16**-1014, **16**-1017, **16**-1076, **16**-1345, **16**-1493, **16**-1613, **16**-1653, **16**-1760, **16**-1767, **16**-1801, **16**-1824, **16**-1855, **16**-1868, **16**-1875, **16**-1955, **16**-1984, **16**-2003, **16**-2166, **16**-2216, **16**-2249, **17**-3, **17**-8, **17**-50, **17**-107, **17**-128, **17**-135, **17**-151, **17**-154, **17**-176, **17**-178, **17**-244, **17**-293, **17**-300, **17**-313, **17**-346, **17**-371, **17**-392, **17**-405, **17**-430, **17**-453, **17**-461, **17**-491, **17**-502, **18**-1, **18**-99, **18**-125, **18**-186, **18**-203, **18**-219, **18**-223, **18**-306, **18**-317, **18**-335, **18**-426, **18**-632, **18**-654, **18**-758, **18**-788, **18**-807, **18**-934, **18**-937, **18**-941, **19**-6, **19**-22, **19**-45, **19**-63, **19**-97, **19**-252, **19**-274, **19**-287,

19-374, **19**-413, **19**-609, **19**-690, **19**-716, **19**-727, **19**-769, **19**-773, **19**-785, **19**-826, **19**-879, **19**-893, **19**-1079, **19**-1106, **19**-1122, **19**-1266, **19**-1332, **19**-1360, **19**-1461, **19**-1527, **19**-1544, **19**-1558, **19**-1577, **19**-1613, **19**-1618
Patat, F. **10**-403, **10**-1180
Patchornik, A. **16**-1930
Patel, B. **16**-1408
Patel, B.A. **13**-467
Patel, B.K. **10**-886, **10**-1156, **16**-131, **16**-1878, **19**-682
Patel, B.P. **10**-122
Patel, D.B. **19**-14
Patel, J.J.B. **19**-1229
Patel, K.M. **18**-205
Patel, M. **15**-2295
Patel, P. **15**-292
Patel, P.K. **10**-747
Patel, R. **11**-397, **18**-342
Patel, R.C. **6**-49, **6**-55, **6**-58, **6**-59, **10**-1255
Patel, S. **19**-73, **19**-289, **19**-832
Patel, S.T. **15**-1979
Patel, S.V. **10**-1373
Patel, U.C. **15**-1564
Patel, V. **12**-670
Pater, R.H. **15**-1948
Paternò, E. **15**-2454
Paterson, E.S. **10**-1626, **12**-456, **12**-497, **15**-884, **16**-3
Paterson, I. **16**-576, **16**-1063, **16**-1077, **16**-1098
Pathak, B. **1**-84
Pathak, U. **16**-229
Patil, A.V. **16**-2022
Patil, B.R. **10**-1178
Patil, G. **16**-1524
Patil, G.S. **10**-112
Patil, K. **15**-1289
Patil, K.M. **19**-1054
Patil, N.R. **19**-616
Patil, N.S. **11**-438
Patil, N.T. **15**-365, **15**-405, **15**-947, **15**-952
Patil, P.N. **16**-1647
Patil, S.N. **10**-1068
Patil, S.R. **15**-1858
Patil, V.D. **15**-700
Patil, V.J. **16**-1323
Patil, Y.P. **13**-683
Patkar, L.N. **16**-1800
Patman, R.L. **10**-1575
Paton, R.M. **15**-2105
Patonay, T. **12**-332, **15**-1912
Patra, P.K. **11**-340
Patricia, J.J. **12**-655, **12**-656, **15**-916
Patrick, B.O. **2**-407, **15**-309
Patrick, D.W. **17**-293
Patrick, J.B. **19**-1486
Patrick, T.B. **11**-308, **14**-149, **14**-478, **15**-2467
Patrie, W.J. **19**-136
Patro, B. **11**-340, **15**-1362
Patsch, M. **18**-416, **18**-545
Pattabhi, V. **3**-6
Pattenden, G. **10**-746, **15**-825, **15**-1366, **16**-1302
Patterson, A.W. **16**-928
Patterson, J.M. **19**-741
Patterson, W. **17**-195
Patterson, W.I. **4**-58
Pattison, F.L.M. **15**-1670
Pattison, J.B. **10**-1124
Pattison, V.A. **18**-445
Patton, D.S. **19**-1303
Patwardhan, B.H. **15**-21
Patwari, S.B. **11**-259
Patz, M. **16**-1065
Pau, C. **8**-252
Pau, C.F. **15**-2229
Pauer, F. **5**-183
Paugam, J.P. **15**-2484
Paukstelis, J.V. **4**-242, **10**-1262, **16**-968, **19**-1128
Paul, A. **15**-2684
Paul, D.B. **10**-1059, **15**-423, **15**-1757
Paul, D.F. **11**-276
Paul, E.W. **19**-694
Paul, I.C. **2**-286, **2**-302, **2**-356, **4**-189, **4**-194
Paul, K. **17**-520, **17**-522
Paul, N.C. **10**-792
Paul, R.P. **16**-871
Paul, S. **10**-610, **11**-447, **11**-502, **11**-591, **12**-119, **12**-120, **19**-601
Paul, V. **11**-240, **11**-442
Paul, V.L. **16**-1865
Pauling, L. **1**-8, **1**-26, **2**-409, **5**-294
Paulmier, C. **12**-250, **17**-293
Paulose, B.J. **16**-898
Paulsen, H. **16**-1866
Paulson, J.F. **10**-365
Paulson, K.L. **16**-2072
Paulus, E.F. **3**-144
Pauson, P.L. **2**-185, **15**-1539, **15**-1548
Pavam, C.H. **16**-796
Paventi, M. **11**-271, **11**-272
Pavia, A.A. **10**-668
Pavlenko, N.V. **19**-931
Pavlides, V.H. **18**-302
Pavlov, S. **16**-2059
Pavlova, L.A. **10**-553
Pavlova, N.N. **10**-830
Pawar, D.M. **4**-334, **4**-403, **4**-405, **4**-407
Pawar, R.P. **10**-611, **10**-1178, **18**-395
Pawar, S.S. **16**-800
Pawêka, Z. **3**-16
Paxton, R.J. **16**-1440
Payeras, A.M. **19**-167
Payette, J.N. **15**-2252
Payne, A.H. **15**-197
Payne, B.J. **18**-144
Payne, D. **4**-537
Payne, M.M. **15**-2621
Payne, N.C. **10**-306
Payzant, J.D. **10**-355
Pazmiño, D.E.T. **18**-389
Pazos, J.F. **18**-212
Peach, M.E. **10**-810, **13**-139
Peachey, S.J. **4**-29
Peacock, J.L. **15**-1374
Pearce, G.T. **4**-108
Pears, D. **19**-869
Pearson, A.J. **3**-92, **19**-112
Pearson, D.E. **9**-36, **10**-1256, **11**-224, **11**-438, **12**-605
Pearson, M.M. **12**-363
Pearson, R. **14**-207
Pearson, R.G. **6**-9, **6**-59, **8**-48, **8**-164, **8**-165, **8**-166, **8**-168, **8**-169, **10**-30, **10**-358, **10**-369, **10**-429, **10**-1402
Pearson, R.J. **15**-2213
Pearson, S.C. **17**-460
Pearson, W.H. **12**-542, **12**-595, **18**-325
Pease, A.R. **3**-197
Pease, J.E. **16**-463
Peat, A.J. **10**-1496
Peatt, A.C. **16**-614, **16**-909
Pecher, J. **15**-2015
Pechet, M.M. **12**-765, **14**-153, **18**-929
Pechhold, E. **5**-178
Pecoraro, J.M. **10**-104
Pecul, M. **4**-311
Pedersen, C.J. **3**-106, **3**-108
Pedersen, C.M. **16**-1982
Pedersen, H.L. **15**-775
Pedersen, J.A. **10**-103
Pedersen, S.F. **15**-1975, **19**-1641, **19**-1642, **19**-1659
Pedersen, T.M. **15**-2676, **16**-1372
Pedersen, U. **16**-1920
Pedersen, U.S. **16**-224
Pedireddi, V.R. **8**-13
Pedoussaut, M. **10**-1932, **16**-1646
Pedregal, C. **19**-1482
Pedrielli, P. **1**-110
Pedrini, P. **19**-223, **19**-842
Pedro, F.M. **16**-1436
Pedrosa, R. **16**-857, **16**-2076
Pedulli, G.F. **1**-116, **1**-110, **5**-331, **18**-73, **19**-578
Peel, J.B. **2**-465
Peel, T.E. **8**-18
Peelen, T.J. **15**-1107
Peeling, E.R.A. **11**-151
Peeling, J. **3**-60
Peerdeman, A.F. **4**-100
Peerlings, H.W.I. **12**-779
Peerzada, N. **11**-410, **16**-726
Pees, K.J. **15**-1217

Peet, J.H.J. **16**-1390
Peet, N.P. **12**-196, **15**-2506, **16**-2123
Peeters, D. **15**-2186, **15**-2233
Peeters, J. **19**-408
Pegg, G.G. **18**-587
Pégot, B. **15**-2329, **16**-801
Pehk, T. **19**-501
Pei, B.-G. **10**-647, **10**-1933
Pei, D. **16**-2076
Pei, T. **15**-944, **15**-951
Pei, W. **16**-821
Peiffer, G. **14**-204, **15**-640
Peiris, S. **5**-133, **12**-681
Pejchal, V. **16**-1993
Pekelny, U. **11**-128
Peled, P. **10**-256
Peles, D.N. **18**-579
Pelikán, P. **14**-6, **14**-7
Pelka, S. **13**-194
Pel'kis, P.S. **10**-1090
Pellacani, L. **15**-2044, **15**-2049, **15**-2050
Pellegrinet, S.C. **15**-1267
Pellerite, M.J. **8**-17, **10**-374
Pellet-Rostaing, S. **15**-892
Pellet, M. **10**-571, **16**-2055
Pelletier, J.D. **10**-1131
Pelliccia, A.R. **15**-1895
Pellissier, H. **4**-197, **10**-1765, **13**-49, **15**-1082, **15**-2337, **15**-2511
Pellón, R.F. **16**-1249
Pelter, A. **4**-82, **10**-1827, **10**-1870, **12**-344, **12**-451, **12**-465, **14**-433, **14**-437, **15**-671, **15**-728, **15**-1255, **16**-736, **16**-1039, **16**-1063, **16**-1925, **18**-451, **18**-460, **18**-461, **18**-462, **18**-465, **18**-468, **18**-489, **18**-491, **19**-847, **19**-851, **19**-858
Peltier, H.M. **16**-306
Peltzer III, E.T. **17**-366
Pelucchini, C. **15**-1716
Pemberton, R.P. **2**-214, **2**-277
Peña-Cabrera, E. **12**-261
Pena, J.M. **15**-943
Peña, M.E. **12**-203, **12**-734
Pena, P.C.A. **18**-156
Peñafiel, I. **12**-434
Penalva, V. **13**-310
Penco, S. **19**-1352
Pendalwar, S.L. **15**-498
Pendola, K.A. **13**-157
Penenory, A. **5**-249
Peñéñory, A.B. **10**-101, **16**-210
Peng, J. **16**-134, **18**-348
Peng, K. **19**-238
Peng, L. **10**-1223, **14**-129, **18**-773
Peng, Q. **13**-434
Peng, S.-M. **19**-723
Peng, X. **11**-141
Peng, Y. **16**-1235, **16**-1902
Peng, Z.-Y. **16**-1433
Peng, Z.-Z. **16**-79
Penhoat, M. **16**-1496
Penkett, C.S. **10**-1649
Penmasta, R. **10**-54, **19**-392, **19**-521, **19**-823
Penn, J.H. **19**-1102
Penner-Hahn, J.E. **10**-1403
Penner, G.H. **3**-60
Penney, J.M. **13**-581
Pennington, L. **18**-302
Pensak, D. **14**-44
Penso, M. **10**-994, **19**-1241
Penton, J.R. **11**-34, **11**-44, **11**-54, **11**-123, **11**-164, **11**-165
Penzien, K. **4**-146
Peoples, P.R. **5**-141
Pepermans, H. **15**-2646
Peralez, E. **5**-329
Peran, N. **15**-607
Percac, K. **10**-128
Percec, V. **13**-548
Perchonock, C. **2**-260
Perchyonok, V.T. **19**-979
Perciaccante, R. **15**-1415
Percina, N. **10**-1161
Percy, J.M. **4**-173, **4**-299
Perdih, M. **4**-103
Perdikomatis, G.P. **11**-451
Perdoncin, G. **19**-934
Perederyna, I.A. **11**-289
Peregudov, A.S. **13**-165, **14**-393
Pereira, C.M.P. **14**-362, **16**-240
Pereira, S.I. **16**-794
Perepelkova, T.I. **3**-3
Perepichka, D.F. **15**-2302
Perera, S.A. **3**-47
Peres, Y. **15**-1597
Perevalova, E.G. **2**-185
Pereyre, M. **12**-14
Pérez-Andrés, J.A. **17**-167, **17**-171, **17**-402
Pérez-Blanco, D. **16**-1271
Pérez-Carvajal, A. **16**-560
Pérez-Castells, J. **15**-1549, **15**-1558, **15**-1561, **15**-1563, **15**-2683, **18**-820
Pérez-Encabo, A. **16**-857, **16**-2076
Pérez-Flores, J. **18**-241, **19**-961
Pérez-Fuertes, Y. **4**-112
Pérez-Galán, P. **15**-2517
Pérez-Lorenzo, M. **12**-100
Pérez-Luna, A. **16**-1819
Perez-Prieto, J. **15**-383
Perez-Rubalcaba, A. **16**-516
Pérez-Sánchez, I. **15**-2526
Pérez-Serrano, L. **15**-1558, **15**-1563
Perez-Torralba, M. **2**-479
Pérez-Torrente, J.J. **4**-64
Perez-Velasco, A. **3**-46
Pérez, A. **16**-857
Pérez, D. **10**-1496, **15**-628
Pérez, E. **15**-1070
Pérez, E.G. **15**-2038
Perez, F. **19**-673
Pérez, I. **13**-337
Pérez, J.A. **15**-2065
Pérez, J.M. **15**-2334
Pérez, M. **13**-542
Pérez, P. **10**-35, **10**-36, **10**-37, **10**-95, **13**-771, **15**-2181, **15**-2292
Pérez, P.J. **12**-375, **15**-2507, **15**-2517, **19**-535
Pérez, S. **2**-488
Peri, F. **15**-230
Periasamy, M. **4**-165, **12**-477, **12**-555, **13**-178, **13**-660, **13**-751, **14**-421, **15**-690, **15**-980, **15**-1507, **15**-1531, **16**-2087, **18**-468, **19**-18, **19**-610, **19**-1466
Periasamy, M.P. **10**-1014, **16**-2249
Pericàs, M.A. **2**-381, **7**-95, **10**-962, **15**-1557, **15**-2421, **15**-2588, **16**-682, **17**-422
Périchon, J. **10**-1485, **10**-1515, **10**-1966, **13**-484, **13**-355, **13**-450, **15**-1221, **15**-1506, **16**-709, **16**-715, **16**-2036
Périé, J.J. **15**-325, **15**-329
Perin, G. **15**-314
Peringer, P. **10**-1073
Perinis, M. **10**-189
Peris, E. **19**-952
Peristeraki, A. **16**-1725
Perjéssy, A. **2**-483
Perkampus, H. **11**-5
Perkins, J. **3**-85
Perkins, M.J. **4**-243, **5**-123, **5**-221, **13**-830, **14**-46, **14**-48, **14**-368, **14**-369, **18**-194, **19**-489
Perkins, N.A. **11**-374
Perkovic, T. **13**-400
Perl, S. **2**-71
Perlin, A.S. **19**-301
Perlmutter-Hayman, B. **4**-194
Perlmutter, P. **15**-267, **15**-1607, **15**-1628
Pernak, J. **9**-137
Pernazza, D. **16**-775
Pérollier, C. **19**-569
Perosa, A. **10**-941, **12**-784, **13**-391, **9**-111
Perraud, R. **16**-529
Perret, R. **16**-2019
Perreten, J. **18**-918
Perreux, L. **16**-1900
Perrier, H. **18**-645
Perrin, C.L. **3**-14, **3**-25, **3**-30, **3**-38, **4**-387, **4**-388, **8**-89, **11**-29, **11**-57, **11**-103, **11**-106, **11**-108, **16**-32
Perrin, D.D. **8**-25, **8**-52, **8**-175, **8**-186
Perrio, S. **12**-248
Perron R. **10**-491
Perrot, M. **19**-1083, **19**-1091
Perroux, Y. **16**-378, **16**-1845

Perry, D.A. **16**-215
Perry, J.J. **16**-103
Perry, N.B. **18**-22, **18**-102
Perry, R.A. **12**-670
Perry, S.S. **2**-243
Perseghini, M. **13**-517
Persiani, D. **15**-907
Person, W.B. **3**-86, **3**-87, **3**-105, **4**-398
Persson, B.A. **15**-276
Persson, E.S.M. **10**-1361, **10**-1507
Persson, I. **8**-161
Persson, J. **10**-879
Persson, P. **8**-161
Perst, H. **10**-122, **10**-410, **10**-767
Persy, G. **2**-362, **2**-445, **5**-440, **7**-23
Pertici, P. **15**-1832
Perumal, P.T. **11**-501, **15**-710, **15**-2316, **15**-2332, **18**-474, **19**-204
Perumal, S. **11**-575
Peruncheralathan, S. **10**-999
Perutz, R.N. **2**-190
Peruzzini, M. **15**-278, **15**-2645
Pervukhina, N.V. **5**-275
Pesce, G. **10**-1611
Pesce, L. **13**-652
Pesch, J. **15**-1487, **16**-722
Pesciaioli, F. **11**-314
Pescitelli, G. **4**-121
Petasis, N.A. **11**-154, **13**-106, **13**-272, **16**-1411, **16**-1415, **16**-1417, **16**-1418, **16**-1419
Petch, W.A. **13**-858
Pete, J.-P. **15**-1118
Pète, J. **17**-281, **19**-1392
Pete, J.P. **16**-9, **16**-1579
Peter-Katalinić, J. **4**-253
Peter, R. **10**-1453
Peters, D.A.V. **15**-1670
Peters, E.-M. **8**-94
Peters, E.N. **5**-96, **9**-9, **10**-211
Peters, G.A. **16**-178
Peters, J.A. **19**-1082
Peters, K. **4**-306, **5**-243, **8**-94, **10**-1771
Peters, K.S. **10**-32, **10**-77, **16**-2209
Peters, M.W. **15**-1907
Peters, N.K. **15**-576
Peters, S.J. **2**-268
Petersen, B.L. **5**-80
Petersen, C.J. **3**-108
Petersen, H.E. **18**-283
Petersen, J.L. **16**-324
Petersen, J.M. **18**-288
Petersen, J.S. **4**-152, **15**-715, **16**-1097
Petersen, N.O. **16**-1768
Petersen, S.B. **3**-83
Petersen, T.B. **13**-495
Petersen, W.C. **19**-1210
Peterson Jr., M.R. **1**-51
Peterson, B. **17**-235
Peterson, D.J. **12**-618, **16**-1289
Peterson, E.A. **11**-409
Peterson, H.J. **5**-73, **8**-134, **15**-756
Peterson, J.J. **13**-473
Peterson, J.O. **19**-914
Peterson, J.R. **2**-388, **4**-91, **15**-1857, **15**-2039
Peterson, K.B. **15**-2283
Peterson, K.P. **15**-414
Peterson, M.J. **10**-621
Peterson, P.E. **5**-97, **10**-125, **10**-126, **10**-128, **10**-149, **15**-272, **18**-259
Peterson, S.M. **12**-275
Petersson, A. **15**-964
Pethrick, R.A. **4**-287
Petillo, P.A. **4**-250
Petiniot, N. **10**-659
Petit, A. **10**-499, **13**-119, **16**-351, **16**-1797, **18**-762
Petit, F. **15**-640, **15**-834, **18**-884
Petit, J. **10**-70
Petit, M. **15**-1342, **15**-2612, **18**-884
Petit, Y. **10**-1623
Petneházy, I. **16**-1921, **17**-489
Peto, A.G. **11**-430, **11**-464
Petragnani, N. **10**-1696, **12**-251
Petricci, S. **10**-994
Pétrier, C. **12**-638, **15**-1213, **16**-472
Petrillo, D.E. **19**-118
Petrillo, G. **8**-183, **17**-60
Petringa, A. **3**-144
Petrini, M. **10**-870, **15**-1051, **15**-1388, **16**-91, **16**-94, **16**-606, **17**-164, **19**-642
Petro, C. **5**-75
Petrosyan, V.E. **5**-387
Petrosyan, V.S. **12**-47
Petrov, A.A. **15**-61, **15**-82, **15**-1740, **15**-1771, **16**-1364
Petrov, A.D. **16**-2060
Petrov, E.S. **8**-175
Petrova, K.V. **13**-513
Petrovanu, M. **12**-442
Petrovic, G. **15**-1289
Petrovich, J.P. **19**-1666
Petrovlskii, P.V. **13**-165
Petrovski, Z. **10**-1645
Petrovskii, P. **10**-1977
Petrovskii, P.V. **14**-393
Petrzilka, M. **15**-2186
Petterson, R.C. **16**-1978
Pettersson, C. **4**-180
Pettersson, G. **4**-180
Pettersson, M. **4**-309
Pettiette-Hall, C.L. **19**-17
Pettit, G.H. **11**-552
Pettit, G.R. **11**-677, **14**-439, **19**-1443, **19**-1450, **19**-1559
Pettit, R. **2**-148, **2**-236, **2**-252, **2**-254, **18**-535, **18**-536, **18**-675
Pettit, R.J. **16**-1410
Pettitt, D.J. **17**-228
Pettman, A. **19**-1034
Petty, R. **1**-44
Peverley, J. **15**-1246
Pevzner, M.S. **14**-400
Pews, R.G. **4**-443
Peyman, A. **5**-243
Peynircioglu, N.B. **5**-123
Peyrat, J.-F. **10**-1110, **13**-606, **15**-214
Peyroux, E. **13**-528
Pezacki, J. P. **5**-414
Pfab, J. **12**-740
Pfaltz, A. **4**-153, **10**-1546, **13**-386, **13**-443, **15**-449, **16**-1220
Pfau, M. **15**-1101
Pfeffer, M. **10**-904
Pfeffer, P.E. **10**-717, **10**-1802, **16**-1308
Pfeifer, W.D. **10**-271
Pfeiffer, P. **17**-10
Pfennig, D.R. **10**-1292
Pfenninger, A. **15**-1969
Pfister, J.R. **10**-944, **18**-307
Pflum, D.A. **15**-643
Pfohl, W.F. **10**-1301
Pfordte, K. **14**-318
Pfrengle, W. **16**-2262
Pfriem, S. **17**-512
Pfyffer, J. **15**-2235
Phadke, R. **11**-397
Pham, D.K. **8**-92
Pham, K.M. **16**-339
Pham, M.P. **16**-1608
Pham, T.N. **10**-106, **12**-656, **12**-660
Phan, N.T.S. **13**-521
Phan, T.B. **10**-393, **10**-394, **10**-395
Phanstiel IV, O. **18**-600
Phanstiel, O. **18**-544
Phapale, V.B. **10**-1463
Phelan, N.F. **2**-51
Phelps, J.C. **15**-1774
Phelps, M.E. **10**-1115
Phenix, B. **13**-285
Philip Jr., J.B. **14**-490
Philip, D. **15**-2213
Philippi, K. **15**-1878
Philippot, K. **10**-1532
Philips, J.C. **8**-56, **17**-359, **17**-360, **18**-98
Philips, N.G. **15**-2637
Phillips, A.M.F. **18**-381
Phillips, B.A. **11**-405
Phillips, B.T. **17**-465
Phillips, C.J. **16**-975
Phillips, D.D. **5**-145
Phillips, D.L. **3**-174, **15**-1311, **15**-2556, **15**-2567, **19**-1118
Phillips, E.M. **15**-1431
Phillips, G.W. **16**-1252
Phillips, H. **10**-9, **10**-10
Phillips, I.M. **15**-2250, **15**-2475
Phillips, J.B. **2**-304

Phillips, J.H. **15**-291
Phillips, L. **4**-297
Phillips, N.H. **12**-658
Phillips, O.A. **15**-162
Phillips, R. **11**-87
Phillips, R.E. **1**-44
Phillips, R.R. **12**-199
Phillips, W.G. **19**-624
Phillips. N.H. **5**-190
Philouze, C. **16**-1451
Philp, D. **3**-216
Phipps, R.J. **11**-429
Phong, L.T. **19**-1037
Phopase, J. **13**-534, **16**-2311
Photis, J.M. **17**-518
Phuan, P.-W. **16**-666
Phukan, M. **16**-1205
Phukan, P. **16**-618
Phukan, P. **16**-939
Pi, R. **10**-1698, **12**-578
Piacenti, F. **10**-1979
Pialssa, C. **15**-943
Piancatelli, G. **15**-1683, **19**-81, **19**-199, **19**-712, **19**-1747
Piantini, U. **16**-663
Piao, F. **19**-1186
Piarulli, U. **16**-943, **16**-1488
Piatak, D.M. **11**-677
Piattelli, M. **3**-128, **3**-133, **3**-144, **4**-95
Piazza, C. **10**-1427
Picard, C.J. **15**-2054
Piccinini, A. **16**-1441
Piccirilli, J.A. **4**-261
Piccolo, O. **10**-1588, **11**-381, **11**-539
Picher, M.T. **15**-2242
Pichler, S. **7**-107
Pick, R.M. **10**-752
Pickard, P.L. **16**-996
Pickardt, J. **15**-2378
Pickering, D. **5**-147
Pickering, D.A. **11**-339
Pickering, R.A. **10**-784
Pickles, G.M. **13**-105
Picoul, W. **16**-1286
Picq, D. **10**-1102
Picquet, M. **18**-835
Picraccini, D. **15**-1653
Pictet, A. **11**-406
Pidathala, C. **16**-1108
Pidgeon, C. **10**-811
Piecuch, P. **18**-669
Pielichowski, J. **10**-608, **15**-1904
Pienta, N.J. **5**-75
Pieraccini, D. **10**-442, **11**-244
Pieraccini, S. **15**-163
Pierini, A.B. **10**-101, **13**-57, **13**-66, **13**-354
Pierini, M. **12**-82
Pierlot, C. **14**-255
Piermatti, O. **15**-2211
Pierre, J. **4**-252, **16**-529, **19**-1000
Pierrefixe, S.C.A.H. **1**-6, **2**-7, **2**-111
Pierres, C. **15**-2335
Piers, E. **10**-1948, **12**-576, **15**-1195, **18**-519
Piers, W.E. **12**-329, **18**-893, **19**-1130
Piersanti, G. **15**-2380
Pierson, C. **14**-173
Pierson, G.O. **18**-212
Piet, J.J.N. **15**-1801
Pieter, R. **19**-1269
Pietra, F. **2**-174, **2**-180, **4**-66, **4**-159, **13**-62
Pietra, S. **13**-76, **19**-756, **19**-1526
Pietroni, B.R. **11**-338
Pietrusiewicz, K.M. **18**-832
Piette, L.H. **15**-59
Piettre. S. **15**-2388, **15**-2432
Piffl, M. **5**-192
Pigeon, P. **10**-1106, **17**-309
Pignataro, L. **16**-776, **16**-1081
Pigou, P.E. **10**-53
Piguel, S. **15**-1719
Pigulla, M. **15**-158
Pihko, M. **3**-2
Pihko, P.M. **12**-137, **16**-1020
Pihlaja, K. **4**-408, **10**-677, **10**-776, **10**-1121, **16**-1767
Pike, D.C. **16**-1615
Pike, K.G. **15**-1548, **19**-120
Pikulin, S. **18**-598, **18**-599
Pilard, S. **10**-995
Pilati, T. **2**-296, **2**-305
Pilcher, G. **1**-99, **1**-100, **1**-105
Pilipauskas, D.R. **10**-1258
Pilkington, J.W. **18**-35
Pillai, M.K. **16**-1232
Pillai, S. **10**-905
Pillai, S.M. **15**-828
Pillai, T.P. **12**-741, **12**-742
Pillai, U.R. **15**-1892, **15**-1893
Pillai, V.N.R. **16**-1930
Pilli, R.A. **12**-292, **16**-1412
Pilling, M.J. **5**-320
Pillinger, K.S. **18**-147
Pillon, F. **10**-1952
Pilot, J.F. **16**-1317, **16**-1354
Pilotti, Å. **13**-382
Pimenta, D.C. **13**-577
Pimentel, G.C. **3**-36, **5**-289, **5**-290
Pincock, J.A. **5**-328, **15**-15, **17**-507, **17**-509, **18**-907, **19**-129
Pincock, R.E. **4**-97, **4**-470, **10**-164, **10**-159, **10**-163, **10**-1303
Pinder, A.R. **19**-1277, **19**-1287
Pindur, U. **5**-53, **10**-551, **15**-2210, **19**-1699
Pine, R.D. **16**-1410
Pine, S.H. **13**-847, **13**-852, **13**-854, **16**-1410, **16**-1413, **18**-411, **18**-422
Pinel, C. **10**-613
Pines, H. **12**-57, **12**-74, **15**-325, **15**-754, **15**-755, **15**-756, **15**-827, **17**-146, **19**-409
Pineschi, M. **10**-837, **10**-996, **10**-1002, **10**-1647, **10**-1891
Pinet, J.-L. **19**-146
Pinet, S. **16**-978
Pinet, S.U. **16**-948
Pinetti, A. **12**-115, **15**-1654, **15**-1732
Ping-Guo, M. **15**-467
Ping, Y.Y. **16**-863
Pingali, S.R.K. **12**-122
Pinhas, A.R. **12**-794, **18**-537
Pinheiro, S. **15**-2520
Pinhey, J.T. **13**-271, **14**-371
Pinho, P. **15**-414
Pini, D. **4**-121
Pinkus, A.G. **12**-157, **16**-531
Pinnick, H.W. **10**-301, **16**-88
Pino, P. **10**-1979, **12**-313, **13**-664, **14**-485, **15**-1597, **15**-1611, **15**-1623, **15**-1625, **18**-896
Pinschmidt Jr., R.K. **15**-2308, **18**-533
Pinson, J. **13**-59
Pinto, D.C.G.A. **7**-129
Pinzino, C. **5**-339
Pioch, R.P. **12**-455
Piotrowski, A.M. **16**-485
Piotrowski, H. **15**-2690
Pippel, D.J. **6**-37
Piquer, Ma.J.A. **7**-95
Piqueras, M.C. **2**-204
Piqueur, J. **10**-902
Piras, L. **15**-561
Pirkle, W.H. **4**-178, **4**-181, **4**-204, **4**-215, **4**-218, **4**-219, **4**-264
Pirogowa, G.N. **17**-155
Pironti, V. **19**-738
Pirozhkov, S.D. **10**-1975, **15**-1494
Pirrung, F.O.H. **15**-934
Pirrung, M.A. **12**-330
Pirrung, M.C. **9**-93
Pisanenko, D.A. **15**-25
Pisano, D. **2**-101
Pisano, L. **19**-1519
Pischel, U. **2**-176
Píškala, A. **16**-1355
Piskunova, Z. **10**-278
Pistarà, V. **16**-51, **16**-204
Pistorius, R. **14**-461
Piszkiewicz, L. **14**-73
Pitacco, G. **16**-259
Pitcher, R.G. **4**-211
Piteau, M. **10**-1258
Pitman, I.H. **12**-762
Pitram, S.M. **18**-965
Pitre, S. **19**-1046
Pitre, S.V. **19**-583
Pittelkow, M. **10**-1092
Pitteloud, J.-P. **10**-1728
Pittman Jr., C.U. **2**-232, **5**-35, **5**-48, **5**-38, **10**-131, **16**-667

Pitts Jr., J.N. **7**-13, **7**-29, **7**-42, **7**-69, **19**-1662
Pitts, M.R. **10**-1187, **15**-585, **15**-586, **19**-1231
Pitzer, R.M. **4**-288
Piva, O. **12**-173, **15**-160, **19**-467
Piveteau, E. **12**-537
Pivsa-Ast, S. **13**-329
Piwoński, H. **2**-480
Pizey, J.S. **10**-654, **10**-768, **10**-878, **10**-1120, **11**-281, **11**-290, **11**-471, **11**-494, **12**-112, **13**-744, **13**-746, **14**-165, **14**-192, **14**-229, **14**-272, **15**-184, **15**-429, **15**-670, **15**-1663, **15**-1690, **15**-1856, **16**-236, **16**-1988, **19**-10, **19**-23, **19**-849, **19**-1278
Pizzano, A. **15**-649, **19**-1143
Pizzato, F. **16**-1284, **16**-1285
Pizzo, F. **10**-690, **10**-974, **10**-987, **10**-1221, **10**-1236, **15**-1817, **15**-1968, **15**-2211, **19**-1249
Pizzolatti, M.G. **12**-750
Pizzotti, M. **12**-786, **19**-1719
Pla-on, K. **11**-303
Pla-Quintana, A. **13**-372, **13**-432
Place, D. **3**-181
Placzek, A.T. **10**-974
Planas, A. **18**-195
Plancher, J.M. **10**-575
Planinsek, Z. **19**-666
Plankl, W. **12**-714
Plant, A. **15**-2296
Plaquevent, J.-C. **9**-137, **17**-320
Plat, M. **10**-1079
Plate, A.F. **18**-650
Plath, P. **18**-19
Platone, E. **11**-262
Platts, J. A. **3**-4
Platz, M.S. **5**-398, **5**-405, **5**-414, **5**-439, **5**-440, **5**-441, **5**-317, **5**-369, **5**-378, **5**-416, **18**-228
Plaut, H. **10**-712
Plavšić, D. **2**-118, **5**-159
Plé, G. **2**-485, **4**-79, **10**-1496, **17**-320
Plé, K. **16**-534
Plechkova, N.V. **9**-139
Pleixats, R. **13**-542, **13**-544
Plenio, H. **13**-588
Plepys, R.A. **19**-894
Pleskov, Y.V. **15**-572
Plesniar, B. **5**-323
Plesnicar, B. **15**-1869, **18**-379
Plessi, L. **19**-377
Plesske, K. **2**-187
Pletcher, D. **19**-105
Pletnev, A.A. **13**-693
Plexats, R. **13**-432
Plieninger, H. **15**-2264
Plietker, B. **10**-1514, **15**-956, **15**-1532
Pluempanupat, W. **10**-1162, **10**-1168
Pluim, H. **15**-1911
Plum, H. **15**-2184
Plumb, J.B. **19**-196
Plumet, J. **16**-1504
Plummer, B.F. **16**-115
Plummer, E.L. **4**-108
Plummer, M. **18**-919
Plunkett, K.N. **18**-883
Plusquellec, D. **16**-1822
Plzak, K. **5**-147
Pmies, O. **15**-452
Poater, A. **18**-892
Poater, J. **2**-9, **2**-146, **2**-170, **2**-340
Pochapsky, T.C. **4**-178
Pochini, A. **11**-389
Pöchlauer, P. **10**-1073
Pock, R. **15**-30, **15**-1770, **15**-2095
Pocker, Y. **12**-437, **12**-707, **18**-149, **18**-150
Podder, S. **11**-333, **11**-337
Podgoršek, A. **14**-187
Podlech, J. **16**-1015, **16**-2241
Podoplelov, A.V. **10**-1395
Podraza, K.F. **10**-1753
Poeth, T. **10**-1310
Pogodin, S. **2**-401
Pogorelyi, V.K. **3**-18, **3**-50, **3**-55
Pohl, D.G. **14**-171
Pohl, M. **16**-1590
Pohmakotr, M. **19**-267, **19**-505
Poignée, V. **4**-488
Poindexter, M.K. **18**-548
Poirier, D. **10**-1131
Poirier, J. **10**-1340, **12**-320
Poirier, R.A. **2**-309, **15**-2247
Poisson, J.-F. **15**-915
Pojarliev, P. **16**-394
Pojer, P.M. **15**-429, **19**-1511
Pokrovskaya, S.V. **16**-1545
Pola, J. **19**-350, **19**-368
Polach, S.A. **12**-376
Poláčková, V. **11**-473
Polášek, M. **2**-463
Polanc, S. **11**-232, **16**-1790
Polanyi, J.C. **6**-16
Polanyi, M. **15**-480, **16**-1657
Polas, S. **15**-1621
Polasek, M. **13**-244
Polat, M.F. **10**-1173
Polavarapu, P.L. **4**-114
Polborn, K. **16**-925
Poleshchuk, O.Kh. **3**-86
Polet, D. **10**-1359, **10**-1522, **10**-1546, **15**-1204
Polezhaeva, N.A. **2**-94, **16**-1470
Poli, G. **10**-1523, **10**-1573, **13**-160
Poli, M. **10**-512
Poli, S. **19**-223
Poliakoff, M. **9**-99, **9**-113
Poliart, C.D. **8**-97
Poling, B. **15**-2505
Poliskie, G.M. **19**-1276
Politanskii, S.F. **10**-1137
Politzer, I.R. **10**-1846, **10**-1849
Politzer, P. **2**-37
Polivkova, J. **4**-112
Polizzi, C. **15**-378
Polla, E. **10**-147
Pollack, R.M. **5**-121, **12**-59, **12**-60, **12**-91, **16**-1698
Pollard, D. **19**-1014
Pollard, D.J. **19**-993
Pollart, D.F. **17**-188
Pollasatri, M.P. **10**-1160
Pollet, P. **15**-651
Pollex, A. **18**-436
Pollicino, S. **10**-691, **16**-976
Pollini, G.P. **15**-2385
Pollock, C.M. **16**-1011
Pollock, L. **4**-397
Polniaszek, R. **16**-1942, **16**-1947
Polshettiwar, V. **10**-859, **13**-384, **16**-113, **16**-221, **16**-2177
Polster, R. **12**-442
Polt, R.L. **12**-433
Pombeiro, A.J.L. **19**-460
Pombo-Villars, E. **11**-128, **16**-1900
Pomelli, C.S. **9**-120, **15**-2225
Pomerantz, M. **1**-87
Pommelet, J. **17**-361
Pommer, H. **16**-1311
Pommier, J. **2**-477
Ponaras, A.A. **10**-682
Ponaskik Jr., J.A. **10**-1536
Ponec, R. **3**-69, **9**-61, **15**-2299, **19**-348
Pongdee, R. **10**-735
Ponomarchuk, M.P. **10**-1399, **19**-606
Ponomareva, E.A. **10**-40, **10**-437
Ponomarov, A.B. **13**-580
Pons, J. **19**-1683
Ponsold, K. **9**-43
Ponti, F. **19**-89, **19**-425
Ponticello, G.S. **4**-214
Pook, L.M. **14**-34
Poole Jr., C.P. **5**-218
Poole, H.G. **11**-150
Poole, J.S. **5**-317
Poon, C. **2**-270
Poon, K.W.C. **10**-711
Poon, N.L. **15**-200
Poondra, R.R. **10**-1028, **13**-511
Poonian, M.S. **18**-39
Poorheravi, M.R. **12**-139
Pooyan, M. **10**-1229
Popa, C. **18**-685
Pope, W, J. **4**-29
Popik, V.V. **16**-2146
Pople, J.A. **1**-55, **2**-9, **2**-14, **2**-16, **2**-115, **2**-219, **2**-232, **2**-414, **4**-297
Popov, A.F. **10**-278
Popov, E.M. **2**-34, **2**-39
Popov, S.I. **16**-434
Popp, F.D. **19**-1113
Poppinger, D. **2**-419, **5**-25

Poranski Jr., C.F. **13**-9
Porcelloni, M. **16**-988
Porcheddu, A. **16**-1811, **16**-1901, **16**-2064, **16**-2224, **17**-484, **19**-649
Porcu, G. **7**-46
Pore, D.M. **16**-1209
Poretti, M. **15**-478
Porri, L. **18**-882
Porshnev, Yu.N. **2**-201
Porta, F. **12**-786, **19**-1719
Porta, O. **14**-111, **14**-382, **14**-385, **16**-9, **16**-121, **16**-1532, **19**-947, **19**-1641
Portella, C. **16**-9, **16**-1107, **16**-1579
Portella, G. **2**-340
Porter, D.W. **10**-1280
Porter, G. **19**-1665
Porter, G.B. **7**-13
Porter, H.K. **19**-1195
Porter, H.Q. **1**-16
Porter, N.A. **5**-281, **5**-331, **14**-27, **14**-108, **15**-66, **15**-1119, **15**-1288, **15**-1298
Porter, R.D. **5**-41, **5**-95, **11**-15
Porter, T.A. **12**-404
Portlock, D.E. **10**-1031
Portnoy, M. **10**-1967, **15**-1553
Portnoy, R.C. **10**-1846
Posey, I.Y. **10**-1712
Poshkus, A.C. **16**-2301
Posner, G. **15**-1168
Posner, G.H. **10**-684, **10**-827, **10**-1406, **10**-1408, **10**-1411, **10**-1415, **10**-1417, **10**-1424, **10**-1425, **10**-1442, **10**-1443, **10**-1505, **10**-1621, **15**-1136, **15**-1136, **15**-1146, **15**-1147, **15**-1166, **15**-1168, **15**-1181, **15**-2153, **15**-2370, **16**-1198, **16**-2004, **16**-2005, **17**-242
Pospelov, M.V. **19**-331
Pospíšil, J. **15**-1254
Post, A.J. **18**-370
Posteher, F. **4**-455
Poster, H. **10**-733
Posternak, A.G. **11**-453
Postigo, J.A. **18**-516
Postnikova, B.J. **8**-187
Postovskii, I.Ya. **13**-231, **13**-722
Potapov, V.A. **11**-354
Potapov, V.M. **4**-148
Potapova, I.M. **16**-541
Potdar, M.K. **11**-211, **11**-400
Potenza, J.A. **2**-224
Potini, C. **10**-706
Potnick, J.R. **15**-1076
Pötter, B. **1**-102
Potter, G.J. **15**-1682
Potter, S.E. **18**-417
Potthast, A. **16**-349
Potts, A.W. **1**-19, **1**-22
Potts, K.T. **2**-221
Potvin, P.G. **3**-124
Poulard, C. **15**-2560
Poulsen, C.S. **18**-889
Poulsen, T.B. **10**-1915, **11**-314, **12**-230, **15**-1954
Poulter, C.D. **5**-50, **18**-571
Poulton, D.J. **18**-48
Poupaert, J.H. **19**-1768, **19**-1773
Poupko, R. **4**-395, **18**-656
Pourali, A.R. **19**-740
Pourayoubi, M. **16**-1872
Pourcin, J. **18**-234
Poutsma, M.L. **14**-39, **14**-77, **14**-145, **15**-109
Poux, M. **16**-102
Pouységu, L. **11**-190
Powell, A.L. **19**-1737, **19**-1739
Powell, D.A. **12**-268, **13**-721
Powell, D.L. **2**-377
Powell, D.R. **12**-492
Powell, H.K.J. **9**-30
Powell, M.F. **6**-69, **6**-94, **8**-117, **8**-118
Powell, N.A. **16**-633
Powell, P. **3**-89
Powell, R.E. **1**-3
Power, P.P. **5**-118, **5**-183
Powers, D.B. **16**-752
Powers, J.P. **4**-370, **4**-383, **5**-292
Powers, J.W. **19**-616
Poyer, J.L. **5**-273
Pozharskii, A.F. **2**-164, **13**-761
Pozsgay, V. **12**-731
Pozzi, D. **14**-17, **15**-519
Pozzi, G. **13**-389, **15**-2514, **19**-179, **19**-1752
Prabagaran, N. **18**-867
Prabhakar, S. **15**-2051, **15**-2063, **15**-2072
Prabhakaran, E.N. **15**-1374
Prabhudas, B. **16**-566
Pradhan, S.K. **19**-933
Prados, P. **19**-1168
Praeger, D. **4**-342
Prager, R.H. **10**-1871, **15**-683, **16**-2297
Prajapati, D. **9**-114, **10**-868, **10**-1482, **10**-1637, **13**-612, **16**-375, **16**-922, **16**-977, **16**-1236, **16**-1244, **16**-1309, **16**-2030, **16**-2110, **18**-350, **19**-295, **19**-1256, **19**-1537, **19**-1669
Prakash, C. **12**-132
Prakash, G.K.S. **5**-7, **5**-15, **5**-44, **5**-59, **5**-87, **5**-89, **5**-94, **5**-100, **8**-18, **8**-20, **10**-152, **10**-186, **10**-195, **10**-204, **10**-214, **10**-886, **10**-1198, **10**-1250, **10**-1251, **11**-123, **11**-154, **11**-210, **11**-221, **11**-241, **11**-434, **11**-569, **12**-48, **12**-50, **12**-164, **12**-356, **13**-106, **13**-272, **14**-409, **15**-1761, **16**-93, **16**-166, **16**-447, **16**-2057, **16**-2066, **16**-2160, **16**-2170, **18**-118, **19**-751, **19**-1423, **19**-1425
Prakash, I. **12**-753, **19**-392, **19**-619, **19**-823
Prakash, O. **15**-1735, **19**-198, **19**-493, **19**-494, **19**-821
Prakash, P.K.S. **11**-500
Prakash, S.J. **9**-91, **10**-1003
Prakasham, R.S. **16**-574
Prall, M. **18**-664
Praly, J. **4**-379
Prandi, C. **15**-1084
Prandi, J. **18**-141
Prantz, K. **17**-409
Prapurna, Y.L. **10**-1048
Prasad, A.R. **10**-1003, **10**-1266, **14**-336, **16**-1635, **19**-992
Prasad, A.S.B. **19**-1466
Prasad, B.A.B. **10**-704, **16**-1535
Prasad, B.V. **2**-478
Prasad, D.J.C. **13**-124
Prasad, E. **15**-1363, **19**-941, **19**-945
Prasad, K. **11**-257, **16**-1939
Prasad, K.G. **19**-1052
Prasad, R. **15**-2109
Prasad, R.S. **19**-1500, **19**-1603
Prashad, M. **18**-267, **19**-652
Prashanthi, S. **16**-315
Prasuna, G. **16**-1379
Pratap, T.B. **15**-2616
Pratelli, C. **4**-121
Prather, J. **19**-1370
Prathima, P.S. **10**-937
Prati, F. **10**-1260, **16**-2246
Pratt, B.C. **15**-1624
Pratt, D.A. **2**-26, **5**-281, **5**-331
Pratt, D.V. **2**-449, **18**-733
Pratt, D.W. **4**-307
Pratt, E.F. **10**-674
Pratt, L.M. **5**-179, **5**-265, **8**-228, **8**-229, **10**-323, **10**-1702, **12**-421, **16**-1056, **16**-1066, **17**-318, **19**-911
Pratt, N.E. **16**-776
Pratt, R.J. **12**-32
Pratt, W.E. **4**-453
Praveen, C. **19**-683
Praveen, V.B. **10**-539
Pravst, I. **12**-114
Prechtl, F. **15**-1927, **19**-514
Preciado, A.B. **18**-623
Preda, D.V. **18**-555
Pregel, M.J. **16**-2276
Preiss, T. **16**-2045
Preite, M.D. **16**-560
Prelog, V. **3**-213, **4**-44, **4**-101, **4**-134, **4**-135, **4**-169, **17**-407, **18**-51
Premalatha, K. **16**-250
Presser, N. **18**-534
Pressman, D. **17**-11

Prestat, G. **10**-1277, **10**-1573, **13**-160
Prestly, M.R. **19**-1156
Preston, S.B. **10**-1872
Pretty, A.J. **18**-417
Pretzer, W. **2**-293, **2**-294
Prévost, N. **18**-58
Prewitt, M.L. **14**-106
Prewo, R. **4**-481
Prey, V. **19**-1734
Prezhdo, O.V. **2**-168
Pri-Bar, I. **12**-773, **13**-669
Pric, J.M. **12**-52
Price, A. **13**-469
Price, C.C. **13**-792
Price, D.A. **15**-2162
Price, G.J. **7**-70
Price, J.D. **4**-503, **15**-1865, **15**-2493
Price, K.E. **16**-792
Price, M.D. **19**-1022
Price, R. **13**-276, **13**-282
Price, R.C. **17**-68, **19**-1441
Price, W.C. **1**-19
Priebe, H. **10**-1061
Priefer, R. **16**-339, **19**-1631
Prien, O. **16**-676
Priesner, C. **10**-421, **10**-427
Priest, D.N. **17**-162, **17**-463
Priest, W.J. **4**-429
Prieto, A. **15**-1051, **15**-2517
Prieto, J.A. **10**-1750, **15**-1883
Prieto, M. **13**-517
Prieto, P. **15**-2119
Prikazchikova, L.P. **15**-46
Prilezhaeva, E.N. **15**-50, **15**-119
Prim, D. **13**-378, **15**-333
Principe, L.M. **15**-1541, **15**-1569
Pringle, J.M. **9**-140
Prins, W.L. **17**-2
Prinsen, W.J.C. **4**-70, **4**-72
Prinzbach, H. **4**-468, **12**-397, **15**-2411, **15**-2442, **15**-2451, **16**-2278, **19**-62
Prior, D.V. **3**-19
Prior, M.J. **16**-1292
Prisyahnyuk, V. **15**-1338
Pritchard, G.J. **12**-425
Pritchard, J.G. **16**-1881
Pritt, J.R. **10**-433
Pritzkow, H. **5**-189
Pritzkow, W. **15**-25
Privett, O.S. **19**-356
Priyakumar, U.D. **16**-8
Procházka, M. **10**-1942
Procopio, A. **10**-974, **10**-1189, **15**-910, **15**-1716, **16**-136, **16**-1723
Procopiou, P.A. **10**-745, **10**-760, **10**-1043, **18**-820, **18**-871, **19**-1746
Procter, D.J. **19**-1065, **19**-1754
Proctor, A.J. **10**-727
Proctor, G. **18**-956
Prodger, J.C. **10**-1805, **15**-1167
Prodolliet, J. **19**-349
Proença, M.F.J.R.P. **11**-562
Prokes, I. **11**-236
Prokipcak, J.M. **10**-225
Prokof'ev, A.K. **5**-399
Prokopiou, P.A. **19**-1390, **19**-1391
Prolingheuer, E. **18**-27
Proops, W.R. **14**-333
Proskow, S. **4**-19, **15**-2437
Pross, A. **1**-118, **5**-408, **8**-156, **9**-1, **10**-101, **10**-879
Pross, E. **10**-489
Proto, A. **15**-1971
Protopopova, M.N. **12**-387
Protschuk, G. **16**-2124
Provencal, D.P. **10**-1744
Proverb, R.J. **17**-494
Provot, O. **13**-704, **15**-214, **15**-781
Prudent, N. **4**-142
Pruitt, J.R. **15**-269
Pruitt, K.M. **13**-13
Pryor, W.A. **14**-2, **14**-42, **14**-77, **14**-110, **18**-54, **19**-340, **19**-343
Przemetchi, V. **19**-607
Przystas, T.J. **10**-567
Psarras, T. **5**-109, **8**-69
Ptock, A. **19**-1695
Pu, D. **15**-2058, **16**-341
Pu, J.Y. **19**-726
Pu, L. **16**-667, **16**-670, **16**-680
Pu, Y.-M. **16**-240
Puar, M.S. **10**-352
Pucheault, M. **12**-346, **15**-1279
Puchta, R. **2**-117, **2**-172, **2**-473, **16**-2127
Puckette, T.A. **16**-1252
Pudjaatmaka, H. **8**-66, **8**-71
Puente, Á. **15**-1106
Puerta, J.E. **10**-519
Puerta, M.C. **15**-284
Pugh, D. **10**-3
Pugh, J.K. **8**-232
Pugh, R.L. **14**-499
Pugia, M.J. **10**-501
Pugin, B. **19**-214
Puglia, G. **11**-386, **11**-389, **11**-519
Puglis, J. **19**-1283
Puglisi, A. **16**-1081, **19**-179
Pugnaud, S. **15**-2295
Pugsley, J.S. **19**-211
Pujol, M.D. **10**-964, **19**-688
Puke, C. **16**-1352
Pulay, A. **17**-62
Pulling, M.E. **15**-1317
Pullman, A. **2**-3, **2**-7
Pullman, B. **2**-99, **2**-193, **2**-229
Pulpoka, B. **3**-145
Pungente, M.D. **10**-786
Punniyamurthy, T. **13**-149, **16**-125, **16**-1214, **16**-1755, **19**-128, **19**-524, **19**-560, **19**-653, **19**-787
Punta, C. **5**-331, **16**-1532, **19**-578
Punzalan, E.R. **12**-646
Punzi, A. **10**-1903, **16**-2015
Pupowicz, D. **15**-2574
Pupyshev, V.I. **15**-179
Purcell, J. **14**-392
Purcell, K.F. **10**-474
Purchase, M. **16**-1667
Purdie, N. **4**-118
Purdon, J.G. **15**-512
Purkarthofer, T. **16**-1212
Purmort, J.I. **12**-438
Purnell, H. **15**-271
Purohit, V.G. **10**-1711
Purpura, M. **10**-1499
Purrington, S.T. **11**-308, **11**-309, **12**-168, **12**-185, **14**-149
Pursiainen, J. **3**-179
Puterbaugh, W.H. **13**-852, **16**-1188
Putinas, J.M. **16**-2267
Putzas, D. **8**-94
Puzitskii, K.V. **10**-1975
Py, S. **15**-1078
Pyatin, B.M. **10**-410, **10**-710
Pyatnitskii, Yu.I. **19**-397
Pye, C.C. **15**-2247, **19**-1606
Pyne, S.G. **16**-1246, **16**-1577
Pyor, W.A. **15**-51
Pyryalova, P.S. **19**-1175
Pytkowicz, J. **16**-899
Pyun, C. **10**-1878
Pyun, S.-J. **10**-1268
Pyun, S.Y. **17**-447
Pyykkö, P. **1**-3

Qadir, M. **13**-386
Qafisheh, N. **19**-837
Qaseer, H.A. **15**-1660
Qi, H. **15**-66
Qi, J.Y. **15**-1997
Qi, M.-J. **16**-958
Qi, N. **19**-1636
Qian, C. **10**-1239, **16**-376
Qian, H. **15**-233, **15**-416, **15**-419
Qian, M. **10**-1909, **12**-306
Qian, R. **16**-637
Qian, W. **14**-299, **19**-184, **19**-202
Qian, X. **16**-429, **16**-1235
Qian, Z.-s. **19**-1033
Qian, Z. **13**-262
Qiao, K. **15**-751
Qiao, S. **16**-612
Qiao, X.-C. **16**-746
Qiao, X. **2**-80
Qin, B. **16**-1497, **16**-1515
Qin, C. **16**-944, **19**-686
Qin, H. **15**-406, **15**-1382
Qin, J. **16**-973, **16**-1610
Qin, L. **16**-341
Qin, T. **13**-496
Qin, X.-Y. **10**-1522
Qin, Y.-C. **16**-667
Qin, Y. **16**-675. **16**-897
Qing, F.-L. **15**-244, **16**-445
Qing, J. **10**-1732
Qiu, D. **11**-241

Qiu, H.-Y. **16**-165
Qiu, J. **19**-1182
Qiu, L.-Q. **15**-643, **15**-1997
Qiu, Z. **11**-463, **15**-2675
Qu, B. **15**-452, **16**-882
Qu, G. **16**-2256
Qu, J. **10**-599, **19**-1055
Qu, Z. **19**-1614
Quach, T.D. **10**-649, **13**-225
Quack, M. **4**-4
Quadbeck, G. **15**-268
Quadrelli, P. **15**-1100
Quadri, M.L. **17**-373
Quan, L.G. **15**-2596, **16**-607
Quan, P.M. **13**-228, **13**-483, **15**-2178
Quang, Y.V. **15**-2150
Quaranta, E. **16**-1951
Quartieri, S. **15**-2127
Quasdorf, K.W. **13**-513, **13**-548
Quast, H. **10**-1054, **18**-678, **18**-679
Quayle, O.R. **16**-1660
Quayle, P. **11**-520
Que Jr., L. **15**-1803, **15**-1808
Quebatte, L. **15**-1728
Queffelec, J. **15**-2387
Quèguiner, G. **13**-350
Querci, C. **19**-441
Quesnel, Y. **10**-575
Quest, D.E. **12**-722
Qui, N.T. **12**-565
Quian, Y. **16**-663
Quici, S. **5**-266, **10**-500, **13**-389, **19**-170, **19**-179, **19**-1752
Quiclet-Sire, B. **15**-413, **15**-1301
Quideau, S. **11**-190
Quiles, F. **18**-935
Quillinan, A.J. **10**-1902
Quin, J.F. **16**-123
Quinero, L. **10**-1231
Quinet, C. **15**-349, **15**-356
Quinkert, G. **18**-922
Quinn, J.F. **10**-574, **15**-618
Quiñoá, E. **4**-108, **4**-110, **4**-111
Quiñonero, D. **13**-23
Quint, S. **10**-916
Quintanar-Audelo, M. **16**-1130
Quintard, J.-P. **11**-258
Quintard, J. **16**-2116
Quintavalla, A. **15**-2241, **19**-1044
Quintero, L. **16**-681
Quintin, J. **13**-317
Quiram, E.R. **15**-111
Quirante, J. **15**-1336
Quirk, R.P. **8**-40, **8**-131
Quiroga-Feijoo, M.L. **16**-516
Qureshi, M.I. **4**-515

Ra, C.S. **12**-718
Raab, V. **8**-98
Raabe, G. **1**-12
Raabe, G. **15**-1910
Raaen, V.F. **18**-40
Rabalais, J.W. **1**-16
Raban, M. **4**-33, **4**-207, **4**-210, **4**-212, **4**-259
Rabani, G. **19**-1156
Rabbat, P. **10**-1123
Rabenstein, D.L. **2**-278
Raber, D.J. **10**-61, **10**-66, **10**-89, **10**-755
Raber, J.C. **12**-623
Rabideau, P.W. **2**-400, **2**-401, **2**-403, **2**-404, **4**-362, **15**-565, **15**-570, **15**-576, **15**-578
Rabinovich, D. **2**-321
Rabinovich, E.A. **12**-61
Rabinovitch, B.S. **5**-362, **12**-402
Rabinovitz, M. **2**-191, **2**-203, **2**-300, **2**-302, **2**-326, **2**-327, **2**-363, **4**-74, **5**-52, **10**-486, **10**-488, **15**-564, **17**-309, **19**-1161, **19**-1174
Rabinowitz, J.L. **15**-1639, **18**-363
Rabinowitz, M. **2**-272
Rabjohn, N. **4**-537, **19**-448, **19**-547
Rablen, P.R. **1**-114, **2**-40, **4**-314, **4**-317, **4**-321, **16**-2129
Racela, W. **8**-30
Racharlawar, S.S. **13**-494
Racher, S. **7**-84
Racherla, U.S. **12**-585, **15**-696, **16**-753, **18**-278
Rachoń, J. **5**-382, **18**-19
Rack, E.P. **14**-66, **15**-1640
Raczynska, E.D. **8**-97, **12**-84
Rad, A.A.R. **18**-353
Rad, M.N.S. **10**-1066, **16**-1900
Radeglia, R. **4**-40
Radell, J. **3**-167
Rademacher, P. **4**-275, **4**-479
Raders, S.M. **10**-1731
Radford, D.V. **3**-104
Radhakrishna, A.S. **18**-302
Radhakrishna, P. **16**-1778
Radhakrishnan, U. **13**-628, **15**-1507, **15**-2603
Radinov, R. **15**-1119
Radke, C.M. **18**-680
Radke, K.R. **13**-203
Radkiewicz-Poutsma, J.L. **18**-399
Radkowski, K. **15**-542
Radlick, P. **2**-283, **18**-295, **19**-429
Radner, F. **11**-104, **11**-157
Radom, L. **1**-118, **2**-14, **2**-191, **2**-205, **2**-219, **2**-419, **4**-297, **5**-25, **8**-251, **15**-555, **18**-228
Radtke, R. **19**-24
Radzik, D.M. **17**-242
Radziszewski, J.G. **2**-243, **4**-518, **4**-519, **5**-286
Raeissi, M. **13**-602
Raeppel, S. **13**-666
Raev, V.A. **7**-123
Raevskii, O.A. **3**-157
Raevsky, O.A. **3**-115
Rafei, M. **16**-1749
Rafel, S. **16**-791, **16**-800, **16**-813
Rafferty, P. **16**-2069
Rafi, S. **16**-1004
Rafiee, F. **9**-141
Rafikov, S.R. **16**-1546
Ràfols, C. **8**-86
Ragagnin, G. **15**-1996
Ragain, R.M. **10**-221
Ragauskas, A.J. **5**-133, **13**-503, **17**-436, **19**-128
Raghavachari, K. **10**-219
Raghavan, A.S. **18**-508, **18**-579
Raghavan, K.V. **11**-251, **19**-759
Raghavan, M. **19**-712
Raghavendra, S. **10**-1653
Raghunath, O.R. **13**-124
Ragnarsson, U. **10**-1041
Ragoussis, N. **16**-1027
Ragoussis, V. **16**-1027
Ragunathan, K.G. **3**-123
Rahaim, Jr., R.J. **10**-1907
Rahaman, H.U.R. **19**-992
Rahaman, R. **10**-1011
Rahaman, R.O. **12**-242
Raheem, I.T. **7**-131, **11**-409
Rahm, A. **12**-14
Rahman, A.-u. **10**-890
Rahman, A. **19**-1299
Rahman, M. **16**-1865
Rahman, S.M.A. **10**-794
Rahmati, A. **19**-36
Rahn, B.J. **10**-1366
Rai, A.N. **10**-651
Rai, G. **19**-1190
Rai, R. **12**-277
Rai, R.S. **19**-1081
Raimondi, L. **15**-1836, **16**-1085
Raimondi, M. **2**-133
Rainer, J.D. **15**-1361
Raines, R.T. **6**-54, **18**-850
Rainier, J.D. **15**-1905, **18**-821, **18**-837
Rainsford, A.E. **17**-447
Rainville, D.P. **12**-15
Rairama, R. **16**-685
Raithby, P.R. **3**-21
Raj, K.S. **10**-1003, **10**-1266
Raj, M. **16**-1085
Raj. C.P. **15**-2204
Rajabi, A. **16**-1007
Rajabi, F. **19**-602
Rajabi, J. **19**-246
Rajadhyaksha, S.N. **19**-742
Rajaei, A. **10**-1066
Rajagopal R. **11**-242
Rajagopal, D. **16**-1116
Rajagopal, S. **5**-441, **10**-480, **10**-482
Rajagopalan, S. **15**-1258
Rajakumar, P. **4**-80
Rajan, S. **12**-215, **13**-632
RajanBabu, T.V. **15**-53, **15**-832, **15**-837, **15**-881
Rajanna, K.C. **11**-126
Rajappa, S. **16**-1800, **18**-737

Rajaram, J. **15**-462
Rajaram, S. **19**-1622
Rajasekhar, K. **10**-847
Rajca, A. **5**-299
Rajca, S. **5**-299
Raje, V.P. **16**-989
Rajendar **9**-91, **15**-1442
Rajendran, V. **7**-93
Rajesh, K. **11**-268
Rajewski, R. A. **9**-101
Rajkumar, A.B. **15**-625
Rajkumar, G.A. **19**-86
Rajkumar, M. **10**-984
Rajogopal, R. **11**-132
Rajput, A.S. **1**-82
Raju, A. **15**-310
Raju, A.K. **16**-357
Raju, T. **11**-227
Rajzmann, M. **5**-333, **10**-474
Rak, M.A. **12**-588
Rakhmankulov, D.L. **5**-53, **10**-559, **16**-1553
Rakitin, O.A. **13**-772
Rákos, L. **10**-683
Rakshit, A.B. **8**-254
Raksis, J.W. **18**-293
Raksit, A.B. **10**-365, **10**-366
Ralbovsky, J. **16**-1953
Ralph, E.K. **8**-237
Ram, R.N. **16**-367
Ram, S. **16**-350, **19**-1196, **19**-1426
Ram, S.R. **19**-1199, **19**-1248, **19**-1250, **19**-1529
Rama Rao, A.V. **18**-357
Rama Rao, K. **13**-151
Rama, K. **10**-1609
Ramachandar, T. **10**-1003, **16**-1723
Ramachandraiah, G. **11**-294
Ramachandran, B. **16**-1056
Ramachandran, J. **16**-875
Ramachandran, P.V. **15**-681, **15**-709, **16**-324, **19**-1007, **19**-1046
Ramachary, D.B. **15**-1430, **16**-914
Ramadas, S.R. **16**-875
Ramaiah, D. **7**-66, **7**-67
Ramaiah, M. **14**-2
Ramaiah, P. **19**-751
Ramakers, J.E. **4**-506
Ramakrishnan, V.T. **12**-741, **17**-385
Ramalingam, T. **19**-294, **19**-1244, **9**-1731
Ramalingam, V.T. **16**-150
Ramalingan, C. **18**-340
Ramamurthy, V. **7**-21, **7**-23, **7**-43, **7**-48, **11**-595, **14**-252, **15**-2362, **15**-2445
Raman, J.V. **2**-57
Ramana, K.V. **16**-74
Ramana, M.M.V. **11**-124
Ramanathan, B. **10**-936
Ramanathan, C. R. **4**-165
Ramani, T. **16**-1087
Ramarao, C. **15**-443, **15**-1804, **19**-121, **19**-869
Ramart-Lucas, P. **18**-131
Ramaswamy, A.V. **11**-238, **12**-116
Rambaud, M. **12**-650
Rambo, E. **15**-1966
Rambo, R.S. **16**-1084
Ramchandani, R.K. **13**-394
Ramesh, C. **13**-678, **13**-679, **16**-294, **16**-1629, **16**-1630, **16**-1636, **17**-444
Ramesh, G. **10**-1172
Ramesh, N. **12**-132
Rameshkumar, C. **15**-1507, **15**-1531
Raminelli, C. **12**-300
Ramírez-López, P. **16**-776, **16**-1490
Ramirez, A. **10**-1769, **13**-46, **13**-734, **16**-1180, **17**-306
Ramirez, F. **16**-1317, **16**-1354
Rammler, D.H. **16**-1825
Ramn, R.S. **15**-203
Ramnarayan, K. **19**-930
Ramnauth, J. **17**-511
Ramón, D.J. **10**-1721, **16**-1084, **16**-1526
Ramón, R.S. **16**-112
Ramondenc, Y. **10**-1496
Ramos, A. **18**-607, **18**-917
Ramos, B. **17**-387
Ramos, E.C. **15**-1151
Ramos, J. **17**-160
Ramos, J.H.R. **10**-1946, **15**-1451, **15**-2355
Rampalli, S. **15**-917
Rampoldi, A. **10**-368
Ramsay, D.A. **1**-55
Ramsay, O.B. **4**-1, **17**-45
Rämsby, S. **16**-1941
Ramsden, C.A. **2**-10, **2**-376
Ramsden, H.E. **12**-481
Ramsden, P.D. **4**-166
Ramsey, B. **10**-178, **10**-179
Ramsey, B.G. **1**-16
Ramu, R. **10**-971, **16**-1630
Ran, Y.-F. **15**-2616
Rana, K.K. **11**-250
Rana, S. **16**-335
Ranaivosata, J.-L. **5**-314, **5**-255
Rancourt, J. **15**-54
Randad, R.S. **16**-462, **16**-752
Randall, L.H. **2**-57
Randell-Sly, H.E. **15**-1481
Rander, K.D. **11**-188
Randic, M. **2**-103, **2**-121, **4**-437
Randl, S. **18**-870
Rane, A.M. **10**-806, **15**-1802
Raner, K.D. **7**-121, **14**-136, **14**-139, **14**-142, **14**-180
Raneri, A. **15**-862
Ranes, E. **11**-145
Rang, H. **4**-458
Rangaishenvi, M.V. **15**-704, **19**-1510
Ranganathan, D. **15**-2391, **19**-384
Ranganathan, K. **15**-1337
Ranganathan, S. **15**-2391, **19**-384
Ranganayakulu, K. **5**-51
Rangappa, K.S. **6**-91
Rangarajan, R. **19**-551
Rani, K.S. **10**-1283
Rank, B. **19**-314
Rankin, K.N. **19**-645
Rantanen, T. **4**-161
Ranu, B. **19**-900, **19**-910
Ranu, B.C. **10**-835, **10**-1149, **10**-1230, **10**-1293, **10**-1719, **10**-1732, **13**-497, **14**-425, **15**-298, **15**-544, **15**-611, **15**-613, **15**-653, **15**-1129, **15**-1448, **16**-50, **16**-348, **16**-554, **16**-1625, **16**-1627, **16**-1943, **17**-216, **17**-376, **17**-378, **17**-383, **18**-138, **18**-167, **19**-905, **19**-, **19**-916, **19**-1312, **19**-1321, **19**-1357
Rao, A.B. **19**-992
Rao, A.J. **16**-785
Rao, A.S. **10**-525, **14**-313
Rao, B.N. **11**-595
Rao, C.G. **9**-9, **10**-337, **15**-700
Rao, C.L. **9**-91
Rao, C.N.R. **2**-417
Rao, C.T. **10**-1197
Rao, C.V. **16**-1635
Rao, G.V. **10**-947, **19**-1257, **19**-1362, **19**-1619, **19**-1668
Rao, H.S.P. **15**-1425, **16**-145
Rao, H.S.P.R. **16**-1004
Rao, J.M. **11**-128, **14**-313, **15**-2462, **18**-462, **18**-468, **19**-1020
Rao, K. **10**-1003
Rao, K.R. **10**-689, **10**-707, **10**-967, **10**-974, **10**-1003, **19**-192, **19**-251, **19**-251
Rao, K.V. **10**-1266, **19**-992
Rao, K.V.R. **19**-129
Rao, M.L.N. **12**-129, **13**-326, **13**-362, **16**-2037
Rao, N.V. **10**-1204
Rao, P.B. **15**-1912, **15**-1916
Rao, P.D. **16**-790
Rao, P.P. **10**-1266
Rao, P.S. **16**-627, **16**-1865
Rao, R. **11**-239
Rao, R.J. **10**-1189
Rao, R.S. **11**-459, **15**-2346, **16**-330
Rao, S. **11**-128
Rao, S.A. **14**-421, **15**-980, **15**-983, **16**-571
Rao, S.N. **5**-82, **10**-490
Rao, T.S. **11**-274
Rao, V.D. **4**-165
Rao, V.V.R. **14**-436
Rao, W. **10**-821
Rao, Y. **16**-1838

Rao, Y.G. **15**-1385, **16**-574
Raphael, R.A. **4**-472
Rapoport, H. **16**-1930, **16**-1936, **16**-2140, **19**-1070
Rapoport, Z. **17**-461
Raposo, C. **15**-2111
Rapp, M. **10**-1728
Rapp, M.W. **10**-461
Rappa, A. **13**-761, **15**-582
Rappaport, S.M. **2**-374
Rappe, A.K. **4**-413
Rappe, C. **12**-150, **17**-346, **18**-203, **18**-211
Rappoport, H. **13**-827
Rappoport, Z. **1**-48, **2**-41, **2**-378, **2**-445, **2**-447, **2**-448, **2**-449, **2**-452, **2**-453, **2**-455, **2**-461, **3**-102, **3**-130, **4**-27, **4**-48, **4**-426, **4**-427, **4**-428, **4**-441, **4**-452, **4**-456, **4**-485, **4**-527, **5**-69, **5**-126, **5**-143, **5**-252, **5**-267, **5**-334, **5**-336, **5**-436, **7**-68, **8**-68, **8**-78, **9**-32, **10**-127, **10**-149, **10**-252, **10**-255, **10**-256, **10**-257, **10**-259, **10**-260, **10**-262, **10**-263, **10**-264, **10**-280, **10**-281, **10**-332, **10**-421, **10**-434, **10**-454, **10**-471, **10**-863, **10**-1094, **10**-1300, **10**-1331
Rappoport, Z. **10**-1929, **11**-230, **11**-375, **11**-470, **12**-59, **12**-82, **12**-84, **12**-91, **12**-733, **13**-29, **13**-39, **13**-54, **13**-57, **13**-776, **14**-329, **15**-36, **15**-38, **15**-39, **15**-40, **15**-76, **15**-78, **15**-107, **15**-461, **15**-500, **15**-591, **15**-1623, **15**-1952, **15**-2105, **15**-2175, **15**-2444, **15**-2470, **15**-2494, **16**-14, **16**-1017, **16**-1226, **16**-1493, **16**-2249, **16**-2249, **17**-50, **17**-59, **17**-154, **17**-300, **17**-371, **17**-392, **17**-430, **17**-453, **17**-461, **18**-160, **19**-22, **19**-252, **19**-609, **19**-716, **19**-773, **19**-785, **19**-893, **19**-1161, **19**-1174, **19**-1544
Raptis, M. **19**-95
Rarig, R.-A.F. **15**-707
Rasanen, M. **4**-309
Rashatasakhon, P. **13**-241, **15**-1349
Rashchupkina, Z.A. **10**-1683
Rasheed, M.A. **18**-642
Rashid, S.M.K. **15**-2369
Rasmussen, J.K. **10**-1757, **12**-205, **16**-1494, **16**-2234
Rasmussen, K.G. **16**-983
Rasmussen, S.C. **13**-203
Rasmussen, S.E. **10**-8
Rasmussen, T. **16**-678
Rasne, R.M. **15**-1047
Raspoet, G. **18**-335
Rassat, A. **5**-271, **16**-1344, **19**-933
Rassias, G.A. **15**-1909
Rassu, G. **16**-1029
Rasteikiene, L. **15**-1731
Rastelli, A. **15**-1874, **15**-1876, **15**-1879, **15**-2119, **15**-2127, **19**-483
Rastetter, W.H. **15**-1871
Rastogi, A. **15**-1396
Raston, C.L. **9**-84, **9**-143, **9**-144, **10**-1357, **12**-604, **12**-609, **12**-611, **15**-977, **16**-614, **16**-909
Rasul, G. **5**-100, **11**-123, **11**-241
Ratajczak, H. **18**-28, **18**-46
Ratajczyk, T. **4**-311
Ratcliffe, A.J. **10**-568
Ratcliffe, P.D. **16**-1448, **19**-120
Ratcliffe, R. **10**-1184
Rath, N.P. **7**-66
Rathjen, H. **12**-360
Rathke, M.W. **4**-533, **10**-1699, **10**-1737, **10**-1858, **10**-1859, **10**-1864, **10**-1867, **10**-1874, **12**-184, **12**-512, **16**-830, **16**-833, **16**-1179, **16**-1305, **16**-2118, **16**-2125, **16**-2134, **16**-2135, **18**-458, **18**-463, **18**-464, **19**-52, **19**-818
Rathmell, R.E. **15**-913
Rathore, R. **10**-1390, **19**-264, **19**-553
Ratjen, L. **16**-363
Ratnikov, M. **12**-360
Ratovelomanana-Vidal, V. **4**-155
Ratts, K.W. **15**-423
Ratusky, J. **11**-664, **11**-665, **11**-666, **11**-667
Rau, A. **18**-652
Rau, H. **7**-11
Raubo, P. **19**-1375
Raucher, D.J. **15**-2645
Rauchfuss, T.B. **16**-218
Raudenbusch, W. **17**-406, **17**-459
Rauhut, M.M. **6**-40, **6**-41, **13**-843, **16**-817
Rauk, A. **1**-107, **4**-34, **4**-37, **4**-256, **5**-81, **8**-159, **10**-296, **12**-237, **18**-174
Rauleder, G. **18**-28
Raulins, N.R. **18**-627, **18**-691
Rausch, B.J. **15**-1567
Rausch, M.D. **2**-185, **12**-414
Raut, S.V. **17**-267
Rautenstrauch, C.W. **9**-94
Rautenstrauch, V. **14**-259, **18**-438, **18**-776, **19**-933, **19**-935
Ravard, A. **17**-320
Ravasio, N. **19**-1428
Raveendran, P. **9**-102
Ravenek, W. **15**-1617
Ravenscroft, M.D. **13**-38
Ravikumar, K.S. **19**-920
Ravindar, K. **15**-310
Ravindran, N. **12**-517, **12**-519, **15**-695
Ravindran, T. **19**-1270
Ravindranath, B. **16**-1880, **17**-204
Ravindranath, N. **16**-1629, **16**-1630, **16**-1636
Ravindranathan, M. **9**-9, **10**-337, **15**-828, **18**-106, **18**-107
Ravindranathan, T. **10**-1132, **15**-2047, **15**-2391, **18**-482
Raw, A.S. **19**-1659
Raw, S.A. **16**-1475, **19**-110
Rawal, V.H. **10**-1082, **14**-326, **15**-1056, **15**-2186, **19**-1118
Rawalay, S.S. **19**-639
Rawat, M. **15**-2651
Rawlinson, D.J. **11**-180, **14**-168, **14**-219, **14**-268, **14**-271, **14**-271, **14**-273, **18**-924
Rawson, R.J. **15**-2553
Ray Jr., W.J. **13**-869
Ray, A. **19**-1586
Ray, R. **15**-1798
Ray, S. **16**-1716
Rayanakorn, M. **15**-271
Rayez, J.-C. **6**-47
RayMahasay, S. **11**-58
Raymo, F.M. **2**-342, **3**-210
Rayner, C.M. **13**-430, **15**-2220
Raynie, D.E. **9**-100
Raza, A. **16**-764
Razdan, R.K. **14**-421
Razin, V.V. **16**-1786, **17**-353
Razinger, M. **4**-103
Razumovskii, S.D. **19**-331, **19**-344
Razuvaev, G.A. **9**-20, **12**-461, **14**-322
Razzano, D.A. **15**-618
Razzuk, A. **13**-85
Rea, D.G. **4**-391
Read de Alaniz, J. **16**-724
Read, D. **4**-257, **4**-258
Read, R.A. **17**-98
Read, R.W. **10**-1083
Reader, J.C. **15**-2274
Readio, P.D. **14**-207, **14**-55, **15**-125
Readman, J.M. **11**-61
Readshaw, S.A., **4**-379, **4**-380
Ready, J.M. **10**-601, **12**-510, **15**-893, **15**-1860
Reagan, M.T. **8**-135, **19**-1264
Reale, A. **19**-1687
Reardon Jr., E.J. **15**-2575
Rebeiro, G.L. **11**-450, **13**-114
Rebeiro, G.LO. **18**-763
Rebek Jr., J. **3**-157, **15**-2206
Rebek, J. **16**-1911, **16**-1930, **18**-651
Rebeller, M. **19**-1401
Rebiere, F. **19**-799
Reboul, E. **16**-1126
Recanatini, M. **15**-1084
Recca, A. **19**-1687
Rechsteiner, B. **16**-267
Rector, C.L. **5**-331

Recupero, F. **19**-167, **19**-320, **19**-578, **19**-1040
Red'ko, A.N. **8**-103
Reddy, A.C. **10**-879
Reddy, A.R. **15**-1385, **16**-574
Reddy, A.S. **16**-1858
Reddy, A.V.N. **10**-1087
Reddy, B.V.S. **16**-330
Reddy, B.M. **12**-774
Reddy, B.S.N. **19**-1256
Reddy, B.S.P. **19**-1256
Reddy, B.V.S. **9**-133, **10**-705, **10**-846, **10**-847, **10**-894, **10**-1003, **10**-1003, **10**-1009, **10**-1069, **10**-1266, **10**-1626, **10**-1653, **11**-217, **11**-459, **13**-167, **13**-174, **13**-742, **14**-336, **15**-1058, **15**-1385, **15**-1438, **15**-1456, **15**-1696, **15**-1736, **15**-2346, **16**-150, **16**-250, **16**-357, **16**-574, **16**-619, **16**-782, **16**-1234, **16**-1235, **16**-1563, **16**-1635, **17**-370, **17**-401, **18**-328, **18**-642, **18**-699, **19**-294, **19**-1532, **19**-1731
Reddy, C.K. **15**-1214
Reddy, Ch.G. **10**-1197
Reddy, Ch.K. **10**-246
Reddy, Ch.R. **10**-1189, **16**-77, **16**-329
Reddy, Ch.S. **10**-847, **16**-156
Reddy, Ch.V. **13**-186, **19**-759
Reddy, D.R. **9**-91, **15**-1442, **19**-493
Reddy, D.S. **3**-76, **18**-324, **19**-1362
Reddy, E.B. **16**-302
Reddy, E.J. **16**-980
Reddy, G.D. **15**-1309, **15**-2441
Reddy, G.J. **11**-332, **19**-1021, **19**-1024
Reddy, G.R. **16**-1858
Reddy, G.S. **16**-1410, **16**-1713, **16**-1717, **16**-1859, **16**-2034, **16**-2284, **19**-1580
Reddy, G.S.K.K. **10**-970, **19**-992
Reddy, G.V. **16**-627, **19**-1257
Reddy, G.V.S. **10**-947, **19**-1619
Reddy, J.P. **19**-1136
Reddy, J.S. **16**-2292
Reddy, J.S.S. **15**-2346, **16**-619
Reddy, K.B. **10**-970, **14**-336
Reddy, K.R. **16**-315
Reddy, K.S.K. **11**-295
Reddy, K.S.R. **11**-285
Reddy, K.V. **16**-56, **16**-1472, **18**-737, **19**-388
Reddy, L.R. **10**-967, **10**-974, **10**-1003
Reddy, M.A. **10**-967, **10**-974, **10**-1003, **19**-192
Reddy, M.M. **16**-1401, **16**-1859, **19**-1532
Reddy, M.R. **16**-2087
Reddy, M.S. **10**-707, **16**-819, **19**-251
Reddy, M.S.R. **12**-129
Reddy, M.V. **16**-77, **16**-1723, **19**-1228
Reddy, M.V.R. **19**-583
Reddy, N.K. **15**-1677
Reddy, N.P. **12**-786, **19**-212
Reddy, N.R. **13**-390, **16**-819
Reddy, P.G. **12**-768
Reddy, P.M. **13**-742
Reddy, P.S. **12**-116, **19**-1523
Reddy, P.S.M.M. **10**-581
Reddy, P.T. **16**-295, **16**-1235
Reddy, P.V. **10**-1003
Reddy, R.M. **16**-826
Reddy, R.P. **15**-2666
Reddy, R.S. **15**-650, **19**-687
Reddy, S. **11**-626, **16**-1555
Reddy, T.I. **16**-1238
Reddy, V.P. **15**-2234, **11**-123, **13**-151, **18**-584
Reddy, V.R. **12**-774
Reddy, V.S. **10**-840, **11**-286
Reddy, Y.R. **18**-639
Redecker, T. **5**-182
Redgrave, A.J. **15**-1867
Redlich, O. **3**-168
Redlich, S. **13**-400
Redman, R.P. **17**-106
Redmore, D. **17**-510, **18**-160, **18**-182, **18**-203, **18**-225, **18**-247
Redpath, J. **15**-917
Redvanly, C.S. **18**-233
Redwine, O.D. **5**-229
Reece, P.A. **10**-1871
Reed, C.A. **5**-8, **5**-9, **8**-91, **8**-119, **9**-123
Reed, D. **13**-726
Reed, J.N. **12**-541
Reed, J.W. **18**-606
Reed, L.L. **2**-181
Reed, N.N. **15**-1973
Reed, S.A. **4**-402
Reed, S.C. **5**-377
Reedich, D.E. **17**-508
Reedijk, J. **19**-169
Reek, J.N.H. **15**-1609
Rees, C.W. **2**-295, **2**-298, **5**-348, **15**-2053, **15**-2547
Rees, N.V. **19**-936
Reese, C.B. **16**-77, **16**-1541, **18**-544, **19**-1114
Reese, O. **15**-1184
Reetz, M.T. **10**-1453, **10**-1455, **10**-1584, **10**-1715, **11**-443, **14**-64, **15**-638, **15**-966, **15**-1203, **16**-461, **16**-604, **16**-608, **16**-609, **16**-655, **16**-657, **16**-698, **16**-755, **16**-799, **16**-985, **16**-1078, **16**-1125, **16**-1135, **16**-1137, **16**-1260, **18**-389, **18**-953
Reeve, W. **8**-57, **17**-397
Reeves, J.T. **13**-348, **16**-599, **16**-1507
Reeves, R.L. **16**-240, **16**-1014
Reeves, W.P. **10**-1060, **11**-239
Refvik, M.D. **19**-1508
Regen, S.L. **7**-84, **7**-91, **10**-500, **10**-501, **10**-737, **10**-832
Reginato, G. **15**-1141, **17**-213
Regis, R.R. **12**-194
Regitz, M. **1**-12, **4**-500, **5**-392, **5**-411, **10**-420, **12**-219, **13**-778, **15**-2585, **16**-2296, **17**-284, **17**-496, **18**-223, **18**-530, **18**-531, **19**-290
Régnier, S. **18**-350
Regnourf-de-Vains, J.-B. **3**-130
Reguillo, R. **19**-1167
Rehan, A.H. **16**-1355
Rehborn, D.C. **13**-492
Rei, M. **15**-262, **15**-263
Reich, C.J. **10**-548
Reich, H.J. **5**-126, **5**-148, **5**-181, **5**-185, **5**-190, **15**-1191, **10**-126, **10**-1826, **12**-658, **17**-293, **17**-295, **17**-296, **18**-779, **19**-806
Reich, I.L. **10**-126, **17**-296
Reich, N.W. **15**-237
Reichardt, C. **10**-430, **10**-459, **10**-461, **10**-474, **10**-476, **10**-477, **10**-478, **14**-134
Reichel, C.J. **16**-385
Reichenbach, T. **15**-888
Reichenbacher, P.H. **18**-43
Reichle, R. **18**-24
Reichle, W.T. **12**-1
Reichmanis, E. **2**-285
Reichwein, J.F. **15**-1564
Reid, C.S. **10**-1630
Reid, D.H. **2**-147, **19**-99
Reid, G. **3**-119
Reid, I. **12**-81
Reid, M. **16**-1332, **19**-110
Reider, P.J. **4**-204, **9**-112, **13**-416, **13**-473, **15**-466, **15**-1113, **16**-251, **19**-647, **19**-650, **19**-1135
Reiding, D.J. **11**-635
Reif, L. **11**-642
Reiff, H. **16**-1101
Reihs, S. **15**-1992
Reijnders, P.J.M. **10**-1319
Reimlinger, H. **12**-57
Rein, T. **14**-274, **16**-1363, **16**-1372, **16**-1386
Reinecke, M.G. **13**-54
Reineke, C.E. **18**-44
Reingold, J.A. **16**-742
Reinhardt, L.A. **5**-347, **16**-1695
Reinheimer, J.D. **13**-91
Reinhold, U. **16**-888
Reinhoudt, D.N. **3**-118, **3**-181, **9**-86, **15**-2371
Reinke, L.A. **5**-273

Reinmuth, O. **10**-1298, **10**-1357, **10**-1606, **10**-1617, **12**-586, **12**-604, **16**-455, **16**-863, **16**-880, **16**-992, **16**-2012, **16**-2048, **16**-2051
Reinscheld, T.K. **12**-623
Reis, A.E.S. **13**-577
Reis, Ö. **13**-552, **19**-527
Reisch, J. **15**-374
Reisdorf, D. **19**-813
Reisenauer, H.P. **2**-183
Reiser, O. **12**-261, **16**-1210, **16**-1363, **16**-1386
Reisinger, C.M. **15**-1921
Reisse, J. **7**-79, **7**-80, **7**-84, **7**-86
Reisser, M. **15**-795
Reißig, H.-U. **16**-732
Reissig, H.-U. **16**-696
Reissig, H. **4**-428, **15**-129
Reist, E.J. **10**-1185, **17**-224
Reister, S. **11**-247
Reiter, M. **15**-1434
Reiter, R.C. **2**-319
Reitman, M. **13**-599
Reitsma, B.H. **4**-129, **4**-150, **15**-635
Reitz, A.B. **16**-1311, **16**-1350, **16**-1355, **16**-1381, **16**-1384, **16**-1385
Reitz, D.B. **5**-131, **10**-1832
Reitz, O. **6**-68
Rekasheva, A.F. **10**-551, **10**-590
Rekowski, V. **5**-304
Rele, S. **19**-1681, **19**-1688
Rella, M.R. **19**-227
Reller, A. **15**-487
Remanick, A. **18**-100
Remar, J.F. **10**-827
Rembaum, A. **2**-28
Remenar, J.F. **10**-1703
Remennikov, G. **10**-375
Remington, R.B. **2**-67
Remion, J. **16**-1990
Remorova, A.A. **11**-329
Rempala, P. **5**-422
Remuson, R. **10**-1283
Ren, H. **16**-665
Ren, J. **16**-242
Ren, L. **15**-1512
Ren, P.-D. **15**-531, **15**-610, **16**-592, **19**-1309
Ren, P. **12**-370, **15**-2664
Ren, P.D-D. **19**-1217
Ren, R.X. **10**-1147, **13**-121, **13**-277, **16**-285, **18**-348
Ren, S.-K. **19**-83
Ren, S.K. **18**-155
Ren, T. **13**-591
Ren, W. **19**-722
Ren, Y. **10**-381, **19**-1026
Renaldo, A.F. **18**-655
Renard, M. **19**-1773
Renard, P.-Y. **10**-873
Renato Noto, R. **8**-84
Renaud, J.-L. **10**-1535, **10**-1615, **15**-453, **16**-1084, **19**-1473
Renaud, P. **14**-16, **14**-17, **14**-18, **14**-21, **15**-519, **15**-1286, **15**-1332, **15**-1356, **15**-1357, **15**-1359, **15**-2158, **17**-299
Rendenbach, B.E.M. **15**-1098
Render, D. **16**-36
Rendleman, J. **14**-48, **14**-368
Renehan, M.F. **15**-1983
Renga, J.M. **17**-296
Renger, B. **13**-209, **10**-1833, **19**-1269
Renk, E. **14**-121
Renko, Z.D. **15**-1858
Renneboog, R. **8**-249
Renneke, R.F. **14**-309
Rennels, R.A. **11**-179, **13**-727, **13**-729
Renner, R. **14**-188
Rennie, R.A.C. **19**-843
Reno, D.S. **4**-204
Renslo, A.R. **15**-2321
Rentea, C.N. **19**-607
Rentzsch, M. **10**-146
Renugopalakrishnan, V. **4**-314
Renz, M. **18**-377
Répási, J. **13**-583
Repič, O. **10**-749, **11**-257, **15**-2554, **16**-1939, **18**-267, **19**-652
Répichet, S. **11**-438
Repinskaya, I.B. **15**-657
Reppe, C. **12**-152
Reppe, W. **15**-2586
Rerick, M.N. **19**-844, **19**-1368, **19**-1369
Reshef, D. **15**-213
Reshotova, I.G. **15**-565
Resnick, P. **12**-198
Resouly, S.M. **13**-309, **13**-560
Respondek, J. **16**-1388
Resta, S. **15**-2008
Rétey, J. **10**-1250
Rettig, S. **4**-404
Réty, J. **4**-156
Reuben, D.M.E. **19**-1001
Reuchlein, H. **2**-90
Reucroft, J. **16**-1381
Reuliaux,V. **16**-1958
Reum, M.E. **15**-2488
Reuman, M. **12**-429
Reusch, W. **18**-205, **19**-1406, **19**-1434
Reutov, O.A. **4**-26, **5**-106, **5**-136, **8**-16, **8**-17, **10**-360, **10**-509, **10**-515, **10**-520, **10**-798, **10**-1391, **12**-2, **12**-34, **12**-37, **12**-43, **12**-45, **12**-655, **12**-703, **13**-274, **16**-1353, **18**-44, **18**-259, **18**-439
Reutrakul, V. **16**-404, **19**-267
Reuvers, J.T.A. **17**-298
Revell, J.D. **15**-1056, **16**-1084
Revial, G. **15**-1101
Revis, A. **16**-1124
Revuelta, J. **19**-1222
Rewicki, D. **5**-106, **8**-17
Rey, M. **15**-2423, **15**-2423, **18**-420
Rey, P. **5**-305
Reye, C. **12**-622
Reyes, E. **15**-1401, **16**-1084
Reyes, N. **10**-670
Reymond, J.-L. **15**-1908
Reymond, S. **15**-2191, **16**-2178
Reynolds-Warnhoff, P. **19**-959
Reynolds, J. **12**-751
Reynolds, J.D. **9**-49
Reynolds, N.J. **16**-256, **16**-497
Reynolds, T.E. **15**-1056, **16**-1192
Reynolds, W.F. **2**-39, **9**-41, **9**-52, **9**-64
Reza-Elahi, S. **15**-535
Rezaei, H. **15**-2172
Rezaeifard, A.-R. **19**-796
Rezai, N. **18**-343
Rezende, M.C. **8**-90, **10**-753, **10**-875, **11**-524, **12**-706, **16**-1738
Reznichenko, A.L. **15**-338
Reznikov, V.A. **5**-267, **5**-274, **5**-275
Rheault, T.R. **15**-1308
Rhee, C.K. **19**-915, **19**-917, **19**-919
Rhee, E.S. **18**-789, **18**-801, **18**-802
Rhee, H. **11**-695, **16**-350, **18**-351, **19**-676
Rhee, I. **12**-558, **13**-688
Rhee, J.U. **15**-1490
Rhee, S. **15**-745, **18**-448
Rheingold, A.L. **15**-2027
Rho, M.M. **9**-9
Rhoads, S.J. **18**-627, **18**-691
Rhode, O. **19**-519
Rhodes, C.J. **5**-258, **5**-344
Rhodes, R.A. **10**-1258
Rhodes, S. **10**-530
Rhodes, Y.E. **10**-161, **10**-163, **10**-211, **19**-824
Rhom, D. **10**-254
Ribagorda, M. **12**-493, **13**-572, **15**-163
Ribas, J. **3**-82, **3**-85
Ribe, S. **9**-97, **18**-698
Ribeiro, A.A. **16**-1041
Ribeiro, C.M.R. **15**-275, **16**-850
Riber, D. **15**-1454
Ribière, P. **15**-421
Ribo, J. **18**-231
Ricart, S. **10**-1906
Ricci, A. **10**-1568, **13**-108, **15**-1141, **16**-976
Ricci, M. **19**-441
Ricci, P. **15**-1106
Rice, G. **2**-405
Rice, J.E. **2**-67
Rice, K. **15**-2679

Rice, K.C. **11**-565, **16**-130
Rice, S.A. **6**-11
Rice, S.N. **5**-435
Rich, A.E. **16**-255
Rich, B. **13**-594
Rich, J.D. **14**-465
Richard, C. **5**-380
Richard, J.P. **5**-12, **5**-20, **5**-101, **5**-102, **8**-70, **10**-1, **10**-68, **10**-93, **10**-94, **10**-310, **10**-592, **12**-44, **12**-97, **18**-333
Richard, T.J. **15**-1871
Richards Jr., C.A. **5**-352
Richards, C.J. **2**-108, **16**-1510
Richards, D.H. **10**-792
Richards, J.J. **13**-567
Richards, K.E. **11**-110
Richards, R.M. **4**-93
Richards, S.N. **19**-98
Richards, W.G. **2**-14
Richardson, D.B. **12**-405
Richardson, D.E. **10**-434, **10**-756
Richardson, J. **16**-1382, **16**-1383, **16**-1452, **19**-250
Richardson, K.S. **2**-8, **2**-420, **5**-26, **16**-46
Richardson, P.F. **15**-1656
Richardson, P.R. **15**-1655
Richardson, R.D. **19**-532
Richardson, W.H. **5**-326, **12**-668, **14**-99, **17**-128
Riche, C. **15**-2444
Richens, D.T. **19**-486
Richert, S.A. **19**-485
Richey Jr., H.G. **5**-34, **5**-35, **5**-47, **5**-49, **5**-69, **5**-115, **5**-125, **10**-142, **10**-205, **13**-30, **15**-107, **15**-886, **16**-486, **16**-509, **16**-975
Richey, J.M. **5**-69, **13**-30
Richheimer, S.L. **10**-1850
Richman, J.E. **10**-1699, **10**-1810, **15**-1464
Richmond, G.D. **10**-1675
Richter-Addo, G.B. **15**-1749
Richter, M.J. **15**-1927
Richter, R. **16**-1868
Richter, W.J. **12**-101
Rickards, B. **15**-1564, **15**-1565
Rickborn, B. **10**-528, **12**-533, **12**-579, **18**-94, **18**-281, **19**-903
Ricks, A.M. **5**-10
Rickter, D.O. **18**-25
Rico, I. **10**-1060
Rico, J.G. **19**-1682
Ridd, J.H. **11**-30, **11**-31, **11**-45, **11**-46, **11**-68, **11**-87, **11**-98, **11**-104, **11**-107, **11**-123, **11**-129, **11**-146, **11**-153, **11**-616, **11**-681, **13**-781, **13**-782, **13**-783
Riddell, F.G. **4**-331, **4**-367, **4**-370, **4**-395
Ridder, A. **15**-346
Rideout, D. **9**-96
Ridvan, L. **3**-195
Rieber, M. **12**-442
Rieche, A. **11**-517, **13**-251, **13**-252, **13**-254
Ried, W. **16**-535, **16**-2164, **17**-513
Riedel, M. **16**-265
Rieder, C.J. **15**-1090, **15**-1095
Riediker, M. **16**-663, **16**-663
Riedrich, M. **15**-1431
Riefling, B. **14**-427
Rieger, A.L. **14**-207
Rieger, R. **15**-2246
Riego, J.M. **16**-1794, **18**-336
Riehl, J.J. **12**-325
Rieke, R.D. **12**-591, **12**-624, **12**-626, **12**-627, **12**-628, **12**-629, **12**-630, **12**-631, **13**-481, **16**-604, **16**-833, **16**-837, **16**-2011, **16**-2035, **19**-1638, **19**-1683
Rieker, A. **5**-242, **5**-246, **13**-789
Riela, S. **15**-229
Riener, M. **13**-513
Rienstra-Kiracofe, J.C. **1**-29, **5**-415
Riente, P. **10**-1722, **15**-507, **16**-344
Riera, A. **7**-95, **10**-736, **10**-962, **15**-1557, **15**-2588
Riera, J. **5**-269
Riermeier, T. **11**-521
Riermeier, T.H. **16**-317, **16**-352, **19**-1150
Ries, M. **15**-2087
Riesen, A. **18**-515
Riesgo, L. **15**-2133, **18**-276
Riesz, P. **7**-71
Rieth, R.D. **13**-315
Rietz, E.G. **10**-558
Riezebos, G. **19**-356
Rifi, M.R. **2**-173, **10**-1308
Rigaudy, J. **14**-242, **15**-2360
Rigby, J.H. **10**-632, **15**-1367, **15**-2677
Riggleman, S. **13**-515
Riggs, J.C. **11**-604, **13**-46
Riggs, N.V. **2**-205
Righetti, P.P. **15**-991, **15**-1100, **18**-713
Righi, G. **10**-706, **10**-1219, **10**-1222, **10**-1242, **17**-218
Righi, P. **15**-230, **16**-212, **16**-1202
Rigo, P. **13**-503, **17**-269
Riguera, R. **4**-108, **4**-110, **4**-111, **4**-112
Rihs, G. **4**-468
Rihs, G. **16**-663
Rijnberg, E. **13**-732
Rijs, A.M. **17**-5
Riley, C.M. S. **17**-466
Riley, E.F. **16**-1200
Rimmelin, P. **8**-26
Rinalde, S. **11**-483, **16**-610
Rinaudo, J. **13**-836
Rinderknecht, H. **16**-1828
Rinehart Jr., K.L. **2**-185, **11**-67, **12**-592, **17**-501
Ring, D.F. **12**-402
Ring, R.N. **15**-77
Ringer, A.L. **4**-435
Rintoul, G.B. **16**-616
Riordan, J.C. **16**-1702
Riordan, P.D. **19**-1540
Ríos, J.V. **19**-777
Rios, R. **15**-1402, **15**-2078
Ripka, W.C. **16**-441
Ripmeester, J.A. **3**-165
Ripoll, J. **2**-468
Ripoll, J.L. **15**-2278, **16**-238
Riquet, E. **10**-1494
Risch, N. **4**-148, **16**-386
Rise, F. **4**-406
Risgaard, T. **16**-1221
Rispens, M.T. **19**-470
Rissanen, K. **3**-125, **3**-179
Rist, Ø. **14**-483
Ritchie, C.D. **6**-59, **6**-94, **8**-111, **8**-129, **10**-346, **10**-372
Ritchie, E. **19**-1511
Ritchie, G.L.D. **2**-156
Ritieni, A. **10**-1041
Ritsner, I. **15**-1365
Rittberg, B.R. **17**-448
Ritter, A. **16**-343
Ritter, J.J. **16**-2170
Ritter, R.H. **12**-408
Ritter, T. **12**-527, **13**-801, **15**-804
Ritter, W. **4**-302
Rittner, R. **4**-366
Rivard, D.E. **12**-727
Riveiros, R. **10**-1549
Rivera-Otero, E. **10**-1008
Rivera-Fortin, M.A. **16**-2204, **16**-2210
Rivera, I. **10**-1876
Rivera, N.R. **16**-251
Rivero, M.R. **10**-1897, **15**-1537, **15**-1540
Riveros, J.M. **8**-248, **8**-251, **10**-12, **16**-1671
Rivers, G.T. **17**-274
Rivers, P. **4**-51
Rivière, H. **15**-1239, **16**-2005
Rix, D. **16**-645, **18**-821
Rizk, M. **18**-776
Rizzo, C.J. **15**-2210
R'kyek, O, **13**-587
Ro, R.S. **17**-403
Robak, M.T. **16**-1222
Robaugh, D.A. **5**-236
Robb, E.W. **7**-109
Robb, M.A. **15**-2298, **15**-2421, **15**-2454, **18**-906
Robbins, C.R. **13**-865
Robbins, H.M. **10**-89
Robbins, J.D. **18**-913
Robbins, M. **16**-1899
Robbins, M.D. **16**-1690, **17**-96
Robert-Peillard, F. **15**-2068
Robert, F. **15**-1557, **15**-1572
Robert, M. **5**-319

Roberts, B.A. **7**-123
Roberts, B.P. **10**-769, **14**-20, **14**-20, **14**-69, **14**-73, **14**-116, **15**-792, **15**-1470, **19**-1287, **19**-1395
Roberts, D.D. **10**-206, **10**-207
Roberts, D.K. **17**-97, **17**-98
Roberts, D.W. **15**-2430
Roberts, E. **18**-781
Roberts, F.E. **10**-70, **16**-190
Roberts, J.D. **1**-43, **4**-298, **4**-437, **4**-531, **5**-327, **6**-62, **10**-214, **10**-333, **10**-655, **13**-40, **13**-84, **13**-97, **14**-122, **15**-2371
Roberts, J.L. **15**-1822, **16**-1039
Roberts, J.T. **14**-449, **17**-448, **19**-1575
Roberts, K. **10**-342, **10**-469, **10**-343
Roberts, K.A. **16**-1677
Roberts, L. **15**-1366
Roberts, N.K. **15**-456
Roberts, R. **10**-422
Roberts, R.M. **11**-313, **11**-367, **11**-383, **18**-760
Roberts, R.M.G. **15**-5, **11**-637, **11**-638
Roberts, R.S. **16**-1367
Roberts, S. **13**-184, **15**-2423
Roberts, S.M. **15**-452, **15**-1957, **15**-1958, **15**-1962, **15**-2423, **18**-156
Roberts, S.W. **15**-1905
Roberts, T.D. **16**-2293
Roberts, V.A. **15**-2665
Roberts, W.J. **15**-1475
Robertson, A.J. **16**-1748
Robertson, B.D. **12**-335
Robertson, D.E. **10**-602
Robertson, G.B **1**-67, **4**-501
Robertson, J. **15**-1246, **15**-1341, **18**-160, **18**-183
Robertson, J.D. **4**-221
Robertson, J.M. **2**-65
Robertson, K.N. **19**-129
Robertson, P.W. **15**-84, **15**-1664
Robertson, R.E. **6**-64, **6**-77, **10**-40, **10**-41, **10**-88, **10**-548, **19**-1711
Robey, R.L. **19**-391
Robiette, A.G. **4**-462
Robiette, R. **15**-2186, **15**-2233, **16**-792, **16**-1382, **16**-1383
Robin, M.B. **1**-18, **1**-19
Robin, S. **15**-1717
Robins, M.J. **19**-1382
Robinson, B. **18**-761
Robinson, C.N. **9**-78
Robinson, D.A. **18**-528
Robinson, D.L. **4**-364
Robinson, E.A. **11**-512
Robinson, G.C. **10**-63
Robinson, G.M. **18**-768
Robinson, J.A. **4**-156
Robinson, J.E. **10**-916, **10**-1544
Robinson, J.K. **6**-69
Robinson, J.M. **15**-376
Robinson, J.W. **1**-21
Robinson, K.D. **3**-65
Robinson, L. **10**-453
Robinson, L.A. **18**-145
Robinson, M.J.T. **4**-370, **18**-117
Robinson, M.K. **13**-828
Robinson, M.W.C. **10**-685, **10**-974, **18**-147
Robinson, R. **2**-105, **16**-1187, **18**-768
Robinson, R.A. **8**-59
Robinson, R.I. **15**-1823
Robinson, R.M. **5**-433
Robinson, S.B. **19**-767
Robinson, W.T. **11**-61, **16**-1400
Robles, R. **5**-321, **16**-575
Robson, M.J. **18**-160
Robson, R. **16**-110
Robveille, S. **13**-94
Robvieux, F. **15**-2694
Robyr, C. **16**-1246
Rocek, J. **19**-96, **19**-390, **19**-690, **19**-692
Rocha, J.B.T. **15**-943
Roche, D. **11**-257
Rochester, C.H. **3**-3, **8**-12, **8**-53, **8**-129, **8**-137, **8**-139
Rochlin, E. **12**-82, **16**-1226
Rockett, B.W. **16**-1390
Rockett, J. **12**-455
Rocklin, D. **14**-10
Rockstuhl, A. **15**-1701
Rodehorst, R. **14**-490
Rodewald, H. **4**-458
Rodewald, L.B. **18**-117
Rodger, A. **4**-130
Rodger, P.M. **4**-130
Rodgers, A.S. **15**-2533
Rodgers, L.R. **6**-73
Rodgers, M.A. **15**-2361
Rodgers, M.A.J. **14**-251
Rodig, A. **5**-189
Rodima, T. **8**-86
Rodin, J.O. **15**-2288
Rodin, W.A. **4**-487
Rodina, L.L. **18**-226
Rodler, M. **2**-458, **13**-51
Rodrguez, M.A. **18**-617
Rodrguez, N. **11**-663
Rodrigue, A. **3**-118
Rodrigues, D.C. **18**-692
Rodrigues, J.A.R. **15**-659, **16**-816
Rodrigues, J.P. **16**-247
Rodrigues, O.E.D. **12**-304, **15**-217, **15**-290, **16**-598
Rodrigues, R. **12**-251
Rodriguez-Dafonte, P. **3**-184
Rodríguez-García, C. **15**-2501
Rodríguez-Solla, H. **15**-2527, **15**-2572
Rodríguez-Ranera, C. **16**-727
Rodríguez-Vicente, A. **16**-727
Rodríguez-Solla, H. **17**-167, **17**-171, **17**-402
Rodríguez-Otero, J. **18**-499
Rodriguez, A. **17**-387
Rodriguez, A.L. **10**-1460, **13**-740, **15**-953
Rodríguez, B. **10**-962, **16**-393, **16**-1084
Rodríguez, D. **10**-1480, **10**-1490, **10**-1549, **15**-2235, **19**-1058
Rodriguez, H.R. **10**-1349, **12**-409, **13**-725
Rodriguez, J. **12**-67, **18**-851
Rodríguez, J.F. **11**-269
Rodríguez, J.R. **10**-974, **18**-869
Rodríguez, M.A. **12**-509, **15**-1673, **19**-1679
Rodríguez, N. **11**-658, **11**-663, **17**-230
Rodríguez, R. **10**-918
Rodriguez, S. **15**-452, **16**-599
Rodriques, K.E. **15**-1723
Rodríquez, M.A. **15**-2655
Roduner, E. **5**-258
Roe Jr., R. **15**-2424
Roe, D.C. **15**-1625
Roe, S.P. **5**-151
Roelens, S. **4**-213
Roelofsen, D.P. **16**-246
Roesch, A. **16**-760
Roesch, K.R. **15**-2624
Roesler, R. **5**-373
Roeterdink, F. **13**-54
Roeterdink, W.G. **17**-5
Roger, P. **19**-1234
Rogers-Evans, M. **10**-1334
Rogers, D. **4**-100
Rogers, D.W. **1**-97, **2**-42, **2**-54, **2**-362, **2**-387, **2**-388, **4**-483, **5**-253, **5**-282
Rogers, D.Z. **10**-684
Rogers, E. **18**-263
Rogers, H.R. **12**-634
Rogers, M. **12**-78
Rogers, M.M. **15**-329, **15**-346
Rogers, M.T. **5**-156, **5**-294
Rogers, P. **10**-565
Rogers, R.D. **9**-121, **9**-139
Rogers, R.J. **12**-634, **13**-808
Rogers, W.J. **17**-462
Rogic, M.M. **10**-1860, **10**-1858, **10**-1859, **10**-1863, **10**-1864, **10**-1866, **10**-1867, **10**-1874, **12**-512
Roginskii, V.A. **5**-278
Roglans, A. **13**-372, **13**-432, **13**-498, **13**-544, **15**-1070
Rogne, O. **16**-2286
Rogozhin, S.V. **4**-178, **10**-553, **16**-1929
Roh, E.J. **10**-986, **11**-321, **15**-1989
Roh, S.-G. **3**-195
Rohatgi-Mukherjee. K.K. **7**-1
Rohitha, C.N. **11**-253, **11**-295

Rohr, W. **16**-1776, **19**-1116
Rohrbaugh, P.E. **13**-91
Rohrer, C. **19**-1626
Röhrig, P. **2**-324
Röhrling, J. **16**-349
Rohwer, M.B. **16**-791
Roig, A. **2**-488
Roitman, J.N. **12**-29
Rojas, G. **10**-1695
Rojas, J. **15**-303
Rojo, J. **19**-1168
Rokhlin, E.M. **16**-43
Roland, K. **16**-815
Roland, S. **16**-901
Rolando, C. **10**-2006, **19**-818
Rölfing, K. **16**-698
Roling, P.V. **16**-516
Rolla, F. **10**-1033, **10**-484, **10**-1126, **10**-1182, **15**-172, **17**-373, **19**-105, **19**-1247
Rollet, P. **13**-590
Rollin, Y. **10**-1966, **13**-484
Rolston, J.H. **15**-13
Rom, R. **18**-667
Roman, E. **16**-1332
Roman, F. **18**-935, **18**-936
Roman, L. **15**-1066
Romanelli, M.G. **2**-184, **17**-429
Romanenko, V.D. **1**-12
Romano, A. **19**-223
Romano, L.J. **14**-178
Romanova, V.S. **19**-1288
Romanovich, A.Ya. **19**-71
Romański, J. **16**-1467
Romão, C. **18**-381
Romão, C.C. **19**-793, **19**-1589
Romão, C.R. **19**-981
Rombolà, O. **13**-236
Rombouts, G. **13**-196
Romea, P. **16**-1906, **16**-2057
Romeo, A. **19**-135
Romeo, R. **16**-1723
Romera, J.L. **10**-884
Romeril, S.P. **13**-446
Romero, J.A.C. **10**-1503
Romero, P.E. **18**-893
Romero, R.H. **15**-1547
Romers, C. **4**-378
Romesberg, F.E. **8**-219, **8**-220, **8**-222
Romine, J.L. **16**-462
Rømming, C. **13**-774, **16**-216
Romney-Alexander, T.M. **13**-275
Romo, D. **15**-2455, **16**-1190
Romsted, L.S. **10**-560
Ron E. **15**-1011
Ron, M. **6**-82
Rona, P. **15**-2662
Ronald, B.P. **18**-149
Ronald, R.C. **16**-437
Roncaglia, F. **14**-23
Ronco, G. **10**-70
Rondan, N.G. **2**-388, **5**-131, **15**-2665, **18**-911
Rondestvedt Jr., C.S. **10**-544, **13**-819
Rongsi, C. **2**-132
Rongsi, C. **2**-132
Rönn, M. **10**-1385, **15**-234
Rönnqvist, M. **3**-63
Roobeek, C.F. **12**-358, **15**-135
Rooney, J.J. **15**-479, **18**-114, **18**-894
Roos, E.C. **16**-1844
Roos, G.H.P. **16**-790
Root, K.S. **12**-635
Roothaan, C.C.J. **1**-4
Rop, D. **10**-512
Roper, T.D. **16**-1095
Ropp, G.A. **11**-661
Ropp, S. **15**-1434
Roque, J.-P. **10**-668, **16**-188, **18**-221
Roques, N. **11**-218, **11**-438, **16**-2142, **19**-1300
Rosa, C. **15**-185
Rosa, E. **12**-743, **13**-517
Rosa, J.N. **16**-801, **19**-687
Rosado, I. **10**-806
Rosado, O. **16**-1881, **18**-936
Rosales, A. **5**-321, **15**-1330
Rosas, N. **10**-1330
Rosati, O. **10**-974, **12**-757, **15**-1482, **15**-1758
Rosato, D. **15**-862
Rosato, F. **12**-769
Rosauer, K.G. **16**-1034
Rösch, N. **15**-1877, **15**-1882, **15**-2107, **19**-123
Roschangar, F. **16**-1891
Roschek, Jr., B. **5**-331
Roscher, N.M. **14**-230
Roschmann, K.J. **15**-1987
Rose, A. **3**-200
Rose, C.A. **16**-1591
Rose, J. **3**-86
Rose, J.B. **17**-13
Rose, M. **13**-241
Rose, M.E. **10**-1668
Roseblade, S. **15**-1341
Roseblade, S.J. **5**-372, **15**-449
Roselln, A. **13**-613
Rosen, W. **2**-283
Rosenau, T. **16**-349
Rosenbaum, C. **18**-764
Rosenberg, A. **1**-42
Rosenberg, A.M. **16**-1669
Rosenberg, D.E. **13**-823
Rosenberg, R.E. **2**-40
Rosenberg, S.D. **12**-481
Rosenberger, M. **2**-203
Rosenblatt, D.H. **15**-1744, **19**-727
Rosenblum, L.D. **16**-2097
Rosenblum, M. **2**-185, **2**-190, **10**-1738, **13**-844
Rosenfeld, J. **5**-21, **18**-22
Rosenfeld, J.C. **18**-546
Rosenfeld, M.N. **13**-805
Rosenfeld, S.M. **2**-66, **12**-682
Rosenman, H. **14**-491
Rosenmund, K.W. **15**-463
Rosenquist, N.R. **9**-62, **9**-63
Rosenstein, I.J. **14**-108
Roses, J.B. **18**-632
Rosés, M. **8**-86
Rosingana, M. **16**-1947
Rosini, C. **4**-115, **15**-1832
Rosini, G. **15**-230, **16**-1199, **19**-1515
Roskamp, E.J. **12**-343
Roskos, P.D. **18**-372
Rösler, K. **19**-24
Rosnati, V. **19**-1407, **19**-1440
Rosner, T. **13**-443
Rosokha, S.V. **2**-138, **11**-20
Ross Jr., B. **19**-485
Ross, C.B. **16**-1556
Ross, D.A. **13**-787
Ross, D.S. **11**-152, **19**-98
Ross, M.M. **2**-393
Ross, N.A. **16**-835
Ross, P. **10**-13
Ross, S.D. **13**-4, **13**-91
Ross, S.K. **9**-113
Rossa, L. **17**-516
Rossen, K. **11**-521
Rosset, S. **15**-1204
Rossetti, Z.L. **4**-345
Rossi, E. **15**-2633
Rossi, I. **16**-774
Rossi, L. **10**-744, **10**-1222, **12**-783
Rossi, M.H. **16**-288
Rossi, R. **4**-67, **10**-1888, **13**-489, **13**-582, **18**-882
Rossi, R.A. **10**-101, **10**-105, **10**-108, **11**-688, **13**-57, **13**-66, **13**-70, **13**-255, **13**-354, **13**-631, **13**-632, **19**-1354
Rossi, R.C. **16**-796
Rossiter, B.E. **15**-1240, **15**-1969
Rossky, P.J. **10**-81
Rosso, G.B. **12**-292
Rostamizadeh, M. **4**-312
Rostkowski, M. **10**-4
Rostovshchikova, T.N. **15**-24, **15**-168
Rotger, C. **13**-23
Roth, A.S. **15**-580
Roth, B.D. **16**-322, **19**-1444
Roth, E.A. **1**-79
Roth, G.P. **10**-1434, **12**-261
Roth, H.D. **2**-292, **5**-339, **5**-426, **7**-1, **12**-406, **12**-407
Roth, J.P. **16**-2229
Roth, M. **15**-67
Roth, P. **15**-2060
Roth, W. **4**-71
Roth, W.R. **5**-304, **10**-188, **15**-2442, **18**-572, **18**-588, **18**-590, **18**-625, **18**-658, **18**-668, **18**-670, **18**-908
Rothenberg, G. **14**-102

Rothenberg, M.E. **10**-94
Rothgery, E.F. **15**-2494
Rothstein, S.D. **13**-203
Rotinov, A. **17**-137
Rotiroti, L. **11**-283
Rotstein, D. **19**-1283
Röttele, H. **2**-302, **2**-345
Rotter, H.W. **8**-94
Roudeau, R. **16**-666
Rouden, J. **16**-430, **16**-1876, **16**-2016
Rouillard, M. **19**-1236
Roulleau, F. **16**-1822
Roumestant, M. **10**-1504
Roumian, C. **10**-858
Rounds, W.D. **16**-104, **16**-1886
Roush, W.R. **4**-126, **15**-2169, **16**-633, **16**-752, **16**-757, **16**-1055, **16**-1111
Rousseau, A.D. **7**-58
Rousseau, B. **15**-600, **19**-872
Rousseau, G. **15**-1713, **15**-1717, **15**-1722, **15**-2010, **16**-1329
Roussel, A. **15**-2423
Roussel, C. **3**-19, **4**-526, **9**-65, **9**-68
Roussel, M. **19**-705
Rousset, C.J. **12**-646
Rousset, L. **15**-1138
Rousset, S. **12**-281
Rout, L. **13**-149
Routaboul, L. **15**-330
Routier, S. **19**-1605
Rouvray, D.H. **4**-269
Roux, M.C. **15**-1189
Rovira, C. **5**-269
Rovis, T. **14**-301 **15**-1485, **15**-1487, **15**-1505, **15**-2687, **15**-2687, **16**-721, **16**-722, **16**-724, **16**-730, **16**-2099, **16**-2100, **16**-2102, **19**-1366
Rowan, S.J. **3**-195
Rowe, K. **18**-465
Rowland, E.B. **10**-1008
Rowland, F.S. **18**-70
Rowland, G.B. **10**-1008
Rowland, S.P. **2**-454
Rowlands, D.A. **11**-471
Rowlands, G.J. **14**-1
Rowlands, M. **12**-344
Rowley, A.G. **16**-1381, **19**-1400, **19**-1404, **19**-1528
Rowley, J.M. **10**-1633
Rowsell, E. **13**-547
Roy, A. **13**-549
Roy, A.H. **10**-1309, **13**-349, **15**-1481
Roy, D. **16**-792
Roy, D.A. **14**-395
Roy, D.R. **10**-38
Roy, G. **16**-1296
Roy, J. **18**-793
Roy, M. **13**-494, **13**-509
Roy, P. **12**-204
Roy, R.R. **16**-1815
Roy, S. **10**-1654, **11**-248, **11**-333, **11**-337, **13**-494, **13**-509, **14**-311, **14**-467, **14**-468, **16**-2245, **19**-430
Roy, S.C. **10**-1512, **11**-250, **2**-665, **16**-149
Roy, U.V. **15**-2428
Royer, A.C. **15**-1714
Royer, L. **16**-1538
Royo, B. **19**-793, **19**-981
Royo, J. **19**-777
Royzen, M. **15**-151
Rozantsev, E.G. **5**-240, **5**-268
Rozas, I. **8**-14
Rozen, S. **10**-1057, **10**-1099, **11**-571, **12**-111, **12**-145, **14**-149, **14**-153, **14**-154, **14**-156, **15**-1645, **15**-1709, **19**-283, **19**-749, **19**-754
Rozenberg, V.I. **16**-680
Rozental, E. **10**-27, **10**-117, **19**-147
Rozhkov, I.N. **14**-150, **15**-1755
Rozhkov, V.V. **11**-177
Rozsondai, B. **5**-238
Rozwadowska, M.D. **16**-1589
Rozzell, D. **16**-362
Ruan, J. **12**-347, **13**-381
Ruane, M. **17**-74, **17**-81
Ruano, J.L.G. **10**-1946, **15**-1451, **15**-2355
Ruano, M. **10**-1548
Ruasse, M.-F. **19**-788
Ruasse, M. **9**-21, **15**-12, **15**-14, **15**-16, **16**-2270
Ruben Martin, R. **10**-1309
Rubenstein, P.A. **8**-66
Rubiales, G. **16**-1407
Rubin, A.E. **15**-1835
Rubin, M. **10**-1502, **10**-1928, **15**-777, **15**-880, **15**-2582, **15**-2603, **19**-1429
Rubin, M.B. **7**-48, **15**-2542
Rubin, R.M. **18**-677
Rubín, S.G. **15**-851, **15**-2685
Rubina, M. **15**-860, **15**-2603
Rubino, M. **10**-1133
Rubino, M.E **15**-1924
Rubinshtein, B.I. **14**-181
Rubio, E. **15**-372
Rubio, M. **19**-1143
Ruble, J.R. **18**-674
Rubottom, G.M. **12**-165, **14**-275, **16**-858, **19**-10, **19**-301, **19**-507
Rubow, M. **15**-1769, **15**-1770
Rucando, D. **10**-1937
Ruch, R.R. **19**-960
Rüchardt, C. **1**-113, **4**-306, **4**-399, **4**-422, **5**-243, **5**-244, **5**-280, **5**-313, **13**-35, **14**-9, **14**-77, **18**-35, **18**-74, **18**-407, **18**-434, **18**-435, **19**-24, **19**-1545
Ruck, R.T. **5**-403, **5**-406, **15**-1020, **17**-464
Rücker, C. **4**-446, **4**-459, **15**-2289
Rücker, G. **4**-446
Rückert, A. **18**-864
Ruckle Jr., R.E. **12**-221
Rudakov, E.S. **10**-215, **10**-455, **10**-456
Rudchenko, V.F. **4**-43
Rudd, E. **15**-1782
Ruderman, W. **14**-179
Rüdiger, V. **3**-115
Rudkevich, D.M. **12**-733
Rudler, H. **12**-726
Rudloff, I. **14**-307
Rudolph, D.A. **13**-517
Rudolph, J. **15**-1938, **15**-2012, **16**-549, **16**-669, **16**-746, **16**-748, **16**-1656
Rudolph, S. **16**-343
Rudorf, W.-D. **15**-1121
Rudorf, W. **15**-2118, **16**-181, **16**-426, **16**-1306
Rudra Das, A.P. **16**-1788
Rudrawar, S. **10**-964, **10**-965, **16**-210
Rudy, T.P. **14**-133
Rudzinsci, J. **17**-48
Rüedi, G. **18**-613
Rüedi, G. **19**-550
Rueping, M. **10**-1718, **16**-400, **16**-1223, **16**-1530, **18**-643, **18**-748, **19**-1152
Rufa, L. **19**-1721
Rufanov, K.A. **15**-2142
Ruff, F. **10**-33
Ruffo, F. **15**-1170
Rufińska, A. **5**-170
Ruge, B. **7**-49
Rüger, W. **15**-87
Ruggiero, P.L. **15**-1094
Rugmini, P. **15**-1074, **15**-2084, **19**-901
Rühl, T. **5**-146
Ruhlandt-Senge, K. **5**-183
Rühlmann, K. **19**-1708
Ruiz-Pérez, C. **4**-488
Ruiz-Hitzky, E. **10**-723
Ruiz-López, M.F. **10**-1702, **15**-2244
Ruiz, A. **10**-1522
Ruiz, J. **16**-2078
Ruiz, J.R. **13**-643, **18**-383
Ruiz, N. **15**-1401
Ruiz, V.R. **15**-242
Rulíšek, L. **16**-776
Rumthao, S. **10**-913
Runcio, A. **19**-219
Rundel, W. **10**-957
Rundle, R.E. **5**-166
Runge, W. **4**-67
Ruo, T.C.S. **14**-60
Ruoho, A.E. **10**-1066, **10**-1148, **10**-1167, **11**-142, **11**-198,

11-298, **16**-48, **16**-72, **19**-91, **19**-797
Rupilius, W. **15**-1605
Ruppel, J.V. **15**-2516
Rusch, G.M. **18**-172
Rush, D.J. **4**-314, **4**-320
Rusiniak, L. **15**-2513
Ruske, W. **11**-557, **11**-561
Russ, M. **16**-2001
Russel, G.A. **18**-68
Russell-Maynard, J.K.L. **10**-1113
Russell-King, J. **18**-22, **18**-102
Russell, A.E. **19**-1733
Russell, A.T. **16**-1330
Russell, C.J. **16**-1155
Russell, C.R. **5**-137
Russell, G.A. **5**-336, **10**-1396, **11**-353, **12**-751, **13**-753, **14**-52, **14**-77, **14**-105, **14**-107, **14**-135, **14**-207, **14**-248, **14**-426, **15**-500, **19**-1734, **19**-1765
Russell, J.A. **10**-104
Russell, K.E. **13**-4
Russell, R.A. **19**-79
Russell, R.K. **2**-283
Russell, R.L. **11**-175
Russell, S.W. **19**-50
Russell, T. **16**-559
Russey, E. **19**-1234
Russo, A. **19**-490
Russo, B. **16**-92
Russo, F. **16**-1952
Russo, M. **15**-232
Rutar, I. **15**-1697
Ruther, F. **19**-450
Rutherford, D.R. **13**-22
Rutherford, J.L. **5**-191, **6**-37, **8**-216, **8**-224, **13**-727, **13**-729
Rutjes, F.P.J.T. **18**-834
Rutledge, P.S. **12**-169, **14**-473, **15**-1682, **15**-1715, **15**-1733, **15**-1734, **15**-1759, **15**-1764, **15**-1822
Rüttimann, A. **17**-417
Ruwet, M. **17**-180
Růžička, A. **16**-1993
Ruzicka, L. **15**-817, **16**-2168, **16**-2168, **18**-113
Ruzsicska, B.P. **5**-385
Ruzziconi, R. **10**-1522, **17**-33, **17**-36, **17**-54, **17**-116, **19**-822
Ryabov, A.D. **13**-367
Ryabova, K.G. **10**-1975
Ryabova, V. **13**-318, **13**-609
Ryan, J. **15**-843
Ryan, K.M. **15**-1983
Ryan, P.W. **15**-581
Ryang, H.S. **14**-137
Ryang, M. **12**-558, **13**-688, **15**-1459
Ryba, T.D. **19**-881
Rybachenko, V.I. **8**-103
Rybakova, N.A. **11**-560
Ryberg, P. **17**-41
Rybinskaya, M.I. **2**-160, **10**-258
Rychly, J. **14**-6, **14**-7
Rychnovsky, S.D. **4**-370, **4**-383, **5**-147, **5**-266, **5**-292, **14**-95, **15**-919, **15**-1040, **16**-1554, **16**-1565, **18**-640, **19**-166
Rychtman, A.C. **8**-1
Rydon, H.N. **10**-1157
Rylander, P.N. **14**-281, **14**-487, **15**-428, **15**-433, **15**-440, **15**-489, **15**-663, **16**-318, **19**-13, **19**-845, **19**-863, **19**-927, **19**-1057, **19**-1081, **19**-1122, **19**-1181, **19**-1230, **19**-1299, **19**-1333
Ryou, S.S. **14**-76
Rys, P. **11**-29, **11**-99
Rytting, J.H. **3**-113
Ryu, D.H. **15**-2196, **16**-1173, **16**-1497, **16**-1514
Ryu, E.K. **10**-641, **17**-432
Ryu, H.-C. **10**-1714, **13**-324, **13**-556, **13**-622, **13**-692
Ryu, I. **10**-1982, **10**-1996, **12**-558, **13**-597, **13**-684, **13**-688, **14**-25, **15**-304, **15**-321, **15**-1355, **15**-1372, **15**-1486, **15**-2075, **16**-2004, **19**-53, **19**-580, **19**-593
Ryu, J.-S. **15**-353, **15**-2024
Ryu, S.R. **19**-884
Ryu, Z.H. **10**-435, **16**-1615
Ryzhkov, L.R. **5**-312
Rzasa, R.M. **15**-2320
Rzepa, H.S. **2**-374, **2**-375, **15**-2306

Saá, C. **15**-851, **15**-2627, **15**-2685, **15**-2688
Saá, J.M. **12**-410, **13**-244, **16**-1217, **19**-245
Saadioui, M. **3**-144
Saalfrank, R.W. **15**-1992
Saavedra, J.E. **4**-228, **12**-733
Sabacky, M.J. **5**-245, **15**-454
Sabarre, A. **15**-309
Sabat, M. **15**-2027, **15**-2260
Sabater, M.J. **15**-242
Sabek, O. **11**-107
Sabel, A. **19**-699
Sabesan, A. **16**-531
Sabharwal, A. **19**-451
Sabila, P. **19**-1542
Sabin, J.R. **3**-61
Sabitha, G. **10**-1003, **10**-970, **10**-984, **16**-1401, **16**-782, **19**-992
Sablier, M. **5**-216
Sabo-Etienne, S. **19**-1167
Sabol, M.A. **4**-30, **16**-2271
Sabol, M.R. **19**-452
Sabot, C. **16**-1937
Sabourault, N. **15**-767
Saburi, H. **10**-1189
Sacchetti, G. **19**-842
Sacha, H. **16**-1058
Sachdev, H.S. **17**-425
Sachdeva, R. **5**-317
Sacher, E. **1**-46
Sachs, D.H. **19**-1302
Sachs, F. **16**-1310
Sacks, C.E. **16**-76
Sackur, O. **18**-215
Sada, M. **16**-1430
Sadakane, M. **16**-2242
Sadakari, N. **2**-324
Sadalai, A. **19**-730
Sadashiv, K. **10**-705, **13**-167
Sadasivam, D.V. **15**-1363
Sadavarte, V.S. **10**-1170, **10**-803, **11**-448, **16**-1707, **16**-1787, **16**-1790, **19**-944
Sadayori, N. **10**-1625
Sadd, J.S. **5**-364
Sadeghi, M.M. **10**-924, **16**-68, **19**-30, **19**-31
Sadeghi, M.M.M. **12**-139
Sadeghipour, M. **14**-323
Sadek, P.C. **11**-339
Sadekov, I.D. **3**-49
Sadhu, K.M. **10**-1878, **16**-1459
Sadighi, J.P. **13**-315, **15**-1648
Sadílek, M. **2**-463
Sadlej, J. **4**-311
Sadow, A.D. **15**-1426
Sadowski, J.S. **13**-128
Sadri, A.R. **11**-637
Sadun, C. **15**-1895
Sadykov, A.S. **13**-468
Sadykov, R.A. **15**-1750
Saebo, S. **16**-667
Saeed, M.A. **17**-132
Saegusa, T. **10**-958, **14**-484, **15**-1632, **15**-2576, **19**-820, **19**-1742
Saejueng, P. **12**-305
Saeki, H. **16**-1766
Saeki, N. **16**-1423
Saeki, T. **13**-624
Saeki, Y. **10**-289, **10**-290, **10**-434, **10**-471, **10**-472
Saengchantara, S.T. **18**-517
Saenger, W. **3**-183, **3**-187, **3**-188, **16**-1623
Saenger, W.V. **3**-183
Sæthre, L.J. **11**-42, **11**-47, **15**-97
Saettel, N.J. **15**-2197
Sáez, J.A. **15**-2282
Safaei, H.R. **19**-781
Safaei, S. **19**-91
Safarov, M.G. **16**-1546, **16**-1549
Safarowsky, O. **3**-193
Safavy, K.K. **10**-70
Saferstein, R. **10**-121
Saffert, A. **19**-477
Safont, V.S. **15**-2242
Sagal, J.F. **10**-1160
Sagar, A.D. **19**-313
Sagatys, D.S. **17**-162
Sagdeev, R.Z. **10**-1395
Saggio, G. **18**-873

Saha-Möller, C. **15**-1883
Saha-Moller, C.R. **15**-1912, **15**-1980, **15**-1916, **15**-1987, **19**-200, **19**-230, **19**-474, **19**-476, **19**-477
Saha, A. **19**-1542
Saha, C. **12**-425
Saha, D. **13**-497
Saha, J.G. **11**-72, **13**-831
Saha, M. **11**-248, **15**-1129
Saha, P. **13**-149, **16**-1214
Sahab, S. **17**-236
Sahai, M. **16**-1985
Sahali, Y. **15**-2459
Sahamieh, R.Z. **11**-659
Sahara, T. **19**-946, **19**-1131
Sahasrabudhe, K. **18**-324
Sahle-Demessie, E. **15**-1892, **15**-1893
Sahli, A. **19**-697
Sahli, M.S. **17**-132
Sahoo, A.K. **13**-705
Sahu, P.R. **10**-584, **16**-212
Sahu, S.G. **10**-1673
Sahyun, M.R.V. **17**-85, **17**-262, **19**-1412
Saicic, R.N. **10**-1645
Saidi, M.R. **10**-959, **10**-966, **10**-1650, **15**-1450, **16**-1224, **19**-236, **19**-897, **19**-1673
Saidi, O. **12**-347, **13**-381
Saiganesh, R. **11**-268
Saigo, K. **16**-232, **16**-579, **16**-842, **16**-843, **16**-1174, **18**-130
Saikia, A.K. **16**-1751, **16**-1804
Saikia, P. **10**-868, **16**-2110
Saikia, P.P. **16**-1213
Saimoto, H. **14**-443
Sain, B. **15**-2064, **15**-2077, **15**-2386, **15**-2561, **16**-369, **16**-2216, **19**-123, **19**-237, **19**-761, **19**-762, **19**-764
Saindane, M. **16**-519
Saini, R. **19**-787
Saini, R.K. **19**-110, **19**-201, **19**-774, **19**-886
Sainsbury, D.M. **10**-192
Saint-Clair, J.-F. **13**-519
Saint, R.E. **12**-388
Saint, S.L. **12**-388
Saiparakash, P.K. **11**-126
Saisho, H. **11**-533
Saito, A. **10**-1522, **15**-204, **16**-941, **18**-328
Saito, B. **10**-1498, **15**-1206, **19**-800
Saito, E. **16**-423
Saito, H. **15**-814
Saito, I. **15**-2358, **15**-2360, **19**-59
Saito, K. **10**-316, **16**-580, **16**-1533, **18**-130, **18**-328
Saito, N. **11**-577, **15**-806
Saito, S. **2**-458, **4**-285, **4**-313, **11**-329, **11**-420, **11**-421, **14**-312, **15**-971, **15**-1509, **15**-2275, **15**-2327, **15**-2377, **15**-2615, **15**-2640, **16**-101, **16**-885, **16**-1074, **16**-1091, **16**-1105, **16**-1191, **17**-166, **17**-288, **18**-738, **19**-948
Saito, T. **10**-624, **10**-813, **10**-1592, **10**-1594, **10**-1726, **14**-268, **15**-1802
Saito, Y. **10**-184
Saitoh, T. **10**-711, **12**-728, **15**-306, **19**-943
Saiz, J.L. **8**-144
Sajiki, H. **11**-686, **11**-694, **12**-263, **13**-589, **14**-356, **15**-438, **19**-499, **19**-1355, **19**-1356
Sajimon, M.C. **7**-66, **7**-67
Sajus, L. **19**-675
Sakaba, A. **13**-503
Sakabe, M. **13**-11
Sakabe, Y. **12**-648
Sakaguchi, K.-e. **10**-1540
Sakaguchi, S. **10**-621, **11**-536, **11**-577, **12**-216, **12**-217, **13**-386, **13**-407, **15**-204, **15**-388, **15**-656, **15**-794, **15**-1175, **15**-1302, **15**-1521, **15**-1995, **16**-1518, **16**-326, **16**-2181, **18**-341, **19**-306, **19**-546
Sakai, D. **10**-1709, **16**-1596
Sakai, H. **15**-1646
Sakai, M. **11**-672, **12**-575, **13**-283, **15**-1452, **18**-899, **18**-902
Sakai, N. **13**-590, **15**-1614, **15**-346, **16**-547, **19**-685, **19**-1448, **19**-1477
Sakai, S. **19**-895
Sakai, T. **15**-1395, **19**-993
Sakajiri, T. **10**-615
Sakaki, S. **16**-1220
Sakakibara, H. **16**-643
Sakakibara, K. **9**-76, **11**-537
Sakakibara, N. **15**-839, **18**-835, **18**-885
Sakakibara, Y. **12**-575, **13**-281, **13**-283, **13**-295
Sakakura, A. **16**-1727, **16**-1742
Sakakura, T. **10**-2010, **10**-2012, **11**-535, **14**-407, **19**-56
Sakamoto, K. **16**-912
Sakamoto, M. **4**-171, **10**-1522, **13**-496, **13**-496, **16**-1793
Sakamoto, S. **3**-195, **5**-167, **16**-1085, **19**-1654
Sakamoto, T. **7**-87, **11**-577, **11**-191, **11**-193, **11**-342, **11**-577, **13**-286, **13**-452, **15**-199, **15**-370
Sakamura, H. **19**-1171
Sakane, S. **18**-367
Sakat, S. **16**-2054
Sakata, G. **16**-275
Sakata, Y. **2**-302, **2**-325, **15**-1692, **15**-1955, **19**-132
Sakate, S.S. **16**-1632
Sakavuyi, K. **16**-324
Sakizadeh, K. **10**-89, **10**-91, **10**-416
Sakthivel, S. **16**-1214
Sakuma, K. **8**-220
Sakuma, S. **15**-1271
Sakuraba, H. **16**-1247
Sakurada, I. **15**-1694, **15**-2030
Sakuragi, H. **6**-14
Sakuragi, R. **15**-911
Sakurai, H. **4**-524, **4**-539, **5**-258, **5**-262, **10**-1325, **11**-427, **13**-721, **15**-1210, **15**-1246, **16**-1062, **19**-1346
Sakuratani, K. **19**-182
Saladino, R. **15**-1895
Salagre, P. **18**-305
Salahuddin, S. **19**-1250
Salakhutdinov, N.F. **11**-92
Salaman, A.M. **16**-419
Salamone, M. **5**-324, **14**-15, **14**-117, **18**-55
Salaris, M. **16**-1901, **17**-484
Salas, G. **10**-1463
Salaskar, A. **16**-846
Salaun, J. **16**-142, **18**-160, **19**-1702
Salaun, J.R. **18**-217
Salbaum, H. **16**-1404
Sale, A.A. **10**-675
Salehi, P. **10**-674, **10**-923, **16**-2171, **18**-343, **19**-81, **19**-85, **19**-835
Salehzadeh, S. **12**-739
Salem, G. **10**-1357, **12**-604, **12**-611, **15**-977
Salem, L. **7**-43
Salem, M.R. **16**-1188
Salem, R.B. **15**-998, **16**-1525
Salerno, G. **12**-770, **15**-243, **15**-316
Sales, M. **16**-1072, **16**-1509
Salfeld, J.C. **13**-477
Salguero, T.T. **18**-895
Salih, K.S.M. **15**-409
Salinger, R. **5**-109, **8**-69
Salinger, R.M. **5**-165, **12**-599
Saller, H. **2**-60
Salmon-Legagneur, F. **18**-131
Salmón, M. **10**-1330
Salmond, W.G. **1**-24
Salomaa, P. **10**-536, **10**-617, **10**-677, **10**-776, **10**-1121, **16**-82, **16**-1767
Salomé, C. **16**-1757
Salomon, C. **15**-1607
Salomon, C.J. **18**-314
Salomon, M.F. **10**-772
Salomon, R.G. **10**-772, **10**-1583, **11**-390, **19**-430
Salomone, A. **16**-498
Salomone, R.A. **16**-2239
Salov, B.V. **13**-117
Salter, K.M. **10**-975
Saltiel, J. **7**-58

Salunkhe, A.M. **12**-548
Salunkhe, M.M. **11**-211, **11**-400, **11**-592, **16**-1230, **16**-1647, **19**-313
Saluzzo, C. **10**-1191, **15**-892, **16**-2050
Salvador, L.A. **5**-57
Salvadori, P. **4**-121, **15**-1832
Salvataore, R.N. **17**-236
Salvatella, L. **15**-2238, **15**-2244
Salvatore, R.N. **10**-812, **10**-849, **10**-889, **10**-891, **10**-920, **10**-1021, **16**-1976
Salvino, J.M. **8**-216
Salzbrunn, S. **13**-106
Salzer, A. **5**-152
Salzmann, T.N. **17**-297
Salzner, U. **4**-385, **4**-386, **4**-388
Sam, D.J. **10**-493, **19**-375
Samajdar, S. **16**-193, **16**-254, **19**-216
Samal, A.K. **10**-886
Samanich, D. **15**-1814
Samant, S.D. **11**-299, **13**-385, **16**-1890, **19**-616
Samanta, A. **7**-24
Samanta, S. **7**-35, **10**-835, **15**-611, **15**-613, **16**-554, **16**-1084, **16**-1084, **16**-1220, **19**-905, **19**-1321
Samanta, T. **19**-92, **19**-94
Sambri, L. **10**-616, **10**-972, **10**-1125, **11**-314, **11**-483, **15**-1065, **15**-1106, **15**-1182, **15**-1388, **16**-610, **16**-1723, **17**-164, **19**-969
Samec, J.S.M. **19**-1133
Sames, D. **10**-1890, **11**-323, **12**-691, **13**-316, **13**-517, **15**-759, **19**-280
Samii, Z.K.M.A.E. **15**-2004
Samimi, H.A. **19**-244
Samkoff, N. **13**-821
Sammakia, T. **10**-570
Sammelson, R.E. **17**-265
Sammes, M.P. **17**-506
Sammes, P.G. **10**-1042, **15**-992, **16**-1381
Sammis, G.M. **15**-800
Sammonds, L. **16**-1066
Samoilov, D.V. **6**-9
Samoilova, N.A. **16**-1929
Samoilova, R. **5**-276
Samokhvalov, G.I. **15**-65
Samoshin, V.V. **4**-346, **4**-373
Sampedro, D. **15**-2655, **18**-617
Sample Jr., T.E. **15**-2279
Sampson, P. **16**-492
Samsel, E.G. **15**-502
Samuel, C.J. **18**-913
Samuel, D. **13**-846
Samuel, P.A. **18**-428
Samuelson, A.G. **3**-41
Samuelsson, B. **10**-1150, **10**-1677, **19**-753
Samuni, U. **19**-348, **19**-368
San Filippo Jr., J. **10**-771, **10**-1423, **11**-618, **14**-178, **14**-420, **18**-798, **18**-800, **19**-89
Sanada, T. **13**-713
Sanbri, L. **15**-910
Sancassan, F. **4**-326, **4**-397, **8**-183
Sanchez-Jimenezy, G. **12**-441
Sánchez-Baeza, F. **19**-371
Sanchez Jr., G.V. **11**-324, **15**-2622
Sanchez, A.M. **11**-595
Sánchez, B. **15**-1320
Sanchez, B.L. **13**-852
Sanchez, C. **16**-1771
Sánchez, F. **10**-757
Sánchez, L.R. **10**-146
Sanchez, M. de N de M. **16**-29
Sanchez, R. **16**-244, **16**-1926
Sanchez, R.A. **16**-1542
Sançon, J. **18**-781
Sanda, J.C. **4**-523
Sandall, J.P.B. **11**-104, **11**-616
Sandefur, B.J. **10**-920
Sandefur, L.O. **15**-1166
Sander, G.E. **16**-1978
Sander, M.R. **11**-597
Sander, W. **4**-498, **5**-71, **5**-217, **5**-434, **19**-351
Sanderfer, P.O. **17**-503
Sanders, A.W. **5**-181, **5**-185
Sanders, C.J. **15**-2045, **15**-2070
Sanders, D.P. **18**-858, **18**-860
Sanders, W.J. **15**-291
Sanderson, A. **6**-37
Sanderson, J.R. **17**-520, **17**-522, **17**-523, **17**-524
Sanderson, R.T. **1**-26, **1**-27
Sanderson, W.R. **15**-1931
Sandford, G. **10**-640, **11**-312, **16**-446
Sandhu, J.S. **10**-868, **15**-2386, **16**-375, **16**-1236, **16**-1244, **16**-1309, **16**-2030, **16**-2110, **16**-2216, **18**-350, **19**-295, **19**-1256, **19**-1413, **19**-1537, **19**-1730
Sandler, S.R. **10**-778, **18**-175
Sandlers, Y. **10**-34
Sandorfy, C. **3**-3
Sandoval, C.A. **19**-1014, **9**-1017
Sandri, J. **10**-1158
Sandri, S. **19**-89
Sandrinelli, F. **12**-248
Sandro Cacchi, S. **15**-906
Sandrock, D.L. **11**-549, **13**-573
Sandrock, G. **10**-78
Sands, R.D. **9**-11
Sandström, J. **4**-236, **4**-237, **4**-283, **4**-526, **4**-536
Sandström, M. **8**-161
Sandu, J.S. **10**-1482, **16**-977, **19**-1669
Sanematsu, F. **10**-73
SanFilippo, L.J. **17**-516, **17**-526
Sanford, M.S. **13**-136, **13**-444, **14**-197, **18**-891, **19**-463, **19**-525
Sang, X. **10**-883
Sangani, P.K. **19**-575
Sanger, F **13**-185
Sangi, M.S. **13**-506
Sangiorgi, C. **18**-327
Sangster, D.F. **14**-218
Sangu, K. **15**-2601
Sankar, G. **11**-579
Sankaranarayanan, J. **16**-1408
Sankararaman, S. **11**-104, **16**-1139, **18**-137
SanMartin, R. **15**-2099
Sannicolo, F. **18**-761
Sano, A. **14**-11
Sano, H. **10**-1970
Sano, T. **10**-1042
Sanrame, C. N. **5**-119
Sansano, J.M. **15**-917, **15**-2114
Sanseverino, A.M. **15**-1704
Sansone, E.B. **19**-1223
Sansottera, G. **19**-993
Sansoulet, J. **16**-1646, **17**-309
Santa, L.E. **16**-473
Santaballa, J.A. **12**-83
Santacruz-Juárez, E. **10**-1231
Santagostino, M. **13**-284, **19**-190, **19**-191
SantaLucia, Jr., J. **16**-1766
Santamaria, J. **14**-242
Santana, M. **19**-1418
Santaniello, E. **15**-535, **16**-1795, **19**-89, **19**-425
Santarsiero, B.D. **15**-12
Santella, N. **18**-634
Santelli, M. **10**-1706, **10**-1765, **10**-1882, **13**-49, **13**-382, **13**-409, **13**-429, **13**-528, **13**-590, **13**-607, **14**-363, **15**-806, **15**-2373, **16**-647, **16**-1910, **19**-1683
Santhi, V. **19**-1020
Santi, C. **10**-694, **10**-1522, **15**-234
Santi, R. **13**-652
Santiago, A.N. **10**-105
Santiago, B. **10**-1877, **12**-349
Santiago, C. **11**-29
Santiago, M.V. **18**-935
Santinelli, F. **15**-1968
Santini, S. **11**-497
Santo, K. **16**-1494
Santoni, G. **16**-1363
Santora, B.P. **15**-442
Santos, A.G. **15**-2231, **16**-801
Santos, L.L. **15**-242
Santos, L.S. **12**-292, **16**-1412
Santos, M. **11**-269
Santos, P.P. **15**-185
Santos, R.C.D. **15**-2126
Santos, R.P. **15**-1198
Santosusso, T.M. **19**-632
Santra, M. **10**-2008

Santry, L.J. **16**-29
Sanuki, R. **15**-643
Sanyashi, S. **16**-1214
Sanz-Tejedor, A. **11**-269
Sanz, D. **2**-479
Saotome, H. **10**-1522
Sapountzis, I. **13**-233, **16**-470
Sapra, P. **13**-183
Saracoglu, N. **10**-598
Saraiva, M.F. **18**-928
Sarancha, V.N. **10**-1137
Sarandeses, L.A. **10**-1480, **10**-1490, **10**-1549, **13**-337, **15**-1212
Sarapa, D. **10**-576
Saravanan, P. **16**-153, **16**-1723
Saravanan, V. **16**-1851
Saravanani, P. **11**-341
Sarda, P. **19**-1342
Sardina, F.J. **5**-195
Sarel-Imber, M. **10**-205
Sarel, S. **10**-205, **15**-145
Sargent, G.D. **10**-186, **15**-29, **18**-104
Sargent, M.V. **2**-99, **2**-300, **18**-401
Sarich, M. **11**-521
Saritha, B. **10**-866, **16**-802
Sarkar, A. **10**-1293, **10**-1878, **13**-495, **15**-653, **16**-348, **16**-1627, **17**-376
Sarkar, A.R. **19**-1037
Sarkar, B.R. **15**-1499
Sarkar, D.C. **16**-50, **16**-1625, **19**-916
Sarkar, N. **15**-2344
Sarkar, S.D. **19**-173
Sarkar, T.K. **13**-613, **16**-1558
Sarkar, U. **10**-38
Sarkice, A.Y. **8**-132
Sarlah, D. **15**-2255, **18**-820
Sarma, D.N. **17**-206
Sarma, J.C. **16**-332, **17**-334
Sarma, K. **15**-1861
Sarma, K.D. **11**-685
Sarmah, G.K. **19**-222
Sarmah, P. **10**-1171
Sarner, S.F. **17**-495
Sarpong, R. **15**-1083
Sarshar, S. **15**-2243
Sartamaría, J. **15**-2206
Sarthou, P. **10**-520
Sartillo-Piscil, F. **10**-1231
Sartori, G. **11**-386, **11**-389, **11**-416, **11**-430, **11**-519, **11**-526, **15**-1930, **16**-212, **16**-1202, **19**-466
Sartorio, R. **15**-1930
Sarussi, S.J. **19**-987, **19**-1193
Sarvari, M.H. **11**-438, **11**-457, **16**-284, **16**-296, **17**-441, **17**-445
Sarvestani, M. **19**-1542
Sarzi-Amadè, M. **15**-1874, **15**-1876, **15**-1879, **19**-483
Sasabe, H. **3**-192
Sasahara, T. **12**-648
Sasai, H. **15**-1913, **16**-955, **16**-1051
Sasaki, H. **10**-1877, **16**-1938
Sasaki, K. **11**-672, **12**-575, **13**-281, **13**-482, **13**-872, **14**-223, **14**-227, **16**-1062, **19**-611, **19**-978
Sasaki, M. **10**-1627, **10**-1949, **16**-199, **18**-964
Sasaki, R. **16**-448, **16**-1420
Sasaki, S. **16**-1992
Sasaki, T. **10**-1358
Sasaki, Y. **3**-143, **10**-1762, **15**-281
Sasakura, K. **11**-391, **11**-558, **11**-559, **16**-1102
Sasaoka, M. **2**-448, **14**-201
Sasaoka, S. **10**-1509, **19**-1235
Sase, S. **10**-1456
Sashima, M. **18**-369
Sashiwa, H. **14**-443
Sasidharan, M. **17**-156
Sasmal, P.K. **16**-1072
Sassaman, M.B. **16**-166, **19**-1495
Sasse, M.J. **19**-1216
Sasson, R. **19**-283
Sasson, S. **15**-2310
Sasson, Y. **10**-489, **10**-1130, **10**-489, **10**-628, **10**-723, **10**-1073, **11**-139, **11**-260, **11**-510, **14**-102, **17**-309, **19**-837
Sastry, G.N. **2**-401, **2**-402, **10**-348, **16**-8
Sastry, K.A.R. **12**-520
Sastry, M.N.V. **15**-1444, **15**-1445
Sastry, V.V.S.K. **16**-875
Satchell, D.P.N. **8**-161, **10**-554, **10**-578, **10**-580, **11**-478, **11**-561, **12**-311, **12**-315, **15**-180, **15**-200, **15**-268, **16**-16, **16**-171, **16**-172, **16**-370, **16**-414, **16**-1616, **16**-1617, **16**-1618, **16**-1619, **16**-1832, **16**-1856, **16**-1955
Satchell, R.S. **8**-161, **10**-554, **10**-580, **12**-311, **12**-315, **15**-180, **15**-200, **15**-268, **16**-16, **16**-171, **16**-172, **16**-370, **16**-414, **16**-1955
Sathaiah, G. **16**-1865
Sathe, S.S. **15**-2575
Satheesh, G. **10**-1626
Sathyamurthy, N. **7**-35
Sathyanarayana, B.K. **4**-129, **4**-150
Satish, A.V. **8**-94
Sato, A. **10**-1497, **15**-787, **16**-908, **18**-585, **18**-737
Sato, F. **10**-1449, **12**-562, **14**-423, **15**-840, **15**-854, **15**-889, **15**-976, **15**-2382, **15**-2592, **15**-2647
Sato, H. **15**-2221, **16**-1126
Sato, K. **12**-496
Sato, K.-I. **15**-304, **15**-321
Sato, K. **3**-15, **10**-695, **11**-551, **13**-55, **13**-479, **15**-563, **15**-1468, **15**-1774, **15**-1800, **18**-775, **19**-677, **19**-681
Sato, M. **10**-1449, **10**-1876, **12**-562, **13**-399, **13**-451, **13**-535, **13**-597, **14**-423, **15**-735, **15**-1259, **15**-1998, **15**-2046, **16**-1507, **16**-1582
Sato, N. **13**-300, **16**-1537
Sato, O. **13**-399, **18**-128
Sato, S. **7**-62, **11**-214, **19**-1371
Sato, T. **6**-4, **10**-742, **10**-834, **10**-1588, **12**-309, **15**-156, **15**-532, **15**-715, **15**-793, **15**-1050, **15**-1197, **15**-1312, **15**-1347, **16**-196, **16**-967, **16**-1114, **16**-1723, **16**-2020, **18**-398, **18**-551, **18**-786, **19**-654, **19**-1053, **19**-1094
Sato, Y. **10**-1522, **10**-1531, **11**-113, **13**-850, **13**-852, **15**-209, **15**-806, **15**-1201, **15**-2599, **15**-2639, **15**-2683, **16**-705, **16**-2243, **18**-885
Satoh, A. **11**-556
Satoh, H. **14**-401, **15**-1556
Satoh, J.Y. **12**-170, **12**-182, **15**-1821
Satoh, M. **10**-1877
Satoh, T. **10**-1596, **10**-1995, **11**-260, **13**-329, **14**-189, **15**-845, **15**-2596, **16**-1276, **18**-203, **19**-1163
Satoh, Y. **15**-1259, **16**-735, **16**-2222, **18**-299
Satsumabayashi, K. **12**-116, **19**-482
Sattely, E.S. **18**-829, **18**-845
Sattur, P.B. **16**-2234
Satyamurthy, N. **10**-1115
Satyanarayana, T. **16**-785
Satyender, A. **16**-1788
Sauer, E.L.O. **10**-1638
Sauer, G. **16**-1120
Sauer, J. **13**-93, **13**-258, **15**-, **15**-2184, **15**-2280, **15**-2289, **15**-2294, **15**-2350
Sauermann, D. **15**-1674
Sauermann, G. **5**-154, **5**-160
Sauers, R.R. **5**-60, **5**-366, **5**-389, **5**-421, **5**-423, **8**-167
Saugé, L. **19**-1605
Saullo, P. **10**-442
Saulnier, M.G. **10**-883
Saunders Jr., W.H. **6**-66, **12**-94, **10**-424, **17**-3, **17**-8, **17**-28, **17**-29, **17**-30, **17**-34, **17**-61, **17**-64, **17**-68, **17**-87, **17**-88, **17**-94, **17**-100, **17**-105, **17**-178, **17**-246, **17**-392, **18**-309, **18**-310, **18**-693, **18**-931, **19**-812
Saunders, D.G. **5**-293
Saunders, Jr., W.H. **17**-6
Saunders, M. **2**-260, **2**-406, **4**-360, **4**-483, **5**-2, **5**-21, **5**-103, **5**-104,

10-194, **10**-213, **10**-1016, **18**-2, **18**-8, **18**-22, **18**-27, **18**-49, **18**-546, **18**-677
Saupe, T. **8**-198, **8**-199, **8**-200
Saus, A. **19**-1776
Saussine, L. **15**-1917
Sauter, F. **11**-684
Sauthier, M. **15**-1574
Sauvage, J.-P. **3**-191, **3**-207, **3**-210, **3**-211, **3**-217, **3**-218, **4**-251
Sauvage, J. **19**-1715
Sauve, D.M. **15**-497, **16**-633
Savarin, C. **13**-158, **13**-623
Savarin, C.G. **16**-998
Savéant, J.-M. **5**-319, **10**-67, **13**-57, **13**-61
Savéant, J. **10**-101, **13**-57, **13**-59, **13**-63, **13**-94
Savedoff, L.G. **10**-353
Savelli, G. **10**-438, **10**-725, **11**-497, **15**-1817, **15**-1968, **19**-273
Savelova, V.A. **16**-2286, **16**-2301
Savenko, T.V. **15**-1878
Savige, W.E. **19**-768
Savignac, M. **15**-1008, **19**-1600
Savile, C.K. **4**-186
Saville, B. **10**-862, **12**-749
Savin, V.I. **4**-45
Savinykh, Yu.V. **10**-332
Savle, P.S. **15**-1993
Sävmarker, J. **12**-282
Savoia, D. **12**-727
Sawa, Y. **15**-1459
Sawada, A. **19**-1285
Sawada, M. **10**-73, **10**-183, **10**-346
Sawada, S. **4**-480
Sawada, T. **10**-537, **15**-2528
Sawada, Y. **15**-1886, **18**-964
Sawaguchi, M. **10**-1102, **10**-1103, **15**-1646
Sawaki, R. **16**-705
Sawaki, Y. **15**-1948, **18**-405, **19**-311, **19**-370
Sawama, Y. **10**-573
Sawamoto, H. **15**-1193
Sawamura, M. **10**-1884
Sawant, D.N. **13**-615
Sawistowska, M.H. **15**-511
Sawyer, D.T. **19**-485
Sawyer, J.R. **15**-868
Sawyer, J.S. **12**-598, **13**-181, **15**-2578
Sawyer, R. **10**-670, **19**-619
Saxena, I. **16**-332
Saxena, M.P. **19**-337
Saxena, N. **19**-553
Saxton, R.G. **2**-264
Sayal, P.K. **19**-451
Sayce, I.G. **19**-5
Sayed, S.H. **15**-1863
Sayer, J.M. **16**-83, **16**-289, **16**-290
Saygili, N. **11**-422
Sayigh, A. **10**-15
Sayo, N. **19**-1016
Sayrac, T. **14**-280
Sayre, L.M. **12**-41
Sayyed, F.B. **2**-25
Sayyed, I.A. **13**-162
Sbarbati, N.E. **12**-563
Scaiano, J. **7**-1
Scaiano, J.C. **5**-119, **5**-299, **7**-1, **7**-51, **14**-239, **18**-73
Scalzi, F.V. **12**-176
Scamehorn, R.G. **13**-654, **18**-207
Scammells, P.J. **19**-1606
Scanio, M.J.C. **15**-2676
Scanlan, E.M. **14**-17, **15**-519
Scannon, P.J. **8**-76, **8**-81
Scapecchi, S. **10**-691
Scardovi, N. **15**-230
Scarpati, R. **15**-2115
Scarpello, J.T. **13**-387
Scarpi, D. **15**-1084, **16**-680
Scartozzi, M. **15**-401
Scettri, A. **15**-1683, **15**-1967, **16**-773, **16**-776, **19**-81, **19**-712
Schaad, L.J. **2**-119, **2**-248, **3**-3
Schaaf, T.K. **15**-1711
Schaal, W. **7**-126
Schaap, A. **10**-1617, **15**-2364
Schaap, A.P. **15**-2369
Schaart, B.J. **12**-633
Schaasberg-Nienhuis, Z.R.H. **11**-202
Schacherer, L.N. **14**-19, **19**-1387
Schachtschneider, J.H. **18**-535
Schade, C. **5**-74, **5**-138, **5**-15312 -418, **12**-578, **15**-1769
Schade, G. **16**-1341
Schade, M.A **10**-1463
Schade, O. **5**-217
Schade, P. **2**-351
Schädler, H.D. **17**-478
Schadt, F.L. **10**-171, **10**-175, **10**-298, **10**-452, **10**-464
Schaefer III, H.F. **1**-1, **1**-29, **1**-84, **2**-67, **2**-110, **2**-191, **2**-219, **2**-220, **2**-279, **2**-280, **2**-289, **2**-290, **2**-473, **4**-290, **5**-352, **5**-358, **5**-413, **5**-415, **7**-17, **11**-35, **11**-226, **15**-11, **16**-1955
Schaefer, A.D. **16**-1962
Schaefer, F.C. **16**-14, **16**-178
Schaefer, J.P. **2**-181, **13**-259, **16**-1483, **16**-2138, **19**-587
Schaefer, T. **3**-60
Schaefer, W. **4**-525
Schaeffer, M.W. **3**-77
Schaeffer, W.D. **4**-23, **10**-428
Schäfer, G. **10**-461, **10**-477
Schäfer, H. **14**-461, **18**-442, **19**-95
Schäfer, H.J. **14**-175, **14**-456, **15**-2180, **17**-514, **19**-586
Schäfer, L. **3**-35
Schäfer, U. **17**-512
Schäfer, W. **4**-511, **15**-2465, **15**-2466, **15**-2469, **18**-529
Schaffers, T. **18**-668
Schaffner, A.-P. **14**-17, **14**-21
Schäffner, B. **13**-98
Schaffner, K. **18**-915, **18**-919, **18**-922
Schaffrodt, H. **18**-19
Schakel, M. **10**-739, **15**-44, **18**-625
Schaller, G.R. **4**-54
Schaller, H.F. **10**-39, **10**-48
Schaller, J. **15**-2235
Schaller, R. **16**-1982, **16**-2158
Schaller, R.J. **2**-372
Schallner, O. **5**-90
Schaltegger, A. **18**-199
Schambach, R.A. **11**-654
Schamlz, H.-G. **15**-1064
Schamp, N. **16**-1280
Schank, K. **10**-773, **10**-863, **13**-772, **16**-2150, **19**-785
Schapiro, V. **15**-2441
Schareina, T. **13**-288
Scharf, D.J. **15**-2575
Scharf, G. **11**-676
Scharf, H. **15**-2184
Schat, G. **12**-596, **12**-614
Schatz, B. **18**-759
Schatz, J. **15**-2350
Schaub, B. **16**-5, **16**-1384, **16**-1388
Schaub, F. **15**-1133
Schauble, J.H. **15**-1669, **19**-710
Schauer, D.J. **16**-1370
Schaumann, E. **15**-2441, **16**-2, **16**-2217, **16**-2218
Schaus, J.V. **12**-280
Schaus, S.E. **10**-1950, **16**-398, **16**-737, **16**-751
Scheer, J.C. **17**-138
Scheeren, H.W. **15**-2228
Scheeren, J.W. **15**-2398, **16**-219, **16**-2203
Scheffer, A. **15**-1910, **15**-1950
Scheffer, J.R. **4**-146, **5**-299, **16**-2215
Scheffler, K. **5**-246
Scheffold, R. **17**-220
Scheibye, S. **16**-216, **16**-217, **16**-224
Scheideman, M. **15**-706, **15**-707
Scheidt, K.A. **4**-126, **13**-224, **15**-798, **15**-1031, **15**-1056, **15**-1431, **15**-1455, **15**-1487, **16**-722, **16**-894, **16**-1192, **16**-2061, **19**-687
Scheiner, P. **17**-505
Scheiner, S. **3**-24
Scheinmann, F. **10**-1902, **18**-691
Scheiper, B. **10**-1384
Scheithauer, S. **16**-1833
Schellenberger, H. **19**-315
Schellman, J.A. **4**-277
Schelpe, A. **15**-169
Schemenaur, J.E. **19**-975
Schenck, G.O. **14**-257, **15**-2356
Schenck, T.G. **18**-743

Schenerman, M.A. **19**-1176
Schenk, W.A. **15**-2002
Schenk, W.N. **16**-1641
Schenkel, L.B. **16**-306
Schenkluhn, H. **15**-2661
Schepers, R.G. **18**-927
Schepp, N.P. **2**-435, **2**-437, **2**-438, **12**-93, **12**-160
Scheppele, S.E. **10**-183, **18**-104
Scherrer, R.A. **13**-256
Schetter, B. **16**-1020, **16**-1060
Schetty, G. **18**-133
Scheuermann, H. **4**-382
Scheuermann, J.E.W. **10**-998
Scheuplein, S.W. **18**-784
Scheurer, P.G. **10**-541
Schiaffo, C.E. **19**-339
Schiano, A.-M. **16**-1599
Schiavelli, M.D. **10**-268, **10**-1461, **15**-220
Schiavoni, M.M. **2**-433
Schick, H. **10**-519
Schick, U. **12**-285
Schieb, T. **2**-312
Schiemenz, G.P. **16**-1312, **16**-1320
Schiess, M. **16**-387, **16**-1787
Schiess, P.W. **17**-405
Schiesser, C.H. **4**-371, **5**-84, **5**-86, **12**-643, **14**-25, **14**-266, **15**-104, **15**-1365
Schiff, H. **12**-486
Schiffers, I. **4**-161
Schiffers, R. **18**-739
Schikora, E. **5**-384
Schill, G. **3**-190, **3**-202, **3**-204, **3**-205, **4**-96, **10**-1810
Schilling, P. **14**-188
Schiltz, A. **16**-2260
Schimmel, H. **10**-375
Schimperna, G. **16**-1125
Schindbauer, H. **16**-1923
Schindler, J. **4**-160
Schindler, S.R. **16**-1402
Schinz, H. **16**-2168
Schinzer, D. **15**-1246
Schipper, D.J. **15**-905
Schipper, P. **10**-165
Schippers, P.H. **4**-224
Schiraldi, D.A. **11**-671
Schirmer, H. **15**-2652
Schissler, D.O. **15**-476
Schlag, E.W. **5**-362, **7**-24
Schlama, T. **13**-618
Schlapbach, A. **16**-736
Schläpfer-Dähler, M. **4**-481
Schlatter, A. **19**-1036
Schlatter, M.J. **4**-486
Schlegel, H.B. **1**-106, **4**-318, **14**-51, **14**-83
Schleicher, K.D. **15**-803
Schleifenbaum, A. **2**-82
Schleker, W. **15**-2184
Schlemenat, A. **18**-908
Schlemper, H. **8**-94, **17**-307
Schlenk Jr., W. **4**-104, **4**-170, **5**-164
Schlenk, W. **5**-164
Schlessinger, R.H. **10**-1699, **10**-1810, **15**-1464
Schleyer, P.v.R. **1**-1, **1**-11, **1**-36, **1**-57, **2**-14, **2**-43, **2**-98, **2**-106, **2**-110, **2**-116, **2**-117, **2**-172, **2**-174, **2**-219, **2**-220, **2**-232, **2**-279, **2**-289, **2**-290, **2**-338, **2**-340, **2**-370, **2**-373, **2**-385, **2**-390, **2**-414, **2**-419, **2**-429, **2**-473, **3**-64, **4**-385, **4**-386, **4**-513, **5**-2, **5**-10, **5**-14, **5**-23, **5**-25, **5**-30, **5**-34, **5**-37, **5**-40, **5**-47, **5**-54, **5**-61, **5**-69, **5**-79, **5**-81, **5**-83, **5**-87, **5**-91, **5**-131, **5**-138, **5**-153, **5**-155, **5**-161, **5**-184, **5**-203, **5**-358, **5**-415, **6**-87, **8**-10, **8**-123, **10**-14, **10**-49, **10**-61, **10**-66, **10**-89, **10**-92, **10**-131, **10**-133, **10**-141, **10**-142, **10**-144, **10**-146, **10**-166, **10**-171, **10**-175, **10**-177, **10**-186, **10**-190, **10**-191, **10**-205, **10**-209, **10**-210, **10**-212, **10**-213, **10**-219, **10**-221, **10**-271, **10**-272, **10**-296, **10**-297, **10**-298, **10**-404, **10**-410, **10**-425, **10**-430, **10**-452, **10**-464, **10**-1122, **10**-1698, **11**-5, **11**-226, **12**-9, **12**-418, **12**-431, **12**-578, **12**-721, **13**-30, **13**-52, **14**-120, **15**-107, **15**-141, **15**-665, **15**-683, **15**-2123, **18**-2, **18**-7, **18**-9, **18**-29, **18**-45, **18**-48, **18**-105, **18**-114, **18**-115, **18**-116, **18**-117, **18**-120, **18**-545, **18**-546, **19**-8
Schlicher, J.W. **19**-1179
Schlögl, K. **4**-81, **4**-86
Schlögl, R. **15**-487
Schlosberg, R.H. **5**-31, **11**-15
Schlosser, M. **8**-100, **10**-1393, **11**-43, **12**-413, **12**-416, **12**-417, **12**-448, **12**-579, **16**-1315, **16**-1349, **16**-1355, **16**-1381, **16**-1384, **16**-1388, **16**-1391, **16**-1392, **17**-26, **17**-28, **17**-312, **18**-449
Schlubach, H.H. **15**-1753
Schlummer, B. **15**-402
Schlund, R. **12**-62
Schlüter, A. **4**-452
Schlüter, K. **15**-95
Schmalstieg, L. **2**-310
Schmalz, D. **2**-352, **5**-155
Schmalzing, D. **4**-180
Schmeising, H.N. **2**-423
Schmerling, L. **15**-746, **15**-757, **15**-1769
Schmickler, H. **2**-111, **2**-312, **2**-324, **2**-351, **2**-357, **2**-361
Schmid, A. **15**-1907
Schmid, B. **16**-129
Schmid, G.H. **10**-135, **15**-1, **15**-21, **15**-27, **15**-80, **15**-88
Schmid, H. **15**-, **18**-691, **18**-745, **18**-759
Schmid, J. **19**-353
Schmid, P. **13**-16
Schmid, W. **15**-939
Schmidbaur, H. **4**-534
Schmidlin, J. **15**-1237
Schmidlin, R. **5**-345
Schmidt, A. **12**-652
Schmidt, A.H. **2**-382, **16**-2001
Schmidt, B. **18**-859
Schmidt, D. **18**-678
Schmidt, D.M. **13**-863
Schmidt, E.W. **14**-293
Schmidt, F. **4**-161, **16**-746, **16**-748
Schmidt, G. **16**-689
Schmidt, G. **4**-402
Schmidt, G.M.J. **2**-321, **4**-146
Schmidt, H. **4**-494, **19**-586
Schmidt, J. **10**-1303
Schmidt, J.A.R. **10**-1632
Schmidt, K. **2**-312
Schmidt, L.M. **4**-324
Schmidt, M. **16**-1624
Schmidt, M.W. **1**-11
Schmidt, R.D. **11**-177
Schmidt, R.R. **2**-264, **5**-142, **10**-1847, **15**-2319, **15**-2352
Schmidt, S. **10**-1751
Schmidt, S.E. **10**-889
Schmidt, T. **12**-70
Schmidt, U. **16**-1764
Schmidt, W. **2**-249, **15**-2259
Schmidtchen, F.P. **4**-252, **4**-254
Schmiedel, R. **2**-231, **3**-212
Schmierer, R. **10**-1744
Schmink, J.R. **7**-118
Schmitt, R.J. **12**-743
Schmittel, M. **5**-313
Schmittou, E.R. **10**-548
Schmitz, C. **17**-292
Schmitz, E. **4**-39, **16**-120, **18**-925
Schmitz, P.H. **10**-1773
Schmitz, R. **19**-1201
Schmitz, R.F. **10**-739
Schmuff, N.R. **5**-150, **10**-1551
Schmutzler, R. **12**-372
Schnabel, W. **2**-176
Schnack, L.G. **18**-542
Schnakenburg, G. **16**-1060
Schneebeli, S.T. **15**-1934
Schneemeyer, L.F. **3**-59
Schneider, A. **18**-117
Schneider, C. **10**-988, **10**-693, **10**-999, **10**-1627, **15**-1184, **18**-636
Schneider, G. **8**-74
Schneider, H.-J. **3**-115, **4**-402
Schneider, H. **1**-45, **4**-343, **4**-354, **9**-10, **15**-13, **15**-1878, **19**-441
Schneider, J.A. **4**-144
Schneider, K. **4**-522, **18**-531

Schneider, M.F. **18**-825
Schneider, M.P. **18**-651, **18**-652
Schneider, P. **12**-607
Schneider, P.H. **16**-666, **16**-677, **16**-1084
Schneider, R. **13**-210, **13**-213, **15**-1769
Schneider, S. **7**-24
Schneider, U. **16**-738, **16**-751
Schnell, H. **5**-243, **11**-387
Schnell, H.W. **5**-42
Schnider, P. **10**-1766
Schnorrenberg, G. **16**-1933
Schnürch, M. **12**-691
Schnurpfeil, D. **15**-1701
Schnyder, A. **11**-543
Schöbel, G. **16**-1283
Schobert, R. **18**-721
Schoemaker, H.E. **15**-934, **18**-834
Schoenberg, A. **10**-1995
Schoenebeck, F. **15**-2135, **19**-1565
Schoeneck, W. **13**-767
Schoepke, F.R. **16**-400
Schoffstall, A.M. **15**-2105
Schofield, K. **11**-34, **11**-44, **11**-54, **11**-58, **11**-59, **11**-97, **11**-99, **11**-100, **11**-123, **18**-362
Scholes, G. **19**-423
Scholl, M. **18**-817, **18**-887
Scholl, P.C. **19**-589
Schöllkopf, U. **12**-9, **15**-2471, **16**-1254, **16**-1255, **16**-1340, **18**-416, **18**-428, **18**-441, **18**-442, **18**-539, **18**-545, **18**-776
Scholte, A.A. **10**-1050
Scholz, D. **12**-249
Scholz, M. **5**-340
Scholz, U. **13**-125
Schön, M. **16**-495
Schön, U. **16**-422
Schönberg, A. **7**-45, **12**-66, **15**-2356, **16**-1465, **19**-1662
Schönberger, A. **19**-255
Schönowsky, H. **14**-352
Schoofs, A.R. **4**-222, **10**-241
Schoolenberg, J. **15**-436
Schore, N.E. **14**-346, **15**-2586, **19**-1022
Schotten, T. **13**-507
Schoustra, B. **17**-2
Schowen, K.B. **16**-1548
Schowen, R.L. **6**-94, **6**-95, **16**-22, **16**-1548, **16**-1584, **16**-1699
Schrader, W. **11**-443
Schrage, K. **15**-481
Schräpler, U. **19**-1708
Schreader, L. **19**-1347
Schreck, J.O. **9**-71, **9**-81
Schreckenberg, M. **10**-1773, **16**-722
Schreiber, J. **10**-751, **10**-1246, **12**-35, **16**-382, **16**-384, **17**-426
Schreiber, M.R. **17**-94
Schreiber, S.L. **15**-2445, **19**-192
Schreier, P. **19**-474, **19**-476, **19**-477
Schreiner, P.R. **2**-219, **5**-335, **10**-840, **10**-1122, **14**-4, **14**-163, **14**-169, **15**-1093, **15**-2602, **16**-126, **18**-664, **19**-1124
Schrekker, H.S. **16**-689
Schrems, M.G. **15**-449
Schriesheim, A. **5**-43, **11**-385, **17**-289, **17**-291, **19**-771, **19**-839
Schrimpf, M.R. **12**-492
Schrive, J. **14**-255
Schriver, G.W. **5**-2, **10**-190
Schrock, R.R. **18**-804, **18**-807, **18**-812, **18**-818, **18**-821, **18**-829, **18**-843, **18**-845, **18**-854, **18**-884, **18**-894
Schröder, B. **18**-909
Schröder, F. **15**-993
Schröder, G. **2**-302, **2**-327, **2**-345, **2**-354, **4**-200, **15**-1841, **18**-671, **18**-672, **18**-674
Schröder, K. **15**-1885
Schröder, M. **3**-119, **15**-1790, **16**-576
Schrøder, S. **17**-6
Schröder, U. **16**-1255
Schroeck, C.W. **16**-1453, **16**-1454
Schroeder, G.M. **10**-1717, **10**-1720
Schroeder, G.M. **10**-1736
Schroeder, H.E. **3**-108
Schroeder, J.D. **10**-991, **19**-150
Schroeter, S. **14**-257
Schroll, G. **10**-948, **15**-497
Schroth, W. **2**-130, **17**-478, **19**-1771
Schrott, W. **12**-538
Schrumpf, G. **4**-293, **10**-1617
Schubert, H. **4**-147
Schubert, J.W. **15**-23
Schubert, P.F. **7**-83, **7**-85, **7**-92
Schubert, R.M. **19**-867
Schubert, U. **4**-534, **15**-819
Schubert, U.S. **7**-114
Schubert, W.M. **2**-412, **11**-49, **11**-469, **11**-648, **11**-649, **14**-489, **15**-26, **19**-413
Schuchardt, U. **19**-486
Schuda, P.F. **15**-2322
Schug, R. **15**-2433
Schugar, H.J. **2**-224
Schuld, C.L. **15**-1865
Schulenberg, J.W. **2**-457, **18**-934
Schulenberg, N. **15**-350
Schuler, R.H. **5**-294
Schulman, D.R. **16**-42
Schulman, E.M. **16**-42
Schulman, J.M. **4**-451
Schulman, M.F. **15**-666
Schulmeier, B. **11**-239
Schulmeier, B.E. **15**-2280
Schult, K.E. **15**-374
Schulte-Frohlinde, D. **7**-58
Schulte-Elte, K.H. **12**-695, **14**-259
Schulte II, J.P. **19**-985
Schulte, T. **15**-1439
Schultz, A.G. **5**-343, **15**-569, **18**-193, **18**-506, **18**-919
Schultz, F. **11**-649
Schultz, H.P. **16**-2167
Schultz, J.C. **5**-76
Schultz, M.J. **15**-226, **15**-1825, **19**-128
Schultz, P.G. **18**-637
Schultz, S.C. **15**-436
Schultz, T. **13**-386
Schultze, L.M. **16**-2221
Schulz, H. **19**-544, appendixa-17
Schulz, J.G.D. **19**-406
Schulz, L. **10**-1690
Schulz, M. **19**-513
Schulz, T. **13**-98
Schulz, W.H. **2**-312
Schulze, A. **19**-656
Schulze, P.D. **5**-368
Schulze, S.M. **18**-634
Schulze, V. **16**-460
Schumacher, R. **16**-1489
Schuman, M. **18**-839
Schumann, H. **11**-364, **13**-360, **15**-807
Schumann, W. **10**-890
Schumers, J.-M. **15**-784
Schummer, A. **4**-252
Schüngel, F.-M. **5**-335
Schürer, S.C. **18**-853
Schurig, V. **4**-38, **4**-178, **4**-180, **4**-219
Schüßler, M. **19**-513
Schuster, A. **4**-455
Schuster, D.I. **7**-68, **15**-2448, **15**-2464, **18**-915, **18**-920
Schuster, G.B. **1**-45, **5**-371, **5**-432, **14**-266
Schuster, H.F. **4**-138, **4**-502, **10**-246, **15**-107, **15**-469, **15**-2389, **16**-2213, **17**-386, **18**-179
Schuster, I.I. **5**-92
Schuster, K. **18**-270
Schuster, O. **11**-336
Schuster, P. **3**-3
Schut, J. **14**-445, **19**-1570
Schütz, T. **16**-720
Schüürmann, G. **10**-441
Schwab, J.W. **16**-1670
Schwab, P. **18**-816
Schwan, A.L. **19**-1508
Schwarm, M. **19**-1063
Schwartz, A. **4**-186
Schwartz, H.S. **10**-752
Schwartz, J. **16**-1410, **16**-1427, **17**-419, **19**-1644
Schwartz, J.L. **18**-752
Schwartz, L.M. **8**-179
Schwartz, M. **4**-294
Schwartz, M.A. **19**-1221
Schwartz, S. **8**-26

Schwarz, H. **5**-2, **5**-68, **10**-146, **10**-519, **18**-77
Schwarz, H. **19**-59
Schwarz, J. **8**-82
Schwarz, R. **15**-1121
Schwarz, S. **10**-519
Schwarz, W. **13**-789
Schwarz, W.H.E. **1**-6
Schwarzenbach, K. **15**-2545
Schwebel, H. **10**-873
Schweig, A. **2**-240, **4**-494
Schweikert, N. **3**-204
Schweinsberg, F. **14**-58
Schweiter, M.J. **15**-1974
Schweitzer, D. **2**-337
Schweizer, E.E. **15**-2472, **17**-260
Schweizer, S. **13**-494, **13**-509
Schweizer, W.B. **4**-525, **5**-201, **16**-387
Schwellnus, K. **16**-1260
Schwemlein, H.P. **3**-89
Schwendeman, R.H. **1**-55, **1**-85
Schwenker, R.P. **7**-30
Schweppe, A. **19**-805
Schwesinger, R. **8**-94, **17**-307
Schwetlick, K. **12**-778, **14**-246, **14**-321
Schwier, T. **10**-1502, **15**-777
Schwierz, H. **3**-198
Schwörer, U. **15**-2159
Schwyzer, R. **16**-1684
Scialpi, R. **19**-1258
Scilly, N.F. **16**-2085
Sclafani, J.A. **13**-561, **16**-1089
Sclove, D.B. **18**-212
Scoccitti, T. **19**-1130
Scola, P.M. **15**-2319
Scolan, A.L.B. **15**-530
Scopes, D.I.C. **15**-380
Scopes, P.M. **4**-104
Scorrano, G. **5**-72, **8**-11, **8**-124, **8**-142, **16**-1682
Scott J.L. **9**-84
Scott, A.D. **10**-6, **16**-1667
Scott, A.I. **13**-325
Scott, A.P. **2**-205, **18**-228
Scott, C.B. **10**-370, **17**-201
Scott, D.A. **15**-191, **15**-197, **15**-627
Scott, F.L. **5**-54
Scott, I.L. **15**-1547
Scott, J.A. **8**-248, **8**-253
Scott, J.L. **9**-117, **9**-126, **9**-143, **18**-525
Scott, J.M.W. **6**-64, **10**-40, **10**-41, **10**-88, **11**-626
Scott, J.W. **4**-137, **4**-139
Scott, K.J. **17**-98
Scott, K.W. **18**-809, **18**-812
Scott, L.T. **1**-74, **2**-299, **2**-350, **2**-387, **2**-399, **2**-401, **14**-129, **18**-63, **18**-555, **18**-683
Scott, M.E. **13**-302
Scott, P. **15**-336, **15**-2045
Scott, S.L. **15**-326
Scott, W.B. **4**-470, **10**-1303
Scott, W.J. **10**-1419, **12**-261, **12**-265, **12**-267, **12**-287
Scouten, C.G. **10**-195
Scremin, M. **16**-1738
Screttas, C.G. **9**-59, **10**-1995, **12**-570, **14**-452, **16**-1010, **18**-201
Screttri, A. **15**-232, **15**-1883, **15**-1971
Scribner, R.M. **16**-441
Scriven, E.F.V. **5**-427, **5**-443, **10**-1059, **10**-1064, **11**-146, **12**-241, **15**-2105, **16**-1727, **18**-309, **19**-1247
Scroggins, S.T. **16**-1085
Seabury, M. **15**-2429
Seabury, N.J. **13**-80
Searle, C.E. **17**-498
Searle, R. **2**-63
Sears, P.G. **8**-258
Seayad, A.M. **11**-409, **15**-1824, **16**-278
Seayad, J. **11**-409, **15**-325, **15**-1824
Sebastian, J.F. **1**-50
Sebastian, R. **3**-60
Sebastián, R.M. **15**-1044, **15**-1070
Sebastiani, G.V. **11**-278, **17**-33, **17**-36, **17**-54, **17**-116
Šebelius, S. **12**-473
Šebesta, R. **9**-130
Sechrest, R.C. **4**-375
Seco, J.M. **4**-108, **4**-110, **4**-111
Seconi, G. **12**-45
Secor, R.M. **4**-192
Sedaghat-Herati, M.R. **10**-324, **11**-30
Seddighi, B. **10**-674
Seddon, K.R. **9**-120
Seddon, K.R. **9**-123, **9**-139
Sedelmeier, G. **15**-2411
Sedighi, M. **16**-1756
Sedlmeier, J. **19**-699
Sedrani, R. **10**-1600
Seebach, D. **4**-134, **4**-135, **4**-139, **4**-444, **5**-155, **5**-201, **10**-579, **10**-1775, **10**-1776, **10**-1805, **10**-1809, **10**-1813, **10**-1820, **10**-1833, **10**-1844, **10**-1900, **15**-1192, **16**-205, **16**-387, **16**-609, **16**-1059, **16**-1199, **16**-1787, **16**-2124, **16**-2151, **19**-1269, **19**-1683
Seeboth, H. **13**-103, **13**-251, **13**-252, **13**-254
Seefelder, M. **18**-678
Seekircher, R. **19**-406
Seel, C. **3**-212
Seeley, D.A. **15**-2309
Seelhammer, T. **13**-305
Seely, F.L. **14**-34
Seeman, J.I. **4**-276, **9**-12, **18**-520
Seetz, J.W.F.L. **12**-596, **12**-612
Sefcik, M.D. **12**-51
Segal, G.A. **2**-16
Segall, Y. **15**-525
Seganish, W.M. **10**-1284, **13**-699, **13**-718
Segebarth, N. **7**-79, **7**-84
Seger, A. **19**-1023
Segi, M. **16**-1167
Segmuller, B. **4**-540
Segorbe, M.M. **12**-271
Segovia, A. **19**-342
Segre, A. **3**-85
Seguineau, P. **16**-1361
Segura, P. **11**-653
Sehgal, A. **18**-704
Sehgal, C. **7**-83
Sehgal, C.M. **7**-83
Sehmi, P. **5**-6, **6**-53, **13**-494
Seib, R.C. **10**-183
Seibel, W.L. **17**-328
Seibert, K.A. **16**-825
Seibl, J. **10**-18
Seiche, W. **15**-1601, **15**-1613
Seid, M. **18**-298
Seidel, C.F. **16**-2168
Seidel, D. **15**-1054, **15**-1408
Seidel, G. **13**-488
Seidel, W.C. **15**-1625
Seigal, B.A. **18**-859
Seigfred, C. **2**-38
Seijo, E. **16**-1187
Seikaly, H.R. **15**-180, **15**-200, **15**-268
Seike, H. **13**-554
Seiler, P. **3**-51
Seiler, S.T. **4**-452
Seip, H.M. **4**-329
Seip, R. **3**-56
Seites, P.G. **10**-1254
Seitz Jr., E.P. **10**-1500
Seitz, G. **2**-231
Seitz, T. **16**-1876
Sekar, G. **10**-704, **10**-974, **10**-1000, **10**-1008, **13**-124, **15**-2512, **19**-469
Sekhar, Ch.V.R. **16**-620
Sekhar, E.R. **10**-1048
Sekhar, K.C. **11**-396, **19**-1205
Seki, A. **16**-1023
Seki, H. **3**-203
Seki, M. **13**-382, **16**-2098, **16**-2101, **16**-2102
Seki, T. **19**-1740, **19**-1741, **19**-1749
Seki, Y. **10**-183
Sekifuji, M. **16**-1202
Sekiguchi, A. **1**-75, **4**-524, **5**-188, **5**-337, **10**-813, **13**-584
Sekiguchi, S. **11**-166, **13**-17, **13**-171, **16**-1698
Sekiguchi, Y. **15**-1052
Sekine, A. **15**-1071
Sekiya, A. **13**-796, **15**-175

Sekiya, K. **10**-1445
Sekljic, H. **16**-1885
Selassa, R.P. **16**-1499
Selegue, J.P. **2**-407
Seliger, H.H. **15**-2370
Selikson, S.J. **19**-1402
Selim, A. **10**-1744
Selinka, C. **2**-90
Selitsianos, D. **16**-1365
Sell, T. **19**-940
Sella, A. **10**-338
Sellers, C. **13**-804
Sellers, C.E. **10**-922
Sello, G. **16**-848, **16**-1319
Sello, J.K. **16**-2263
Selman, S. **18**-197
Seltzer, R. **10**-519, **10**-520
Seltzer, S. **15**-2287
Selva, A. **14**-382
Selva, M. **9**-111, **10**-443, **10**-941, **12**-784, **13**-391
Selvakumar, K. **13**-382, **19**-1676
Selve, C. **10**-946
Selvi, S. **11**-500
Selwood, T. **16**-1664
Semenischeva, N.I. **13**-795
Semenov, A.O. **14**-138
Semenow, D. **10**-425
Semenow, D.A. **13**-40, **13**-84
Semmelhack, M.F. **2**-56, **10**-1318, **10**-1320, **10**-1322, **13**-656, **15**-2661, **17**-342
Semmingsen, D. **2**-381
Semones, A.M. **13**-472
Sen Gupta, K.K. **19**-691
Sen Gupta, S. **19**-691
Sen, A. **14**-282
Sen, D. **3**-110
Sen, K.D. **1**-25, **1**-28, **1**-31
Sen, S. **10**-1372
Senaiar, R.S. **15**-2614
Senanayake, C.B.W. **12**-269
Senanayake, C.H. **13**-348, **15**-452, **16**-452, **16**-599, **16**-1507, **16**-2012, **19**-1542
Senapati, B.K. **16**-1173
Senatore, L. **16**-2274, **16**-2275
Senboku, H. **10**-2005, **14**-469, **14**-481, **15**-1504, **17**-384
Senda, T. **15**-1281
Senda, Y. **15**-123
Senders, J.R. **15**-2584
Sene, M. **19**-181
Senet, J. **10**-1258
Seneviratne, V. **19**-746
Seng, F. **16**-1403, **16**-1476
Senglet, N. **19**-489
Sengmany, S. **16**-399
Sengupta, D. **12**-722
Sengupta, K.K. **19**-92, **19**-94
Sengupta, S. **12**-427, **13**-388, **13**-813
Senju, T. **16**-460
Senn, M. **12**-101, **14**-143
Sennhenn, P.C. **15**-1938, **15**-2012
Senra, J.D. **13**-379, **13**-497
Senthilkumar, P. **17**-479
Senthilnathan, V.P. **5**-369
Senzaki, M. **15**-2275
Senzaki, Y. **18**-680
Seo, H. **19**-1449
Seo, J.W. **10**-532
Seo, K. **16**-1634
Seo, M.J. **19**-945
Seo, S..Y. **15**-238
Seo, S.H. **10**-1723
Seo, S.Y. **19**-689
Seoane, G. **15**-2493
Seoane, G.A. **15**-1693
Seoane, P. **15**-2155
Seomoon, D. **13**-689, **15**-855, **15**-958
Sepioł, J. **2**-480
Seppelt, K. **1**-102
Seppo, E. **18**-52
Sera, A. **6**-57, **9**-86, **10**-506, **19**-1245
Seradj, H. **10**-585, **16**-143, **16**-148, **16**-155
Serbanovic, A. **15**-1807
Sercel, A.D. **16**-322
Serdyuk, L. **17**-258
Sereda, G.A. **15**-1667
Sérée de Roch, I. **19**-675
Seregin, I. V. **13**-318, **13**-609
Seregina, V.F. **13**-117
Serelis, A.K. **15**-105
Sergeev, N.M. **4**-346
Sergeev, A.G. **11**-507, **13**-98
Sergeev, G.B. **12**-638, **15**-24, **15**-168, **15**-179
Sergeeva, Z.I. **19**-1267
Sergeyev, S. **15**-161
Sergi, V. **10**-565
Sergovskaya, N.L. **15**-1702
Serguchev, Yu.A. **19**-418
Seri, N. **3**-135
Serianni, A.S. **3**-48
Serieys, A. **16**-1819
Serino, C. **10**-1345
Serizawa, H. **15**-1259
Serjeant, E.P. **8**-25, **8**-175
Serna, S. **15**-2099
Serra-Zanetti, F. **17**-431
Serra, M. **18**-305
Serratosa, F. **2**-381, **2**-382
Serravalle, M. **11**-182, **14**-140, **14**-405
Serva, L. **19**-1234
Servano, J. **16**-682
Servesko, J.M. **15**-630
Servi, S. **15**-535
Servino, E.A. **13**-437
Sesana, G. **14**-385
Sesenoglu, Ö. **19**-309
Seshadri, S. **14**-212
Seshita, T. **10**-1297
Sessions, R.B. **4**-248, **4**-249, **4**-250
Sestelo, J.P. **10**-1480, **10**-1490, **10**-1549, **13**-337
Seter, J. **10**-164
Seth-Paul, W.A. **9**-47
Seth, S. **17**-267
Sethi, K. **16**-1269
Sethi, P. **16**-2147
Sethna, S. **11**-397, **11**-430, **11**-467
Sethofer, S.G. **10**-964
Sethuraman, M.R. **11**-433
Setiarahardjo, I.U. **13**-13
Seto, H. **13**-262
Setoguchi, H. **15**-969
Setzer, W.N. **5**-155
Seubert, J. **18**-532
Seubold Jr., F.H. **18**-56, **18**-65
Seung, Y.J. **17**-447
Severin, K. **15**-1728
Severin, T. **19**-591, **19**-1201
Seville, J.P.K. **15**-2126
Sevin, A. **15**-2444, **18**-52
Sevlapalam, N. **16**-1796
Sewgobind, N.V. **11**-409
Sexsmith, S.R. **15**-2642
Sexton, A. **12**-610, **12**-626
Sexton, G. **8**-113
Sexton, K.E. **19**-1058
Seybold, G. **2**-247, **2**-249
Seybold, P.G. **8**-191
Seydel, R. **11**-361
Seyden-Penne, J. **15**-1042, **15**-1189, **17**-118, **19**-1000, **19**-1278, **19**-879
Seyferth, D. **12**-398, **12**-557, **15**-1460, **15**-1461, **15**-2480, **15**-2482, **15**-2483, **16**-503, **16**-504, **19**-1293
Sezen, B. **13**-316, **19**-280, **19**-526
Sferrazza, A. **13**-608
Sfouggatakis, C. **18**-965
Sfulcini, A. **15**-991
Sha, C.-K. **15**-1340, **15**-1345
Sha, C. **16**-532
Shaabani, A. **19**-113, **19**-556, **19**-781
Shaapuni, D.Kh. **19**-1341
Shabana, R. **16**-216, **19**-1768
Shabat, D. **15**-1109
Shadakshari, U. **15**-1210
Shaefer, C.G. **19**-1082
Shaffer, C.J. **15**-2017
Shaffer, D.K. **14**-230
Shafir, A. **13**-205, **13**-206
Shafran, Yu.M. **16**-1521
Shah, A.C. **16**-1922
Shah, B.K. **2**-343
Shah, M.H. **12**-175, **16**-2229, **16**-2230
Shah, R.D. **16**-340
Shah, S.K. **10**-1826
Shah, S.T.A. **10**-814
Shahak, I. **10**-1073, **10**-1215
Shahbazi, F. **11**-199, **11**-441
Shahi, S.P. **19**-583

Shaik, S. **10**-879, **14**-94, **17**-6
Shaik, S.S. **2**-6, **2**-44, **8**-156, **10**-100, **10**-111, **10**-378
Shaikh, N. **10**-1309
Shaikh, N.S. **19**-1037
Shaikh, T.M. **15**-2061
Shain, S.A. **16**-24
Shainyan, B.A. **2**-476, **10**-252, **10**-259, **10**-276, **19**-1766
Shair, M.D. **18**-695
Shakespeare, W.C. **4**-507
Shakib, F.A. **5**-372
Shakirov, M.M. **18**-6, **18**-11
Shakoori, A. **19**-832
Shalaev, V.K. **19**-814
Sham, T.-K. **19**-129
Shamma, M. **10**-827
Shamsuddin, K.M. **19**-1088
Shan, Z. **16**-1083, **19**-1158
Shanbhag, G.V. **15**-368
Shandro, C.A. **18**-368
Shang, J.-Y. **4**-155
Shang, X. **16**-1184
Shang, Z. **14**-75, **15**-1046
Shani, A. **2**-287, **2**-293
Shankar, B.K.R. **4**-464
Shanklin, J.R. **16**-1453, **16**-1454
Shanklin, M.S. **15**-1600
Shanmugam, P. **10**-1627
Shanmugasundaram, M. **13**-456, **15**-2597, **15**-2613
Shannon, I.J. **17**-267
Shannon, P.T. **7**-58, **15**-2660
Shao, D. **16**-592
Shao, H. **16**-1044, **19**-555
Shao, J.-G. **15**-2187
Shao, L.-Y. **16**-79
Shao, L. **18**-704
Shao, M. **19**-235
Shao, P.-L. **19**-1262
Shao, R. **4**-209
Shapiro, G. **16**-1843
Shapiro, I.O. **5**-111
Shapiro, M. J. **4**-133
Shapiro, N.D. **18**-275
Shapiro, R.H. **17**-270, **17**-272, **17**-276, **17**-277
Shapland, P. **15**-702
Shapley, J.R. **15**-2410
Sharada, D.S. **16**-826, **19**-1727
Sharafutdinova, D.R. **19**-800
Sharanin, Yu.A. **16**-1477
Sharf, B. **7**-24
Sharf, V.Z. **16**-1553
Sharghi, H. **10**-1229, **10**-1234, **11**-438, **11**-457, **11**-586, **16**-284, **16**-296, **16**-1903, **17**-445, **18**-353, **18**-697
Sharifi, A. **14**-340
Sharifi, R. **19**-1726
Sharifi, T. **11**-30
Sharma, A.K. **12**-423, **19**-1764
Sharma, D.K. **7**-57
Sharma, G.T. **9**-74
Sharma, G.V.M. **10**-1197, **16**-803, **16**-811, **16**-1778
Sharma, J. **18**-220
Sharma, J.P. **19**-81, **19**-94
Sharma, L. **16**-1633
Sharma, M. **18**-601, **19**-72, **19**-449
Sharma, N.K. **19**-573
Sharma, P. **10**-1330, **15**-2212, **19**-304, **19**-1305
Sharma, P.K. **14**-94
Sharma, R. **16**-2072, **19**-1464
Sharma, R.K. **14**-374
Sharma, R.P. **17**-206, **17**-334, **19**-907
Sharma, R.R. **10**-1343
Sharma, S. **10**-1428, **12**-600, **16**-1870
Sharma, S.D. **16**-2223
Sharma, S.N. **19**-443
Sharma, V. **15**-1735
Sharma, V.B. **16**-369, **19**-123, **19**-237, **19**-762
Sharma, V.K. **19**-1203
Sharma, V.L. **19**-1469
Sharma, V.B. **15**-2077
Sharnin, G.P. **13**-72
Sharp, J.T. **13**-833
Sharp, K.G. **5**-370
Sharp, M.J. **13**-314
Sharp, R.L. **15**-686, **15**-683, **15**-703
Sharpe, L.R. **13**-654
Sharpless, K.B. **4**-200, **7**-130, **10**-525, **10**-527, **10**-529, **10**-697, **10**-842, **10**-895, **10**-1074, **10**-1578, **10**-1580, **12**-226, **12**-227, **12**-254, **14**-198
Sharpless, K.B. **15**-1689, **15**-1793, **15**-1799, **15**-1830, **15**-1831, **15**-1832, **15**-1835, **15**-1837, **15**-1838, **15**-1840, **15**-1841, **15**-1843, **15**-1874, **15**-1883, **15**-1938, **15**-1969, **15**-1970, **15**-1971, **15**-1974, **15**-1975, **15**-1976, **15**-2011, **15**-2012, **15**-2013, **15**-2014, **15**-2020, **15**-2022, **15**-2032, **15**-2136, **17**-293, **17**-331, **19**-80, **19**-450, **19**-451, **19**-453, **19**-454, **19**-579, **19**-588, **19**-709, **19**-711, **19**-866, **19**-892
Sharts, C.M. **10**-542, **10**-1099, **10**-1100, **10**-1214, **12**-763, **15**-165, **15**-1668, **15**-1754, **15**-2371, **15**-2419, **15**-2483
Shastin, A.V. **15**-2086
Shatavsky, M. **10**-143
Shatenshtein, A.I. **5**-111, **5**-155, **11**-118, **12**-61
Shaterian, H.R. **10**-873
Shatskaya, V.A. **16**-2286
Shaughnessy, E.A. **15**-2249
Shaughnessy, K.H. **13**-526
Shaw, A. **18**-544
Shaw, J.E. **13**-144, **10**-717
Shaw, J.T. **10**-1907, **16**-1092, **16**-1195
Shaw, W.J. **19**-484
Shawl, C.E. **2**-423
Shchegolev, A.A. **18**-2
Shchukina, M.V. **16**-2273
She, J. **15**-1046
She, X. **15**-1933, **19**-238
Shea, H.A. **13**-526
Shea, K.J. **4**-512, **14**-56, **14**-57, **15**-143, **18**-657, **18**-687
Shearer, G.O. **15**-1875
Sheats, G.F. **11**-101
Sheats, J.E. **13**-30, **13**-32, **13**-806
Shebaldova, A.D. **18**-535
Shechter, H. **5**-417, **10**-1931, **15**-1752, **16**-2293, **19**-403, **19**-639
Sheeba, V. **15**-1757, **19**-707
Sheehan, J.C. **10**-1033, **10**-1054, **16**-1908
SheHon, D.R. **16**-839
Sheikh, H. **10**-753
Shein, S.M. **10**-1395
Shekarriz, M. **10**-1945, **15**-1705, **15**-2001
Shekhar, A.C. **16**-1865
Sheldon, C.G. **12**-331, **12**-334, **16**-1434
Sheldon, R.A. **11**-246, **14**-219, **14**-237, **14**-240, **14**-268, **14**-474, **15**-1789, **15**-1894, **16**-1499, **16**-1950, **18**-377, **18**-382, **18**-409, **19**-167, **19**-169, **19**-218, **19**-265, **19**-418, **19**-698
Sheldrake, P. **15**-568
Sheldrick, W.S. **4**-280
Shell, B. **19**-414
Shellhamer, D.F. **15**-4, **15**-34
Shelly, D.P. **11**-606, **13**-829
Shelly, K.P. **12**-91
Shelton, G.R. **18**-575
Shelton, J.R. **15**-70
Shelton, J.R. **16**-380, **18**-945
Shemyakin, M.M. **2**-177, **18**-948
Shen, C.-Y. **15**-1340
Shen, C.-X. **16**-445
Shen, C. **19**-164
Shen, C.C.C. **5**-137
Shen, G.S. **16**-1413
Shen, J. **12**-357, **15**-2189
Shen, J.H. **15**-1976
Shen, K. **16**-1496, **18**-593
Shen, L. **10**-1051, **14**-195, **15**-1268
Shen, M. **14**-186
Shen, Q. **13**-147, **13**-186, **13**-187
Shen, S. **2**-224, **5**-416, **19**-1542
Shen, W. **10**-1459, **12**-317, **13**-527
Shen, X.-P. **3**-138
Shen, X. **13**-268, **16**-2200
Shen, Y. **11**-325, **11**-362, **15**-1079, **16**-831, **16**-832, **16**-854, **16**-1201, **16**-1503

Shen, Z.-L. **15**-1222, **16**-1508, **16**-1527
Shen, Z. **19**-168, **19**-502, **19**-622
Shene, A.L. **17**-182
Sheng, E. **14**-303
Sheng, J. **19**-529
Sheng, Q. **19**-224
Sheng, R. **2**-132
Sheng, S. **15**-215
Sheng, S.J. **18**-73
Shenglof, M. **13**-360
Shenhav, H. **15**-78
Shepelavy, J.N. **12**-240
Shepherd, B.D. **1**-13
Shepherd, R. **18**-32
Shepherd, R.G. **13**-75
Sheppard, A.C. **19**-511, **19**-519, **19**-713
Sheppard, H.C. **11**-116
Sheppard, N. **2**-36
Sheppard, P.J. **11**-76
Sheppard, W.A. **10**-542, **10**-1099, **10**-1100, **10**-1214, **13**-776, **15**-165, **15**-1668, **15**-1754, **15**-2483, **19**-1737
Shepperson, I.R. **16**-911
Sheradsky, T. **12**-225
Sherbine, J.P. **14**-454
Sherburn, M.S. **15**-2252, **15**-2270, **15**-2276
Sheridan, P.M. **8**-214
Sheridan, R.S. **2**-238, **4**-332, **4**-518, **5**-349, **5**-381, **5**-416, **5**-422, **5**-431, **6**-38, **17**-508
Sherman, J.C. **3**-180, **3**-181, **3**-182
Sherman, S.C. **11**-671
Sherman, V.W. **14**-496
Sherrill, C.D. **3**-79, **3**-80
Sherrington, D.C. **15**-1833, **15**-1972, **16**-1930, **16**-1935
Sherrod, S.A. **6**-81
Sherry, B.D. **13**-361, **15**-416, **18**-275
Sherwin, M.A. **18**-678
Shestopalov, A.M. **16**-1477
Sheu, C. **18**-493, **19**-485, **19**-485
Sheu, H. **10**-468
Sheu, J. **15**-2348
Sheu, R.G. **18**-955
Shevchuk, V.U. **10**-1137
Shevelev, S.A. **10**-514, **11**-177
Shevlin, P.B. **5**-376, **14**-61, **17**-145
Shezad, N. **13**-430, **15**-2220
Shi-ike, T. **16**-431
Shi, D.-P. **19**-235
Shi, F. **13**-107, **16**-59, **16**-59, **16**-134, **16**-1862
Shi, J. **4**-155, **10**-1478, **14**-84, **15**-1024, **15**-1346
Shi, L. **10**-1463, **13**-179, **16**-270, **16**-571, **16**-854, **16**-1085, **16**-1358, **19**-1014, **19**-1364, **19**-1649
Shi, M. **11**-128, **15**-1427, **16**-625, **16**-793, **16**-820, **16**-900, **16**-955, **16**-956, **16**-957, **16**-958, **18**-169, **18**-170, **18**-616, **19**-981
Shi, S.-Y. **10**-1475, **16**-53
Shi, W.-J. **16**-742
Shi, W. **12**-389, **13**-648
Shi, X.-X. **16**-209
Shi, X. **5**-317, **16**-324
Shi, Y.-J. **13**-517
Shi, Y. **12**-275, **15**-367, **15**-597, **15**-1925, **15**-1932, **15**-1933, **15**-1934, **15**-1935, **15**-1936, **15**-1943, **15**-2041, **15**-2562, **15**-2564, **16**-945, **16**-1906, **18**-158
Shi, Z.-J. **10**-1607
Shi, Z. **11**-264, **13**-720, **15**-237, **15**-287, **16**-46, **19**-115, **19**-128
Shi, Z. **19**-1104
Shia, K.-S. **10**-1567, **15**-1178, **16**-303, **16**-1115
Shiba, T. **15**-1595
Shibahara, F. **11**-527, **15**-1486
Shibakami, M. **3**-177, **4**-184, **13**-796, **15**-175
Shibasaki, M. **10**-708, **10**-771, **15**-406, **15**-1034, **15**-1071, **15**-1122, **15**-1382, **15**-1405, **15**-1635, **15**-1694, **15**-1883, **15**-1913, **15**-1918, **15**-1919, **15**-2030, **15**-2328, **16**-396, **16**-403
Shibasaki, M. **16**-411, **16**-552, **16**-737, **16**-780, **16**-940, **16**-942, **16**-1051, **16**-1090, **16**-1150, **16**-1216, **16**-1326, **16**-1449, **16**-1480, **16**-1495, **16**-1523, **19**-1654
Shibata, I. **16**-356, **16**-621, **16**-643, **16**-840, **16**-912, **16**-2032, **19**-1085, **19**-1127, **19**-1285, **19**-1295
Shibata, J. **16**-1175
Shibata, K. **15**-929, **16**-595, **16**-712
Shibata, N. **10**-782, **19**-800, **19**-1758, **19**-1760
Shibata, T. **4**-442, **10**-1456, **13**-330, **13**-677, **15**-1012, **15**-1452, **15**-1565, **15**-1568, **15**-1577, **15**-1830, **15**-2082, **15**-2083, **15**-2196, **15**-2607
Shibata, Y. **15**-845, **19**-1034
Shibatmoi, K. **10**-1545, **11**-273, **12**-166, **14**-196, **16**-645
Shibli, A. **10**-1471
Shibuguchi, T. **16**-942
Shibuta, H. **19**-1034
Shibutani, M. **2**-332, **2**-359
Shibuya, I. **16**-2240
Shibuya, M. **19**-654
Shibuya, S. **15**-1341, **19**-1271
Shichao Yu, S. **19**-1014
Shida, J. **10**-954
Shida, S. **12**-361
Shida, T. **5**-298
Shido, M. **15**-2116
Shie, J.-J. **14**-305
Shieh, C.H. **16**-2232
Shieh, W.-C. **10**-749
Shields, G.C. **8**-185, **8**-191
Shields, G.P. **3**-21
Shiers, J.J. **10**-261
Shiga, H. **15**-2593
Shiga, Y. **19**-1294
Shigemasa, T. **18**-132
Shigemasa, Y. **14**-443
Shigemura, M. **8**-184
Shigetani, T. **2**-39
Shigeyoshi, Y. **10**-1716
Shih, C. **10**-425
Shih, J. **10**-1251
Shih, J.G. **5**-87
Shih, N.C. **15**-515
Shih, Y.-K. **13**-841
Shih, Y. **11**-465
Shiibashi, A. **19**-664
Shiina, I. **16**-1054, **16**-1175, **16**-1913
Shijo, M. **4**-180
Shiju, N.R. **11**-579
Shikaura, J. **15**-1334
Shim, C.S. **9**-21, **10**-320, **16**-1612
Shim, E. **13**-689
Shim, S.B. **12**-730
Shim, S.C. **10**-1574, **13**-668, **16**-2244, **19**-14
Shim, W.H. **11**-321
Shimada, H. **19**-1656
Shimada, M. **11**-458, **15**-858
Shimada, S. **11**-432, **11**-453, **11**-468, **13**-326, **13**-327, **15**-391, **18**-551, **13**-584, **15**-207, **15**-789, **15**-823, **15**-1859, **18**-141
Shimada, Y. **16**-692
Shimagaki, M. **17**-243
Shimamura, T. **16**-1175
Shimamura, Y. **12**-729
Shimane, K. **16**-1423
Shimanouchi, T. **10**-1225
Shimanskaya, M.V. **15**-2485
Shimao, I. **18**-942, **18**-950
Shimazaki, M. **18**-159
Shimazaki, R. **13**-719
Shimazawa, R. **13**-495, **16**-759
Shimizu, H. **15**-2108, **16**-1172, **17**-165, **19**-128, **19**-1154, **19**-1716
Shimizu, I. **11**-342, **16**-1492, **17**-329, **18**-198, **19**-53, **19**-863
Shimizu, K.-i. **16**-1792
Shimizu, K. **10**-1154, **10**-1358
Shimizu, K. **15**-1509
Shimizu, M. **15**-1670, **15**-2513, **16**-595, **16**-712, **16**-912, **16**-963, **16**-982, **16**-1163, **16**-1580, **19**-946, **19**-1131, **19**-1646

Shimizu, N. **10**-176
Shimizu, R. **10**-1926
Shimizu, S. **3**-142, **3**-143, **10**-1762
Shimizu, T. **10**-958, **16**-1770, **16**-2098, **16**-2101, **19**-806
Shimizu, Y. **16**-2032
Shimobayashi, A. **13**-283
Shimoda, K. **15**-660, **16**-1649
Shimoji, K. **10**-1821
Shimomura, O. **13**-591
Shimura, M. **15**-1720
Shimura, Y. **12**-147
Shin-ike, T. **14**-26
Shin, C. **10**-1593, **2**-477
Shin, D.-S. **16**-1447, **19**-543
Shin, D. **15**-257
Shin, E.-k. **16**-849
Shin, H. **10**-1141
Shin, J. **5**-96
Shin, K.K. **7**-14
Shin, S. **15**-881, **16**-1089
Shin, S.I. **10**-889, **10**-1021, **13**-712, **16**-1976
Shin, U.S. **11**-331
Shin, Y.-J. **16**-683
Shindo, M. **10**-1706, **16**-2243
Shine, H.J. **11**-531, **11**-580, **11**-583, **11**-599, **11**-609, **11**-618, **11**-620, **11**-624, **11**-625, **11**-628, **11**-641, **11**-681, **13**-842, **13**-847, **13**-857, **13**-862, **18**-194, **18**-691, **18**-693, **18**-761, **18**-788, **18**-789, **18**-790, **18**-791, **18**-795, **18**-798, **18**-799, **18**-800, **18**-801, **18**-802, **18**-941, **18**-951
Shiner Jr., V.J. **6**-80, **6**-89, **6**-95, **10**-69, **10**-80, **10**-147, **10**-183, **10**-344, **10**-412, **10**-461, **12**-667, **17**-7, **18**-18, **19**-962
Shiner, C.S. **5**-133, **10**-771
Shiner, V.J. **10**-221
Shing~~u~~, K. **4**-68
Shingaki, T. **12**-238
Shingare, M.S. **10**-679
Shingu, H. **10**-83, **10**-325
Shinhama, K. **14**-397
Shinkai, S. **3**-127, **3**-131, **7**-62, **19**-1557
Shinmen, M. **13**-597
Shinmyozu, T. **3**-134
Shinoda, H. **2**-39
Shinohara, A. **15**-1859
Shinohara, Y. **16**-1285
Shinokubo, H. **10**-1273, **10**-1484, **10**-1572, **10**-1626, **10**-1715, **13**-322, **13**-346, **13**-449, **13**-457, **14**-12, **15**-317, **15**-763, **15**-787, **15**-890, **15**-935, **15**-936, **15**-1297, **15**-1299, **15**-1344, **15**-1358, **15**-1778, **15**-1779, **15**-2611, **15**-2638, **16**-576, **16**-1035, **19**-1645
Shintani, R. **11**-330, **15**-1269, **16**-921, **16**-2058
Shioiri, T. **12**-77, **12**-541, **15**-1912, **15**-1953, **16**-1277, **16**-1281, **16**-1287, **16**-1372, **16**-1458, **18**-224, **18**-240, **19**-495, **15**-642, **16**-1183
Shipman, M. **10**-261, **18**-58
Shirae, Y. **13**-496, **16**-1793
Shiragami, T. **10**-1012
Shirai, M. **10**-913, **15**-1435
Shirai, N. **13**-850, **13**-852
Shirai, R. **13**-495, **16**-759
Shirai, Y. **15**-1912, **16**-1287
Shiraishi, D. **15**-288
Shiraishi, K. **5**-299
Shiraishi, M. **16**-1850
Shiraishi, T. **15**-1112
Shiraishi, Y. **11**-577, **18**-736
Shirakawa, E. **10**-1729, **11**-327, **15**-212, **15**-894
Shirakawa, K. **12**-522
Shirakawa, S. **3**-142, **3**-143, **15**-2113, **16**-1128
Shirakura, M. **15**-841
Shirasaki, D. **15**-2322
Shireman, B.T. **16**-1093
Shiri, M. **11**-296
Shirini, F. **16**-80, **19**-88, **19**-241, **19**-776
Shirley, D.A. **12**-419
Shirley, I.M. **15**-443, **15**-1804
Shirley, R.L. **17**-517
Shiro, M. **4**-347, **12**-390
Shirokawa, S.-i. **16**-1149
Shirokova, N.P. **18**-334
Shiroodi, R.K. **16**-1872
Shirota, Y. **15**-2401
Shiroyama, M. **19**-311
Shirwaiker, G.S. **18**-681
Shirzi, J.S. **19**-236, **19**-1673
Shishido, K. **16**-2243
Shishido, T. **10**-915, **15**-392, **15**-765
Shitama, H. **15**-2563
Shitani, R. **15**-1211
Shivakawa, S. **19**-978
Shivanyuk, A. **3**-125
Shivaramayya, K. **15**-1391
Shivasankar, K. **16**-1809
Shivini, F. **12**-739
Shklover, V. **5**-276
Shkurko, O.P. **9**-20
Shlykov, S.A. **2**-450
Shner, V.F. **13**-117
Shoaf, C.J. **19**-1177
Shoair, A.G.F. **19**-378
Shoair, A.G. **19**-380
Shoar, R.H. **19**-34
Shobe, D. **18**-163
Shodai, H. **10**-1297
Shoel, S.Md.A. **15**-2631
Shoemaker, M.J. **18**-421
Shoji, M. **15**-1106, **15**-2210, **15**-2352, **16**-1085, **19**-515, **19**-517
Shoji, T. **18**-271
Shokol, V.A. **16**-1364
Shokouhimehr, M. **13**-383
Shokri, S. **16**-293
Sholle, V.D. **5**-240, **5**-268
Shönberg, A. **15**-2675
Shono, T. **10**-1831, **16**-1578, **17**-375, **19**-1546, **19**-1666, **19**-1671
Shook, B.C. **17**-168, **17**-169
Shook, D.A. **12**-221
Shore, N. **7**-48
Shore, P.A. **14**-225
Shorokhodov, V.I. **11**-292
Short, K.M. **15**-2677
Short, R.P. **16**-1079
Shorter, J. **8**-149, **8**-164, **9**-16, **9**-19, **9**-20, **9**-38, **9**-41, **9**-58, **9**-61, **10**-372, **10**-474, **16**-417
Shortridge, R.W. **4**-430
Shostakovskii, M.F. **10**-680, **15**-255, **15**-294
Shotland, Y. **19**-992
Shoup, T.M. **12**-467, **16**-463
Shovshinev, S.V. **15**-1702
Shpan'ko, L.V. **13**-91
Shreeve, J.M. **12**-144, **13**-312, **15**-1659
Shrestha, M. **15**-1854
Shrestha, R. **13**-358
Shrikhande, J.J. **16**-1872
Shriner, R.L. **4**-14
Shtamburg, V.G. **4**-43
Shteingarts, V.D. **11**-13, **13**-116, **14**-226
Shteinman, A.A. **15**-1808
Shtern, V.Ya. **12**-209
Shu, D. **13**-665
Shu, L. **15**-1932, **15**-1933, **15**-1934
Shubashree, S. **13**-167
Shubert, D.C. **10**-1366
Shubin, V.G. **11**-1, **18**-2, **18**-6, **18**-11, **18**-30, **18**-35
Shubina, E.S. **3**-5
Shucai, L. **10**-709
Shudo, K. **11**-504, **11**-187
Shuekhgeimer, G.A. **15**-2176
Shuford, R.J. **15**-494
Shuikin, N.I. **15**-746, **19**-1351
Shukla, D. **10**-702
Shukla, M.R. **16**-1647
Shukla, R. **3**-123,**18**-79, **18**-508
Shukla, R.K. **11**-288
Shukun, H. **19**-1349
Shulman, E.M. **16**-1198
Shulman, G.P. **17**-149
Shulman, J.I. **16**-1389
Shulman, N. **13**-89
Shul'pin, G.B. **19**-460
Shul'pina, L.S. **19**-460
Shults, R.H. **10**-1355, **10**-1356
Shulyupin, M.O. **15**-385, **15**-397
Shumaker, S.H. **18**-356

Shundo, R. **15**-2089
Shundo, T. **10**-1579
Shunmugasundaram, A. **5**-408
Shushunov, V.A. **12**-456, **12**-461
Shustov, G.V. **4**-37, **4**-40
Shute, R.E. **13**-189, **13**-392, **13**-501
Shuto, S. **16**-1331
Shutt, G.R. **10**-10
Shuttleworth, S. **10**-669
Shvartsberg, M.S. **14**-351, **13**-125
Shvekhgeimer, G.A. **15**-1750
Shvets, V.F. **14**-138
Shvets, V.I. **4**-164
Shvo, Y. **15**-213, **15**-462
Shyamsunder, T. **10**-1003, **15**-430, **15**-464
Si, Y.-G. **16**-542, **16**-902
Siahaan, T.J. **15**-1162
Siam, K. **3**-35
Siani, G. **12**-82
Sibelle, E.C. **11**-466
Sibi, M.P. **14**-17, **14**-45, **15**-1119, **15**-1289, **15**-1290, **15**-1308, **15**-1402, **15**-2110, **15**-2144, **15**-2146, **15**-2147, **15**-2251, **16**-680, **16**-1847, **16**-2072, **19**-1117
Sibille, S. **10**-1485
Sicher, J. **4**-472, **17**-8, **17**-16, **17**-20, **17**-23, **17**-24, **17**-26, **17**-27, **17**-100, **17**-382
Sicken, M. **2**-324
Sicking, W. **1**-96, **15**-2245
Sickles, B.R. **13**-48
Sicre, J.E. **10**-300
Siddall, J.B. **15**-1133, **19**-890
Siddappa, U. **10**-1143
Siddhanta, A.K. **2**-458, **12**-93
Siddiquei, A.S. **11**-77
Siddiqulah, Md. **12**-489
Siddons, D.C. **18**-450
Sidhu, H. **17**-39
Sidot, C. **13**-677
Siebenhaar, B. **16**-1237
Sieber, A. **17**-460
Sieber, J.D. **15**-1260
Sieber, P. **16**-1684
Sieber, R. **19**-699
Sieber, S. **5**-81, **10**-133, **10**-221
Sieber, W. **15**-2309, **16**-1544
Siebert, M.R. **18**-655
Siebert, W. **2**-189
Sieburth, S.M. **18**-634
Sieburth, S.Mc.N. **10**-1372, **15**-796, **15**-2675
Sieczkowski, J. **3**-97
Siedle, A.R. **15**-2658
Siegel, A. **12**-430
Siegel, C. **16**-1077
Siegel, E. **10**-774
Siegel, H. **12**-649
Siegel, J. **4**-20, **4**-525
Siegel, J.J. **11**-83
Siegel, J.S. **2**-78, **2**-88, **2**-403, **3**-210, **8**-184, **11**-84
Siegfried, B. **10**-1953, **13**-820, **14**-396, **16**-1669, **19**-641, **19**-1550
Siegfried, S. **18**-721
Siegl, W.O. **10**-1957
Siegmann, K. **10**-1403
Siehl, H. **5**-68, **6**-79
Sieler, J. **4**-55
Siemeling, U. **5**-182
Siemers, N.O. **19**-1659
Siemsen, P. **14**-328
Sierakowski, C. **18**-90
Sierra, C.A. **13**-401
Sies, C.W. **11**-61
Siesel, D. **11**-376
Sieser, J.E. **15**-329
Sieskind, O. **11**-320
Sifniades, S. **12**-212
Sigalas, M.P. **5**-55
Sigalov, M. **12**-82
Sigeev, A.S. **13**-165, **14**-393
Sigerson, R.C. **19**-1156
Siggel, L. **15**-2680
Siggel, M.R. **2**-58, **2**-59, **8**-186
Sigman, M.E. **5**-432
Sigman, M.S. **15**-226, **15**-908, **15**-1825, **15**-1826, **15**-2341, **15**-2587, **16**-691, **19**-128, **19**-141, **19**-211, **19**-211, **19**-700, **19**-701
Signorella, S. **13**-565
Sih, C.J. **4**-185, **19**-991
Siklosi, M.P. **12**-693
Sikora, D.J. **2**-185
Sikorski, J.A. **18**-484
Sikorski, W.H. **15**-1191
Silber, J.J. **13**-15
Silber, P. **15**-2453
Silberman, L. **6**-18
Silbert, L.S. **10**-717, **10**-774, **10**-1802, **14**-170, **16**-1308
Silbey, R. **7**-24
Silcoff, E.R. **16**-1090
Sild, S. **2**-124
Silina, A. **10**-1788
Silks III, L.A. **18**-930
Sill, P. **15**-877
Sill, P.C. **15**-1564, **15**-1565
Silla, E. **10**-247
Sillion, B. **15**-1691
Silva Jr., J.F. **18**-218
Silva, A.M.S. **7**-129, **16**-794
Silva, D. de O. **16**-266
Silva, M.A. **15**-2187
Silva, M.S. **15**-314
Silva, P.J. **8**-150
Silveira Jr., A. **18**-472
Silveira, A. **17**-195
Silveira, C.C. **12**-300, **12**-304, **15**-217, **15**-290, **15**-297
Silveira, G.P.C. **16**-796
Silveira, P.B. **13**-308
Silver, M.E. **16**-1963
Silver, M.S. **10**-216
Silverberg, L.J. **19**-1016
Silverman, S.M. **15**-2159, **15**-2160
Silvero, G. **15**-2193
Silversmith, E.F. **3**-186, **16**-1198
Silverstein, R.M. **4**-108, **4**-265
Silverthorn, W.E. **3**-96
Silverton, J.V. **2**-298
Silverwood, H.A. **19**-21
Silvester, M.J. **11**-308
Silvestri, M.G. **10**-1579
Silvi, B. **2**-9, **8**-215
Simaan, S. **15**-1602
Simal, F. **15**-1776, **15**-2142
Simamura, O. **18**-404, **19**-1548
Simandan, T. **10**-1023
Simándi, L.I. **14**-329, **19**-385, **19**-716
Simas, A.B.C. **13**-497, **15**-956
Simchen, G. **16**-969
Sime, J.M. **8**-41
Simic, O. **15**-2250
Simion, A.M. **10**-886
Simion, C. **10**-886
Simkin, B.Ya. **2**-234, **2**-316, **5**-348
Simkin, M. **12**-681
Simmonett, A.C. **2**-220
Simmons, H.E. **2**-34, **4**-239, **4**-251, **10**-493, **12**-240, **13**-40, **15**-2437, **15**-2549, **15**-2551, **15**-2556, **15**-2559, **18**-933, **19**-375
Simmons, M.C. **12**-405
Simms, N. **10**-1738
Simões, J.A.M. **1**-104
Simon, A. **2**-374
Simon, E.S. **19**-1237
Simon, H. **17**-63
Simon, J. **13**-106
Simon, J.A. **16**-2180
Simon, J.D. **10**-77
Simon, K. **5**-185
Simon, W.M. **13**-189, **16**-1686
Simonelli, F. **19**-1405
Simonetta, M. **1**-9, **1**-77, **2**-288, **2**-296, **2**-305, **2**-313, **2**-350, **13**-11, **15**-2297
Simonneaux, G. **15**-2525
Simonoff, R. **19**-1498
Simonot, B. **15**-1722
Simonov, A.M. **13**-761
Simons, J. **5**-348
Simons, J.H. **16**-440
Simons, R.W. **15**-1725
Simova, S. **16**-606
Simpkins, N.S. **10**-1743, **12**-104, **12**-109, **15**-41, **15**-320, **16**-880, **16**-1292
Simplício, A.L. **19**-793
Simpson, C.C. **11**-77
Simpson, C.F. **11**-76
Simpson, G.R. **8**-196
Simpson, I.D. **10**-1649
Simpson, L.S. **16**-2285

Simpura, I. **16**-1028, **19**-1751, **19**-1752
Sims, J.J. **19**-429
Sims, L.B. **6**-70, **6**-76, **17**-62, **17**-134
Sinclair, J.A. **14**-437, **15**-1262, **18**-484, **18**-486
Sindona, G. **16**-136
Sinegovskaya, L.M. **4**-307
Sineokov, A.P. **15**-2152
Singaram, B. **10**-912, **10**-964, **10**-1878, **12**-545, **12**-548, **13**-184, **15**-704, **15**-709, **16**-560, **18**-466, **18**-474, **18**-475, **18**-487, **19**-857, **19**-911, **19**-973, **19**-1029, **19**-1110, **19**-1141, **19**-1166, **19**-1483, **19**-1484, **19**-1510
Singaram, S. **15**-728, **19**-857
Singer, R.A. **2**-426, **13**-189, **15**-329
Singer, R.D. **9**-117, **13**-506, **19**-1606
Singer, S.P. **15**-2032l **17**-293
Singer, S.R. **18**-176
Singer, T. **10**-397
Singh, O.V. **10**-1022
Singh, A. **7**-84, **7**-91, **10**-1007, **10**-832, **16**-1222
Singh, B.P. **10**-181, **16**-1626, **18**-73
Singh, C.B. **10**-886
Singh, D.U. **16**-1890
Singh, F.V. **14**-364
Singh, G.P. **15**-1917
Singh, G.S. **15**-2043
Singh, H.K. **19**-1331
Singh, J. **10**-505, **15**-729, **16**-1036, **16**-1119, **19**-72, **19**-449, **19**-451
Singh, J.O. **13**-15
Singh, K. **10**-620
Singh, K.J. **11**-603, **11**-604, **12**-421, **17**-306
Singh, K.N. **12**-423
Singh, M. **19**-735
Singh, M.P. **19**-1624
Singh, N. **19**-243
Singh, N.K. **12**-352
Singh, P. **12**-168, **12**-423
Singh, P.K. **16**-667
Singh, P.N.D. **5**-433, **16**-1408
Singh, P.R. **10**-1399, **14**-399, **16**-1890
Singh, R. **11**-660, **16**-1789
Singh, R.P. **11**-341, **15**-2252
Singh, S. **10**-1372, **11**-311, **15**-360, **15**-2679, **16**-1232, **16**-2119, **19**-1275, **19**-1586
Singh, S.K. **10**-1566, **19**-384
Singh, S.P. **12**-666, **18**-127
Singh, U.K. **13**-190
Singh, V. **10**-505, **12**-259, **16**-1036
Singh, V.K. **10**-704, **10**-974, **10**-1000, **10**-1006, **10**-1008, **10**-1241, **11**-341, **15**-1016, **15**-1956, **15**-2512, **16**-153, **16**-550, **16**-667, **16**-1085, **16**-1535, **16**-1723, **19**-160, **19**-469, **19**-1009
Singhal, G.H. **17**-175
Singhal, N. **16**-100, **19**-205
Singleton, D.A. **15**-698, **15**-994, **15**-2143, **15**-2280, **15**-2312, **15**-2390
Sinha, B. **18**-744
Sinha, J. **14**-482
Sinha, P. **14**-311
Sinha, S. **11**-319, **19**-920
Sinha, S.C. **16**-1100
Sinisterra, J.V. **19**-993, **19**-1736
Sinke, G.C. **1**-99
Sinn, H. **15**-1674
Sinnokrot, M.O. **3**-79, **3**-80
Sinnott, M.L. **10**-433, **16**-31, **16**-32
Sinnreich, J. **15**-1727
Sinou, D. **10**-826, **10**-1161, **10**-1522, **10**-1912, **13**-389, **15**-2514, **15**-2520, **19**-1752
Sinoway, L. **10**-1424
Sinu, C.R. **16**-871
Sinya, J. **15**-567
Sipe Jr., H.J. **11**-213
Sipos, G. **5**-87, **16**-1283
Siquet, C. **11**-277
Sirieix, J. **10**-1457
Siriwardana, A.I. **15**-177, **15**-971
Sirkecioglu, O. **16**-1715
Sirokmán, F. **16**-1283
Siroky, M. **10**-1942
Sironi, M. **2**-133
Siska, S.J. **16**-1074
Siska, S.J. **4**-143
Siskos, M.G. **11**-451
Sisti, A.J. **10**-319, **15**-1687, **18**-171, **18**-172, **18**-173, **18**-376
Sita, L.R. **4**-152, **16**-1097
Sitzmann, M.E. **19**-747
Siu, T. **15**-2052, **15**-2054
Sivakamasundari, S. **16**-172
Sivakumar, M. **17**-479, **19**-671
Sivakumar, S. **4**-165
Sivappa, R. **16**-1785
Sivaram, S. **11**-288, **15**-828
Six, C. **18**-849
Sixma, F.L.J. **11**-382, **11**-644, **17**-138
Sixxa, H. **16**-349
Sizan, O.E. **10**-1994
Sjöberg, B. **16**-182
Sjöberg, K. **10**-484, **16**-182
Sjöholm, Å. **15**-1376
Sjöholm, R. **16**-685
Sjöström, M. **9**-29
Skalit, C. **15**-2479
Skamoto, I. **10**-1816
Skarnulis, A.J. **12**-610, **12**-626
Skarzewski, J. **16**-2121
Skattebøl, L. **11**-499, **15**-2492
Skell, P.S. **5**-350, **5**-365, **9**-47, **9**-50, **10**-425, **12**-625, **14**-55, **14**-56, **14**-57, **14**-138, **14**-207, **14**-209, **14**-212, **15**-56, **15**-58, **15**-125, **15**-143, **15**-2491, **15**-2538, **17**-46, **18**-20, **18**-43, **18**-47, **18**-175
Skelton, B.W. **10**-644
Sket, B. **12**-130
Skidmore, J. **15**-1958, **15**-1962, **18**-156
Skinner, C.J. **11**-312
Skinner, G.A. **11**-57, **11**-108
Skinner, I.A. **12**-73
Skjaerbaek, N. **13**-196
Sklarz, B. **19**-10
Sklenak, S. **15**-1794
Sklorz, C.A. **16**-576
Skobeleva, S.E. **3**-42
Skoglund, M.J. **12**-58
Skolnik, H. appendixa-1
Skonieczny, S. **16**-2276
Skorcz, J.A. **13**-638
Skorobogatova, E.V. **15**-279
Skovronek, H. **16**-1978
Skowroñska, A. **16**-425
Skrabal, P. **11**-29, **13**-38
Skranc, W. **16**-1212
Skrydstrup, T. **10**-1309, **14**-355, **15**-1454, **16**-406
Skucas, E. **10**-1575
Skulski, L. **11**-284
Skwarczynski, M. **15**-872
Slack, D.A. **12**-6
Slade, J. **4**-175
Sladkov, A.M. **13**-580
Slagle, J.D. **10**-1160
Slama, F.J. **5**-97
Slater, C.D. **9**-78, **18**-713
Slatford, P.A. **17**-446
Slaugh, L.H. **18**-64
Slavin, J. **16**-2063
Slawin, A.M.Z. **2**-342, **10**-261
Slayden, S.W. **12**-469, **18**-485
Slebocka-Tilk, H. **15**-6, **15**-12, **15**-22, **15**-1650, **16**-1104, **16**-1700, **16**-1701
Slee, T.S. **4**-436
Sleezer, P.D. **12**-34
Slegt, M. **5**-78
Slieker, L.M. **10**-1544
Slingenfelter, D.S. **4**-168
Sliwnska, A. **15**-412
Sloan Jr., E.D. **3**-19, **3**-164
Sloan, E.D. **3**-173.
Sloboda-Rozner, D. **15**-1883
Slocum, D.W. **12**-430, **12**-623, **13**-724, **13**-725
Slopianka, M. **10**-497, **15**-2378
Slotin, L. **4**-262
Slutsky, J. **17**-495
Smadja, W. **15**-107
Smail, F.R. **9**-113

Small Jr., V.M. **10**-759
Small, A. **18**-610
Small, L.E. **8**-248, **12**-694
Small, P.A. **11**-112
Smalley, R.E. **2**-392, **2**-393
Smalley, R.K. **18**-308
Smallridge, A.J. **11**-144, **15**-1607
Smart, B.E. **2**-418
Smat, R.J. **17**-9
Smentek, L. **18**-579
Smentowski, F.J. **12**-751
Smerz, A.K. **15**-1927
Smidrkal, J. **13**-548
Smidt, J. **19**-699
Smietana, M. **12**-328, **15**-1688
Smil, D.V. **10**-1892, **16**-761, **16**-762
Smiles, S. **13**-867
Smiley, R.A. **10**-517, **10**-1931
Smirnov, V.V. **15**-24, **15**-168, **15**-179
Smirnyagin, V.A. **15**-1750
Smissman, E.E. **16**-1548, **17**-131
Smit, P.J. **14**-395
Smit, W.A. **15**-21, **15**-2205
Smith-Palmer, T. **15**-1759
Smith, R.A.J. **15**-1140
Smith III, A.B. **10**-550, **18**-805, **18**-965, **18**-966
Smith III, M.R. **12**-588, **13**-107, **19**-1555
Smith III, W.J. **4**-126, **13**-181, **16**-1055, **19**-1338
Smith Jr., W.N. **12**-621
Smith, A. **13**-448
Smith, A.D. **19**-1500, **19**-1603
Smith, A.S. **16**-2054
Smith, B. **19**-261
Smith, B.D. **4**-322, **4**-324
Smith, B.H. **4**-81
Smith, B.M. **16**-152
Smith, B.T. **18**-324
Smith, C.A. **16**-325
Smith, C.D. **12**-460, **18**-446, **18**-447
Smith, C.J. **13**-175, **13**-189
Smith, C.P. **16**-1317, **16**-1354
Smith, C.R. **8**-31, **15**-2055
Smith, C.V. **14**-176
Smith, D.A. **15**-536, **15**-1082
Smith, D.C. **16**-226
Smith, D.H. **4**-131
Smith, D.J.H. **19**-706
Smith, D.M. **10**-1503, **14**-395, **15**-1317
Smith, E.M. **10**-1852
Smith, F. E. **7**-105
Smith, F.C. **17**-267
Smith, G. **15**-992
Smith, G.D. **4**-305, **17**-19
Smith, G.G. **12**-673, **17**-128, **17**-151, **17**-492, **17**-493, **18**-627, **18**-691
Smith, G.M. **15**-2208
Smith, G.T. **3**-14
Smith, G.V. **15**-484, **15**-494, **17**-346
Smith, H.D. **12**-221
Smith, H.E. **4**-277
Smith, H.L. **18**-301
Smith, J. **16**-1912
Smith, J.A. **15**-1962
Smith, J.A.S. **11**-496
Smith, J.D. appendixa-29
Smith, J.G. part 2-6, **10**-406, **17**-86, **17**-211
Smith, J.M. **8**-7
Smith, J.S. **17**-9
Smith, J.W. **3**-56, **8**-190, **8**-235
Smith, K. **10**-493, **10**-1827, **10**-1870, **11**-135, **11**-277, **12**-344, **12**-425, **12**-451, **12**-465, **14**-433, **14**-437, **15**-671, **15**-1255, **16**-589, **16**-736, **16**-1039, **16**-1063, **18**-451, **18**-460, **18**-461, **18**-465, **18**-469, **19**-847, **19**-851, **19**-858
Smith, L.A. **13**-17
Smith, L.H.S. **19**-1754
Smith, L.R. **16**-1981
Smith, M.A. **6**-16, **16**-1726
Smith, M.B. **4**-101, **4**-112, **4**-155, **4**-283, **4**-328, **4**-343, **4**-364, **4**-512, **5**-169, **5**-171, **5**-177, **6**-17, part**2**-6, **10**-251, **10**-503, **10**-670, **10**-893, **10**-1023, **10**-1166, **11**-258, **15**-427, **15**-1183 **15**-1292, **15**-1308, **15**-1348, **15**-1831, **15**-1867, **15**-1969, **15**-2154, **15**-2172, **15**-2186, **15**-2202, **15**-2218, **15**-2231, **15**-2242 **15**-2268, **15**-2348, **16**-1003, **16**-1015, **16**-1074, **16**-1123, **16**-1326, **16**-2049, **17**-286, **17**-379, **19**-877, **19**-1013, **19**-1566
Smith, M.D. **19**-121
Smith, M.L. **17**-7
Smith, M.R. **10**-130
Smith, N.W. **10**-1280
Smith, P. **5**-209
Smith, P.A.S. **11**-541, **17**-496, **18**-161, **18**-290, **18**-309, **18**-311, **18**-319, **18**-361, **18**-403
Smith, P.J. **6**-91, **10**-1861, **17**-63, **17**-66, **17**-69
Smith, P.L. **15**-2260
Smith, P.M. **10**-618, **16**-1515
Smith, R.A. **10**-812, **12**-182
Smith, R.A.J. **15**-1240, **15**-1139, **15**-1245
Smith, R.C. **10**-576, **13**-320, **16**-143, **16**-1778
Smith, R.D. **15**-2551, **15**-2559
Smith, R.D.J. **9**-103
Smith, R.G. **5**-245, **10**-1555, **19**-1514
Smith, R.J. **4**-140
Smith, R.K. **4**-175
Smith, R.R. **18**-882
Smith, R.S. **10**-570, **16**-654
Smith, S. **10**-80
Smith, S.C. **8**-207, **15**-443, **15**-1081, **15**-1804, **15**-2523, **18**-450
Smith, S.F. **10**-20
Smith, S.G. **10**-353, **10**-354, **10**-450, **10**-521, **13**-728
Smith, S.M. **15**-705
Smith, S.V. **4**-405, **4**-407
Smith, S.W. **10**-1474
Smith, T.D. **15**-509
Smith, T.L. **12**-521
Smith, W.B. **10**-139
Smith, W.E. **11**-514, **18**-189
Smith, W.N. **10**-1901
Smith. M.B. **10**-893
Smitha, G. **16**-156
Smithen, C.E. **15**-2547
Smithers, R. **12**-452, **15**-1246, **16**-763
Smithers, R.H. **16**-1336
Smithies, A.J. **15**-1366
Smolina, T.A. **18**-44, **18**-259
Smolinsky, G. **5**-430, **5**-431, **12**-239, **17**-491, **17**-493, **18**-589
Smolko, K.I. **16**-917
Smonou, I. **14**-266, **19**-226, **19**-983, **19**-1338
Smoot, J. **19**-1620
Smoter, N.J. **16**-154
Smrcina, M. **13**-244
Smrtka, M. **10**-1937
Smushkevich, Yu.I. **19**-426
Smyth, T. **10**-657
Smyth, T.A. **19**-414, **19**-415
Snagovskii, Yu.S. **16**-1967
Snaith, R. **13**-726
Snajdrova, R. **18**-389
Snapper, M.L. **15**-2403, **16**-672, **16**-776, **16**-899, **16**-1515, **16**-1540, **18**-621, **18**-859, **18**-889
Snatzke, G. **4**-120, **4**-277
Snavely, K. **9**-101
Sneddon, H.F. **19**-1754
Sneeden, R.P.A. **16**-863
Sneen, R.A. **10**-86, **10**-88, **10**-89, **10**-96, **10**-97, **16**-1669, **17**-39
Snelgrove, J.L. **18**-811
Snell, R.L. **15**-2452
Snider, B.B. **15**-937, **15**-1000, **15**-1011, **15**-1351, **15**-2390, **16**-1570, **16**-1571
Snieckus, V. **10**-1334, **10**-1348, **10**-1349, **12**-429, **12**-431, **12**-541, **13**-513, **13**-725, **13**-730, **15**-991, **16**-676, **18**-814
Snoble, K.A.J. **16**-1353
Snoonian, J.R. **5**-378
Snow, A.W. **16**-169
Snow, D.H. **10**-301

Snow, J.T. **18**-478
Snow, J.W. **16**-310
Snow, R.A. **2**-388
Snowden, D.J. **15**-913
Snowden, M. **18**-399
Snowden, R.L. **12**-695
Snushall, B. **3**-222
Snyckers, F. **11**-10
Snyder Jr., R.C. **10**-207
Snyder, C. **12**-465
Snyder, C.H. **14**-434
Snyder, D.C. **10**-1155
Snyder, E.I. **10**-173
Snyder, E.S. **10**-1855
Snyder, G.A. **4**-529
Snyder, H.R. **13**-839
Snyder, J.K. **4**-210, **15**-2295, **15**-2691
Snyder, J.P. **2**-99, **2**-100, **2**-107, **2**-210, **2**-252, **2**-275, **2**-376, **2**-382, **10**-1404, **10**-1438, **15**-1154, **15**-1240
Snyder, L. **15**-848
Snyder, L.C. **10**-144
Snyder, S.A. **15**-2258
So, C.M. **13**-198, **13**-291, **13**-495, **13**-516
So, J.-H. **5**-57
Soai, K. **10**-1034, **16**-462, **16**-605, **16**-679, **16**-1247, **19**-1071, **19**-1460
Soares, L.A. **16**-666
Soares, V.C.D. **16**-247
Sobczyk, L. **3**-16
Sobery, W. **12**-399
Sobkowiak, A. **19**-485
Sobolev, A.N. **3**-129
Sobrio, F. **16**-430
Socaci, C. **2**-485
Socen, H. **10**-985
Sodeoka, M. **12**-147, **16**-388
Södergren, M.J. **15**-2066, **17**-223, **19**-470
Soderquist, J. **10**-806
Soderquist, J.A. **10**-806, **10**-1876, **10**-1877, **12**-593, **15**-685, **15**-688, **15**-701, **15**-710, **15**-1802, **16**-756, **19**-1020
Soejima, T. **16**-1578
Soeta, T. **15**-1204, **16**-933
Sofia, M.J. **15**-282
Sofuku, S. **16**-1730
Sogon, T. **19**-1323
Soheili, A. **13**-718
Sohmiya, H. **7**-87, **7**-102
Sohn, E. **11**-458
Sohn, J.E. **12**-330
Sohn, M.-H. **10**-1114
Sohn, S.C. **10**-330
Sohn, S.S. **14**-302
Sohtome, Y. **16**-1480
Soignier, S. **18**-873
Sokol, A. **11**-139
Sokolov, V.I. **4**-1, **4**-26, **4**-484, **12**-16
Sokolova, T.N. **15**-279
Sokołowska, J. **16**-889
Solà, L. **15**-2588, **16**-682
Solà, M. **2**-9, **2**-146, **2**-170, **2**-340, **10**-879
Solabannavar, S.B. **16**-1209
Solans-Monfort, X. **18**-892
Solash, J. **10**-225
Solastiouk, B. **12**-761
Soldaini, G. **19**-745
Soldermann, N. **18**-734
Soldevilla, A. **18**-617
Soleilhavoup, M. **15**-379
Soler, T. **16**-884
Solin, N. **16**-949
Solis-Oba, A. **10**-1190
Solladié, G. **10**-1674, **10**-1117, **15**-1495, **16**-494, **16**-1176
Solladié, N. **3**-191
Sollenberger, P.Y. **16**-87, **16**-288
Sølling, T.I. **16**-49
Sollner, K. **7**-82
Solly, R.K. **14**-60
Solodenko, W. **16**-422
Solodova, K.V. **11**-171
Solotnov, A.F. **3**-115
Soloveichik, S. **19**-1
Solov'ev, V.P. **3**-115
Solov'yanov, A.A. **5**-136, **10**-360, **12**-703, **18**-439
Soloway, A.H. **12**-474
Solsona, B. **19**-459
Soltani, O. **19**-1183
Soltner, T. **15**-1609
Solv'yanov, A.A. **16**-512
Soman, R. **15**-1784. **19**-334
Somasundaram, M. **11**-268
Somayaji, V. **12**-517
Sombret, B. **14**-255
Sombroek, J. **2**-306
Somers, J.J. **15**-796
Somers, P.K. **16**-878
Somerville, R.F. **15**-1715
Someya, H. **10**-1363
Somfai, P. **5**-85, **10**-963, **15**-1376, **15**-2060, **18**-450, **18**-580, **18**-782, **18**-783
Sominsky, L. **19**-147
Sommazzi, A. **19**-1399
Sommer, H.Z. **10**-895
Sommer, J. **5**-15, **5**-17, **8**-18, **8**-26, **10**-404, **11**-487, **12**-48, **12**-49, **12**-357, **15**-1219, **18**-35
Sommer, K. **15**-966
Sommer, L.H. **10**-1393, **12**-455
Sommer, M.B. **16**-465
Sommers, A.H. **10**-1668
Somorjai, G.A. **15**-485
Somyo, T. **10**-1592
Son, E.-C. **13**-624
Son, H.S. **16**-334
Son, S. **10**-1473, **15**-2672
Son, S.U. **15**-1535, **15**-1550, **15**-1551, **15**-1556, **15**-2254, **16**-742
Son, T. **10**-2009
Son, Y.-C. **4**-112, **19**-232
Sonawane, H.R. **18**-220, **19**-443
Soncini, A. **2**-89
Sondheimer, F. **2**-270, **2**-287, **2**-293, **2**-300, **2**-301, **2**-302, **2**-315, **2**-320, **2**-322, **2**-325, **2**-327, **2**-329, **2**-334, **2**-354, **2**-358, **2**-359, **14**-331
Sone, T. **16**-1449, **16**-1480
Sonenfeld, D. **11**-139
Song, B.D. **16**-1614, **16**-1875
Song, C.-S. **10**-1380, **10**-1995, **13**-675
Song, C. **13**-529, **16**-776
Song, C.E. **10**-442, **10**-532, **10**-986, **11**-321, **11**-331, **15**-1834, **15**-1989
Song, D. **15**-1102
Song, F. **10**-935
Song, G. **16**-429, **16**-1235, **16**-1902, **19**-763
Song, H.-J. **10**-1938
Song, H.-Y. **16**-734
Song, J.-W. **6**-4
Song, J. **11**-314, **15**-1059, **16**-398
Song, J.I. **19**-1097
Song, J.J. **13**-348, **16**-452, **16**-599, **16**-1507
Song, K. **10**-2
Song, K.-S. **1**-115, **1**-117
Song, M.-P. **13**-503
Song, M. **16**-719, **16**-1561
Song, M.S. **19**-1590
Song, Q. **15**-1575, **15**-1576
Song, S.-E. **14**-14
Song, S. **15**-646
Song, S.H. **19**-1453
Song, W.M. **19**-933
Song, X. **13**-455
Song, Y.-L. **12**-479
Song, Y. **12**-478, **13**-397, **16**-322, **16**-1512
Song, Y.L. **12**-476
Song, Z.-L. **19**-83
Song, Z. **13**-728, **15**-2563, **16**-1572, **19**-647, **19**-650
Song, Z.L. **18**-135, **18**-158
Song. D.H. **16**-1496
Songstad, J. **8**-164, **10**-318, **10**-518
Songster, M. **16**-115
Soni, P. **10**-586
Sonmor, E.R. **19**-1130
Sonnet, P.E. **7**-58, **17**-199, **17**-224, **17**-339, **17**-363
Sonnichsen, G. **8**-71
Sonntag, O. **11**-579
Sono, M. **19**-441
Sonobe, H. **15**-1562
Sonoda, A. **14**-436, **19**-870
Sonoda, K. **15**-765

Sonoda, M. **15**-384
Sonoda, N. **3**-166, **10**-838, **10**-851, **10**-854, **10**-1294, **10**-1644, **10**-1971, **10**-1996, **12**-252, **12**-558, **12**-771, **13**-43, **13**-682, **13**-684, **13**-688, **14**-26, **15**-304, **15**-321, **15**-1355, **15**-1519, **15**-2008, **16**-626, **16**-2004, **19**-53, **19**-593, **19**-725, **19**-1574
Sonoda, T. **13**-24, **10**-496
Sonoda, Y. **15**-786
Sonogashira, K. **13**-582
Sonye, J.P. **12**-80, **18**-273
Soong, L.T. **15**-614
Sooriyakumaran, R. **7**-90
Soós, T. **15**-1051, **16**-218
Sørbye, K. **10**-795
Sorensen, C.M. **16**-1817
Sorensen, E.J. **15**-415
Sorensen, J.B. **3**-15
Sørensen, P.E. **10**-561, **16**-46
Sorensen, T.S. **3**-67, **4**-240, **5**-37, **5**-51, **5**-81, **10**-137, **10**-296, **10**-461, **10**-475, **17**-394, **18**-7, **18**-174, **18**-206
Sorenson, M.E. **15**-1412
Sorger, K. **5**-184
Soriano, J.M. **16**-1897
Sorimachi, K. **11**-314, **15**-1014, **15**-1015, **16**-936, **16**-991
Sorm, F. **11**-664
Sormunen, G.J. **16**-706
Sorokin, A.B. **19**-260, **19**-569
Sorokin, V.I. **18**-761
Sorokina, L.P. **19**-1097
Sorrenti, P. **16**-1199
Sorriso, S. **13**-773, **13**-774
Sosa-Rivadeneyra, M. **16**-681
Sosnicki, J.G. **15**-1400
Sosnovsky, G. **11**-180, **14**-168, **14**-219, **14**-247, **14**-268, **14**-271, **14**-273, **14**-320, **16**-96, **17**-523, **18**-924
Sosounk, S.E. **15**-1667
Sotiriou, C. **19**-326
Soto-Delgado, J. **15**-2282
Sotomatsu, T. **8**-184
Sotomayor, N. **16**-2078
Sott, R. **8**-225, **16**-488
Sotzing, G.A. **10**-670
Soucek, J. **15**-739
Soucy, C. **19**-1459
Soueidan, M. **11**-445
Soufi, J. **15**-2378
Soula, G. **10**-494
Soulen, R.L. **2**-266
Soulivong, D. **18**-873, appendixa-26
Souma, Y. **10**-1070, **15**-1500, **15**-1501
Soundararajan, N. **5**-414, **5**-416, **16**-1947
Soundararajan, R. **15**-90, **12**-513, **12**-514, **15**-697
Souppe, J. **16**-2113, **19**-950
Sousa, L.R. **18**-913
South, J.A. **13**-143
Southern, J.M. **15**-1414, **16**-2038
Southwick, P.L. **2**-454, **18**-258
Souto-Bachiller, F.A. **2**-239
Sowinski, A.F. **14**-178
Spaar, R. **10**-266
Spackman, I.H. **17**-65
Spada, G.P. **4**-194, **15**-163
Spafford, M.J. **16**-163
Spaggiari, A. **10**-1260
Spagnol, M. **10**-941
Spagnol, M.D. **10**-1564
Spagnolo, P. **12**-541, **15**-2080, **18**-327, **19**-1258
Spain, V.L. **19**-890
Spanedda, M.V. **16**-936
Spange, S. **9**-119
Spanget-Larsen, J. **2**-199
Spangler, C.W. **18**-560, **18**-592
Spangler, D.P. **10**-1438
Spaniol, T.P. **3**-125
Spanka, G. **4**-479
Spannenberg, A. **11**-507, **13**-98
Spannenberg, A. **15**-647
Sparacino, M.L. **16**-1817
Sparfel, D. **19**-271
Sparks, T. **18**-719
Spatola, A.F. **11**-686
Spawn, C. **10**-1219
Spear, R.J,. **5**-36, **5**-39, **10**-180
Specht, H. **2**-240
Speck, D.H. **3**-107
Speck, J. **11**-128
Speckamp, W.N. **15**-934, **16**-1844
Spector, M.L. **12**-776
Speer, H. **5**-142
Speier, J.L. **15**-739
Spek, A.L. **13**-244, **13**-732, **16**-853, **19**-209
Spellmeyer, D.C. **15**-104, **18**-493, **18**-518
Spencer, A. **13**-368
Spencer, J.B. **15**-150, **15**-1420, **15**-1421, **15**-1422, **15**-1423, **19**-1543
Spencer, J.N. **18**-606
Spencer, N. **3**-214, **3**-216
Spencer, T.A. **17**-55
Spencer, W.T. **13**-567
Spengler, T. **11**-406
Sperandio, A. **17**-218
Sperandio, D. **18**-879
Speranza, M. **10**-12, **10**-274, **10**-275
Speranza, M. **17**-99
Spero, D.M. **15**-2505
Sperotto, E. **13**-148
Sperry, L. **15**-241
Speth, D.R. **19**-450
Spevak, P. **19**-1251, **19**-1624
Spey, S.E. **3**-85
Speybroeck, V.V. **10**-1244
Speziale, A.J. **16**-1278, **16**-1981
Spialter, L. **10**-877, **16**-321, **16**-2065
Spicer, L.D. **19**-1426
Spieciarich, D. **19**-1166
Spiegel, B. I. **10**-1463
Spiegel, D.A. **14**-19, **19**-1387
Spiess, S. **10**-1513
Spietschka, E. **18**-230
Spillane, W.J. **11**-606
Spilling, C.D. **16**-1246, **19**-1197
Spillner, C.J. **5**-50
Spina, E. **16**-2273
Spina, K.P. **10**-1107
Spinacé, E.V. **19**-486
Spindler, J.-F. **13**-293
Spinelli, D. **8**-183
Spinicelli, L.F. **16**-90
Spino, C. **15**-2172, **16**-490
Spirikhin, L.V. **14**-428
Spitler, E.L. **2**-213
Spitzer, U.A. **19**-389, **19**-394, **19**-447
Spitzin, V.I. **17**-155
Spivey, K.M. **15**-1860
Spizzichino, S. **10**-1522
Spletstoser, J.T. **19**-1118
Spohn, R.J. **12**-557
Spolaore, B. **17**-220
Spoor, P. **10**-1546
Spoors, P.G. **16**-167
Spracklin, D.K. **4**-404
Sprecher, M. **10**-15, **16**-160
Spreti, N. **10**-438
Spring, F.S. **18**-113
Springall, H. D. **2**-409
Springer, D.M. **16**-1638
Springer, G. **8**-162
Springer, J.P. **4**-214
Springer, W.R. **18**-207
Sprott, K.T. **15**-2196
Sprules, T.J. **18**-642
Spruyt, P. **13**-606
Spryskov, A.A. **11**-48, **11**-200
Spurlock, S. **19**-429
Sputore, S. **19**-190
Squillacote, M. **4**-332, **4**-490
Squillacote, M.E. **4**-355, **15**-2183
Squires, R.R. **2**-26, **5**-107, **5**-114, **5**-133, **12**-671
Sraidi, K. **3**-19
Srebnik, M. **10**-1228, **12**-545, **15**-678, **15**-679, **15**-681, **15**-709, **18**-455
Sreedhar, B. **11**-223, **12**-116, **13**-205, **13**-509
Sreekumar, R. **11**-442, **15**-1074, **15**-2084, **19**-901
Sreenu, D. **17**-433
Sreeshailam, A. **15**-1401
Sridhar, B. **13**-494
Sridhar, C. **13**-205
Sridhar, M. **16**-1865, **16**-2283, **18**-316, **19**-1623

Sridharan, S. **10**-328
Sridharan, V. **15**-863, **15**-917, **15**-1592
Srihari, P. **10**-1205, **12**-129, **16**-550, **19**-1592
Srikanth, A. **15**-1997
Srikanth, G.S.C. **15**-1284, **15**-1289
Srikrishna, A. **19**-1373
Srinavasa, G.R. **19**-1720
Srinivas, C. **19**-1592
Srinivas, Ch. **13**-742
Srinivas, D. **16**-1235, **16**-1401, **16**-2034
Srinivas, G. **19**-18
Srinivas, K.A. **13**-115, **15**-1900
Srinivas, K.V.N.S. **16**-302, **16**-1750
Srinivas, P. **10**-876
Srinivas, P.V. **11**-128, **14**-313
Srinivas, R. **15**-1401, **19**-294, **19**-1244, **19**-1731
Srinivas, Y. **15**-1662
Srinivasa, G.R. **19**-1196
Srinivasan, C. **5**-408, **11**-575
Srinivasan, K.V. **11**-132, **11**-240, **11**-242, **11**-442, **13**-592, **13**-810
Srinivasan, M. **19**-363
Srinivasan, N.S. **19**-708
Srinivasan, P.S. **16**-875
Srinivasan, R. **4**-450, **7**-58, **8**-154, **19**-90, **19**-1014
Srinivasu, P. **11**-251
Sriramurthy, V. **4**-142, **15**-1418
Srisailas, M. **4**-80
Srivastava, A. **13**-388
Srivastava, N. **15**-1386
Srivastava, P.C. **12**-520, **15**-2386, **16**-2216
Srivastava, R.G. **19**-669
Srivastava, R.R. **10**-1237, **16**-1820
Srivastava, R.S. **12**-228, **15**-337, **15**-1503
Srivastava, S. **15**-120
Srivastava, S.K. **11**-228
Srivastava, V. **16**-1716
Srivastava, V.P. **18**-342
Srogl, J. **13**-158, **13**-623, **16**-2091, **19**-1220
Sromek, A.W. **13**-318, **15**-371, **15**-2582
Srzić, D. **5**-159
St-Onge, M. **10**-1025
St. Jean Jr., D.J. **15**-1331
St. Pierre, M.J. **7**-40
Staab, E. **15**-1994
Staab, H.A. **2**-337, **3**-33, **4**-76, **5**-342, **5**-346, **8**-99, **8**-198, **8**-199, **8**-200, **8**-202, **11**-486, **15**-5, **15**-35, **16**-1776, **19**-1116
Stabba, R. **15**-829
Staben, S.T. **15**-1009, **18**-165
Stabler, S.R. **16**-1817
Stacey, F.W. **15**-296, **15**-1644
Stach, H. **16**-1971
Stachel, S.J. **19**-1439
Stachissini, A.S. **16**-281, **16**-288
Stack, D.E. **12**-591, **12**-630, **16**-2011
Stack, T.D.P. **15**-1873
Stackhouse, J. **4**-35
Stadler, A. **7**-107, **7**-110, **10**-727, **13**-248
Stadler, M. **16**-394
Stadmüller, S. **16**-2208, **16**-2209
Stafford, D.G. **15**-2510
Stafford, R.L. **15**-1932
Stahl, D. **5**-68
Stahl, F. **2**-340, **13**-52
Stahl, M. **19**-1699
Stahl, N. **3**-23
Stahl, R.E. **4**-81
Stahl, S.S. **10**-1030, **15**-329, **15**-346, **15**-419, **16**-1842, **16**-1966, **19**-128, **19**-715
Stähle, M. **12**-417
Stahlecker, H.M. **16**-1408
Stahly, B.C. **13**-754
Stahly, G.P. **13**-754
Staib, R.R. **15**-2319
Stainforth, N.E. **16**-396
Stairs, R.A. **19**-604, **19**-605
Staklis, A. **18**-301
Staley, S.W. **2**-273, **4**-443, **5**-105, **15**-667
Stalick, W.M. **12**-57, **12**-74, **15**-325, **15**-754, **15**-756, **19**-409
Stalinski, K. **15**-1338, **15**-1339
Stalke, D. **2**-90, **5**-184
Stallman, J.B. **15**-918
Stals, J. **1**-56
Stam, C.H. **2**-68, **11**-654
Stambuli, J.P. **15**-2159, **15**-2160
Stamhuis, E.J. **16**-87
Stamm, H. **10**-1646
Stammann, G. **15**-31
Stammler, H.-G. **5**-182
Stanbury, P. **15**-2427
Standen, M.C. **16**-1444
Stanetty, P. **10**-1339, **18**-389
Stanforth, S.P. **13**-651
Stang, P.J. **5**-69, **5**-371, **5**-391, **10**-263, **10**-264, **10**-271, **10**-411, **10**-1461, **11**-348, **13**-29, **13**-440, **13**-543, **13**-582, **13**-628, **15**-36, **15**-107, **16**-1677, **17**-318
Stangeland, E.L. **19**-911
Stangeland, L.J. **10**-518
Stanger, A. **2**-6, **2**-71, **2**-88, **2**-102
Staninets, V.I. **15**-93
Stankovic, S. **19**-520, **19**-522
Stanley, J.H. **14**-496
Stanley, J.P. **14**-77, **18**-789
Stanley, L.M. **15**-2110, **15**-2144, **16**-680
Stanovnik, B. **15**-2105
Stansbury, H.A. **14**-333
Stanton, J.F. **2**-280, **8**-116
Stanton, M.G. **16**-1786
Stanway, S.J. **17**-214
Staples, M.A. **2**-211
Staral, J.S. **2**-191, **2**-231, **10**-214, **11**-16
Starer, I. **18**-20, **18**-47
Starikov, E.B. **3**-75
Starikova, Z.A. **16**-680
Staring, E.G.J. **16**-2198, **16**-2201
Stark, B.P. **17**-427, **17**-499, **17**-502, **17**-510, **17**-516
Stark, T.J. **17**-145
Starks, C.M. **10**-484, **10**-485, **10**-628, **10**-720, **10**-1106, **10**-1708, **10**-1932, **15**-2485, **16**-1281
Starner, W.E. **16**-883
Starnes, S.D. **8**-180
Staros, J.V. **18**-528
Stashenko, E.E. **11**-366
Staude, E. **10**-403, **10**-1180
Staudinger, H. **19**-1259
Stauffer, R.D. **17**-342
Stavber, G. **14**-157
Stavber, S. **11**-309, **12**-114, **12**-133, **14**-157, **14**-187, **19**-666
Staveley, L.A.K. **3**-110
Stavenger, R.A. **10**-1746
Stavrescua, R. **7**-99
Stawinski, J. **10**-633
Stazi, F. **13**-284
Stead, D. **6**-37
Stec, W.J. **16**-1361
Stecher, H. **4**-205
Steckel, T.F. **17**-397
Steckhan, E. **14**-456, **15**-2286, **19**-596
Steel, A.J. **14**-73, **14**-116
Steel, P.G. **12**-588
Steel, P.J. **15**-135, **15**-139
Steele, B.R. **12**-570, **10**-1995, **16**-1010
Steele, F. **2**-472
Steele, W.R.S. **8**-96
Steele, W.V. **4**-243
Steenken, S. **5**-12, **9**-67, **10**-47, **10**-346
Steensma, R.W. **16**-2310
Steenwinkel, P. **4**-95
Steere, J.A. **7**-101
Stefane, B. **10**-1619, **16**-1790, **17**-367
Stefanelli, S. **15**-1836
Stefani, A. **14**-112
Stefani, H.A. **7**-70, **13**-577, **14**-361, **14**-362, **14**-364, **15**-1436, **16**-240, **16**-266
Stefania, R. **16**-1872
Steffens, C. **15**-949
Stefinovic, M. **18**-814
Stegel, F. **13**-9
Stegemann, J. **2**-193
Steglich, W. **16**-1727
Stegmann, V.R. **16**-2210, **16**-2211
Stehle, N. **10**-1345

Stein, A.R. **10**-88, **10**-89, **10**-94, **16**-2250
Stein, D. **19**-1293
Stein, K. **18**-572
Stein, M. **5**-242
Stein, S.E. **5**-236
Stein, Z. **1**-71
Steinbach, R. **10**-1453, **10**-1455, **10**-1584
Steinbauer, E. **19**-1734
Steinbeck, K. **12**-369, **12**-653
Steinberg, H. **11**-644, **19**-1728
Steiner, A. **15**-1958
Steiner, D. **10**-964, **16**-560
Steiner, D.D. **12**-148
Steiner, E. **2**-89, **15**-1775
Steiner, G. **15**-2433, **15**-2438
Steiner, R.P. **18**-494
Steiner, T. **3**-6, **3**-16, **3**-40, **3**-75
Steinhoff, B.A. **19**-128
Steinman, D.H. **15**-2158
Steinmann, J.E. **15**-291
Steinmetz, A. **19**-396
Steinmetz, M.G. **7**-58
Steinreiber, A. **10**-727
Stella, L. **5**-256, **18**-924
Stelter, E.D. **11**-29
Stelzer, F. **15**-853
Stemerick, D.M. **10**-925
Stemke, J.E. **17**-273, **17**-278
Stemmler, R.T. **15**-1269
Stemmler, T.L. **10**-1403
Stemp, G. **15**-1816
Stengel, P.J. **19**-1507
Stenkula, M. **15**-274
Stensland, P. **17**-125
Stent, M.A.H. **10**-1619
Stenzel, J. **10**-670, **11**-258
Stenzel, W. **13**-507
Stepanenko, V. **19**-972, **19**-1234
Stepanov, N.F. **15**-179
Stephan, D.W. **19**-1123
Stéphan, E. **16**-487
Stephan, H. **3**-144
Stephan, M. **16**-1963
Stephens, G.M. **15**-662
Stephens, J.R. **12**-708
Stephens, P.J. **4**-115, **4**-119
Stephens, R.D. **13**-580
Stephenson, B. **10**-284, **10**-1117, **18**-98
Stephenson, C. **18**-645
Stephenson, C.R.J. **15**-1269
Stephenson, D.S. **4**-382
Stephenson, L.M. **14**-250, **14**-263, **19**-450
Stephenson, P.T. **16**-1600
Stepien, B.T. **2**-207
Stepień,B.T. **2**-61
Stepukhovich, A.D. **18**-54
Stercho, Y.P. **19**-1471
Sterk, H. **15**-2426
Sterling, J.J. **10**-1425, **10**-1443, **15**-1147
Stern, A.G. **18**-88
Stern, C.L. **15**-2025, **15**-2027
Stern, E.W. **12**-776
Sternativo, S. **10**-694
Sternbach, D.D. **10**-1824
Sternberg, H.W. **15**-1496
Sternhell, S. **4**-531
Sternhell, S. **14**-371, **12**-750
Sternson, L.A. **13**-858
Sterrenburg, J.G. **18**-848
Stetter, H. **10**-1773, **12**-653, **15**-1462, **15**-1462, **15**-1487, **16**-722, **16**-1588
Stevenazzi, A. **15**-1539, **15**-1560
Stevens, C.L. **16**-371, **17**-175, **19**-82
Stevens, E.S. **4**-129, **4**-150
Stevens, I.D.R. **5**-414, **10**-353
Stevens, I.W. **5**-20
Stevens, J.A. **13**-21
Stevens, J.B. **16**-1702
Stevens, M.F.G. **12**-746
Stevens, R.M. **10**-1049
Stevens, R.R. **17**-248, **17**-282
Stevens, R.V. **6**-46, **19**-234
Stevens, T.S. **11**-607, **13**-847, **13**-862, **18**-1, **18**-309, **18**-411, **18**-415, **18**-443
Stevens, W. **11**-488, **16**-1729
Stevens, W.R. **15**-1625
Stevenson, C.D. **2**-213, **2**-244, **2**-268, **2**-319
Stevenson, D.P. **15**-477
Stevenson, G.R. **2**-99, **2**-365
Stevenson, J.P. **5**-325
Stevenson, P. **10**-1311
Stevenson, R. **18**-113
Stevenson, S. **2**-405
Stevenson, T. **10**-1745
Stevenson, T.A. **4**-418
Steward, O.W. **15**-1179, **17**-185
Stewart, A.T. **19**-1738
Stewart, D.R. **3**-136
Stewart, E.T. **1**-4
Stewart, I.C. **15**-1429, **18**-861
Stewart, J.D. **18**-389
Stewart, J.J.P. **2**-18, **2**-19, **15**-2283
Stewart, J.M. **16**-1932
Stewart, R. **1**-35, **3**-28, **8**-1, **8**-32, **8**-33, **8**-55, **8**-148, **8**-154, **12**-91, **19**-2, **19**-92, **19**-314, **19**-447
Stewart, S.G. **10**-974
Stewart, S.K. **12**-518
Stewart, T.E. **4**-108
Stewen, U. **5**-249
Stgring, P. **13**-521
Stickley, K.R. **5**-342
Stickney, C.A. **19**-574
Stien, D. **15**-1378
Stiff, C.M. **16**-889
Stigliani, W.M. **4**-486
Stiles, M. **16**-1302, **16**-1303
Stiles, P.J. **3**-104, **4**-128
Still, I.W.J. **19**-1597
Still, W.C. **4**-144, **15**-691, **16**-1681
Stille, J.K. **10**-1434, **10**-1461, **10**-1462, **10**-1488, **10**-1508, **10**-1967, **10**-1969, **12**-261, **12**-287, **12**-289, **13**-246, **16**-1061, **16**-2032, **17**-330
Stille, J.R. **18**-642
Stilz, H.U. **16**-6
Stimson, C.C. **11**-335
Stimson, V.R. **12**-65
Stinson, S.R. **19**-847
Stirling, C. **4**-48, **5**-126, **10**-863, **19**-773, **19**-785
Stirling, C.J.M. **2**-94, **4**-30, **4**-48, **4**-49, **6**-15, **9**-5, **10**-239, **10**-408, **10**-431, **15**-21, **16**-1470, **17**-49, **17**-106, **17**-121, **17**-121, **18**-492
Stock, L.M. **10**-331, **11**-25, **11**-31, **11**-49, **11**-51, **11**-85, **11**-93, **11**-95
Stockenhuber, M. **11**-579
Stöckigt, J. **16**-1312
Stockmann, V. **15**-1095
Stocky, T.P. **19**-1058
Stoddard, G.J. **18**-657
Stoddart, J.-F. **2**-342, **3**-106, **3**-194, **3**-195, **3**-196, **3**-197, **3**-199, **3**-201, **3**-210, **3**-214, **3**-216, **3**-220, **4**-169
Stodola, F.H. **16**-1704
Stofer, E. **14**-476
Stoffregen, S.A. **16**-1439
Stofko Jr., J.J. **18**-49
Stohrer, W. **10**-242
Stoicheff, B.P. **1**-76, **2**-36
Stokes, S. **17**-190
Stokes, S.S. **18**-621
Stoll, M. **16**-2168
Stolle, W.T. **16**-1264
Stolow, A. **5**-127
Stolow, A. **6**-16
Stolow, R.D. **4**-382
Stoltz, B.M. **8**-92, **10**-1520, **10**-1735, **17**-282
Stolz, L.A. **18**-695
Stončius, S. **19**-1156
Stone, A.J. **18**-556
Stone, D.A. **16**-1842
Stone, F.G.A. **2**-196, **12**-287
Stone, R.M. **9**-36
Stoner, E.J. **10**-621
Storch, D.M. **2**-20
Storch, E.C. **16**-847
Storer, J.W. **17**-55
Storer, R.I. **16**-358, **16**-1848
Storesund, H.J. **18**-22, **18**-102
Storey, J.M.D. **16**-1583, **16**-2067
Stork, G. **5**-197, **10**-241, **10**-583, **10**-1118, **10**-1324, **10**-1740, **10**-1754, **10**-1771, **10**-1777, **10**-1791, **10**-1796, **10**-1797, **12**-433, **15**-817, **15**-1467, **15**-2273, **16**-1119, **16**-1336

Storr, R.C. **15**-2297, **15**-2371, **18**-506
Story, P.R. **2**-385, **10**-142, **10**-144, **14**-286, **17**-520, **17**-521, **17**-522, **17**-524, **19**-357, **19**-363
Story, R.R. **18**-105
Stothers, J.B. **5**-132, **5**-133, **6**-74, **18**-94, **18**-203
Stotter, P.L. **12**-162, **19**-889
Stottlemeyer, T.R. **7**-72
Stoughton, R.W. **4**-59
Stout, C.W. **15**-2351
Stoute, V. **18**-404
Stoutland, P.O. **10**-379
Stowell, J.C. **5**-105, **10**-1264, **16**-455, **16**-1014
Stowers, K.J. **13**-136
Stoyanov, E. **8**-119
Stoyanov, E.S. **8**-91
Stoyanova, I.V. **8**-91
Stoye, D. **16**-1866
Stępień, B.T. **2**-153
Strachan, A.N. **11**-101, **11**-148
Strachan, W.S. **18**-113
Stracke, M.P. **15**-1436
Stradiotto, M. **15**-335
Strand, J.W. **10**-908, **11**-183
Strange, J.H. **4**-395
Strassner, T. **15**-270, **15**-2106, **19**-458
Stratakis, M. **14**-260, **14**-262
Stratton, B. **5**-408
Strauss, C.R. **7**-109, **7**-121, **7**-123, **11**-188, **19**-949
Strauss, H.L. **4**-336
Strauss, M.J. **13**-9, **13**-10
Strauss, U. **1**-100
Strausz, O.P. **5**-385, **15**-1947, **18**-231, **18**-233, **18**-235
Strazzari, S. **5**-225
Strazzolini, P. **12**-735, **16**-1821, **19**-219
Street, L.J. **12**-387
Streeter, D.L. **18**-122
Strege, P.E. **2**-48, **2**-49, **10**-1524
Strehmel, V. **9**-119
Streib, H. **13**-851
Streib, W.E. **15**-2645
Streicher, H. **5**-96
Streicher, W. **13**-88, **13**-840
Streiner, T. **3**-54
Streith, J. **15**-1775, **16**-297, **18**-515
Streitwieser Jr., A. **1**-52, **2**-2, **2**-28, **2**-59, **2**-127, **4**-23, **5**-137, **5**-157, **6**-90, **7**-17, **8**-16, **8**-17, **8**-60, **8**-65, **8**-66, **8**-71, **8**-75, **8**-76, **8**-77, **8**-78, **8**-80, **8**-81, **8**-186, **10**-11, **10**-99, **10**-299, **10**-428, **11**-642, **16**-191
Streitwieser, A. **2**-24, **4**-323, **5**-202, **5**-203, **8**-15, **8**-67, **8**-81, **8**-86, **8**-229, **8**-232, **10**-1, **10**-3, **10**-232, **10**-244, **10**-285, **10**-293, **10**-303, **10**-1682, **16**-454
Strekowski, L. **14**-387, **16**-1291
Strelenko, Y.A. **4**-373
Streuff, J. **15**-2021
Strickland, J.B. **16**-736
Strickland, S.M.S. **18**-930
Strieter, E.R. **13**-190, **13**-191
Strijtveen, B. **4**-213
Strine, J. **13**-285
Strobel, E. **16**-1953
Strobel, T.A. **3**-19, **3**-164
Stroh, R. **11**-360, **11**-361
Strohmeier, W. **12**-86
Strologo, S. **13**-652
Ström, P. **16**-1941
Strömberg, S. **13**-423
Stromquist, P. **19**-1595
Strömqvist, M. **16**-263
Strong, J.M. **8**-83
Strongin, R.M. **13**-817
Stropnik, T. **11**-232
Strotman, N.A. **10**-1730
Stroud, M.A. **11**-76
Stroud, S.G. **19**-442
Strozier, R.W. **2**-388, **15**-81
Strub, H. **2**-243
Strübing, D. **11**-521
Struble, J.R. **15**-2340
Struchkov, Y. **5**-276
Strukelj, M. **15**-21
Strunk, S. **18**-449
Struzynski, C.P. **10**-883
Stryker, J.M. **16**-1121
Strzalko, T. **15**-1042
Stuart, A.M. **15**-1610
Stuart, R.S. **12**-55
Stubbs, M.E. **18**-682
Stucchi, E. **15**-1141
Stuchal, F.W. **10**-301
Stuckwisch, C.G. **15**-2105
Studabaker, W.B. **15**-2498
Stüdemann, T. **10**-1470
Studer, A. **11**-423, **13**-593, **14**-432, **18**-57, **19**-173, **19**-1661
Studer, M. **11**-543, **16**-1237
Studzinskii, O.P. **10**-420
Stuermer, R. **12**-484
Stuhr-Hansen, N. **19**-1690
Stull, D.R. **1**-99
Stupp, S.I. **17**-450
Stupperich, C. **2**-480
Sturla, S.J. **15**-1001, **15**-1559
Stürmer, R. **15**-733, **16**-752
Styler, S.A. **10**-916
Su, A.C.L. **15**-833
Su, C.-Y. **19**-1118
Su, C. **16**-1230
Su, D. **13**-106
Su, F.-Y. **16**-1746
Su, H. **15**-2252, **17**-220
Su, J. **15**-2094, **15**-2697
Su, J.T. **19**-188
Su, K.-X. **15**-1906
Su, L. **15**-1218
Su, M.-D. **18**-626
Su, M. **15**-176, **16**-1378
Su, M.D. **4**-173, **4**-299
Su, Q. **10**-1478, **15**-66
Su, T.M. **18**-545, **18**-546
Su, W. **10**-634, **10**-801, **12**-660, **16**-743, **16**-910, **16**-944, **19**-686, **19**-1678
Su, X.-P. **10**-863
Su, X. **13**-129, **16**-776
Su, Y. **13**-431
Su, Z. **16**-1084
Suarez, A. **12**-288, **15**-649, **19**-1143
Suarez, J. **10**-1750
Suarez, P.A.Z. **9**-122, **16**-247
Subasi, N.T. **11**-422
Subba Rao, B.C. **12**-465, **19**-965, **19**-1615
Subba Rao, G. **15**-565
Subba Rao, G.S.R. **11**-370
Subba Rao, O. **5**-437
Subba Rao, Y.V. **11**-686
Subba Reddy, B.V. **10**-707, **10**-1656, **11**-192, **15**-310, **16**-1555, **19**-1244, **19**-1592
Subbaraj, A. **5**-437
Subbaraman, J. **10**-392
Subbaraman, L.R. **10**-392
Subbarao, Y.T. **16**-1785
Subbotin, O.A. **4**-346, **9**-34
Subedi, R. **16**-1608
Subhas, M.S. **13**-494
Subhash, P.V. **16**-1892
Subong, A.P. **19**-729
Subotkowski, W. **11**-599, **18**-800, **18**-951
Subrahmanyam, C. **12**-517
Subramaniam, B. **9**-101
Subramaniam, R. **15**-1290
Subramanian, L.R. **5**-69, **10**-263, **10**-264, **10**-411, **10**-1435, **11**-498, **13**-29, **15**-36, **15**-107, **16**-2174
Subramanian, R. **5**-416, **10**-1711
Subrmanyam, R.V.K. **10**-947
Suchan, S.D. **10**-1292
Suchanek, P. **16**-1101
Suda, H. **4**-182
Suda, K. **18**-142, **18**-154, **18**-369
Suda, M. **2**-198, **2**-245
Sudalai, A. **10**-679, **10**-1132, **11**-240, **11**-288, **11**-442, **13**-394, **15**-299, **15**-1768, **15**-2047, **15**-2061, **15**-2062, **16**-1780, **19**-319, **19**-621
Sudha, R. **16**-1139
Sudhakar, C. **15**-1662
Sudo, R. **10**-944
Sudo, T. **15**-789
Sudo, Y. **15**-2322
Sudrik, S.G. **18**-220
Sue, R.E. **12**-609
Sueda, T. **19**-533
Suehiro, T. **14**-114

Suematsu, H. **12**-395, **15**-2515
Suemitsu, R. **12**-568, **10**-1761, **10**-1960, **10**-1962, **12**-561, **13**-686
Suemune, H. **15**-1481
Suen, T. **15**-1291
Suenaga, M. **3**-134
Suenaga, T. **15**-2248
Suenaga, Y. **16**-1913
Suenram, R.D. **19**-349, **19**-370
Suero, M.G. **15**-2526
Suga, S. **10**-1830, **11**-381, **14**-53, **14**-327, **15**-2347, **16**-1492
Sugahara, H. **18**-535
Sugai, S. **17**-183
Sugamoto, K. **15**-198, **15**-199
Sugasawa, S. part 2-6
Sugasawa, T. **11**-391, **11**-558, **11**-559, **11**-564, **16**-1102
Sugathapala, P.M. **15**-2677
Sugawara, A. **18**-141
Sugawara, M. **10**-326
Sugawara, S. **15**-2603
Sugawara, Y. **13**-401
Sugden, J.K. **19**-1229
Sugden, S. **10**-330
Suggs, J.W. **19**-81
Sugi, Y. **13**-678, **13**-679
Sugihara, H. **15**-1403, **19**-1756
Sugihara, T. **11**-329, **15**-872, **15**-1546, **15**-1578, **15**-2595, **16**-1634
Sugihara, Y. **7**-23, **15**-1998, **15**-2000, **17**-368
Sugimoto, A. **3**-31, **16**-1276
Sugimoto, H. **10**-741, **16**-1799
Sugimoto, M. **16**-1537
Sugimoto, O. **12**-617
Sugimoto, T. **10**-2008, **15**-1852, **15**-2115
Sugimura, T. **10**-728
Sugino, E. **19**-1271
Suginome, H. **10**-903, **15**-358, **18**-364, **19**-59
Suginome, M. **10**-713, **15**-841, **16**-704, **16**-1168, **16**-2252
Sugiono, E. **16**-400, **16**-1530, **19**-1152
Sugita, K. **15**-452
Sugita, N. **13**-677, **19**-1716
Sugita, T. **11**-381, **12**-648
Sugiura, F. **11**-513
Sugiura, M. **10**-1534, **15**-1277, **15**-1419, **15**-1437, **15**-1508, **16**-359, **16**-776, **16**-947, **16**-952, **16**-953
Sugiura, T. **5**-312
Sugiyama, E. **19**-1127
Sugiyama, J. **14**-289
Sugiyama, T. **15**-1684
Sugoh, K. **12**-791
Suguro, M. **13**-719
Suh, D.J. **10**-893
Suh, J.M. **16**-986
Suh, Y.S. **16**-837, **16**-1610
Suh. W.H. **15**-1558
Suhendra, M. **19**-1184
Suhr, H. **13**-89
Sui, J.K. **19**-1022
Suib, S.L. **19**-232
Suk, J.Y. **18**-226
Sukata, K. **10**-1019, **16**-1494, **16**-2163
Sukcharoenphon, K. **2**-473
Sukirthalingam, S. **15**-917
Sukumar, R. **10**-679
Sukumaran, K.B. **18**-506
Sulikowski, G.A. **12**-310, **12**-391
Sulikowski, M.M. **12**-391
Sullivan, A.B. **19**-841
Sullivan, D.F. **16**-1179, **16**-2134, **19**-52
Sullivan, E.L. **16**-2303
Sullivan, G.R. **4**-216
Sullivan, P.J. **5**-215
Sullivan, R.J. **11**-304
Sulmon, P. **16**-1280
Sultana, S.S. **10**-703, **13**-390, **16**-802
Sulzbach, H.M. **2**-279, **2**-289, **2**-290
Sulzbach, R.A. **12**-582
Sumbler, B.L. **16**-339
Sumi, S. **19**-107
Sumida, S.-i. **16**-640
Sumida, Y. **10**-1576
Sumihara, H. **16**-2141
Sumino, Y. **10**-1971, **19**-1574
Sumitani, K. **10**-1309
Sumitani, N. **15**-57
Sumiya, T. **10**-1970, **16**-1085, **19**-515
Sumiyoshi, Y. **3**-15
Summerhays, K.D. **8**-243
Summers, B. **14**-125, **14**-127
Summerville, R.H. **10**-272
Sumonja, M. **2**-263
Sumpter, C.A. **2**-299
Sun, B. **15**-1921
Sun, C. **12**-523
Sun, C.-L. **13**-517
Sun, C.-S. **17**-234
Sun, C. **8**-229, **16**-489
Sun, F. **4**-240, **13**-148, **13**-205
Sun, G.-r. **15**-1889
Sun, G.-F. **16**-591
Sun, G. **11**-334, **16**-1084
Sun, H.-B. **11**-137
Sun, H. **9**-92
Sun, H.H.Y. **15**-2136
Sun, I.-W. **13**-500
Sun, J. **10**-976, **16**-1879, **19**-1041, **19**-1156
Sun, K.-L. **16**-322
Sun, K. **19**-1026
Sun, L. **10**-2, **19**-1017
Sun, N. **19**-168, **19**-1158
Sun, P. **13**-450
Sun, S.F. **16**-89
Sun, W.-H. **15**-2660
Sun, W. **10**-1224, **15**-351, **15**-1980, **16**-407, **16**-1498
Sun, X.-L. **16**-1481, **16**-1597, **18**-148
Sun, X. **5**-191, **10**-109, **10**-1224, **10**-1703, **15**-1829, **16**-1180, **16**-2012, **16**-2307, **19**-1014
Sun, Y. **5**-405, **15**-460, **19**-1017, **19**-1142
Sun, Z.-P. **10**-1607
Sun, Z. **13**-620, **16**-776
Suna, E. **10**-1464, **12**-107, **13**-523
Sunagawa, M. **16**-2143
Sundaralingam, M. **5**-91
Sundararajan, G. **10**-974, **18**-867
Sundberg, R.J. **18**-761
Sundén, H. **19**-516
Sunderhaus, J.D. **10**-714
Sundermeier, M. **13**-860
Sundermeier, U. **19**-231
Sundermeyer, J. **8**-98, **15**-1882
Sundgren, A. **10**-1189
Sung, B.S. **15**-1559
Sung, D.D. **16**-1615
Sung, H.R. **15**-974
Sung, S.-y. **10**-1489, **10**-1546, **15**-1248, **16**-563
Sunjic, V. **15**-635, **10**-910
Sunkel, J. appendixa-22, appendixa-23
Sunko, D.E. **6**-76, **6**-79, **6**-83, **10**-128, **10**-133, **10**-198, **10**-221
Sunley, G.J. **18**-873
Sunner, J. **10**-447
Sunoj, R.B. **16**-792, **16**-984, **18**-229
Suorsa, T. **3**-179
Superchi, S. **4**-115
Suppan, P. **7**-36, **19**-1665
Supsana, P. **17**-438
Surampudi, V. **11**-154
Surendra, K. **10**-689, **19**-192
Suresh Babu, V.V. **16**-1085
Suresh, C.H. **2**-25, **2**-31, **15**-100
Suri, J.T. **16**-961, **16**-1081
Suri, S.C. **12**-743
Suriaatmaja, M. **19**-380
Suriano, J.A. **15**-1538
Surivet, J.-P. **15**-847
Surman, P.W.J. **2**-226
Surmina, L.S. **10**-1683
Surridge, J.H. **13**-691
Suryavanshi, G. **15**-2061
Surzur, J. **15**-53, **19**-100
Suschitzky, H. **13**-476, **13**-802, **13**-804, **19**-291
Sushko, T.P. **18**-226
Suslick, K.S. **7**-70, **7**-73, **7**-74, **7**-75, **7**-76, **7**-83, **7**-85, **7**-92
Suslova, E.N. **15**-305, **19**-1766
Süss, H.U. **2**-198, **2**-199
Süsse, M. **16**-1970

Sustmann, R. **5**-256, **5**-304, **15**-2245, **15**-2280, **15**-2289, **15**-2385
Susuki, S. **5**-291
Susuki, T. **10**-472
Susz, P.B. **11**-476
Sütbeyaz, Y. **10**-985, **19**-379
Suter, C. **18**-571
Sutherland, A.G. **17**-349
Sutherland, A.J. **12**-279
Sutherland, I.O. **3**-106, **3**-158, **18**-417, **18**-420, **19**-1443
Sutherland, R.G. **5**-427, **7**-83
Suto, Y. **14**-297, **16**-403
Sutton, A.E. **18**-859
Suvorov, N.N. **19**-426
Suwa, A. **10**-1091
Suwa, T. **16**-356, **16**-643, **19**-1127
Suwinski, J. **13**-44
Suyama, T. **16**-1816
Suzu, T. **15**-1998
Suzuka, T. **10**-1529
Suzuki, A. **10**-1876, **10**-1877, **10**-1878, **10**-1978, **12**-515, **12**-566, **13**-486, **13**-487, **13**-490, **13**-694, **13**-790, **13**-805, **14**-114, **15**-671, **15**-729, **15**-735, **15**-1256, **15**-1259, **15**-1264, **15**-1282, **16**-735, **16**-1182, **17**-165, **18**-451, **18**-473, **18**-479, **18**-484
Suzuki, D. **15**-2592, **15**-2647
Suzuki, H. **10**-944, **10**-1098, **10**-1272, **11**-123, **11**-141, **11**-418, **12**-529, **13**-145, **13**-159, **13**-261, **13**-646, **13**-768, **13**-840, **19**-1517, **19**-1716
Suzuki, K. **13**-55, **14**-225, **16**-1506, **18**-13, **18**-159, **18**-254, **19**-1260
Suzuki, M. **10**-1752, **10**-1809, **10**-1970, **16**-1148, **18**-151
Suzuki, N. **15**-989
Suzuki, R. **13**-496, **16**-355
Suzuki, S. **6**-90, **10**-1644, **14**-327, **16**-458, **16**-1252, **19**-629, **19**-1163
Suzuki, T. **10**-695, **10**-1762, **12**-116, **12**-147, **13**-171, **13**-401, **13**-500, **15**-222, **15**-1038, **15**-1193, **16**-601, **16**-1090, **16**-1146, **16**-1202, **16**-1792, **16**-2139, **18**-385, **19**-144, **19**-482, **19**-864
Suzuki, Y. **13**-326, **13**-327, **16**-1281, **16**-1507, **16**-1582
Svanholm, U. **18**-716
Švec, P. **16**-1993
Svedendahl, M. **15**-1110
Svendsen, B.H. **15**-775
Svendsen, J.S. **15**-1830, **15**-1840
Svensen, H. **13**-766
Svensson, M. **13**-423, **13**-427
Svensson, S. **15**-97
Svensson, T. **18**-40
Sveshnikova, E.B. **7**-30
Svetlakov, N.V. **10**-1112
Svinivas, D. **16**-1713
Sviridov, S.I. **15**-1702
Svoboda, J.J. **5**-32, **5**-56, **5**-62
Svoboda, M. **17**-20, **17**-32, **17**-100, **17**-261, **17**-382
Svyatkin, V.A. **4**-346
Swafford, A.M. **15**-1714
Swafford, R.L. **18**-914
Swager, T.M. **3**-200, **5**-234
Swain, C.G. **6**-95, **9**-62, **9**-63, **9**-64, **10**-370, **11**-275, **12**-678, **13**-30, **13**-32, **13**-806, **13**-808, **19**-1737, **19**-1739
Swain, C.J. **5**-149
Swain, M.S. **9**-62, **9**-63
Swallow, S. **16**-777
Swamer, F.W. **16**-2126
Swami, S.S. **17**-435, **19**-938, **19**-944
Swaminathan, S. **10**-247, **16**-1116, **18**-270
Swamy, N.R. **10**-1003
Swamy, T. **11**-217, **16**-1555
Swan, J.M. **10**-857, **10**-862
Swann, B.P. **19**-391
Swann, E. **18**-765
Swansborough, K.F. **19**-10
Swanson, D.R. **12**-646
Swanwick, M.G. **19**-1202
Swapna, G.V.T. **15**-2462
Swapna, K. **13**-151
Swarbrick, M.E. **18**-391, **18**-450, **18**-741
Swarnalakshmi, S. **19**-1056
Swartz, J.E. **13**-64
Swartz, T.D. **10**-192
Swartzendruber, J.K. **12**-227
Swarup, S. **10**-388
Sweany, R.L. **15**-502
Sweat, F.W. **19**-614
Swedlund, B.E. **11**-271, **15**-1759, **15**-1764
Swedo, R.J. **19**-96
Sweeney, J.B. **18**-781
Sweeney, W.A. **2**-412, **11**-469
Sweeney, Z.K. **16**-730
Sweeting, L.M. **4**-215, **4**-216
Sweetman, B.J. **16**-189
Sweigart, D.A. **16**-742
Sweis, R.F. **10**-1729
Swensen, W.E. **16**-1339
Swern, D. **10**-768, **10**-773, **10**-774, **12**-461, **14**-219, **14**-244, **14**-247, **14**-268, **14**-271, **15**-28, **19**-148, **19**-154, **19**-157, **19**-625, **19**-632, **19**-674, **19**-696, **19**-1764
Swett, L.R. **10**-1668, **16**-1837
Swierczek, K. **13**-44
Swierczewski, G. **10**-1588
Swiger, R.T. **10**-301
Swinborne-Sheldrake, R. **2**-145
Swinbourne, E.S. **17**-128
Swindell, C.S. **10**-122
Swinnen, D. **16**-1897
Swisher, J.V. **17**-359
Swiss, K.A. **16**-1069
Swiątek, A. **16**-1467
Swoboda, W. **19**-359
Sy, A.O. **18**-293
Syamala, M.S. **11**-595
Syatkovskii, A.I. **15**-2498
Sygula, A. **2**-401, **2**-404
Syha, Y. **5**-66
Sykes, P. **6**-1
Symons, M.C.R. **2**-416, **3**-42, **5**-149, **5**-298, **5**-339, **10**-41
Synerholm, M.E. **10**-16
Syper, L. **18**-401, **19**-597
Szabó, A. **13**-583
Szabo, A.L. **16**-1657
Szabo, H. **14**-291
Szabó, K.J. **12**-473, **16**-615, **16**-949
Szabo, W.A. **16**-2234
Szabó, Z.G. **6**-52
Szafran, M. **2**-101
Szajáni, B. **17**-489
Szarek, W.A. **4**-376
Szeimies, G. **19**-691
Szeja, W. **10**-646
Szejtli, J. **3**-185, **3**-186
Székelyhidi, Z. **13**-683
Szele, I. **6**-83, **11**-162, **11**-167, **13**-37, **13**-770
Szentpály, L.V. **10**-34
Szeto, C.-P. **16**-1122
Szeto, W.T.A. **16**-1998
Szeverényi, Z. **19**-385
Szilagyi, P. **5**-62
Szilagyi, S. **10**-588
Szillat, H. **15**-853
Szmant, H.H. **15**-2005, **19**-1439
Szmuszkovicz, J. **10**-750, **10**-1791
Szöllõsy, Á. **16**-1268
Szulejko, J.E. **10**-13
Szumigala Jr., R.H. **13**-273
Szwarc, H. **18**-447
Szwarc, M. **5**-13, **10**-61
Szymanska-Buza, T. **18**-884
Szymanski, M.J. **15**-994
Szymanski, W. **16**-2255
Szymoniak, J. **15**-912, **15**-2673, **16**-886, **16**-1482, **16**-1569, **19**-1647

Taagepera, M. **4**-249, **8**-243, **8**-252
Taba, K.M. **4**-362
Tabacco, S.A. **10**-1503
Tabaei, M.H. **10**-585
Tabar-Hydar, K. **19**-72, **19**-248
Tabata, A. **15**-1856
Tabata, M. **14**-437
Taber, D.F. **10**-1695, **11**-433, **12**-221, **12**-393, **12**-685, **15**-902,

15-991, **15**-2169, **18**-289, **19**-1016, **19**-1439
Taber, T.R. **16**-1058
Tabet, J.-C. **15**-1572
Taboonpong, P. **10**-1162
Tabuchi, H. **11**-588, **11**-630
Tabuchi, N. **15**-1457, **16**-580
Tabuchi, T. **17**-207, **19**-1398
Tabushi, I. **2**-357, **3**-106, **3**-183, **12**-112, **14**-165, **19**-758
Tacconi, G. **15**-2319, **15**-2385, **18**-713
Tachi, K. **16**-612
Tachibana, K. **16**-2214
Tada, M. **10**-1013, **15**-324, **15**-1634, **19**-1353
Tada, N. **14**-201
Tadaki, M. **13**-711
Tadami, S. **16**-867
Tadano, K.-i. **15**-2267
Taddei, M. **7**-46, **16**-1765, **13**-108, **15**-561, **16**-2224
Tadjer, A. **2**-272
Tae, J.S. **15**-1489
Taeschler, C. **10**-137
Tafesh, A.M. **15**-1497
Taffer, I.M. **10**-531
Taft, B.R. **13**-129, **15**-630
Taft, R.W. **3**-19, **3**-20, **8**-104, **8**-145, **8**-175, **8**-176, **8**-192, **8**-234, **8**-240, **8**-243, **8**-252, **9**-20, **9**-37, **9**-47, **9**-50, **9**-51, **9**-52, **9**-54, **9**-55, **9**-63, **10**-460, **10**-463, **10**-474, **10**-479, **10**-555
Tafurt-García, G. **11**-366
Taga, T. **10**-249, **15**-410, **19**-1716
Tagaki, W. **14**-225, **16**-2279
Tagarelli, A. **15**-910, **16**-136
Tagashira, J. **13**-199
Tagat, J.R. **16**-2310
Tagaya, H. **10**-744, **19**-1437
Taggi, A.E. **12**-175, **16**-2226, **16**-2228, **17**-322
Tagliavini, E. **12**-727, **16**-774
Tagliavini, G. **16**-571
Taguchi, H. **13**-711, **16**-502, **17**-416
Taguchi, T. **8**-217, **10**-1497, **10**-1964, **12**-186, **13**-234, **15**-1236, **15**-1457, **15**-1718, **16**-580, **16**-908, **18**-737
Taguchi, Y. **15**-1321, **16**-2240
Tahara, K. **2**-154
Taher, A. **13**-401
Tahmasebi, D.P. **10**-674
Tahshiro, M. **19**-1425
Tai, A. **4**-1
Tai, C.-L. **16**-1115
Tai, C.C. **13**-500
Taigounov, A.A. **19**-906
Taigounov, I.R. **19**-906
Taillefer, M. **11**-698, **13**-129, **13**-293, **13**-611, **13**-647
Taira, A. **15**-1050, **15**-1250
Tait, B.D. **15**-121
Tait, S.J.D. **19**-105
Tajbakhsh, M. **10**-1135, **13**-123, **13**-235, **16**-127, **16**-337, **16**-338, **19**-114, **19**-598, **19**-776, **19**-832
Tajik, H. **11**-287
Tajik, M. **16**-208
Tajima, K. **16**-1825
Tajima, T. **14**-457
Tajmehri, H. **11**-287
Takaba, D. **16**-1328
Takabe, K. **15**-1056, **16**-1085, **16**-1253
Takacs, J.M. **15**-705, **15**-831, **15**-835
Takada, E. **15**-1264
Takada, H. **16**-1451
Takada, S.C.S. **16**-247
Takada, T. **15**-1210
Takagaki, T. **19**-1317
Takagi, H. **16**-1328
Takagi, J. **19**-677
Takagi, K. **10**-1097, **10**-1312, **10**-1456, **13**-281, **13**-283, **13**-295, **13**-330, **13**-482, **13**-568, **14**-360, **15**-1012, **15**-1565, **15**-1568, **15**-1577, **15**-2607, **16**-2022
Takagi, R. **16**-1285
Takagi, Y. **10**-1282, **12**-748
Takagishi, H. **15**-2629
Takagishi, S. **12**-413, **16**-144
Takaguchi, Y. **16**-1362
Takahahsi, T. **15**-2643
Takahara, J.P. **16**-464
Takahara, P.M. **19**-1641
Takahashi, E. **15**-1704, **16**-389
Takahashi, H. **10**-1456, **10**-1821
Takahashi, H. **13**-568, **16**-841, **19**-399
Takahashi, J. **16**-1085
Takahashi, K. **15**-2000, **16**-2057, **19**-840
Takahashi, M. **13**-234, **19**-208
Takahashi, N. **15**-830
Takahashi, O. **15**-146
Takahashi, S. **10**-1544, **15**-1517, **15**-1525, **15**-1584, **15**-1585, **15**-1586, **15**-1595, **19**-1069
Takahashi, T. **10**-1451, **10**-1911, **15**-230, **15**-398, **15**-740, **15**-782, **15**-838, **15**-843, **15**-846, **15**-986, **15**-988, **15**-989, **15**-2069, **15**-2604, **15**-2634, **16**-593, **16**-2111, **18**-523, **18**-824, **19**-499
Takahashi, T.T. **15**-1684
Takahashi, Y. **10**-1976, **10**-1978, **12**-181, **15**-153, **15**-1206, **16**-911, **16**-1008, **19**-667
Takahata, H. **19**-141, **19**-475
Takahori, T. **15**-2194, **16**-1050
Takai, K. **10**-1908, **15**-408, **15**-2487, **16**-690, **16**-693, **16**-1425, **16**-1431, **16**-2137, **19**-39, **19**-134
Takai, T. **15**-1991, **16**-841, **19**-519
Takai, Y. **10**-73, **10**-183, **16**-662
Takaki, K. **10**-915, **15**-392, **15**-765, **15**-1446
Takakis, I.M. **10**-161
Takaku, M. **11**-373
Takakura, M. **19**-1640
Takakura, N. **16**-170
Takamatsu, K. **11**-40
Takami, K. **10**-1481, **12**-526, **13**-457, **15**-308
Takamine, K. **19**-1632
Takamizawa, S. **19**-1172
Takamoto, N. **1**-73
Takamoto, Y. **10**-1098
Takamura, N. **13**-779
Takanami, T. **18**-154
Takanami, T. **18**-142
Takano, H. **10**-1282, **12**-147
Takano, K. **11**-186
Takano, M. **15**-2528
Takano, S. **15**-1976, **19**-1371
Takanohashi, Y. **19**-1465
Takao, H. **11**-329, **15**-872, **15**-1578, **15**-2595
Takao, K.-i. **15**-2267
Takao, T. **11**-418
Takaoka, K. **19**-1517
Takaoka, R. **4**-171
Takaoka, T. **17**-476
Takasaki, K. **10**-534
Takasaki, M. **19**-1182
Takase, K. **15**-1686
Takase, M. **19**-1071
Takashima, K. **10**-13, **16**-1671
Takashima, Y. **3**-215
Takasu, K. **15**-1384, **15**-2372, **15**-2397
Takasugi, J.J. **16**-1335
Takata, K. **16**-2137
Takata, T. **3**-192
Takatsuki, H. **16**-1165
Takatsuto, S. **4**-120
Takaya, A. **4**-129, **4**-150, **15**-635
Takaya, H. **13**-554, **15**-1614, **19**-1015, **19**-1016, **19**-1031
Takaya, J. **15**-330, **15**-1499, **15**-2116, **16**-390, **16**-866, **16**-867, **16**-1164
Takaya, K. **19**-1750
Takaya, Y. **15**-1199, **15**-1263, **15**-1281
Takayama, R. **7**-60
Takayama, T. **18**-261
Takayanag, H.i **19**-400
Takazawa, O. **16**-1038
Takeba, M. **15**-1519
Takechi, N. **16**-717
Takeda, A. **15**-2603
Takeda, H. **15**-223, **15**-1476
Takeda, K. **11**-690, **18**-964

Takeda, M. **10**-1174, **15**-392, **15**-2210, **16**-921, **19**-993, **19**-1458
Takeda, T. **10**-1282, **10**-1511, **13**-711, **15**-840, **15**-1985, **16**-448, **16**-1299, **16**-1420, **16**-1423, **16**-1839, **19**-281
Takeda, Y. **15**-1333
Takegami, Y. **10**-1987, **19**-1103, **19**-1748
Takehira, K. **10**-915, **15**-392, **15**-765
Takei, H. **10**-1505, **16**-2054
Takei, I. **19**-1233
Takeishi, S. **16**-1071
Takemiya, A. **10**-1838, **15**-347
Takemoto, K. **3**-166, **3**-177, **4**-184
Takemoto, T. **19**-103
Takemoto, Y. **10**-1527, **15**-962, **15**-963, **15**-1053, **15**-1340
Takemura, H. **3**-134
Takemura, S. **19**-613
Takenaga, N. **19**-198 **19**-1657
Takeoka, Y. **3**-57, **15**-815
Takeshima, T. **16**-214
Takeshita, M. **13**-610
Takeshita, T. **14**-153, **17**-15
Takeuchi, H. **5**-243, **11**-186
Takeuchi, K-i. **5**-120
Takeuchi, K. **2**-176, **2**-178, **4**-476, **5**-88, **5**-124, **5**-210, **10**-138, **10**-315, **10**-317, **15**-1593, **16**-1381, **18**-680
Takeuchi, M. **10**-1709
Takeuchi, N. **15**-1955
Takeuchi, R. **10**-931, **10**-954, **15**-1508
Takeuchi, T. **15**-1692
Takeuchi, Y. **1**-94, **19**-534
Takeyama, T. **16**-501
Takezawa, E. **19**-306
Takezawa, F. **15**-2518
Takhi, M. **16**-1723
Taki, H. **19**-278
Takikawa, H. **16**-1091
Takimoto, M. **15**-806, **15**-836, **15**-1509
Takinami, S. **18**-479
Takino, T. **10**-163
Takita, R. **16**-552
Takiyama, N. **15**-2573, **16**-511
Takizawa, J.-i. **19**-504
Takizawa, S. **16**-955, **19**-141
Takizawa, Y. **14**-289, **16**-1023
Takken, H.J. **17**-278
Taksande, K.N. **16**-1632
Taktak, S. **16**-716
Takui, T. **5**-271
Takuma, Y. **19**-1171
Takumi, H. **10**-663
Tal, L. **15**-1088
Talami, S. **18**-492
Talbert, J. **16**-2009
Talbot, R.J.E. **16**-16, **16**-1613, **16**-1619, **16**-1693
Talbott, R. **11**-649
Tale, R.H. **19**-1054
Talinli, N. **16**-1715
Tallant, M. **12**-310
Talley, J.J. **10**-316
Talley, P. **12**-525
Tallier, C. **16**-2075
Tallman, K.A. **5**-331
Tal'Rose, V.L. **8**-83
Talukdar, B. **16**-1878
Talukdar, S. **16**-309, **19**-1442, **19**-1601, **19**-1688
Talybov, G.M. **15**-264
Tam, I. **18**-538
Tam, J.P. **16**-1931
Tam, K. **4**-425
Tam, N.C. **19**-1588
Tam, W. **15**-2376
Tamada, M. **19**-591
Tamada, Y. **13**-554
Tamaddon, F. **16**-2176
Tamagaki, S. **14**-225
Tamagawa, K. **2**-32, **16**-1126
Tamami, B. **10**-844, **10**-981, **10**-1233, **15**-2001, **16**-64, **16**-65, **19**-885
Tamamura, H. **10**-249
Tamao, K. **10**-712, **10**-1309, **10**-1317, **13**-624, **15**-849, **18**-883
Tamaru, Y. **10**-1968, **14**-306, **15**-1724, **16**-595, **16**-712, **16**-982, **16**-1560, **16**-2031
Tamaru, Y. **18**-787
Tambade, P.J. **13**-615, **13**-683
Tamborra, P. **6**-15
Tamborski, C. **12**-645
Tamhankar, B.V. **11**-252
Tamiaki, H. **15**-2467
Tamiri, T. **11**-139
Tamm, C. **19**-504
Tämm, K. **10**-228
Tamm, M. **2**-179 **3**-40, **3**-75, **12**-372
Tamm, T. **10**-228
Tamura, H. **15**-2405
Tamura, K. **18**-149
Tamura, M. **10**-1401, **10**-1943, **13**-451, **13**-796, **14**-417, **15**-175, **15**-1131
Tamura, O. **15**-1333, **16**-1316
Tamura, R. **5**-291, **10**-1552, **19**-1518
Tamura, S. **6**-74, **16**-806
Tamura, T. **15**-1106
Tamura, Y. **10**-875, **11**-555
Tan, B. **4**-304
Tan, C.-H. **4**-122, **4**-124, **4**-125
Tan, C.-W. **16**-1074, **16**-1075
Tan, C.K. **15**-1720
Tan, J. **11**-404, **19**-715
Tan, K.-T. **16**-565, **16**-590
Tan, K.-T. **16**-614
Tan, L.C. **10**-831, **16**-1986
Tan, L.K. **11**-477, **15**-1786
Tan, L.Y. **5**-289
Tan, T.-L. **12**-90
Tan, X.J. **15**-1976
Tan, Z. **13**-348, **13**-432, **16**-452, **16**-599, **16**-1507, **19**-1614
Tan. C.-H. **15**-2189
Tanabe, K. **3**-77
Tanabe, M. **10**-1761, **17**-424
Tanabe, Y. **12**-328, **16**-1143, **16**-1181, **16**-1745, **16**-2130, **16**-2131, **16**-2132, **16**-2141
Tanaka, A. **10**-1203, **12**-791, **18**-328
Tanaka, C. **19**-1378
Tanaka, D. **13**-373, **13**-446, **15**-806, **15**-2683
Tanaka, F. **11**-314, **15**-1052, **15**-1056, **16**-395, **16**-958, **16**-961, **16**-1080, **16**-1081, **16**-1085
Tanaka, H. **13**-308, **14**-201, **15**-1802, **15**-2008, **15**-2249, **15**-2590, **16**-695, **16**-2242, **18**-523, **19**-27, **19**-439, **19**-1467
Tanaka, I. **15**-946
Tanaka, J. **13**-11
Tanaka, K. **1**-71, **1**-72, **1**-73, **5**-188, **9**-143, **9**-145, **10**-355, **10**-1535, **15**-845, **15**-1488, **15**-1724, **16**-538, **16**-809, **16**-1118, **16**-1259, **18**-271, **18**-500, **19**-213, **19**-831, **19**-927, **19**-1171
Tanaka, M. **1**-75, **2**-76, **10**-1070, **10**-1462, **10**-2008, **10**-2010, **10**-2012, **11**-503, **11**-535, **12**-560, **13**-326, **13**-327, **14**-407, **15**-223, **15**-369, **15**-395, **15**-396, **15**-1476, **15**-1481, **15**-1500, **15**-1785, **15**-1788, **15**-1800, **16**-695, **16**-1227, **16**-2161, **19**-56, **19**-593
Tanaka, N. **6**-88
Tanaka, R. **5**-271, **5**-272, **15**-343, **15**-976, **15**-2592
Tanaka, S. **4**-82, **10**-1189, **10**-1238, **10**-1943, **15**-2115, **16**-352
Tanaka, T. **5**-337, **10**-794, **10**-1635, **10**-1884, **13**-323, **13**-326, **13**-327, **15**-815, **15**-1193, **16**-674, **16**-1243, **16**-1992, **19**-475
Tanaka, W. **16**-838
Tanaka, Y. **10**-1522, **15**-793, **15**-1432, **15**-1433, **19**-1271
Tandon, A. **16**-1716
Tanemura, K. **12**-116, **13**-568, **19**-482
Tang, B.-X. **12**-284, **13**-588
Tang, D. **19**-1381

Tang, D.Y.H. **5**-295, **18**-81
Tang, F.Y. **14**-110
Tang, J. **10**-1626, **15**-890, **16**-132, **18**-169, **19**-502, **19**-622
Tang, J.Y. **14**-342
Tang, K.-H. **15**-1310, **15**-1364
Tang, K. **12**-425
Tang, L. **13**-148, **15**-1052, **16**-631
Tang, M.-W. **15**-1926
Tang, M. **19**-529, **19**-1017
Tang, Q. **13**-354, **11**-189
Tang, R.H. **14**-110
Tang, S. **4**-304
Tang, T.P. **16**-934, **16**-935
Tang, W.-J. **15**-452
Tang, W. **13**-410, **15**-439, **15**-452, **15**-457, **15**-641, **16**-599, **18**-495
Tang, X.-Q. **16**-725
Tang, X. **16**-1084, **16**-1364
Tang, Y. **14**-186, **15**-619, **15**-1094, **15**-1200, **15**-2563, **16**-855, **16**-1359, **16**-1461, **16**-1481, **16**-1597, **18**-148
Tang, Y.S. **2**-435, **8**-64, **8**-118
Tang, Z. **11**-356, **16**-1082, **16**-1084
Tangari, N. **16**-500
Tangestaninejad, S. **10**-688, **15**-1981, **15**-1999
Tanguy, G. **10**-1965, **10**-1987
Tani, H. **10**-944
Tani, K. **12**-67, **8**-92
Tani, M. **11**-577, **13**-386, **13**-407
Tani, S. **10**-872, **18**-778, **19**-1561
Tanida, H. **10**-159, **10**-183
Tanigaki, K. **18**-234
Tanigawa, Y. **10**-946, **10**-1063, **10**-1065, **10**-1356, **14**-276
Taniguchi, H. **10**-267, **11**-375, **11**-522, **11**-534, **17**-325
Taniguchi, K. **19**-1632
Taniguchi, M. **11**-373, **15**-643
Taniguchi, N. **13**-164
Taniguchi, S. **10**-405
Taniguchi, T. **19**-1599
Taniguchi, Y. **2**-324, **10**-1063, **10**-1065, **10**-1238, **15**-1446
Tanikaga, R. **19**-1756
Tanikawa, S. **10**-70, **10**-84
Tanimizu, H. **15**-2503
Tanimoto, S. **15**-1852
Tanino, K. **10**-1627, **10**-1949, **15**-999
Tanio, M. **10**-875
Tanizawa, D. **19**-1127
Tanji, K. **12**-617
Tank, R. **16**-229
Tankguchi, N. **13**-153
Tanko, J. **4**-428, **15**-129, **18**-162, **18**-606, **18**-615, **18**-650
Tanko, J.M. **4**-442, **5**-226, **5**-325, **14**-73, **14**-81, **14**-138, **14**-148, **14**-180, **14**-323, **18**-606
Tann, C.-H. **12**-298, **18**-571
Tanner, D. **2**-336, **2**-357, **5**-85, **13**-196, **14**-355, **15**-1981
Tanner, D.D. **14**-60, **14**-177, **14**-207, **19**-1331, **19**-1516
Tanner, M.E. **2**-237
Tantillo, D.J. **3**-69, **15**-1083, **15**-2272, **18**-164, **18**-574, **18**-623, **18**-655, **18**-657, **18**-676, **18**-952
Tanturli, R. **15**-1832
Tanuma, M. **19**-819
Tanuwidjaja, J. **16**-306
Tanyeli, C. **19**-526, **19**-528
Tanzawa, T. **17**-419
Tao, B. **13**-525
Tao, C.-Z. **10**-1067
Tao, E.V.P. **15**-272
Tao, F. **12**-478
Tao, H. **15**-594
Tao, L.-M. **12**-284
Tao, W.-T. **15**-1228
Taoka, B.M. **16**-398
Taoufik, M. **18**-873, **18**-873, appendixa-26
Tapi, O. **10**-247
Tapolczay, D. **15**-1366
Tapolczay, D.J. **15**-1414
Tapuhi, E. **12**-157
Tapuhi, Y. **4**-194
Taqian-Nasab, A. **11**-134
Taquet, J.-P. **10**-1513
Tarakanova, A.V. **18**-650
Tarantelli, F. **17**-57
Tararov, V. **16**-317
Tararov, V.I. **19**-1150
Tarassoli, A. **13**-386
Tarbell, D.S. **11**-41, **19**-838
Tarbin, J.A. **19**-748
Tardella, P.A. **15**-2044, **15**-2049, **15**-2050
Tardif, O. **15**-769
Tardy-Delassus, A. **11**-491
Tarhouni, R. **12**-650
Tarino, J.Z. **13**-837
Tarnopolsky, A. **15**-598
Tarr, A.W. **6**-16
Tarrade-Matha, A. **10**-1952
Tarrant, P. **15**-2374
Tarratt, H.J.F. **18**-117
Tarrian, T. **10**-683
Tarsis, E. **16**-788
Tartakovskii, V.A. **19**-1180
Tarui, A. **15**-1468
Tasche, K.K. **16**-137
Taschner, M.J. **15**-2243, **19**-1444
Tashika, H. **10**-1962
Tashino, Y. **19**-679
Tashiro, H. **19**-1425
Tashiro, M. **11**-634, **15**-551, **10**-537, **10**-886, **11**-634
Tashtoush, H. **5**-61, **11**-481
Taskinen, A. **8**-83
Tasler, S. **13**-212
Tasneem, Ali, M.M. **11**-126
Tasneem, Rajanna, K.C. **11**-500
Tatamidani, H. **10**-2004, **16**-2092, **16**-2093, **19**-1492
Tatchell, A.R. **19**-1236
Tateishi, A. **14**-289
Tatemitsu, H. **2**-333, **2**-335
Taticchi, A. **2**-165, **15**-2174, **15**-2186
Tatlock, J.H. **19**-718
Tatlow, J.C. **15**-1644
Tato, J.V. **12**-734
Tatsami, K. **15**-1625
Tatsukawa, A. **10**-577, **10**-1680
Tatsuki, S. **18**-736
Tatsumi, K. **12**-289
Tatsuoka, T. **12**-511
Taube, H. **15**-556
Tauh, P. **15**-1314
Taura, K. **1**-72
Taurins, A. **16**-420
Tautermann, C. **10**-795
Tautou, H. **10**-761
Tavares, P. **15**-669
Taveras, A.G. **5**-343
Taverner, S.J. **9**-120
Tavernier, D. **4**-134
Tavor, D. **19**-992
Tawara, Y. **2**-228
Taya, H. **16**-1797
Taya, K. **10**-656, **16**-235
Tayal, S.R. **10**-1399
Tayama, E. **10**-1709, **16**-1949, **17**-183
Tayama, O. **15**-388, **15**-794
Tayano, T. **16**-735
Taylor, S.H. **19**-459
Taylor, A. **18**-719
Taylor, B.F. **4**-385
Taylor, B.J. **15**-1154
Taylor, D. **10**-627
Taylor, D.K. **4**-454
Taylor, D.R. **8**-15, **8**-80, **10**-246, **15**-107, **17**-386
Taylor, E.C. **11**-235, **13**-109, **13**-110, **13**-270, **13**-297, **13**-747, **14**-377, **14**-412, **16**-1483, **16**-1710, **16**-2120, **16**-2159, **19**-391
Taylor, G.A. **18**-954
Taylor, H.T. **15**-1782
Taylor, J.A. **14**-348
Taylor, J.B. **16**-1473, **16**-1474
Taylor, J.E. **15**-1812, **15**-1814
Taylor, J.M. **11**-262
Taylor, K.G. **5**-371
Taylor, M. **19**-1135
Taylor, M.J. **2**-226
Taylor, M.S. **15**-1043, **15**-1105
Taylor, N.J. **15**-1268, **16**-468
Taylor, P.G. **11**-100, **15**-292, **16**-1293
Taylor, P.J. **3**-19, **9**-47
Taylor, P.N. **4**-258
Taylor, P.W. **4**-402

Taylor, R. **1**-55, **1**-68, **2**-33, **2**-392, **2**-414, **3**-21, **3**-27, **3**-29, **3**-33, **9**-28, **11**-2, **11**-30, **11**-53, **11**-69, **11**-76, **11**-79, **11**-111, **11**-115, **11**-201, **11**-212, **11**-271, **11**-369, **11**-475, **11**-648, **11**-651, **11**-668, **11**-673, **11**-701, **12**-675, **13**-745, **17**-128, **17**-139, **17**-140, **17**-151, **17**-198, **17**-493, **19**-387
Taylor, R.A. **15**-442
Taylor, R.B. **4**-537
Taylor, R.C. **13**-91
Taylor, R.E. **16**-594
Taylor, R.E.R. **13**-799
Taylor, R.J. **4**-215
Taylor, R.J.K. **13**-494, **15**-923, **15**-982, **15**-1165, **16**-1332, **16**-1440, **16**-1475, **17**-345, **17**-349, **18**-836, **19**-110, **19**-662
Taylor, R.T. **15**-508
Taylor, S.J. **15**-2387
Taylor, S.K. **11**-339, **16**-1963
Taylor, W.C. **19**-1511, **19**-1686
Taylor. P.G. **1**-48
Taynton, P. **16**-560
Tazaki, M. **11**-551
Tazoe, M. **16**-595
Tchoubar, B. **18**-215, **19**-1000
Teach, E.G. **15**-1725
Teasley, M.F. **15**-2367
Tebbe, F.N. **16**-1410
Teberekidis, V.I. **5**-55
Tedder, J.M. **1**-2, **5**-211, **1**-170, **14**-2, **14**-65, **14**-77, **14**-210, **15**-91, **15**-101, **18**-68
Tedford, M.C. **16**-1624
Tedjo, E.M. **17**-298
Tedrow, J.S. **16**-730, **16**-1092, **16**-1195
Tee, O. **11**-109
Tee, O.S. **11**-271, **11**-272
Teeter, J.S. **15**-1763
Tehrani, K.A. **16**-1416
Teimouri, M.B. **19**-781
Tejero, T. **16**-979
Tekavec, T.N. **15**-2682
Tekawa, M. **18**-198
Teki, Y. **5**-271, **5**-272
Teleman, O. **16**-1270
Telford, R.P. **19**-1086, **19**-1193, **19**-1214
Teller, H. **10**-999
Teller, R.G. **15**-474
Tellitu, I. **15**-2099
Telvekar, V.N. **16**-1853
Temperini, A. **10**-694, **16**-1734
Tempesta, M.S. **4**-537
Temple Jr., D.L. **10**-1857, **10**-1854
Templeton, J.L. **15**-2065
ten Brink, G.-J. **18**-377, **18**-382, **19**-218
Ten Hoeve, W. **4**-25
Tenaglia, A. **15**-2674
TenBrink, R. **10**-512
Tencer, M. **16**-1104
Teng, H.-L. **16**-413
Teng, L. **18**-437
Tenud, L. **10**-18
Teo, K.E. **12**-150
Teo, Y.-C. **13**-205, **16**-560, **16**-590, **16**-639, **16**-1151
Tepe, J. **11**-435
Tepe, J.J. **15**-996
ter Borg, A.P. **18**-585
Ter Halle, R. **15**-892
ter Wiel, J. **15**-1951
Terada, M. **11**-314, **12**-234, **13**-244, **15**-1014, **15**-1015, **15**-1055, **15**-1428, **16**-936, **16**-991, **16**-1574
Terada, T. **19**-138
Teraji, T. **15**-2400
Terakawa, E. **10**-138
Terakura, K. **18**-347
Teranishi, A.Y. **12**-254. **16**-1042. **19**-709
Teranishi, H. **15**-1334
Teranishi, S. **10**-740
Terao, J. **10**-1267. **10**-1309. **10**-1362. **10**-1382, **10**-1388, **10**-1470, **13**-357, **14**-414, **15**-313, **15**-903, **15**-1480. **16**-2044
Terao, T. **12**-361
Terao, Y. **15**-2105
Teraoka, Y. **15**-1334
Terasaki, S. **19**-1203
Terashima, S. **15**-2391, **17**-241
Teratani, S. **10**-656
Teratani, T. **13**-591
Terauchi, N. **15**-1196
Terec, A. **2**-485
Terefenko, E.A. **16**-2063
Terekhova, L.N. **15**-1082
Terenghi, G. **11**-519
Terent'ev, A.B. **18**-69, **18**-80, **18**-84
Terent'ev, A.O. **12**-153
Terent'eva, G.A. **10**-332
Tereschenko, G.F. **18**-320
Ternansky, R. **15**-2679
Ternansky, R.J. **18**-634
Tero-Kubota, S. **5**-337
Terpko, M.O. **19**-1193
Terpstra, J.W. **10**-784, **18**-252
Terrano, D. **19**-465
Terrasson, V. **15**-333
Terrell, C.R. **16**-402
Terrell, R. **10**-1791, **16**-1962
Terrett, N.K. **16**-1600
Terrier, C. **15**-1592
Terrier, F. **5**-110, **8**-188, **10**-386, **10**-388, **10**-399, **13**-6, **13**-9, **13**-10, **13**-756, **19**-193
Terstegen, F. **15**-2507
Tesfu, E. **13**-176
Tesoro, G.C. **15**-77
Testa, A. **13**-391
Testa, B. **4**-1
Testaferri, L. **10**-694, **13**-113, **13**-142, **13**-145, **14**-366, **15**-234, **16**-1734
Tester, J.W. **13**-175. **15**-376
Teston-Henry, M. **8**-161
Tewson, T.J. **11**-30
Texier-Boullet, F. **16**-267
Texier, F. **15**-2150
Tey, C. **16**-2057
Teyssié, P. **10**-659
Tezuka, H. **4**-480
Tezuka, T. **14**-47, **14**-124, **18**-585
Tezuka, Y. **1**-73
Thacker, N.C. **15**-705
Thadani, A.N. **10**-1892, **16**-761, **16**-762
Thakkar, M. **15**-2212
Thakur, A.J. **18**-350, **19**-295
Thakur, V.V. **15**-2062
Thakuria, J.A. **19**-1730
Thaler, T. **16**-849
Thaler, W.A. **14**-54, **14**-145, **14**-199, **15**-170
Thalji, R.K. **15**-967, **16**-1111
Thalmann, A. **16**-1764
Tham, F.S. **9**-123
Thamatloor, D.A. **18**-229
Than, C. **11**-122
Thanh, B.T. **10**-1702
Thanh, G.V. **18**-851
Thavonokham, B. **10**-732, **10**-1418
Thayumanavan, R. **15**-1052, **16**-961
Thayumanavan, S. **5**-196
Thea, S. **16**-2276
Thebtaranonth, C. **15**-53, **16**-1017
Thebtaranonth, Y. **15**-53, **16**-1017, **18**-417
Theerthagiri, P. **16**-2179
Theissmann, T. **19**-1152
Thelan, P.J. **18**-926
Theobald, D.W. **4**-364
Theophanides, T. **11**-479
Théron F. **12**-74, **18**-654
Thetford, D. **10**-1042
Thewissen, D.H.M.W. **15**-550
Thi, H.C.G. **4**-488
Thi, M.P.N. **10**-415
Thiara, P.S. **11**-409
Thiaw-Woaye, A. **16**-564
Thibblin, A. **6**-66, **6**-69, **10**-71, **10**-90, **10**-230, **17**-4, **17**-38, **17**-39, **17**-48, **17**-53, **17**-66
Thibon, A. **15**-1949
Thibonnet, J. **12**-281
Thickitt, C.P. **15**-2070
Thiebaud, S. **10**-605
Thiébault, A. **13**-59, **13**-63, **13**-94
Thiebes, C. **13**-272
Thiede, R.J. **16**-89
Thiel, O.R. **15**-325
Thiel, W. **2**-15, **18**-892.
Thiele, G.F. **2**-351

Thielecke, W. **10**-1690
Thieme, P.C. **16**-1311
Thier, W. **15**-508
Thiery, E. **15**-450
Thiéry, V. **11**-399
Thies, O. **16**-1012
Thies, R.W. **4**-502, **18**-620
Thieser, R. **10**-489
Thijs, L. **6**-36
Thilgen, C. **2**-391
Thilmont, N. **10**-1965
Thimmaiah, M. **16**-2023
Thinggaard, J. **16**-1982
Thirase, G. **5**-160
Thirsk, C. **12**-480
Thiruvengadam, T.K. **12**-298
Thivolle-Cazat, J. **18**-873
Thobe, J. **16**-1320
Thoburn, J.D. **18**-579
Thomas IV, B.E. **15**-998, **15**-999
Thomas, A. **13**-213
Thomas, A.A. **7**-130, **15**-2280
Thomas, A.P. **10**-1501
Thomas, B. **7**-58
Thomas, B.R. **19**-1419
Thomas, C.B. **19**-704, **19**-1774
Thomas, C.R. **15**-1644
Thomas, C.W. **10**-550, **10**-1146
Thomas, D.W. **16**-1995
Thomas, F. **9**-10
Thomas, G. **19**-1081
Thomas, J.A. **11**-611, **11**-614
Thomas, J.M. **15**-271
Thomas, K.G. **7**-67
Thomas, P.J. **10**-339, **10**-1631, **17**-106
Thomas, P.N. **11**-97
Thomas, R. **2**-237, **16**-1361
Thomas, R.C. **6**-18
Thomas, R.D. **5**-205, **5**-157, **5**-158, **8**-219
Thomas, R.J. **16**-23, **16**-24
Thomas, S. **10**-912, **13**-184, **15**-1658, **19**-1166
Thomas, S.J. **10**-657
Thomas, S.P. **15**-715
Thomas, T.D. **2**-58, **8**-186, **8**-251, **11**-42, **11**-47, **15**-97
Thomas, W.A. **4**-358
Thomassin, R. **16**-2169
Thomazeau, C. **8**-126
Thomm, E.W.C.W. **12**-762
Thommen, W. **14**-259
Thommes, K. **15**-1728
Thompson, A. **19**-128
Thompson, A.L.S. **13**-800
Thompson, A.S. **18**-329
Thompson, B.B. **15**-1225
Thompson, C.M. **5**-105, **10**-513
Thompson, D.F. **13**-395
Thompson, D.H.P. **10**-1321
Thompson, D.J. **10**-1974, **12**-67
Thompson, H.W. **15**-1239
Thompson, J. **17**-421
Thompson, J.A. **10**-174
Thompson, J.E. **19**-1735
Thompson, J.L. **15**-2502
Thompson, J.T. **10**-426
Thompson, K.L. **15**-263
Thompson, L.A. **16**-1936
Thompson, M. **1**-16
Thompson, M.M. **19**-16
Thompson, Q.E. **19**-333
Thompson, S.P. **17**-217
Thompson, S.R. **15**-2039
Thomsen, I. B. **16**-1982
Thomsen, I. **10**-992, **16**-217, **16**-224
Thomson, A.D. **7**-115
Thomson, P. **18**-719
Thomson, R.H. **5**-237, **11**-470, **19**-252, **19**-609
Thomson, R.J. **15**-1103
Thomson, S.J. **15**-485
Thonchant, S. **15**-2075
Thondorf, I. **3**-129, **3**-135
Thongsornkleeb, C. **18**-437
Thorarensen, A. **10**-1385
Thorburn, S. **11**-77
Thorhauge, J. **15**-1172
Thorn, D.L. **15**-849
Thornton, E.R. **6**-95, **15**-2246, **16**-1053, **16**-1068, **16**-1077, **19**-493
Thorpe, D.H. **11**-632
Thorpe, F.G. **13**-105
Thorsen, M. **16**-1920
Thorsen, P.T. **19**-1465
Thottumkara, A.P. **19**-194
Thozet, A. **16**-2261
Threadgill, M.D. **19**-1549
Thudium, F. **9**-15
Thuéry, P. **3**-144
Thuillier, A. **16**-1466
Thulin, B. **2**-336
Thurkauf, A. **16**-130
Thurner, A. **17**-213
Thweatt, J.G. **15**-2395
Thyagarajan, B.S. **14**-376
Thyagarajan, G. **16**-1364, **18**-322
Tian, F. **5**-326
Tian, H.-Y. **16**-1140
Tian, H. **15**-1933, **19**-561
Tian, J. **5**-366, **5**-389
Tian, Q. **15**-2587
Tian, S.-K. **16**-1731
Tian, S. **15**-353, **15**-2028
Tian, W. **18**-289
Tian, W.Q. **19**-1259
Tian, X. **13**-548, **15**-277, **19**-1026
Tian, Z. **2**-217, **4**-434
Tichenor, G.J.W. **15**-48
Tichy, M. **3**-43
Ticknor, B.W. **5**-10
Tidwell, T.T. **2**-263, **4**-441, **4**-520, **4**-532, **5**-55, **5**-67, **9**-7, **10**-222, **15**-25, **15**-28, **15**-80, **15**-180, **15**-200, **15**-216, **15**-268, **16**-370, **16**-507, **16**-1104, **16**-1677, **16**-2216, **16**-2236, **17**-321, **19**-614
Tiecco, M. **10**-694., **10**-824, **10**-1180, **13**-113, **13**-142, **13**-145, **13**-145, **14**-128, **14**-366, **15**-234, **16**-1734
Tiekink, E.R. **12**-643
Tierney, J.P. **7**-110, **7**-125
Tietz, H. **12**-778
Tijani, J. **15**-1520
Tijerina, T. **16**-1410
Tikwe, L. **4**-538
Tillack, A. **10**-909, **10**-933, **14**-307, **15**-325, **15**-357, **15**-363, **15**-366, **15**-366
Tillett J.G. **16**-1664
Tilley, T.D. **15**-761, **16**-986
Tillyer, R.D. **15**-1113, **18**-766
Tilstam, U. **19**-61
Timberlake, J.W. **5**-226
Timmer, K. **15**-550
Timmerman, P. **3**-181
Timmins, G. **5**-133, **6**-93, **10**-192, **12**-54
Timmons, C. **15**-2061, **16**-1025
Timmons, C.J. **18**-547
Timmons, D.J. **15**-2580
Timmons, R.J. **15**-514
Timms, A.W. **14**-392, **14**-394
Timms, D.A. **10**-974, **18**-147
Timokhin, V. **15**-1311, **16**-527
Timokhin, V.I. **14**-96, **15**-419, **17**-144
Timokhina, L.V. **16**-213
Timony, P.E. **13**-260
Tin, K. **12**-190
Tinant, B. **11**-356, **16**-1280
Ting, A. **16**-398
Ting, J. **10**-827, **10**-1411
Tingoli, M. **11**-283, **13**-113, **13**-142, **13**-145, **15**-1695
Tinucci, L. **11**-539
Tipper, C.F.H. **5**-387, **6**-11, **6**-52, **6**-55, **6**-58, **6**-59, **6**-60, **7**-48, **8**-108, **8**-114, **8**-148, **10**-226, **11**-2, **11**-111, **11**-201, **11**-212, **11**-271, **11**-580, **11**-648, **11**-651, **11**-668, **11**-673, **11**-700, **12**-2, **12**-24, **12**-38, **12**-57, **12**-448, **12**-533, **12**-579, **12**-668, **13**-4, **13**-745, **14**-77, **15**-479, **16**-16, **16**-1613, **16**-1619, **16**-1653, **16**-1665, **16**-1693, **17**-3, **17**-8, **17**-40, **17**-42, **17**-61, **17**-128, **17**-180, **18**-627, **18**-788, **19**-2, **19**-675
Tippmann, E.M. **5**-405
Tipsword, G.E. **10**-1438
Tipton, A.K. **15**-1803
Tipton, T.J. **5**-293
Tirla, C. **16**-378, **16**-1845
Tirouflet, J. **19**-1083
Tirpak, R.E. **16**-1305, **16**-2125

Tishbee, A. **4**-175
Tishkov, A.A. **10**-39
Tissandié, S. **19**-1234
Tissot-Croset, K. **10**-1359, **10**-1522, **10**-1533
Titov, A.I. **12**-211
Titov, E.V. **9**-48
Titov, Yu.A. **15**-565
Titova, S.P. **11**-621
Tius, M.A. **15**-1082, **15**-1089, **15**-1095
Tiwari, G.B. **19**-197
Tiwari, H.P. **10**-57, **19**-81, **19**-94
Tiwari, S. **15**-2227
Tkachuk, R. **2**-158
Tkatchouk, E. **14**-354
Tlili, A. **13**-129
To, D.C.M. **10**-639, **15**-1915
Toader, D. **17**-258
Tobe, M.L. **13**-57
Tobe, Y. **2**-69, **2**-154
Tobey, S.W. **2**-229, **16**-24
Tobiason, F.L. **1**-85
Tobisu, M. **10**-1286, **15**-2690, **19**-1497
Tobita, Y. **19**-1449
Tobito, Y. **19**-709
Tobler, H.J. **2**-202
Toblert, T.L. **16**-996
Tocher, D.A. **4**-361, **4**-537
Toda, A. **15**-410
Toda, F. **1**-71, **1**-72, **1**-73, **3**-171, **3**-175, **4**-169, **4**-171, **9**-143, **9**-145, **10**-663, **16**-1118, **16**-1446, **16**-2136, **16**-2139, **18**-132, **19**-882, **19**-1729
Toda, M. **11**-325, **19**-1414
Toda, N. **15**-975
Todaro, L. **4**-361
Todd, D. **19**-1409
Todd, G.P. **17**-151
Todd, H.E. **14**-112
Todd, M.J. **10**-57
Todda, F. **5**-291
Todeschini, R. **2**-350
Todesco, P.E. **13**-83, **16**-243. **19**-809
Todo, H. **10**-1470, **14**-414
Todres, Z.V. **5**-333, **6**-39
Toekelt, W.G. **15**-757
Togni, A. **15**-1086, **15**-1402, **15**-1426, **16**-663, **16**-1247
Togo, H. **10**-738, **13**-299, **13**-299, **14**-193, **14**-386, **16**-315, **16**-1748, **19**-182, **19**-266, **19**-272, **19**-532, **19**-659, **19**-679, **19**-1578, **19**-1583, **19**-1610
Toh, H.T. **14**-153
Tohda, Y. **13**-582, **15**-2112
Tohjo, T. **19**-1758
Toi, H. **19**-870
Tojino, M. **15**-1372
Töke, L. **15**-1098, **16**-1268, **16**-1921, **17**-213, **17**-489
Toker, J.D. **15**-2131
Toki, T. **10**-1644
Tokitoh, N. **15**-661, **15**-658, **15**-659
Tokiyama, H. **12**-154
Tokles, M. **4**-210
Tokuda, M. **10**-903, **10**-2005, **12**-661, **13**-460, **14**-469, **14**-481, **15**-358, **15**-1504, **17**-384
Tokuda, O. **16**-397
Tokuda, Y. **11**-576
Tokudomi, M. **15**-1277
Tokumaru, K. **16**-1281
Tokunaga, K. **10**-854, **13**-682
Tokunaga, M. **4**-200, **15**-222, **19**-48
Tokunaga, N. **12**-71, **15**-1209, **15**-1211, **15**-1226
Tokunaga, Y. **19**-643
Tokura, N. **5**-243, **14**-137, **16**-2277, **17**-324, **18**-803, **19**-1328
Tokutake, N. **18**-203
Tokuyama, H. **10**-1206
Tokuyasu, T. **10**-400
Tolbert, L.M. **11**-671, **15**-2256, **15**-2289
Tolgyesi, W.S. **5**-16, **11**-411
Tolkachev, O.N. **19**-1777
Tollenaere, J.P. **9**-47
Tolman, C.A. **15**-492, **15**-1625
Tolnai, G.L. **13**-591
Tolomelli, A. **15**-1415
Tolstikov, G.A. **14**-428, **15**-738, **15**-740, **19**-331
Tolstikova, L.L. **15**-305
Tom, N.J. **13**-189, **16**-1686
Toma, L. **18**-713
Toma, M. **7**-99
Toma, Š. **7**-96, **7**-97, **9**-130, **11**-236, **11**-473, **13**-182, **15**-1064, **15**-1443, **16**-301, **19**-557
Tomar, S. **11**-397
Tomari, M. **17**-490
Tomás, J. **18**-195
Tomás, M. **15**-2133, **15**-2654, **18**-276
Tomaselli, G.A. **16**-2273, **19**-770
Tomasik, P. **9**-38
Tomasik, W. **12**-740
Tomasini, C. **15**-1177, **16**-549
Tomaszewski, J.E. **16**-530
Tomatsu, A. **19**-613
Tombo, G.M.R. **16**-129
Tomezsko, E.S. **19**-442
Tomi, K. **19**-1103
Tomilov, Y.V. **15**-2537
Tomimura, T. **5**-272
Tominack, B.J. **7**-127, **13**-596
Tominaga, Y. **16**-2068
Tomioka, A. **4**-313
Tomioka, H. **5**-357, **5**-359, **5**-401, **5**-410, **18**-237, **19**-134
Tomioka, K. **4**-153, **12**-725, **15**-1168, **15**-1171, **15**-1185, **15**-1204, **15**-1395, **15**-1449, **15**-2248, **16**-405, **16**-892, **16**-933, **16**-1372, **16**-1873
Tomita, D. **16**-780
Tomita, K. **13**-872
Tomita, M. **18**-322, **19**-1290
Tomita, N. **16**-981
Tomita, T. **15**-2503
Tomizawa, G. **12**-196
Tomizawa, M. **19**-654
Tomkins, R.P.T. **2**-229
Tomkinson, N.C.O. **19**-533, **19**-640
Tommasino, M.L. **18**-143
Tomo, Y. **16**-1252
Tomoda, S. **4**-238, **11**-40, **16**-460
Tomoika, H. **18**-231
Tomooka, K. **4**-203, **15**-924, **18**-13
Tonachini, G. **5**-127
Tonazzi, S. **15**-1056
Tonellato, U. **14**-42, **15**-36, **15**-80, **15**-83
Toneva, R. **19**-925
Tong, K.-H. **15**-1899
Tong, X. **15**-882
Tongco, E.C. **16**-2170
Tongkate, P. **10**-1168
Toniolo, L. **11**-505
Tonks, L. **13**-395, **13**-396
Toombes, G.E.S. **10**-1702
Tooze, R. **15**-1621
Top, S. **16**-2175
Topley, B. **10**-17
Topolski, M. **5**-382, **12**-450, **12**-639
Toppet, S. **15**-2423
Topping, C.M. **15**-1163
Topsom, R.D. **1**-55, **8**-176, **8**-252, **9**-2, **9**-39, **9**-49, **9**-51, **9**-52, **9**-55, **9**-64
Tor, Y. **10**-1080
Torborg, C. **13**-98
Torche, S. **18**-266
Torchy, S. **16**-345, **16**-347, **19**-948
Tordeux, M. **16**-449
Tordo, P. **5**-224
Toreki, R. **18**-812
Torenius, H.M. **9**-138, **13**-278
Torgov, I.B. **15**-1082
Tori-i, A. **10**-537
Tori, M. **19**-441
Torigoe, M. **14**-441, **19**-1562
Torii, S. **14**-201, **15**-1802, **16**-144, **16**-2242, **19**-387
Torii, T. **15**-1038
Torisawa, Y. **11**-556, **14**-297
Toriumi, Y. **4**-313
Toriyama, F. **12**-299
Torkiyan, L. **15**-1450
Tormo, J. **16**-1595
Toro-Labbé, A. **10**-36, **10**-37

Toromanoff, E. **4**-141, **15**-500, **16**-11
Torossian, G. **10**-1710
Torraca, K.E. **13**-130, **13**-132
Torre, G. **4**-39, **16**-2246
Torregiani, E. **10**-1125, **15**-1065, **15**-1388, **15**-1397, **17**-164
Torrell, E. **13**-487
Torres, E.C. **17**-160
Torres, G. **15**-1883
Torres, G.H. **13**-619
Torres, L.E. **6**-19
Torres, M. **15**-1947, **18**-231
Torres, N.M. **13**-454
Torres, R.R. **16**-1429
Torres, T. **10**-757
Torres, W. **15**-1883
Torssell, K. **19**-424, **19**-624
Torssell, K.B.G. **10**-797, **15**-2105, **19**-1538
Tortajada, A. **19**-817
Tortoioli, S. **10**-690
Tortorelli, V.J. **15**-2538
Tortosa, M. **18**-757
Toru, T. **10**-782, **16**-1537, **19**-800, **19**-974
Torupka, E.J. **10**-1303
Tosaka, E. **18**-254
Tosaki, S.-y. **15**-1883
Toscanini, M. **11**-314
Toscano, J.P. **5**-398
Toscano, R.A. **4**-374, **13**-150
Toscano, R.M. **19**-770
Toshida, N. **15**-1568
Toshikawa, S. **15**-2487, **19**-39
Toshimitsu, A. **4**-480, **11**-134, **13**-748
Tosi, G. **15**-2575
Toste, F.D. **10**-1521, **15**-416, **15**-847, **15**-867, **15**-870, **15**-1006, **15**-1009, **15**-1429, **15**-1566, **15**-2389, **15**-2608, **18**-165, **18**-275, **18**-330, **19**-1144
Toteva, M.M. **5**-102, **10**-68
Toth, A. **17**-56
Toth, B.R. **10**-192
Tóth, G. **19**-425
Tóth, J. **19**-1206
Totten, G.E. **19**-824
Tottie, L. **10**-683
Touchard, F.P. **16**-1394
Toudou, S. **16**-1580
Touillaux, R. **16**-1295
Toukoniitty, E. **8**-83
Toullec, J. **2**-432, **2**-435, **2**-436, **2**-461, **4**-99, **8**-11, **12**-83, **12**-91, **12**-95
Toullec, P.Y. **16**-746
Toupet, L. **2**-485
Tour, J.M. **15**-498, **16**-485, **19**-731
Toussaint, A. **16**-1220
Towne, T.B. **15**-231
Townes, J.A. **15**-2387
Townsend, J.M. **18**-32
Townsend, R.-J. **15**-2522, **15**-2664
Townson, M. **14**-68
Toy, P.H. **5**-328, **10**-727, **10**-730, **10**-731, **14**-83, **14**-91, **15**-154, **19**-153
Toyao, A. **15**-1333
Toyoda, M. **19**-703
Toyoda, T. **11**-391, **11**-559, **16**-1102
Toyokuni, T. **19**-1208
Toyosaki, T. **12**-792
Toyoshima, T. **10**-1373
Toyota, K. **12**-131, **12**-263, **13**-189
Toyota, M. **15**-809
Toyota, S. **4**-282, **16**-1118, **16**-2136, **19**-1729
Traas, P.C. **17**-278
Trabanco, A.A. **10**-884
Trabocchi, A. **10**-1875, **12**-295
Tracey, M.R. **10**-1051
Tracey, M.R. **10**-1051
Trachtenberg, E.N. **19**-448, **19**-547
Trachtman, M. **2**-30
Tracz, S. **15**-1660
Trætteberg, M. **2**-53, **2**-54
Trahanovsky, W.S. **12**-209, **12**-705, **14**-329, **14**-351, **14**-414, **15**-182, **15**-1869, **17**-293, **18**-379, **18**-779, **19**-2, **19**-10, **19**-104, **19**-122, **19**-301, **19**-318, **19**-377, **19**-411, **19**-421, **19**-579, **19**-597, **19**-672, **19**-806
Trainor, R. **15**-1821
Trainor, R.W. **7**-109
Tramontano, A. **19**-1045
Tramontini, M. **10**-279, **10**-418, **16**-372, **19**-923
Tramper, H.S. **19**-1330
Tran-Dube, M.B. **15**-1487, **16**-722
Tran, A.T. **15**-529
Tran, H.Q. **5**-347
Tran, M.B. **10**-1503
Tran, M.N. **15**-780
Tran, V. **15**-2140
Tranmer, G.K. **13**-506
Tranter, G.E. **4**-6
Trauner, D. **15**-2271, **18**-500, **18**-504, **18**-727, **18**-742
Trauthwein, H. **15**-325, **15**-363
Trautwein, H. **18**-74
Traverse, J.F. **16**-776
Travis, B.R. **19**-329, **19**-382, **19**-671
Traylor, T.G. **2**-423, **12**-8, **15**-115
Traynelis, V.J. **13**-752
Traynham, J.G. **5**-4, **11**-57, **14**-56, **14**-58, **14**-128, **18**-85
Treager, J.C. **2**-262
Trebalón, L. **17**-486
Trecker, D.J. **11**-597, **15**-1869, **15**-1884, **15**-2445, **18**-665, **19**-11, **19**-42, **19**-64, **19**-331, **19**-547, **19**-577, **19**-614
Trècourt, F. **13**-350
Treffers, H.P. **16**-1663
Trehan, S. **10**-1068, **15**-828, **16**-1495
Tremaine, P.H. **16**-97
Tremblay, M.-C. **16**-490
Tremblay, M. **10**-1757
Tremelling, M.J. **13**-657
Trémillon, B. **12**-356
Tremmel, J. **5**-238
Trépanier, V.E. **11**-329
Treptow, B. **4**-448, **15**-931
Tretyak, O.A. **16**-2196
Tretyakov, A.N. **13**-795
Treutwein, J. **15**-1007, **15**-2404
Trevillyan, E.A. **12**-435, **12**-436
Trevisan, R. **13**-766
Triantafyllou, A.S. **11**-451
Tribedi, U. **15**-1660
Trimitsis, G.B. **10**-512
Trinajstic, N. **2**-118, **2**-127, **2**-470
Trincado, M. **15**-372, **16**-943, **16**-1222
Tripathy, P.B. **10**-1878
Tripathy, R. **15**-2246
Tripathy, S. **13**-178
Tripoli, R. **11**-368, **12**-332
Tripoli, R. **16**-1334
Tripoulas, N.A. **10**-1049
Tristram, E.W. **16**-283
Trivedi, E.R. **19**-980
Trivedi, G.K. **15**-2109
Trivedi, N.J. **16**-1879
Trivedi, R. **10**-974, **19**-791
Trofimenko, S. **12**-375, **15**-2507, **19**-535
Trofimov, A. **16**-808
Trofimov, B.A. **10**-680, **10**-804, **10**-1597, **15**-255
Trofimov, B.A. **4**-307
Trofimov, M.I. **1**-32
Trogolo, C. **14**-86, **15**-1351, **15**-2008, **15**-2090, **15**-2092
Troisi, L. **12**-769, **15**-2369
Troitskii, N.A. **12**-153
Trombini, C. **12**-727, **16**-1084
Tromelin, A. **11**-587
Trometer, J.D. **10**-1640, **17**-55
Tromp, J. **11**-654
Tronche, C. **5**-327. **14**-143
Tröndlin, F. **13**-35. **19**-1545
Tropitzsch, R. **17**-356
Trost, B.M. **2**-48, **2**-49, **2**-50, **2**-94, **2**-360, **4**-214, **4**-425, **5**-150, **6**-19, **10**-945, **10**-1510, **10**-1519, **10**-1520, **10**-1521, **10**-1524, **10**-1546, **10**-1551, **10**-1558, **10**-1564, **10**-1674, **10**-1717, **10**-1720, **10**-1736, **10**-1749, **10**-1755, **10**-1999, **12**-70, **12**-246, **12**-258, **12**-542, **13**-439, **14**-276, **15**-404, **15**-420, **15**-543, **15**-780, **15**-785, **15**-793, **15**-847, **15**-849, **15**-864, **15**-925, **15**-931,

Trost, B.M. (*Continued*) **15**-956, **15**-1566, **15**-2003, **15**-2082, **15**-2083, **15**-2155, **15**-2157, **15**-2158, **15**-2159, **15**-2160, **16**-151, **16**-159, **16**-402, **16**-404, **16**-938, **16**-1088, **16**-1089, **16**-1090, **16**-1093, **16**-1441, **16**-1443, **16**-1470, **16**-1474, **16**-1764, **16**-1805, **17**-235, **17**-297, **18**-109, **18**-110, **18**-166, **18**-245, **19**-24, **19**-250
Trotman-Dickenson, A.F. **14**-130, **14**-132
Trotter, J. **1**-80, **3**-181, **4**-146, **4**-404, **4**-471, **5**-299
Troupel, M. **10**-1956, **10**-1963, **13**-155
Troutman, M.V. **15**-451
Troyansky, E.I. **4**-373, **19**-592
Trozzolo, A.M. **5**-349, **14**-49
Trshiska, Ya. **18**-354
Truax, D.R. **4**-363, **4**-270
Truce, W.E. **10**-253, **10**-276, **10**-1825, **10**-1861, **11**-503, **13**-862, **13**-865, **13**-869, **13**-873, **15**-45, **15**-46, **15**-48, **15**-50, **15**-1159, **16**-190, **17**-324, **18**-412
Trucks, G. **15**-1794
Trudeau, S. **15**-1854
Trudell, M.L. **18**-252, **19**-74, **19**-233, **19**-1611
Trueblood, K.N. **2**-299
Truesdale, L.K. **12**-226
Truhlar, D.G. **6**-9, **6**-25, **10**-596
Trullinger, T.K. **19**-1403
Trumbull, E.R. **17**-244, **17**-251, **17**-259
Truong, A. **16**-2213
Truong, P.N. **1**-11
Truong, T.N. **12**-421
Trupp, B. **4**-459
Truppo, M.D. **19**-1014
Trusty, S. **10**-565
Trzoss, M. **4**-140, **18**-828
Trzupek, L.S. **12**-563
Ts, C.e. **4**-428
Tsadjout, A. **12**-757
Tsai, C.-C. **16**-1421, **16**-1422
Tsai, C. **12**-523
Tsai, F.-Y. **10**-1309, **10**-1733, **15**-2634
Tsai, M. **4**-22, **19**-16
Tsai, T.Y.-R. **16**-794
Tsai, Y.-M. **15**-1310, **15**-1364
Tsai, Y. **10**-1299
Tsanaktsidis, J. **10**-53, **14**-476
Tsang, G.T.Y. **10**-306
Tsang, M.W.S. **13**-175
Tsang, W.-Y. **10**-592
Tsang, W.C.P. **11**-542
Tsangaris, M.N. **15**-1698
Tsao, K.-L. **10**-288
Tsao, M.-L. **5**-439, **10**-291, **10**-471
Tsarev, D.A. **13**-553
Tsaroom, S. **10**-1073
Tschaen, D. **10**-1194
Tschaen, D.M. **15**-1113, **19**-647, **19**-650
Tschamber, T. **18**-515
Tscheschlok, K. **15**-2095
Tschöp, A. **10**-693
Tschuikow-Roux, E. **5**-362
Tschumper, G.S. **1**-29
Tse, A. **8**-240
Tse, C. **15**-129, **18**-162, **18**-606, **18**-615, **18**-650
Tse, M.K. **13**-162, **15**-1885, **15**-1901
Tselinskii, I.V. **10**-1093, **12**-745
Tseng, C.C. **4**-151, **10**-1763, **10**-1586
Tseng, C.K. **15**-1725
Tseng, S.-L. **16**-680
Tseng, W.-H. **15**-1340
Tsibouklis, J. **10**-1053
Tsipouras, A. **4**-215
Tsir, Ya. **16**-2060
Tso, H. **15**-2279
Tsoucaris, G. **4**-169, **4**-170
Tsoungas, P.G. **17**-438
Tsubaki, K. **3**-135, **10**-1535, **10**-1724
Tsubata, K. **19**-1546
Tsuboi, S. **10**-1629
Tsubokawa, N. **16**-1202
Tsubouchi, A. **10**-1511, **13**-711, **16**-1299, **16**-1423
Tsubouchi, H. **16**-1882
Tsuboya, N. **15**-2640
Tsuchida, M. **12**-748, **19**-144
Tsuchida, N. **18**-365
Tsuchida, Y. **14**-114, **19**-1596
Tsuchihashi, G. **10**-1809, **12**-188, **12**-189, **12**-193, **18**-13, **18**-159, **19**-1585
Tsuchimoto, T. **11**-327, **15**-212, **15**-933, **18**-255
Tsuchiya, K. **10**-1267
Tsuchiya, S. **1**-90
Tsuchiya, T. **11**-438, **14**-477, **15**-1932, **16**-2040, **16**-2240
Tsuchiya, Y. **10**-993, **15**-642, **15**-762, **16**-1183
Tsuda, K. **19**-1014
Tsuda, T. **14**-484
Tsuge, H. **15**-1953
Tsuge, O. **10**-1090, **15**-2105, **15**-2105, **15**-2105
Tsuge, S. **19**-1094
Tsugeno, A. **10**-315
Tsugoshi, T. **11**-555
Tsui, H.-Y. **15**-1023
Tsui, S.K. **17**-69
Tsuji, H. **15**-946
Tsuji, J. **4**-172, **10**-1518, **10**-1520, **10**-1734, **12**-565, **14**-281, **14**-485, **14**-486, **14**-492, **14**-498, **15**-1497, **15**-1774, **16**-1047, **17**-329, **19**-53, **19**-399, **19**-400, **19**-698, **19**-86, **19**-1294
Tsuji, K. **16**-1882
Tsuji, R. **15**-1919
Tsuji, S. **10**-1716, **16**-196
Tsuji, T. **10**-159, **10**-1300
Tsuji, T. **4**-442, **12**-167, **15**-2470, **16**-921, **19**-1034
Tsuji, Y. **10**-471, **10**-472, **10**-473, **10**-926, **10**-931, **10**-954, **10**-1275, **10**-1943, **15**-1480, **16**-2044, **19**-48, **19**-1238
Tsujimoto, M. **14**-224
Tsukada, N. **10**-1625, **12**-309, **15**-969, **15**-2603
Tsukagoshi, T. **15**-816
Tsukahara, J. **9**-12
Tsukamoto, H. **13**-535
Tsukamoto, K. **10**-1660
Tsukayama, M. **7**-60
Tsukinoki, T. **15**-551
Tsukuda, M. **12**-648
Tsumaki, H. **10**-813, **16**-1867
Tsumiyama, T. **19**-282
Tsumura, S. **19**-462
Tsunawaki, S. **13**-792
Tsuneda, T. **6**-4
Tsuno, Y. **5**-334, **10**-73, **10**-176, **10**-182, **10**-183, **10**-289, **10**-290, **10**-327, **10**-434, **10**-471, **10**-472, **10**-473, **11**-169, **16**-1959, **18**-300
Tsunoda, K. **11**-515, **19**-1034
Tsunoda, T. **10**-729, **10**-1816, **16**-1328, **18**-736
Tsunoi, S. **15**-1355, **19**-593
Tsuritani, T. **19**-1645
Tsurugi, H. **15**-845
Tsurugi, J. **19**-1474
Tsurugi, K. **10**-1519
Tsuruoka, Y. **19**-1203
Tsuruta, T. **14**-9
Tsushima, K. **10**-1420
Tsushima, S. **12**-227
Tsushima, T. **12**-167
Tsutsui, H. **10**-1012
Tsutsui, M. **12**-1
Tsutsui, Y. **15**-2347
Tsutsumi, K. **15**-1568, **19**-1301
Tsutsumi, S. **12**-771, **15**-1459, **19**-725
Tsutsumi, T. **19**-1031
Tsuzuki, H. **15**-551
Tsuzuki, S. **3**-77
Tsvetkov, E.N. **3**-149
Tsyganov, D. **15**-991
Tu, C.-H. **15**-1178
Tu, S.-J. **16**-57, **19**-1073
Tu, Y.
Tu, Y.-Q. **13**-179, **15**-1936, **16**-270, **18**-135, **18**-155, **18**-158,

19-83, **19**-1036, **19**-1364, **19**-1649
Tuaillon, J. **15**-1740
Tubergen, M.W. **15**-166
Tuccarbasu, S. **14**-470
Tuchiya, Y. **15**-2518
Tucker, C.E. **9**-124, **10**-1403
Tucker, G.P. **11**-202
Tucker, J.A. **15**-1127
Tucker, J.L. **15**-522
Tucker, J.R. **15**-2499
Tucker, R.B. **19**-608
Tudge, M.T. **15**-1021
Tueting, D. **16**-2032
Tufariello, J.J. **4**-241, **19**-431
Tufon, C. **13**-13
Tuhina, K. **13**-509
Tuji, H. **10**-521
Tuladhar, S.M. **10**-54, **15**-2007
Tuleen, D.L. **14**-55, **14**-207
Tuli, D. **10**-1668
Tullman, G.M. **14**-470
Tullock, C.W. **16**-441
Tumas, W. **5**-113
Tumas, W. **12**-697, **14**-479
Tümmler, B. **3**-150
Tüncher, W. **19**-284
Tundel, R.E. **13**-98, **13**-188
Tundo, A. **18**-73
Tundo, P. **9**-111, **10**-443, **10**-941, **10**-1669, **12**-784, **12**-784, **13**-391
Tung, C. **17**-515
Tung, C.C. **16**-1278
Tung, H. **19**-485
Tung, J.C. **4**-324
Tung, J.S. **13**-827
Tunge, J.A. **12**-692, **18**-724
Tunney, B.H. **13**-246
Tunoori, A.R. **16**-1895, **19**-1111, **19**-1118
Tuong, H.B. **16**-1388
Tur, F. **16**-1217
Turconi, M. **13**-284
Tureček, F. **2**-463
Turk, A. **10**-1323
Turk, M.R. **2**-268
Turkevich, J. **15**-476
Turley, P.C. **16**-45
Turley, P.C. **18**-210
Turnbull, K. **10**-1059, **10**-1064, **19**-1247
Turner, A.B. **19**-22, **19**-23
Turner, A.T. **11**-697
Turner, D.W. **1**-16
Turner, H.W. **19**-211
Turner, J.M. **16**-961
Turner, J.O. **5**-48, **8**-42
Turner, J.V. **12**-325, **18**-775
Turner, L.M. **12**-32
Turner, N.J. **10**-1028, **13**-511, **19**-1148
Turner, P. **19**-1487
Turner, R.B. **4**-516
Turos, E. **18**-561
Turro, N.J. **5**-218, **5**-299, **5**-303, **5**-356, **5**-397, **7**-1, **7**-21, **7**-23, **7**-27, **7**-31, **7**-43, **7**-44, **7**-48, **10**-1443, **14**-179, **14**-252, **15**-2362, **15**-2445, **15**-2449, **15**-2452, **15**-2464, **15**-2534, **16**-45, **16**-2206, **17**-515, **17**-527, **18**-210, **18**-211, **18**-246, **19**-1662
Tursky, M. **12**-723
Turtaut, F. **13**-611
Turteltaub, J.S. **19**-227
Turunen, B.J. **16**-1895
Tuttle, J.B. **15**-615
Tuttle, T. **19**-1565
Tvaroška, I. **15**-1923
Tverezovsky, V.V. **16**-2073
Tveryakova, E.N. **11**-289
Twamley, B. **13**-312
Tweddle, N.J. **16**-2238
Tweedie, V.L. **19**-1363
Twiddle, S.J.R. **12**-480
Twieg, R.J. **13**-207
Twigg, M.V. **10**-1974, **12**-67
Twigger, H.L. **16**-2069
Twitchett, H. **16**-1869
Twitchin, B. **12**-325
Tye, H. **13**-278, **13**-320, **16**-1765
Tykwinski, R.R. **17**-317, **17**-318
Tyltin, A.K. **15**-2280
Tymonko, S.A. **13**-700, **13**-706, **13**-717, **19**-139
Tymoschenko, M.F. **13**-314
Tyrlik, S. **19**-1685
Tyurina, L.A. **15**-179
Tyutyulkov, N. **2**-272
Tzeng, T. **15**-1444

Uang, B.-J. **16**-1515, **16**-666, **16**-746
Uang, S. **16**-736
Ube, H. **12**-234, **15**-1055, **15**-1428
Ubukata, M. **17**-469
Ucciani, E. **14**-203
Uchibori, Y. **13**-262
Uchic, J.T. **10**-335, **18**-543
Uchida, A. **14**-416
Uchida, M. **10**-1962
Uchida, N. **19**-1034
Uchida, T. **6**-57, **9**-86, **10**-506, **10**-1539, **15**-1852, **15**-2145, **15**-2515, **16**-1940, **16**-1944, **18**-390
Uchida, Y. **5**-126
Uchimaru, T. **3**-77, **16**-395
Uchimura, H. **15**-762
Uchino, N. **13**-283
Uchiro, H. **16**-1099, **19**-865
Uchiyama, K. **11**-213
Uchiyama, M. **11**-301, **15**-768, **15**-776, **15**-779, **15**-1689, **16**-1430
Uchiyama, N. **15**-1223
Uchiyama, T. **19**-198
Uda, H. **16**-1062
Udachin, K. **3**-165
Udenfriend, S. **14**-225
Ueba, M. **19**-1340
Uebel, J.J. **10**-237
Uebelhart, P. **5**-340
Ueda, A. **18**-680
Ueda, H. **10**-1886, **13**-11, **13**-210
Ueda, K. **2**-69, **5**-88, **10**-1999
Ueda, M. **11**-213, **12**-126, **12**-135, **16**-742, **16**-941, **16**-971, **16**-1603, **16**-1604, **16**-1606, **19**-1139
Ueda, N. **19**-1672
Ueda, Y. **15**-1412
Uedo, E. **16**-1105
Uehara, G. **6**-63
Uehara, S. **19**-591
Uehara, T. **15**-2112
Uehlin, L. **16**-1168
Uehling, D.E. **15**-1131
Ueki, H. **10**-1641
Uematsu, Y. **10**-1709, **16**-1528
Uemoto, K. **10**-1816, **15**-288
Uemura, M. **3**-96, **10**-1365
Uemura, S. **4**-480, **10**-819, **11**-134, **11**-332, **13**-298, **13**-323, **13**-551, **13**-746, **13**-748, **15**-236, **15**-1230, **15**-1661, **15**-1733, **15**-1856, **15**-1858, **19**-215, **19**-956, **19**-1233, **19**-1634, **19**-1716
Uemura, T. **19**-1031
Uenishi, J. **18**-386, **19**-874, **19**-1294
Ueno, H. **19**-1322
Ueno, K. **13**-633
Ueno, M. **8**-204, **13**-192, **15**-2372, **16**-355, **16**-1172, **19**-684
Ueno, S. **10**-623, **13**-563
Ueno, T. **10**-84
Ueno, Y. **19**-709, **19**-1378
Ueno. M. **16**-738
Uenoyama, Y. **19**-1565
Ueshima, T. **19**-1742
Ueta, M. **15**-859
Ueta, T. **13**-698
Uff, B.C. **18**-406, **19**-1113
Uffer, P.M. **4**-483
Ugalde, J.M. **16**-852
Uggerud, E. **3**-60, **10**-62, **10**-287, **10**-349, **13**-14
Ugi, I. **10**-1015, **15**-579, **16**-2249, **16**-2253, **16**-2259, **16**-2262, **17**-481, **17**-482
Ugo, R. **11**-534
Uguen, D. **19**-518
Uhm, S.J. **16**-833
Uhm, S.T. **12**-628
Uhm, T.S. **16**-1615
Ujaque, G. **15**-345, **16**-667
Ujihara, Y. **16**-1253
Ujikawa, O. **16**-1575, **16**-1576

Ukai, K. **15**-975, **16**-866, **16**-867, **16**-1425
Ukaji, Y. **19**-581
Ukita, T. **4**-347, **15**-1830
Ulan, J.G. **15**-536
Ulich, L.H. **16**-1991
Ullenius, C. **10**-1426, **15**-1169, **15**-1241, **15**-1241, **18**-666
Ullman, E.F. **13**-846
Ullrich, E.C. **19**-1653
Ulman, M. **18**-891
Ulmen, J. **18**-674
Ulmer II, C.W. **15**-1082
Ulrich, G. **5**-305
Ulrich, H. **16**-1868, **16**-2197
Ulrich, W. **18**-669
Um, I.-H. **10**-389, **16**-1959
Um, I. **10**-378, **10**-388
Um, I.H. **16**-17
Um, J.M. **16**-256, **18**-495
Uma, R. **19**-128
Umani-Ronchi, A. **10**-1544, **12**-727, **16**-1513, **16**-500
Umani, F. **14**-86, **15**-1351
Umbreit, M.A. **17**-3, **19**-451
Umemoto, T. **12**-196
Umen, M.J. **12**-590, **15**-1158
Umeno, M. **13**-262, **18**-940
Umino, A. **15**-2528
Umpleby, J.D. **15**-899
Unelius, C.R. **10**-1053
Uneyama, K. **15**-2600, **19**-1146
Ungaro, R. **11**-389
Unger, D. **10**-169
Unger, J.B. **13**-129, **15**-624, **16**-1109
Unger, S.H. **9**-62, **9**-63, **9**-65, **9**-68
Ungváry, F. **12**-640, **15**-1618, **15**-1619, **15**-1620. **16**-525
Unibertsitatea, E.H. **16**-852
Unni, M.K. **15**-703
Uno, F. **17**-272
Untch, K.G. **2**-115, **2**-347
Unterberg, H. **2**-336
Unverferth, K. **12**-778
Uozumi, Y. **10**-715, **10**-1545, **10**-1781, **11**-695, **18**-746, **19**-1035
Upadhyay, A.K. **10**-1134
Upadhyaya, D.J. **16**-1872
Uphade, B.S. **13**-394
Uphade, T.S.S. **15**-2047
Uppalla, L.S. **10**-803, **10**-1170, **16**-1211, **16**-1707, **16**-1787, **16**-1790
Upton, C.J. **15**-143
Ura, Y. **15**-2689, **16**-2111
Urabe, H. **15**-840, **15**-854, **15**-897, **15**-976, **15**-2042, **15**-2382, **15**-2592, **15**-2647
Uraguchi, D. **10**-1544, **16**-401, **16**-936, **16**-991, **16**-1220
Urankar, D. **15**-1697
Urasaki, I. **11**-305
Urban, F.J. **18**-780
Urban, R.S. **18**-200
Urbanek, L. **14**-122
Urbano, F.J. **13**-643
Urbanowicz, J.H. **16**-104, **16**-1886
Urbańska, N. **16**-1457
UrBas L. **15**-1052, **16**-1199, **16**-376
Urch, C.J. **3**-85
Urey, H.C. **16**-40
Ürge, L. **13**-683
Uriarte, A.K. **7**-58
Uriel, C. **15**-1319
Uriz, P. **18**-305
Urks, M. **16**-2299
Urmann, M. **13**-587
Urpí, F. **16**-1906, **16**-2057
Ursprung, J.J. **18**-111
Urushima, T. **16**-1085
Usacheva, G.M. **4**-45
Usai, M. **13**-563
Ushida, S. **16**-617
Ushijima, S. **13**-299
Ushiki, S. **16**-1247
Ushino, T. **5**-88
Ushioda, N. **18**-577, **19**-1372
Uskoković, M. **4**-211
Usorov, M.I. **19**-426
Usov, V.A. **16**-213
Ussing, B.R. **15**-2390
Ustynyuk, N.A. **15**-2142
Ustynyuk, Yu.A. **9**-34, **15**-279
Usuelli, F. **16**-927
Usugi, S.-i. **10**-1486
Usugi, S. **15**-317
Usui, H. **10**-1589
Usui, S. **4**-279, **11**-301
Usui, Y. **15**-1800
Usyatinskii, A.Ya. **13**-270, **13**-747
Uthe, J.F. **11**-384
Utimoto, K. **14**-17, **15**-778, **15**-975, **15**-1389, **16**-662, **16**-841, **16**-1039, **16**-1425, **16**-1430, **16**-1431, **19**-1395, **19**-1640
Utley, J.H.P. **11**-46, **14**-456
Uto, T. **2**-137
Utsonomiya, M. **15**-330
Utsugi, M. **15**-2528
Utsukihara, T. **19**-993
Utsumi, N. **16**-958, **19**-1301
Utsunomiya, D. **10**-1012
Utsunomiya, M. **10**-929, **13**-186, **15**-342
Uyanik, M. **19**-206
Uyeda, C. **18**-710
Uyeda, R.T. **4**-251, **12**-63
Uyehara, T. **10**-695, **15**-1164, **15**-1241
Uyeo, S. **18**-322
Uzick, W. **5**-248
Uziel, J. **19**-766
Uzio, D. **5**-413, **19**-37
Vaal, M.J. **16**-1642
Vaccari, D. **10**-1260
Vaccaro, L. **10**-690, **10**-974, **10**-987, **10**-1221, **10**-1236, **15**-2211, **19**-1249
Vaccaro, P.H. **4**-16
Vadivel, S.K. **19**-1623
Vågberg, J.O. **10**-240
Vahedi, H. **19**-598
Vahrenholt, F. **15**-2385
Vaichunaite, B.K. **18**-945
Vaid, B.K. **12**-753
Vaidyanathan, R. **5**-266, **16**-1916, **16**-2290, **19**-166
Vaidyanathaswamy, R. **15**-546
Vaijayanthi, T. **19**-1157
Vail, O.R. **10**-148
Vaino, A.R. **15**-1896
Vairamani, M. **15**-1658, **18**-931
Vajda, E. **5**-238
Vakulrskaya, T. **5**-276
Vakulya, B. **15**-1051
Valacchi, M. **17**-213
Valange, P. **15**-2584
Valdés, C. **17**-271
Vale, M. **5**-299
Valeev, E.F. **3**-79
Valencia, S. **19**-951
Valenta, Z. **19**-12
Valente, C. **10**-1309
Valentí, E. **15**-2421, **17**-422
Valentin, E. **16**-259
Valentine Jr., D.J. **4**-46
Valentine, J.S. **10**-771
Valentine, J.S. **19**-443
Valenzuela, J. **5**-346
Valerga, P. **15**-284
Valette, G. **19**-506
Valgimigli, L. **5**-331
Valko, L. **14**-6, **14**-7
Valla, C. **19**-1630
Vallée, Y. **15**-1078, **16**-948, **16**-978, **16**-1539
Valleix, A. **16**-1892
Valleix, F. **15**-1204
Vallin, K.S.A. **12**-298
Vallribera, A. **15**-1044, **15**-1070
Valot, F. **10**-941, **16**-1889
Valoti, E. **11**-539, **11**-381
Valters, R. **6**-14
Valters, R.E. **2**-481
Valverde, S. **10**-1611
Valverde, S. **15**-1319
van Albada, M.P. **11**-208
Van Allen, D. **13**-247
Van Alsenoy, C. **3**-35.
Van Arman, S.A. **19**-195
Van Atta, R.E. **19**-960
Van Auken, T.V. **4**-77, **17**-501
van Beilen, J. **19**-542
van Beilen, J.B. **19**-539
van Bekkum, H. **9**-18, **15**-434, **16**-246, **19**-185, **19**-1082

van Bergen, T.J. **11**-554
van Bommel, A.J. **4**-100
Van Buren II, W.D. **12**-214
Van Calsteren, M.-R. **15**-2203
Van Cleave, W.C. **11**-44
van de Putte, T. **15**-434
van de Ven, L.J.M. **18**-603
Van de Weghe, P. **10**-1071, **16**-1131
van Deidhuizen, J.J. **17**-311
van den Berg, M. **15**-643
van den Engh, M. **19**-122, **19**-377, **19**-411, **19**-579
van den Heuvel, M. **16**-424
van den Hoven, B.G. **15**-1608
van der Donk, W.A. **15**-196, **15**-731
Van der Eycken, E. **7**-126, **7**-127, **7**-129, **13**-219, **13**-598, **15**-2203
Van der Eycken, E.V. **10**-918
van der Gen, A. **4**-95, **16**-1376, **16**-1500
van der Haas, R.N.S. **16**-1220
Van der Kelen, G.P. **12**-535
van der Kerk, G.J.M. **16**-853
van der Lugt, C. **5**-233
van der Maas, J. **3**-40
van der Maeden, F.P.B. **19**-1728
van der Meer, R. **16**-1806
Van Der Mensbrugghe, A. **16**-1958
van der Plas, H.C. **1**-94, **13**-54, **13**-230, **13**-722, **13**-762
van der Sluis, M. **16**-895
van der Veen, J.M. **11**-512
van der Veen, L.A. **15**-1604
van der Vlugt, D. **5**-78
van der Wel, H. **16**-29
van der Wijst, T. **3**-22
van der Zeeuw, A.J. **12**-319
Van Dine, G.W. **10**-209, **18**-545
van Doorn, J.A. **8**-30, **18**-409
Van Doren, J.M. **10**-363
van Dorp, D.A. **19**-356
van Duijneveldt-van de Rijdt, J.G.C.M. **3**-29
van Duijneveldt, F.B. **3**-29
van Duynhoven, J.P.M. **3**-181
van Echten, E. **16**-1257
Van Eenoo, M. **17**-205
van Eerden, J. **3**-118
van Eikkema Hommes, N.J.R. **12**-613
van Elburg, P. **16**-1376
van Eldik, R. **17**-71
van Emster, K. **18**-14
Van Engen, D. **2**-77, **2**-109
van Es, A. **11**-488, **16**-1729
van Gorkom, M. **4**-265
van Halbeek, H. **19**-1259
van Halteren, B.W. **11**-310
van Hijfte, L. **15**-2335
Van Hoozer, R. **17**-163
Van Horn, D.E. **10**-1451, **10**-1463
van Houwelingen, H.C. **9**-57
van Klaveren, M. **10**-1507
van Klink, G.P.M. **13**-148
van Koten, G. **10**-904, **10**-1507, **11**-654, **12**-420, **12**-587, **13**-148, **13**-732
van Kruchten, E.M.G.A. **18**-96
van Langen, L.M. **16**-1499
van Leeuwen, P.W.N.M. **15**-1604, **15**-1609
Van Lente, M.A. **11**-267
van Lenthe, J.H. **13**-52
van Leusen, A.M. **16**-1256, **16**-1257, **16**-1258, **16**-1338
van Leusen, D. **16**-1256, **16**-1257
van Maarseveen, J.H. **10**-917, **11**-409, **16**-1220, **18**-834
Van Mele, B. **15**-2284
van Melick, J.E.W. **16**-1954
van Niel, M.B. **10**-1805, **16**-1484
VanNieuwenhze, M.S. **15**-1831
van Opdenbosch, N. **4**-414
Van Ornum, S.G. **19**-338
van Otterlo, W.A.L. **18**-866
Van Peppen, J.F. **15**-486
van Rantwijk, F. **15**-434, **16**-1499, **16**-1950
Van Sickle, D.E. **15**-2288
van Soolingen, J. **15**-564
Van Speybroeck, V. **14**-113
van Staden, M. **19**-243
van Staveren, C.J. **3**-118
van Tamelen, E.E. **2**-64, **2**-275, **2**-278, **10**-1165, **10**-1328, **10**-1578, **10**-1580, **12**-726, **14**-439, **15**-514, **15**-818, **15**-2469, **16**-89, **18**-529, **19**-429, **19**-875, **19**-1431, **19**-1559
van Veggel, F.C.J.M. **3**-118, **3**-181
van Veldhuizen, B. **1**-94
Van Vliet, M.C.A. **15**-1894
van Vranken, D.L. **12**-367, **12**-380, **15**-407
van Vuuren, E. **18**-848
van Wageningen, A.M.A. **3**-181
van Well, R. **19**-1276
van Zeist, W.-J. **6**-3, **17**-114
van Zijl, A.W. **10**-1447, **16**-466
van Zijl, P.C.M. **2**-67
van Zoeren, C. **19**-234
Vancik, H. **10**-128, **10**-133, **10**-198, **10**-221
Vander Jagt, D.L. **10**-192
Vandercammen, J. **7**-86
Vanderesse, R. **10**-1311, **13**-479, **14**-442, **19**-1563
VanDerveer, D. **12**-722, **18**-122, **18**-123
VanderWerf, C.A. **16**-1356
Vanecko, J.A. **18**-410
Vanemon, P. **19**-688
Vanier, N.R. **5**-112
Vankar, Y.D. **10**-1146, **10**-1197, **10**-1249, **11**-487, **15**-167, **15**-605, **16**-93, **16**-1722, **16**-1995, **17**-454, **19**-583, **19**-631
Vankelecom, I.F.J. **13**-387
Vanlierde, H. **15**-2423
Vannes, G.J.H. **1**-83
VanNieuwenhze, M.S. **4**-126
Vanquickenborne, L.G. **18**-335, **18**-360
Vaňura, P. **3**-146
Vara Prasad, J.V.N. **15**-708, **15**-682, **15**-712, **18**-476
Varadarajan, A. **2**-383, **2**-386
Varala, R. **15**-1067, **18**-384
Varasi, M. **10**-733
Vardanyan, I.A. **19**-675
Vardapetyan, S.K. **19**-374
Varela, J.A. **15**-851, **15**-2627, **15**-2685, **15**-2688
Varescon, F. **15**-1917
Varga, S. **15**-1051
Varga, S.L. **4**-214
Vargas, F. **16**-746
Vargas, J.R. **18**-695
Vargas, S. **19**-1143
Varghese, B. **10**-974, **18**-867
Varghese, J.P. **10**-1471
Varghese, V. **16**-871
Varick, T.R. **14**-93, **15**-1313
Varkony, T.H. **19**-435
Varma, M. **16**-1631
Varma, M. **17**-121
Varma, R.K. **15**-1711
Varma, R.S. **7**-117, **10**-635, **10**-907, **10**-1062, **13**-467, **15**-604, **15**-1492, **15**-1815, **15**-1892, **15**-1893, **16**-113, **16**-269, **16**-1199, **16**-1238, **16**-1631, **16**-1945, **16**-2177, **19**-28, **19**-110, **19**-201, **19**-774, **19**-886, **19**-895, **19**-1206
Varsolona, R. **19**-1542
Varughese, P. **10**-354
Varvak, A. **17**-209
Varvounis, G. **17**-438
Vasapollo, G. **10**-1998, **12**-785, **15**-1518, **15**-1582
Vasbinder, M.M. **16**-815
Vasco, V. **15**-169
Vasconcellos, M.L. **16**-1171
Vasella, A. **19**-450
Vasella, T. **14**-432
Vasil'ev, A.A. **15**-1702
Vasil'ev, G.S. **15**-50
Vasil'eva, S.P. **16**-162
Vasil'eva, V.P. **19**-719
Vasil'tsov, A.M. **10**-804
Vasin, V.A. **16**-1786, **17**-353
Vaskan, R.N. **16**-479
Vasquez, E. **13**-634
Vasquez, P.C. **19**-226
Vass, A. **19**-1206
Vassar, V.C. **15**-453
Vasse, J.-L. **16**-1286
Vassie, S. **10**-169, **18**-24

Vassilikogiannakis, G. **10**-1734, **15**-2258
Vasu, J. **15**-2109
Vasudevan, A. **15**-214, **18**-303
Vatèle, J.-M. **10**-1188, **15**-208
Vaughan, C.W. **13**-84
Vaughan, H.L. **16**-1690
Vaughan, J. **8**-37
Vaughan, K. **12**-746
Vaultier, M. **10**-995, **11**-449, **12**-547, **15**-2524
Vaur, S. **16**-1138
Vauthey, E. **7**-36
Vauthey, I. **16**-1889
Vautravers, N. **19**-1167
Vavřík, J. **17**-197
Vayjooee, M.H.B. **15**-289
Vayner, G. **18**-639
Vayron, P. **10**-873
Vázquez-Villa, H. **10**-686
Vazquez, B. **14**-354
Vázquez, C. **19**-972
Vázquez, J. **19**-292
Vázquez, S. **4**-511
Veale, C.A. **16**-878
Vecchiani, S. **15**-1657
Veciana, J. **5**-269
Vedantham, P. **16**-2192
Vedejs, E. **12**-107, **12**-492, **15**-675, **15**-702, **15**-706, **15**-707, **15**-721, **15**-1827, **15**-1876, **15**-2105, **16**-206, **16**-215, **16**-1264, **16**-1345, **16**-1348, **16**-1353, **17**-202, **17**-342, **18**-773, **19**-504, **19**-1408
Vedernikov, A.N. **15**-2067, **15**-2069
Veenstra, J.S. **15**-715
Veeravagu, P. **16**-1567, **17**-123
Veerendhar, A. **19**-1727
Veglia, A.V. **11**-595
Vegter, G.C. **14**-122
Veitch, G.E. **16**-1938
Vekemans, J.A.J.M. **19**-209
Vela, A. **2**-9
Velaparthi, U. **10**-883
Velasco, L. **10**-1330
Vel'der, Ya.L. **14**-428
Velichko, F.K. **15**-1773
Veljković, J. **16**-2193
Velker, J. **18**-734
Velluz, L. **4**-277
Velmathi, S. **13**-288
Velu, S.E. **15**-1163
Velusamy, S. **16**-125, **16**-1755, **19**-128, **19**-560, **19**-787
Venanzi, L.M. **16**-129
Vendier, L. **19**-1167
Venier, C.G. **12**-187, **19**-798
Venimadhavan, S. **12**-91
Venkanna, G.T. **13**-205
Venkatachalam, C.S. **11**-700
Venkatachalam, T.K. **12**-669
Venkataiah, B. **10**-1571, **16**-758, **16**-1744, **16**-1808
Venkatakrishnan, P. **19**-205
Venkataraman, D. **12**-305, **13**-112, **13**-247
Venkataraman, K. **16**-1990
Venkataraman, S.K. **10**-1452
Venkataramani, P.S. **19**-669
Venkatesan, K. **4**-474, **13**-592, **15**-2445, **16**-7
Venkatesh, V. **16**-2037
Venkateshwar, M. **16**-315
Venkateswarlu, A. **10**-1212
Venkateswarlu, K. **11**-286
Venkateswarlu, Y. **10**-1003
Venkatraman, L. **4**-165, **15**-2251
Venkatraman, M.S. **19**-683
Venkatraman, S. **13**-308, **13**-330, **15**-1231
Vennall, G.P. **15**-1002, **15**-1019, **16**-763
Ventura, D.L. **12**-373
Ventura, S. **11**-182
Venturello, P. **10**-1669
Venturi, M. **3**-194
Venturini, A. **5**-128, **15**-2421
Venturo, V.A. **3**-77
Venugapal, C. **16**-150
Venugopalan, P. **12**-423, **16**-56
Vera, E.L. **10**-1051
Vera, S. **15**-1106
Veracini, S. **8**-17
Verardo, G. **12**-735, **17**-269
Verbicky, C.A. **18**-868
Verbit, L. **4**-22
Verboom, R.C. **15**-276
Verboom, W. **3**-181, **9**-86
Verbrugge, C. **14**-434
Verchere, J. **10**-386
Verdaguer, X. **10**-736, **15**-1557, **19**-1119
Verdaguer, X. **19**-1451
Verdecchia, M. **10**-744
Verdonck, L. **12**-535
Verducci, J. **2**-481
Veregin, R.P. **3**-60
Verenchikov, S.P. **14**-24
Verendel, J.J. **15**-452
Vereshchagin, A.N. **4**-362, **16**-135, **19**-1666
Vereshchagin, L.I. **19**-10
Verevkin, S.P. **4**-399
Verhé, R. **10**-309, **10**-1300, **12**-110, **15**-2470
Verhoeven, J.W. **7**-34
Verhoeven, T.R. **2**-50, **15**-1883
Verkade, J.G. **4**-129, **4**-150, **10**-1731, **13**-186, **13**-639, **15**-635, **16**-767, **16**-1204, **16**-1240, **16**-1798, **16**-1802
Verkade, P.E. **9**-18
Verkruijsse, H.D. **10**-1698, **10**-1839, **12**-418, **12**-506, **16**-2010
Verlhac, J. **16**-2116
Verma, M. **15**-1949
Verma, S.D. **2**-211
Vermeer, P. **10**-245, **10**-1422, **10**-1436, **12**-525, **12**-572
Vermeer, P. **15**-981
Vermeeren, H.P.W. **17**-138
Vermehren, J. **10**-274
Vermeij, R.J. **2**-74
Vermont, G.B. **13**-821
Verna, F. **15**-447
Vernigor, E.M. **19**-814
Vernin, G. **13**-822, **13**-830
Vernon, J.M. **13**-39, **15**-2262
Verny, M. **12**-74, **18**-654
Veronese, D. **16**-796
Verpeaux, J.-N. **10**-1559, **13**-63, **17**-290
Verpeaux, J. **19**-818
Verrall, R.E. **7**-83
Verrinder, D.J. **10**-225
Versichel, W. **3**-29, **3**-33
Versluis, L. **15**-1617
Verter, H.S. **19**-318
Verveer, P.C. **7**-128
Verza, E. **15**-535
Verzas, M.K. **15**-214
Vescovi, A. **19**-199, **19**-1747
Veselov, V.Ya. **10**-383
Veselovskaia, I.K. **13**-253
Veselovskii, A.B. **19**-71
Veselovskii, V.V. **19**-71
Veselovsky, V.V. **15**-2205
Vesely, J. **15**-1402, **15**-2078
Vesley, G.F. **17**-527
Vessière, R. **12**-74, **18**-654
Vest, G. **16**-1926
Veszprém, T. **18**-618
Vetter, W. **3**-205
Veverková, E. **16**-301
Veyron B. **10**-1102
Vial, L. **15**-892
Viala, J. **10**-1158
Vialle, J. **16**-4, **16**-186
Vianello, P. **10**-733
Vianello, R. **8**-133, **15**-607
Vianna, J.F. **12**-706
Viau, R. **5**-126
Vibet, A. **16**-4
Vibhute, Y.B. **11**-259
Vibhute, Y.R. **10**-1178
Vicario, J.L. **15**-1045, **15**-1401
Vicart, N. **10**-1496
Vice, S.F. **10**-1351
Vicens, J. **3**-128, **3**-141, **3**-144, **3**-145
Vicente, R. **18**-276
Viciu, M.S. **13**-195
Vickery, B.D. **16**-777
Vico, R. **11**-693
Vidal-Ferran, A. **15**-1929
Vidal, J.-P. **18**-157
Vidal, M. **15**-614
Vidal, S. **14**-124

Videtta, V. **12**-769
Vidrine, D.W. **10**-149
Viehe, H.G. **1**-9, **2**-64., **4**-492, **5**-256, **5**-258, **10**-1898, **11**-172, **12**-444, **12**-506, **14**-329, **15**-80, **15**-217, **15**-218, **15**-461, **15**-2150, **15**-2253, **15**-2388, **15**-2432, **15**-244, **15**-2530, **15**-2584, **16**-535, **17**-292, **17**-313, **17**-361, **19**-1772
Vieira, A.S. **12**-300, **14**-364
Vieira, N.M.L. **10**-1220
Viel, S. **3**-85
Vierfond, J. **11**-546
Vierhapper, F.W. **1**-94
Vieta, R.S. **18**-649
Vietmeyer, N.D. **18**-520
Viggiano, A.A. **10**-365
Vignola, N. **10**-780, **10**-1678, **10**-1800, **16**-1108
Vignolle, J. **5**-425
Vijayakumaran, K. **19**-82
Vijayamohanan, K.P. **18**-220
Vila, J.M. **10**-1906
Vila, X. **15**-1336
Vilaivan, T. **16**-1872
Vilaplana, M.J. **10**-1252
Vilar, E.T. **11**-498, **16**-2174
Vilarrasa, J. **15**-303, **16**-1906, **16**-1969, **16**-2057
Vilhelmsen, M.H. **12**-532
Villa-Marcos, B. **19**-1143
Villa, M. **11**-646
Villa, P. **10**-70
Villa, R. **19**-223
Villacampa, M. **15**-2334
Villani, C. **4**-53, **4**-62
Villani, R. **15**-1774
Villano, S.M. **5**-338, **17**-35
Villanova, L. **11**-653
Villar, F. **15**-1359, **17**-299
Ville, G. **10**-238
Villegas, C. **10**-1231
Villemin, D. **13**-495, **13**-505, **13**-519, **16**-1827, **19**-615
Villieras, J. **10**-1610, **12**-524, **12**-650, **12**-651, **15**-984, **16**-1361
Villiers, C. **19**-1699
Villiers, P. **10**-1496
Vilsmaier, E. **10**-334, **17**-356
Vimara, E. **14**-405
Vinader, V. **10**-1546
Vinatoru, M. **7**-99
Vincens, M. **15**-614
Vincent Jr., B.F. **19**-1218
Vincent, B.R. **5**-151
Vincent, G. **16**-2261
Vincent, M.A. **2**-474, **18**-704, **18**-708
Vincent, R.L. **3**-65
Vines, S.M. **12**-500
Vineyard, B.D. **15**-454
Vink, J.A.J. **19**-1210
Vinnik, M.I. **15**-181, **17**-178, **18**-352
Vinod, M.P. **13**-394
Vinod, T.K. **19**-194
Vinogradov, A.N. **14**-243
Vinogradov, M.G. **14**-24, **14**-489
Vinter, J.G. **3**-46, **3**-85
Viola, A. **17**-494, **18**-654
Viout, P. **10**-1710
Viózquez, S.F. **16**-1084
Virender. **15**-2561
Vis, J.-M. **18**-382
Visali, B. **16**-1234
Vishnyakova, T.B. **3**-18
Vishnyakova, T.P. **16**-415
Vishwakarma, L.C. **19**-508, **19**-510
Visigalli, M. **16**-1813
Viski, P. **19**-385, **19**-445
Vismara, E. **11**-262, **14**-140, **14**-378, **14**-379, **14**-383, **14**-384, **14**-389
Visnick, M. **16**-1291
Viso, A. **18**-757
Visser, G.W.M. **11**-310
Visser, J.P. **4**-506
Visser, R. **2**-146
Viswajanani, R. **19**-1373
Viswanathan, G.S. **16**-1564
Vit, J. **19**-888
Vitale, A.A. **10**-897, **12**-561
Vitale, A.C. **18**-171
Vitale, D.E. **17**-55
Vitale, M. **10**-1573, **12**-331
Vitale, M.A. **9**-89, **10**-508
Vítek, J. **19**-350
Vitins, P. **17**-495
Viton, F. **15**-2144
Vitt, S. **10**-1977, **14**-160
Vitullo, V.P. **10**-328, **18**-195
Vivanco, S. **15**-2119
Vivarelli, P. **2**-62
Vivekananda, S. **2**-463
Viyayakrishna, K. **10**-974
Vizza, F. **15**-2645
Vlaar, C.P. **15**-1938, **15**-2012
Vladuchick, S.A. **15**-2549
Vlasov, A.V. **16**-2114
Vlasov, V.M. **13**-81
Vlasova, N.N. **16**-2114
Vliegenthart, J.A. **3**-29
Vlietstra, E.J. **16**-1887
Vo-Thanh, G. **15**-970, **15**-2329, **16**-801
Vo, N.T. **15**-1077
Vodichka, L. **18**-354
Voelter, W. **4**-120, **10**-814
Voet, J.G. **4**-475
Vogel, A. **2**-305
Vogel, D.E. **10**-71, **15**-361
Vogel, E. **2**-194, **2**-275, **2**-288, **2**-291, **2**-292, **2**-293, **2**-294, **2**-302
Vogel, E. **2**-303, **2**-305, **2**-306, **2**-310, **2**-312, **2**-324, **2**-351, **2**-357, **2**-361, **2**-364, **3**-193, **4**-488, **17**-303, **18**-503, **18**-682
Vogel, G. **5**-156
Vogel, H. **15**-1470
Vogel, I.A. **19**-1713
Vogel, M.A.K. **17**-197
Vogel, P. **5**-2, **10**-25, **13**-331, **15**-2448, **16**-2299, **16**-2306, **18**-2, **18**-22, **18**-27, **18**-37
Vogel, P.C. **10**-80
Vogel, R. **13**-647
Vogel, S. **13**-160
Vogel, W. **8**-25
Vogelfanger, E. **10**-187
Vogels, C.M. **19**-1588
Vogelzang, M.W. **17**-138
Vogl, E.M. **13**-640
Vogler, E.A. **18**-332
Vogler, T. **15**-2609
Vogt, D. **15**-1625
Vogt, H. **10**-1044
Vogt, M. **15**-1883
Vogt, P.F. **19**-1076
Vögtle, E. **3**-106
Vögtle, F. **2**-66, **2**-328, **3**-222, **3**-106, **3**-117, **3**-124, **3**-150, **3**-151, **3**-159, **3**-193, **3**-198, **3**-208, **3**-212, **4**-70, **4**-169, **4**-253, **4**-530, **14**-456, **16**-1266, **17**-516
Voica, F. **13**-381
Voigt, K. **12**-285
Voigtländer, D. **11**-443
Voigtritter, K. **18**-861
Voigtritter, K.R. **15**-624
Voitenko, Z.V. **15**-2280
Voitsekhovskaya, I.Yu. **16**-1924
Volant, F. **15**-717
Volante, R.P. **12**-759, **13**-273
Volatron, F. **16**-1900
Vold, R.L. **3**-169
Vold, R.R. **3**-169
Volger, H.C. **12**-10, **15**-135
Vol'kenshtein, Yu.B. **11**-411
Volkman, S.K. **16**-935
Volla, C.M.R. **16**-2306
Vollenweider, L. **10**-670
Vollhardt, J. **5**-150
Vollhardt, K.P.C. **2**-6, **2**-24, **2**-82, **2**-87, **2**-233, **4**-5415-2586, **15**-2588, **15**-2623, **15**-2641, **15**-2642, **16**-1396, **17**-229
Vollmar, A. **11**-62
Volmer, M. part 2-6
Volodarsky, L.B. **5**-274, **5**-267
Volod'kin, A.A. **18**-196
Volovik, S.V. **15**-93
Volpe, T. **15**-1101
Vol'pin, M.E. **2**-177, **12**-13, **15**-2532, **16**-863, **19**-1288
Volpp, W. **19**-353
Völter, H. **4**-234

Volz, H. **5**-42. **5**-96, **5**-243
von dem Bussche-Hünnefeld, C. **16**-1936
von Felten, W.C. **10**-184
von J. Hinz, A. **14**-9
Von Lehman, T. **10**-150
von Matt, P. **15**-2249
von Nagy-Felsobuki, E. **9**-52
von Pechmann, H. **11**-397
von Puttkamer, H. **2**-350
von Raumer, M. **7**-36
von Ross, B. **2**-250
von Rudloff, E. **19**-376
von Schenck, H. **13**-409, **13**-427
von Schnering, H. **4**-306
von Schnering, H.G. **5**-243, **8**-94, **10**-1771
Von Seebach, M. **4**-460
Vontor, T. **10**-93
Voorhees, K.J. **17**-492
Vora, H.U. **14**-301
Vorbrüggen, H. **10**-751, **10**-1140, **13**-738, **13**-761, **14**-378, **16**-1727, **16**-1758
Vorlop, K.-D. **16**-1496
Voronenkov, V.V. **14**-243
Voronkov, M. **5**-276
Voronkov, M.G. **3**-119, **15**-296, **15**-305, **15**-1739, **16**-213, **16**-2114
Voronkov, M.V. **10**-923
Vorozhtsov Jr., N.N. **11**-644
Vos, A. **1**-83
Vos, T.J. **17**-311
Vossius, D. **18**-312
Vosswinkel, M. **5**-439
Vostell, M. **16**-1252
Vostrikova, O.S. **15**-738, **15**-740
Vostrowsky, O. **2**-398, **16**-1311, **16**-1397, **17**-356
Voter, A.F. **2**-241
Voth, G.A. **9**-121
Vougioukalakis, G.C. **18**-821
Vovsi, B.A. **17**-323
Vowinkel, E. **10**-673
Voynov, G.H. **19**-1464
Vrancken, E. **10**-1626, **17**-221
Vrang, L. **7**-126
Vranková, K. **19**-1156
Vrcek, V. **5**-103, **10**-155
Vreeke, M. **10**-114
Vreugdenhil, A.D. **5**-169
Vrielink, A. **10**-88
Vrielink, J.J. **10**-739, **15**-44
Vriend, J. **5**-233
Vu, A.T. **15**-2619
Vu, B.T. **15**-2112
Vyas, R. **15**-2063
Vyas, V.A. **17**-63
Vyater, A. **15**-1143
Vyboishchikov, S.F. **18**-892
Vypel, H. **14**-149
Vyse, N. **15**-1555
Vyskoc, F. **7**-121
Vyskocil, S. **13**-244
Vysotskaya, N.A. **14**-218

Waack, R. **12**-438
Wabnitz, T.C. **15**-1421, **15**-1422, **15**-1423
Wack, H. **12**-175, **15**-2386, **16**-2226, **16**-2228, **16**-2229, **17**-322
Wada, E. **10**-1680
Wada, F. **13**-811, **14**-406, **14**-408, **14**-410
Wada, K. **10**-815, **15**-2689, **19**-1455
Wada, M. **10**-1042, **16**-571, **16**-589, **16**-593, **16**-784, **19**-975
Wada, R. **10**-708, **16**-737, **16**-780, **16**-942
Wada, Y. **19**-1541, **19**-684
Wadamoto, M. **15**-1251, **16**-1142, **16**-1172, **16**-780
Waddell, S.T. **4**-452, **15**-144
Wade, K. **2**-190, **5**-152, **12**-50, **12**-356
Wade, P.A. **10**-1556
Wade, R.C. **19**-851, **19**-858
Wadgaonkar, P.P. **11**-252, **16**-1209, **19**-1245, **19**-1422
Wadman, S. **10**-1613
Wadsworth Jr., W.S. **16**-1360, **16**-1361
Wadsworth, K.J. **15**-1072, **16**-2094
Waegell, B. **4**-400, **12**-67, **15**-2548, **17**-275, **18**-206, **19**-1326
Waetzig, S.R. **12**-692
Wagatsuma, N. **10**-828
Wagemann, W. **2**-306
Wagener, K.B. **10**-1695
Wager, C.A. **16**-1771, **19**-940
Wager, T.T. **19**-940
Wagerle, Ty.R. **12**-175
Wagh, Y.S. **13**-615
Waghmode, S.B. **11**-238, **12**-116
Wagle, D.R. **16**-1990
Wagner-Jauregg, T. **15**-2259
Wagner, A. **10**-1161, **10**-1972, **13**-304, **13**-723, **15**-767, **15**-2112, **16**-1892, **17**-475
Wagner, C.D. **15**-477
Wagner, C.K. **6**-73
Wagner, G.W. **16**-1303
Wagner, H. **2**-246, **2**-247, **10**-515
Wagner, J.M. **10**-919
Wagner, K. **10**-421, **10**-427, **17**-513
Wagner, P.J. **5**-234, **7**-26, **7**-41, **7**-48, **7**-50, **7**-51, **7**-52, **7**-56
Wagner, R.S. **1**-60
Wagner, U. **4**-120
Wagner, W.M. **5**-390
Wähälä, K. **10**-833
Wahl Jr., G.H. **1**-51, **13**-30, **13**-36
Wai, C.M. **9**-105
Wai, J.S.M. **15**-1830
Wai, W. **17**-504
Waich, K. **16**-1212
Wailes, J.S. **15**-1933
Wailes, S. **10**-658
Wainschel, L.A. **11**-95
Wainwright, P.G. **15**-1912, **15**-1914, **15**-1960
Wait, A.R. **9**-47
Waite, B.A. **8**-44
Wakabayashi, A. **15**-1578, **15**-2595
Wakabayashi, K. **14**-12, **15**-901, **15**-1299
Wakabayashi, S. **7**-23
Wakabayashi, T. **16**-235
Wakabyashi, H. **16**-851
Wakahara, Y. **16**-1114
Wakai, C. **3**-7
Wakamatsu, H. **13**-610, **18**-804
Wakamatsu, K. **15**-153
Wakamatsu, T. **13**-763
Wakasa, M. **7**-37
Wakasa, N. **19**-1172
Wakasugi, K. **16**-1745
Wakatsuki, Y. **15**-222, **15**-769, **15**-861
Wakchaure, V. **16**-1110
Wakchaure, V.N. **16**-324, **16**-360, **16**-363
Wakefield, B.J. **5**-155, **5**-163, **12**-443, **12**-497, **12**-580, **12**-586, **12**-623, **13**-476, **13**-736, **16**-2061, **19**-1318
Wakharkar, R.D. **10**-679, **13**-394
Waki, Y. **13**-308
Wakiji, I. **15**-865
Wakisaka, A. **9**-135
Wakisaka, K. **10**-828
Wakita, A. **15**-49
Wakita, M. **3**-84
Wakselman, C. **5**-110, **10**-1442, **16**-449
Wakselman, M. **17**-152
Walba, D.M. **3**-202, **4**-92, **4**-93, **4**-209
Walba, D.M. **10**-950
Walborsky, H.M. **5**-143, **5**-206, **5**-287, **5**-382, **10**-1014, **10**-1581, **10**-1684, **12**-18, **12**-32, **12**-450, **12**-639, **12**-641, **14**-498, **14**-499, **15**-666, **16**-2249, **16**-2265, **18**-19
Walburn, J.J. **12**-481
Wälchli, R. **12**-702
Walde, A. **12**-417
Waldeck, D.H. **7**-59
Walden, P. **6**-48, **10**-7
Walder, L. **17**-220
Waldmann, H. **18**-764
Wales, D.J. **18**-556
Walfort, B. **2**-90
Walker, B.J. **16**-792, **16**-1361
Walker, D. **11**-41, **19**-23

Walker, E.R.H. **19**-844
Walker, F. **5**-175
Walker, F.H. **4**-453
Walker, F.J. **10**-697
Walker, F.W. **16**-513
Walker, H. **15**-374
Walker, K.A.M. **10**-820, **15**-446, **19**-1112
Walker, M.A. **16**-1063, **17**-209
Walker, M.P. **18**-371
Walker, S.D. **13**-494
Wall, A. **11**-157, **17**-351
Wall, D.K. **16**-2165
Walla, P. **13**-332
Wallace, B. **16**-1573
Wallace, D.J. **13**-285
Wallace, E.M. **11**-417
Wallace, O.B. **16**-1638
Wallace, R.G. **18**-315
Wallace, T.J. **16**-2277, **17**-289, **17**-324, **19**-771, **19**-839
Wallace, T.L. **17**-291
Wallace, T.W. **18**-517
Wallen, S.L. **9**-102
Wallenfels, K. **10**-1929, **16**-1493, **17**-430, **17**-461
Waller, F.D. **17**-249
Waller, F.J. **11**-136, **19**-124
Wallin, A.P. **12**-433
Walling, C. **10**-190, **11**-574, **14**-29, **14**-122, **14**-138, **14**-181, **14**-199, **14**-207, **14**-215, **14**-220, **16**-518, **19**-100, **19**-265
Wallis, E.S. **18**-294
Wallner, O.A. **16**-615, **16**-949
Wallon, A. **4**-253
Wallraff, G.M. **4**-490
Waloch, C. **16**-917
Walsh, A.D. **1**-31, **7**-17, **15**-86
Walsh, L.M. **16**-807
Walsh, P.A. **2**-440
Walsh, P.J. **15**-1837, **15**-2562, **16**-638, **16**-661, **16**-666, **16**-675, **16**-681, **16**-697, **16**-710
Walsh, R. **5**-410, **15**-179, **18**-87, **18**-608, **18**-625, **18**-684
Walsh, T.D. **10**-99
Walsh, W.L. **18**-258
Walspurger, S. **15**-1219
Walter, D. **18**-442
Walter, D.S. **15**-1366
Walter, D.W. **18**-57
Walter, H. **6**-79
Walter, R. **13**-469
Walter, R.I. **16**-523
Walter, W. **4**-234, **16**-169
Walter, W.F. **14**-439, **19**-1559
Walters, M.A. **18**-614, **18**-736
Walters, M.E. **19**-1354
Walters, M.J. **18**-127
Walthall, D.A. **8**-112
Walton, D.R.M. **11**-33, **12**-499, **13**-685, **14**-349, **14**-350, appendixa-29
Walton, J.C. **5**-211, **5**-220, **14**-2, **14**-46, **15**-51, **15**-101, **15**-1310, **18**-54
Waltz, K.M. **16**-638
Waluk, J. **2**-480
Walz, I. **15**-1086
Wan, B. **13**-148, **16**-546
Wan, C.-W. **13**-604
Wan, H. **18**-410
Wan, J.K.S. **5**-334
Wan, P. **15**-259
Wan, W.B. **2**-317, **2**-331
Wan, X. **11**-264, **13**-720, **19**-115, **19**-128, **19**-722, **19**-1017
Wan, Y.-G. **19**-572
Wan, Y. **10**-836, **13**-206, **13**-595, **13**-671, **19**-1612
Wan, Z.-K. **15**-2295
Wan, Z. **19**-726
Wang H.H. **7**-85
Wang, A.-Z. **14**-342
Wang, A. **15**-1862
Wang, B.-Q. **10**-1607
Wang, B.-S. **15**-852
Wang, B. **9**-92, **13**-206, **15**-811, **15**-1932, **15**-1980, **15**-2058, **15**-2326, **16**-1219, **16**-2043, **19**-269, **19**-800, **19**-976
Wang, B.M. **18**-135, **18**-158
Wang, B.T. **15**-1055
Wang, C.-C. **15**-802, **15**-1216
Wang, C.-J. **15**-2114, **15**-594, **16**-413, **16**-900
Wang, C.-L. **19**-285
Wang, C. **12**-523, **15**-1522, **15**-1576, **16**-151, **19**-1014, **19**-1143, **19**-1156, **19**-1182, **8**-178
Wang, C.C-Y. **15**-1612
Wang, C.J. **16**-441
Wang, C.S. **16**-2294
Wang, D.-P. **12**-267
Wang, D.-q. **15**-2556
Wang, D.-K. **16**-880
Wang, D. **13**-279, **15**-2567, **16**-915, **16**-1140, **19**-1017
Wang, F.-S. **15**-1345
Wang, F. **8**-211, **9**-128, **13**-588, **15**-210, **16**-1084, **19**-83, **19**-763, **19**-1036, **19**-1353
Wang, G.-W. **2**-406, **2**-407, **14**-300, **15**-1057
Wang, G. **15**-287, **15**-706, **16**-129
Wang, G.L. **12**-701
Wang, G.P. **8**-67
Wang, G.Y. **10**-188
Wang, H.-W. **16**-407
Wang, H.-M. **19**-503
Wang, H. **7**-92, **8**-7, **10**-1469, **10**-1905, **13**-148, **13**-166, **13**-168, **13**-205, **15**-597, **15**-1052, **15**-2653, **16**-897, **19**-1017, **19**-1655
Wang, I. **15**-1949
Wang, J. **5**-196, **15**-863
Wang, J.-C. **15**-2156
Wang, J.-Q. **19**-179
Wang, J.-S. **19**-1627
Wang, J.-T. **1**-117
Wang, J.-X. **7**-126, **10**-858, **12**-262, **13**-398, **13**-497, **16**-1823, **16**-2027, **16**-2041, **16**-2046, **16**-2047, **16**-572, **16**-600
Wang, J. **5**-299, **10**-855, **11**-241, **12**-389, **13**-325, **15**-460, **15**-1106, **15**-2215, **15**-2697, **16**-663, **16**-815, **16**-1051, **16**-1084, **16**-1414, **16**-1529, **16**-1822, **16**-1947, **16**-2256, **18**-773, **18**-806, **19**-229, **19**-1118, **19**-1568, **19**-1569, **19**-1614
Wang, J.C. **3**-219
Wang, J.R. **13**-496
Wang, J.Y.C. **14**-167
Wang, K. **5**-261
Wang, K.-H. **12**-262, **13**-497
Wang, K. **12**-256, **15**-2653, **19**-1627
Wang, K.K. **18**-484, **18**-490, **19**-997
Wang, L. **3**-24, **5**-234, **10**-1346, **10**-1459, **13**-616
Wang, L.-C. **15**-2381, **16**-714
Wang, L.-F. **19**-235
Wang, L.-P. **9**-137, **15**-1055
Wang, L.-X. **10**-1475, **10**-660, **15**-470, **15**-643, **15**-2045, **16**-746, **16**-893, **16**-943, **16**-1560, **19**-1014
Wang, L. **10**-540, **10**-1309, **12**-123, **13**-156, **13**-223, **13**-313, **13**-471, **13**-351, **13**-364, **13**-385, **13**-401, **13**-494, **13**-512, **13**-588, **13**-598, **13**-600, **13**-613, **13**-717, **14**-298, **14**-, **14**-339, **15**-1832, **15**-2479, **16**-2043, **16**-2307, **19**-1582
Wang, L.L. **2**-270
Wang, Li.C. **15**-1323
Wang, M.-L. **7**-93
Wang, M. **13**-179, **13**-600, **13**-613, **15**-210, **15**-1492, **16**-202, **16**-270, **16**-596, **16**-1584, **16**-2107, **19**-800, **19**-1649
Wang, M.D. **12**-781
Wang, N. **10**-692, **15**-2119, **19**-174
Wang, P.A. **15**-570, **15**-571
Wang, P.G. **16**-786, **16**-800
Wang, P.S. **5**-365
Wang, Q.-F. **10**-1522
Wang, Q. **10**-1468, **11**-123, **11**-241, **11**-569, **12**-478, **15**-1040, **15**-1179, **15**-1761, **16**-447, **17**-185, **19**-1423
Wang, R. **13**-312, **15**-1305, **16**-544, **16**-545, **16**-666, **16**-670

Wang, S.-Y. **15**-1185
Wang, S.-X. **19**-1627
Wang, S. **9**-105, **10**-1369, **12**-445, **14**-303, **15**-1085, **15**-1980, **16**-1498, **16**-2043, **19**-1198
Wang, S.C. **18**-623
Wang, S.L.B. **15**-2094
Wang, S.Y. **7**-83
Wang, T. **2**-266, **3**-155, **10**-1213, **11**-460, **12**-95, **16**-1523, **19**-150
Wang, T.S. **10**-1668
Wang, W. **8**-110, **8**-118, **8**-121, **10**-855, **12**-256, **12**-656, **13**-592, **13**-698, **15**-503, **15**-916, **15**-1106, **16**-503, **16**-504, **16**-571, **16**-815, **16**-1084, **16**-1358, **19**-128
Wang, W.-B. **15**-562, **16**-1597
Wang, X.-C. **15**-1939
Wang, W.-h. **8**-122
Wang, X.-j. **11**-404, **16**-2012
Wang, X.-L. **13**-524
Wang, X.-X. **15**-607, **19**-285
Wang, X.-Y. **19**-285
Wang, X. **8**-210, **11**-594, **13**-106, **13**-205, **15**-449, **15**-853, **15**-944, **15**-951, **15**-1132, **15**-1347, **15**-1478, **15**-1921, **15**-2421, **15**-2579, **16**-1032, **16**-2109, **17**-258, **17**-387, **18**-784, **19**-171, **19**-174
Wang, Y.A. **19**-1259
Wang, Y.-C. **19**-1298
Wang, Y.-F. **13**-236
Wang, Y.-G. **13**-172, **13**-397, **15**-1794, **19**-175
Wang, Y.-L. **19**-285, **19**-1616
Wang, Y.-M. **14**-88
Wang, Y.-N. **4**-228
Wang, Y.-Q. **11**-314, **15**-2252
Wang, Y.-X. **10**-45
Wang, Y. **10**-1529, **10**-1607, **12**-681, **13**-244, **13**-313, **13**-496, **13**-500, **15**-1052, **15**-1079, **15**-1207, **15**-1835, **15**-2252, **15**-2455, **15**-2697, **16**-398, **16**-469, **16**-612, **16**-1358, **16**-1368, **18**-518, **19**-1253, **19**-1261, **19**-1521
Wang, Z.-Q. **16**-945
Wang, Z.-M. **15**-1793, **15**-1832, **15**-1843, **15**-1925
Wang, Z.-X. **2**-117, **13**-364, **15**-1936
Wang, Z. **10**-599, **10**-977, **10**-1728, **11**-334, **12**-543, **12**-543, **13**-161, **13**-321, **13**-388, **13**-714, **15**-957, **15**-1903, **15**-1971, **15**-2323, **16**-578, **16**-589, **16**-612, **16**-666, **16**-767, **16**-1084, **16**-1208, **16**-2107, **16**-2312, **19**-32, **19**-117, **19**-715, **19**-1008, **19**-1041, **19**-1640
Wang,W. **16**-504
Wann, S.R. **10**-563, **19**-1465
Wannberg, J. **11**-544, **11**-545
Wanner, M.J. **11**-409
Wannere, C.S. **2**-43, **2**-110, **2**-172
Wanzlick, H.-W. **5**-384
Warawa, E.J. **19**-67
Ward Jr., W.J. **16**-1346
Ward, D.E. **16**-1072, **16**-1509, **19**-915, **19**-917, **19**-919
Ward, D.G. **8**-45
Ward, E.L.M. **11**-520
Ward, H.R. **4**-508, **5**-228, **5**-231, **10**-1395, **12**-657, **16**-191, **18**-528
Ward, J.P. **11**-361, **18**-809, **19**-50, **19**-337
Ward, J.S. **18**-675
Ward, P. **18**-194
Ward, R.S. **4**-139, **4**-197, **17**-394
Ward, R.W. **15**-992
Ward, T.J. **18**-412
Ward, T.R. **16**-129
Wardell, J.L. **10**-802, **10**-1626, **12**-409, **12**-443, **12**-456, **12**-497, **12**-577, **12**-587, **12**-594, **12**-623, **12**-644, **13**-743, **15**-293, **15**-884, **15**-909, **16**-3, **16**-571, **19**-1577, **19**-1618
Waring, A.J. **18**-35, **18**-194
Waring, C. **19**-419
Waring, M.J. **15**-197, **15**-627, **15**-1816
Warkentin, J. **5**-414, **5**-424, **14**-89, **15**-1352, **15**-2120, **17**-423, **17**-500
Warmuth, R. **3**-137
Warner, B.P. **16**-765
Warner, P.M. **2**-375, **2**-394, **4**-512, **18**-524, **18**-526, **18**-676
Warner, S. **10**-670
Warnet, R. **15**-47
Warnhoff, E.W. **5**-132, **12**-150, **15**-2473, **18**-94, **18**-203, **18**-251, **19**-959
Waroquier, M. **10**-1244, **14**-113
Warpehoski, M.A. **19**-453
Warren, C.T. **16**-1661
Warren, H.B. **2**-399
Warren, J.A. **4**-276
Warren, R.W. **18**-117
Warren, S. **16**-1387, **18**-32, **18**-259, **19**-1755
Warren, S.E. **15**-113
Warrener, R.N. **19**-79
Warrick, P. **6**-69
Warrington, J.M. **18**-632
Wartenberg, F.-H. **15**-1346
Wartini, A.R. **5**-346
Wartski, L. **15**-1190, **15**-1042, **15**-1189, **15**-1192
Wasa, M. **10**-1028
Waseda, T. **16**-2082
Waser, J. **15**-426
Washington, I. **15**-1941
Washiyama, M. **15**-1137
Wasielewski, M.R. **13**-224
Wassef, W.N. **16**-1617, **16**-1618
Wasserman, A. **15**-2169
Wasserman, B. **10**-352
Wasserman, E. **2**-260, **2**-261, **3**-209, **5**-303, **5**-365, **5**-430, **5**-431, **18**-881
Wasserman, H.H. **12**-675, **14**-250, **14**-251, **14**-252, **14**-263, **15**-2356, **15**-2360, **15**-2361, **15**-2362, **15**-2364, **15**-2366, **15**-2494, **16**-45, **18**-210, **18**-374, **19**-505, **19**-548
Wasserscheid, P. **9**-120
Waszczylo, Z. **6**-91
Wat, E.K.W. **10**-1319
Watabe, H. **10**-1382
Watada, A. **11**-314
Watanabe, A. **16**-307, **18**-151, **18**-390, **19**-1034
Watanabe, F. **11**-690
Watanabe, H. **10**-1388, **10**-1470, **12**-562, **15**-2528, **16**-1047
Watanabe, K. **11**-314, **15**-1056
Watanabe, M. **1**-72, **15**-1052, **15**-1072, **16**-605, **16**-1220
Watanabe, N. **12**-338, **12**-390, **15**-1733
Watanabe, S.-i. **10**-1203
Watanabe, S. **10**-695, **10**-1287, **12**-177, **12**-476, **13**-698, **13**-701, **13**-719, **15**-532, **15**-1913, **16**-961, **19**-802
Watanabe, T. **10**-851, **10**-1294, **13**-490, **15**-2000, **16**-982, **16**-1965, **19**-627
Watanabe, W.H. **10**-680
Watanabe, Y. **10**-577, **10**-926, **10**-931, **10**-954, **10**-1987, **13**-852, **15**-280, **15**-386, **15**-1583, **19**-974, **19**-1103, **19**-1238, **19**-1748
Watanuki, K. **10**-630
Wataya, Y. **16**-355
Waterhouse, A. **10**-1355, **10**-1356
Waterhouse, D.J. **4**-228
Waters, D.N. **11**-647
Waters, W.A. **14**-256, **14**-351, **19**-2, **19**-92, **19**-101, **19**-314, **19**-1202, **19**-1719
Watkin, D.J. **2**-181
Watkin, J.G. **16**-765
Watkins, A.L. **15**-1613
Watkins, C.J. **7**-28
Watkinson, M. **10**-998
Watson, A.J. **11**-122
Watson, A.J.A. **10**-1044
Watson, A.J.B. **12**-322
Watson, D.A. **13**-680
Watson, D.G. **1**-55, **1**-68, **2**-33
Watson, D.J. **15**-452
Watson, I.D.G. **10**-916, **10**-1001
Watson, J.M. **18**-760

Watson, M.P. **18**-744, **18**-747
Watson, S.P. **15**-1548
Watson, S.W. **17**-182
Watson, W.H. **3**-117
Watt, C.I.F. **12**-696, **12**-697, **19**-7, **19**-1737
Watt, D.S. **10**-1695, **10**-1700, **14**-280, **19**-452, **19**-1402
Watts, D.W. **16**-417
Watts, I.M. **5**-410
Watts, L. **2**-236, **2**-254
Watts, P.C. **16**-1304
Watts, W.E. **5**-68, **11**-607, **13**-847, **13**-862, **16**-1741, **18**-1, **18**-309, **18**-411
Waugh, J.S. **2**-109
Wawzonek, S. **18**-926
Wayda, A.L. **2**-282
Waykole, L. **10**-849, **16**-519, **16**-2309
Wayman, M. **12**-762
Waymouth, R.M. **4**-153, **10**-1538
Wayne, R.P. **14**-251
Wayne, R.P. **15**-2361
Wayner, D.D.M. **1**-95, **1**-107, **19**-1516
Weakley, T.J.R. **2**-317, **5**-65
Weatherwax, A. **12**-125, **15**-2386, **16**-2229
Weaver, S.L. **15**-2429
Weaver, W.M. **10**-352, **11**-123, **19**-616
Weavers, L.K. **7**-78
Webb H.M. **8**-241
Webb, D. **11**-670
Webb, G. **15**-479, **15**-485
Webb, G.G. **10**-196, **10**-214
Webb, H.M. **8**-236
Webb, K.S. **16**-1198, **19**-746
Webb, V.L. **4**-349
Weber, A. **16**-2150
Weber, E. **3**-106, **3**-117, **3**-150, **3**-151, **3**-162, **3**-163
Weber, E.J. **16**-463, **16**-774
Weber, H. **2**-285
Weber, J.L. **2**-229
Weber, L. **2**-48, **2**-49, **10**-1524
Weber, M. **14**-361, **14**-364, **16**-598, **16**-1695
Weber, P. **14**-78
Weber, R.T. **5**-307
Weber, S. **10**-334
Weber, T. **4**-139, **11**-380
Weber, V. **14**-17
Weber, W.P. **10**-484, **10**-628, **10**-720, **10**-812, **10**-1015, **10**-1106, **10**-1708, **10**-1932, **15**-2485, **16**-1289, **16**-2163, **19**-1595
Webster, O.W. **2**-160, **15**-2175
Wechter, W.J. **18**-452
Weckerle, B. **19**-474
Wedegaertner, D.K. **12**-17, **14**-500
Wee, A.G.H. **12**-378
Weedon, A.C. **12**-73, **15**-2448, **15**-2458
Weeds, S.M. appendixa-31
Weeks, D.P. **10**-564, **10**-567, **16**-2053
Weetman, J. **15**-2243
Wege, D. **18**-39
Weglein, R.C. **18**-31
Wegner, H.A. **15**-2697
Wehbe, J. **15**-333
Wehle, D. **4**-335, **4**-382
Wehmeyer, R.M. **12**-628
Wehmschulte, R.J. **5**-183
Wehn, P.M. **12**-232, **15**-2059
Wehner, G. **16**-1261, **17**-257
Wehner, W. **3**-150
Wei, B. **13**-398, **16**-2027, **16**-2041, **16**-2046, **16**-2047
Wei, C. **10**-1924, **16**-268, **16**-269, **16**-271, **16**-923, **16**-926
Wei, D. **19**-1017, **19**-1503
Wei, H.-X. **15**-1742, **15**-1746, **15**-2037, **16**-814, **16**-820, **16**-821, **16**-1044, **19**-555
Wei, H.-L. **19**-1025
Wei, J.-W. **15**-1387
Wei, J. **12**-463
Wei, J. **13**-100
Wei, L.-L. **15**-1126, **15**-1383, **15**-1846, **15**-545, **16**-1048, **16**-1156
Wei, L.-M. **15**-545, **16**-1778
Wei, L.L. **16**-391
Wei, Q. **15**-287
Wei, S. **16**-1314, **19**-1041
Wei, T. **19**-1046
Wei, X. **15**-452, **15**-923, **19**-1542
Wei, Y. **10**-348, **16**-311, **19**-720, **19**-1014
Wei, Z.-Y. **10**-1603, **16**-1904
Wei. S. **16**-1371
Weibel, J.-M. **15**-2101
Weiberth, F.J. **16**-993
Weichold, O. **13**-548
Weidlich, T. **16**-1993
Weidmann, B. **16**-609
Weidmann, H. **19**-1626
Weidmann, R. **4**-222
Weidner, J. **10**-334
Weigand, K. **13**-194
Weigel, L.O. **19**-1082
Weigert, F.J. **4**-437
Weihai, W. **16**-1085
Weil, T.A. **13**-664
Weiler, L. **4**-400, **4**-404, **10**-786, **16**-1228, **18**-876
Weill-Raynal, J. **10**-1862, **18**-451
Weinberg, N. **16**-46
Weinberger, B. **10**-1987
Weiner, B. **15**-799
Weiner, D.P. **10**-602
Weiner, H. **10**-97
Weiner, L. **11**-578
Weiner, M.A. **5**-156
Weiner, S.A. **13**-753
Weingarten, H. **13**-125, **16**-245, **16**-1918
Weingärtner, H. **9**-99
Weinheimer, A.J. **15**-518
Weinhold, F. **2**-24
Weinman, S.A. **4**-32
Weinmann, H. **19**-61
Weinreb, S.M. **12**-128, **15**-1378, **15**-1774, **15**-2319, **15**-2319, **16**-316, **16**-1839, **16**-2074, **16**-2080, **18**-838, **19**-381, **19**-1117
Weinshenker, N.M. **19**-164
Weinstain, R. **15**-1109
Weinstein, R.M. **16**-503, **16**-504
Weinstein, S. **4**-175, **4**-177, **4**-194, **4**-195, **17**-50
Weintraub, L. **16**-1962
Weirich, R. **13**-469
Weise, A. **10**-439
Weisel, M. **19**-1142
Weisenburger, G.A. **6**-37
Weiser, J. **4**-339
Weisgerber, G. **10**-1977
Weiske, C appendixa-21
Weisman, G.R. **4**-215, **4**-250, **5**-243
Weisman, R.B. **5**-313
Weismiller, M.C. **19**-511
Weiss, A. **14**-121
Weiss, A.W. **1**-4
Weiss, B. **13**-38
Weiss, C.J. **15**-311, **15**-312
Weiss, D.S. **7**-27, **7**-48, **15**-2445
Weiss, E. **5**-138, **5**-154, **5**-160, **5**-168
Weiss, J. **10**-17, **16**-1829
Weiss, R. **5**-64, **5**-75, **10**-421, **10**-427, **11**-439, **11**-480
Weiss, R.C. **15**-459
Weiss, R.G. **11**-594
Weiss, S. **4**-285, **10**-899
Weissbach, O. appendixa-23
Weissberger, A. **4**-104, **6**-9, **6**-25, **6**-34, **6**-42, **6**-43, **6**-46, **6**-58, **6**-59, **6**-62, **6**-65, **6**-66, **9**-16, **17**-244, **19**-12, **19**-300, **19**-843
Weissbuch, I. **4**-104, **4**-195
Weissenbach, P. **11**-36
Weisser, H.R. **18**-772
Weissermel, K. **15**-1707
Weissman, H. **13**-455, **18**-883
Weissman, P.M. **19**-1099
Weissman, S. **10**-1194
Weissman, S.A. **13**-288, **15**-710
Weitl, F.L. **10**-70
Weitz, E. **15**-1910, **15**-1950
Weitz, I.S. **15**-564
Weitzberg, M. **15**-2370
Weix, D.J. **10**-1786, **13**-358, **16**-945
Welch, C.J. **4**-181, **9**-112
Welch, D.S. **16**-810

Welch, G.C. **19**-1123
Welch, J. **10**-1146, **10**-1249, **16**-1995
Welch, J.T. **15**-167
Welch, M.J. **14**-478
Welch, S.C. **19**-1354
Welch, T.R. **18**-645
Well, P.R. **9**-37
Weller, A. Z. **7**-19
Weller, H.N. **19**-234
Weller, T. **16**-2124
Weller, W.T. **16**-1762
Wells, A. **10**-956
Wells, A.P. **2**-126
Wells, P.B. **15**-147
Wells, P.R. **9**-18, **9**-46, **9**-47, **10**-373, **14**-58
Wells, S. **10**-422
Wells, W.E. **10**-412
Welsh, K.M. **14**-179
Welsher, T.L. **2**-235
Welter, C. **10**-1513
Welton, T. **9**-120, **9**-123, **15**-553, **15**-558, **15**-2225
Welvart, Z. **12**-729, **16**-530, **18**-444, **18**-447
Wen, F. **16**-341
Wen, J. **10**-708, **13**-453
Wen, J.Q. **12**-105
Wen, X. **16**-854
Wen, Y. **16**-1497
Wen, Z. **14**-75
Wencel-Delord, J. **16**-645
Wencewicz, T. **19**-779
Wenchen, H. **2**-132
Wende, R. **10**-840
Wender, I. **10**-1979, **12**-313, **13**-664, **14**-485, **15**-1623, **18**-896
Wender, P. **15**-1496, **15**-1625
Wender, P.A. **10**-1643, **10**-1760, **15**-811, **15**-916, **15**-1543, **15**-1544, **15**-2445, **15**-2671, **15**-2676, **15**-2676, **15**-2679, **15**-2680, **15**-2692, **15**-2696, **15**-2697, **15**-2699, **18**-612, **18**-634, **18**-879
Wenderoth, B. **10**-1453
Wendlandt, J.E. **15**-346
Wendschuh, P.H. **18**-520
Wendt, M.D. **4**-126
Weng, T.Q. **13**-594
Weng, Z. **13**-366
Wengenroth, H. **12**-676
Wenjie, H. **2**-132
Wenke, G. **19**-824
Wenkert, E. **10**-1601, **15**-899, **15**-2174, **15**-2575, **19**-576
Wennemers, H. **15**-1056, **16**-1084
Wennerbeck, I. **4**-237
Wennerström, O. **2**-334, **2**-336, **2**-357
Wensing, M. **12**-654
Went, C.W. **10**-1789
Wentrup, C. **10**-510, **13**-42, **4**-497, **4**-507, **4**-518, **4**-519, **5**-413, **5**-439, **6**-43
Wentworth Jr., P. **12**-340, **15**-2131
Wentworth, A.D. **12**-340
Wenzel, A.G. **18**-895
Wenzel, T.J. **2**-108
Wepster, B.M. **2**-62, **9**-18, **9**-64, **11**-55, **11**-156
Werkman, C.H. **4**-262
Wermeckes, B. **19**-544
Wermer, M. **5**-222
Werner, C. **17**-18
Werner, E.A. **10**-892
Werner, H. **2**-188, **12**-360
Werner, N.D. **14**-62
Werner, N.S. **10**-1491
Werner, T. **19**-498
Werner, U. **3**-159, **4**-253
Werner, W. **16**-1740
Wernett, P.C. **16**-1347
Wersel, O.A. **15**-2309
Werstiuk, N.H. **5**-132, **5**-133, **6**-93, **10**-192, **12**-54, **17**-283, **18**-510
Wertz, J.E. **5**-218
Werz, D.B. **15**-1928
Weskamp, T. **10**-1388
Wessel, H.P. **17**-208, **18**-781
Wessig, P. **15**-2255
Wessig, P. **7**-2
Wessjohann, L.A. **4**-188, **16**-677, **16**-689
West, C.T. **19**-1288, **19**-1427
West, F.G. **15**-1090, **15**-1092, **15**-1095, **15**-1530, **16**-1368, **18**-410
West, J.C. **11**-121
West, K. **8**-162
West, P. **12**-438
West, P.R. **4**-500
West, R. **1**-13, **1**-14, **2**-377, **2**-381, **2**-382, **5**-156
Westaway, K.C. **6**-76, **6**-88, **6**-91, **6**-92, **7**-105, **10**-4, **10**-344, **10**-445, **10**-1930
Westaway, S.M. **10**-1493
Westberg, H.H. **18**-899, **18**-902, **19**-429
Westcott, S.A. **15**-731, **19**-1588
Westdorp, I. **19**-1699
Westerberg, G. **9**-115
Westerkamp, J.F. **16**-2185
Westerlund, C. **10**-1337
Westermaier, M. **10**-398, **10**-399
Westerman, P.W. **5**-64, **5**-39
Westermann, B. **16**-677
Westermann, J. **10**-1453, **10**-1455, **10**-1584, **15**-652, **15**-1128, **16**-655
Westheimer, F.H. **10**-557, **19**-93, **19**-95
Westhus, M. **18**-856
Westlake, P.J. **19**-1516
Westley, J.W. **4**-174, **4**-217
Westman, F. **15**-267
Westmijze, H. **12**-525, **12**-572, **15**-981
Westmoreland, I. **15**-2070
Weston, J. **5**-192
Weston, J.B. **11**-100
Westphal, J. **15**-2264
Westrum Jr., E.F. **1**-99
Westwood, D. **16**-1484
Westwood, N.P.C. **1**-16
Westwood, S.W. **14**-115
Wetterich, F. **5**-255, **14**-72, **14**-109
Wettermark, G. **4**-227
Wetzel, D.M. **5**-130
Weuster-Botz, D. **19**-995
Wexler, S. **14**-253, **14**-256
Weyerstahl, P. **10**-257, **10**-788
Weymuth, C. **19**-550
Whalen, D.L. **5**-121
Whalen, R. **14**-173
Whaley, W.M. **11**-406
Whalley, W. **17**-491, **18**-632, **18**-758
Whangbo, M. **1**-2, **4**-378
Wharton, P.S. **18**-214
Wheatley, A.E.H. **11**-301
Wheatley, P.J. **3**-95
Wheeler, O.H. **16**-1881, **17**-91, **17**-104, **18**-935, **18**-936, **19**-604, **19**-879, **19**-1079, **19**-1461
Whelan Jr., W.P. **10**-15
Whelan, H.M. **16**-2069
Whelan, J. **15**-1478
Wheland, G.W. **2**-1, **2**-144, **2**-156, **2**-409, **4**-128, **18**-12, **18**-30
Wheless, K. **19**-1365
Whetten, R.L. **2**-393
Whiffen, D.H. **1**-56
Whimp, P.O. **4**-501
Whipple, L.D. **12**-17
White, A.H. **10**-644
White, A.J.P. **3**-197, **3**-210, **3**-220, **15**-1932
White, A.M. **5**-41, **5**-61, **5**-94, **8**-10, **10**-200, **10**-559, **18**-108
White, A.W. **11**-220, **15**-916
White, C. G. H. **4**-361
White, C.T. **4**-157
White, D.H. **14**-478
White, D.N.J. **18**-465
White, D.R. **16**-1275
White, E.H. **7**-28, **10**-57, **17**-244, **18**-99
White, E.P. **15**-1664
White, F. **10**-1837
White, H.S. **11**-615, **11**-619
White, J. **18**-161
White, J.B. **15**-537
White, J.D. **4**-514, **19**-892
White, J.M. **1**-67, **4**-250, **16**-1895, **17**-284, **19**-1111, **19**-1118
White, K.S. **18**-732
White, L.S. **13**-387
White, M.A. **19**-129

White, M.C. **19**-472, **19**-473
White, M.G. **11**-671
White, P. **19**-38
White, P.D. **16**-1752, **16**-1753
White, P.S. **4**-374, **15**-1076, **15**-2581
White, R. **15**-2410
White, R.W. **19**-336
White, S. **10**-1768
White, S.B. **11**-213
White, V.A. **11**-626
White, W. **5**-416
White, W.A. **16**-245
White, W.N. **11**-609, **11**-613, **11**-615, **11**-616, **11**-617, **11**-619, **18**-713, **18**-715
Whitehead M.A. **8**-166
Whitehead, A.J. **15**-320
Whitehead, D.C. **15**-1720, **19**-382
Whitehead, M. **18**-302
Whitesell, J.K. **4**-139, **4**-186, **4**-273, **10**-1763, **10**-1785, **10**-1799
Whitesell, M.A. **10**-1763, **10**-1785
Whitesides, G.M. **4**-156, **4**-216, **10**-1404, **10**-1423, **12**-563, **12**-634, **12**-635, **13**-128, **14**-418, **14**-420, **15**-496, **15**-1243, **16**-1624, **16**-1795
Whitesides, T. **19**-429
Whitfield, D.M. **4**-281
Whitham, G.H. **16**-1292
Whiting, A. **12**-518, **12**-480
Whiting, M.C. **3**-96, **10**-433, **10**-1109, **15**-473, **16**-272, **18**-22, **18**-102
Whitley, P.E. **12**-623
Whitlock Jr., H.W. **18**-112
Whitman, D.W. **2**-242
Whitman, G.M. **15**-326, **15**-1624
Whitmire, K.H. **16**-2210
Whitmore, F.C. **18**-3, **18**-13, **16**-506
Whitney, C.C. **18**-478
Whitney, D.B. **16**-1931
Whitney, S. **12**-590
Whitney, S.K. **15**-529
Whittaker, D. **18**-96, **18**-219, **19**-962
Whittaker, D.T.E. **10**-1295, **15**-1347
Whittaker, G. **18**-557
Whittaker, M. **13**-320, **16**-1765
Whittall, J. **15**-452
Whitten, C.E. **10**-1425, **10**-1443, **15**-1146, **15**-1147, **16**-2005
Whittington, B.I. **15**-135, **15**-139
Whittle, A.J. **11**-215, **11**-438, **12**-171
Whittle, R.R. **16**-1355
Whitwood, A.C. **15**-1621
Whitworth, S.M. **3**-67, **10**-296
Wibbeling, B. **16**-1352
Wiberg, A. **2**-489
Wiberg, K.B. **1**-95, **1**-114, **2**-40, **2**-44, **2**-59, **4**-16, **4**-119, **4**-288, **4**-290, **4**-314, **4**-317, **4**-320, **4**-333, **4**-359, **4**-401, **4**-418, **4**-420, **4**-421, **4**-427, **4**-438, **4**-440, **4**-452, **4**-453, **4**-456, **4**-469, **4**-540, **5**-47, **6**-59, **8**-16, **8**-181, **8**-182, **8**-210, **10**-205, **10**-208, **10**-210, **10**-213, **10**-341, **10**-1302, **14**-182, **15**-132, **15**-142, **15**-144, **15**-1794, **17**-428, **18**-163, **19**-2, **19**-3, **19**-92, **19**-95, **19**-96, **19**-187, **19**-301, **19**-410, **19**-446, **19**-606, **19**-691, **19**-1387
Wiberg, N. **1**-12, **15**-515
Wicenec, C. **16**-2305
Wick, A. **17**-417
Wick, A.E. **18**-726
Wickham, G. **12**-37
Wicks, G.E. **19**-750
Widdison, W.C. **14**-499
Widdowson, D.A. **12**-426, **13**-295, **13**-805
Widehem, R. **10**-951
Wideman, L.G. **19**-813
Widenhoefer, R.A. **15**-206, **15**-233, **15**-235, **15**-250, **15**-416, **15**-419, **15**-805, **15**-853, **15**-855, **15**-944, **15**-951
Widing, H.F. **1**-49
Widlanski, T.S. **16**-2285
Widmer, J. **10**-809, **10**-1555, **19**-1514
Widyan, K. **10**-1084
Wiechell, H. **17**-318
Wiechert, R. **16**-1120
Wiedemann, W. **18**-542
Wiegand, N.H. **18**-683
Wieghardt, K. **3**-120, **14**-353
Wieland, G. **16**-969
Wieland, H. **2**-310
Wieland, L.C. **10**-576, **16**-672
Wieland, P. **4**-44, **19**-1005
Wiemer, D.F. **10**-1219
Wiering, J.S. **15**-1911
Wiersum, U.E. **17**-231, **18**-553
Wiesboeck, R. **17**-45
Wieser, H. **4**-270, **4**-363
Wieser, J.D. **1**-65
Wieser, K. **19**-591
Wiesner, M. **15**-1056
Wiest, H. **15**-2184, **15**-2294
Wiest, O. **4**-322, **15**-2197, **15**-2286, **15**-2441
Wife, R. **13**-644
Wife, R.L. **2**-302
Wigal, C.T. **15**-1242
Wigfield, D.C. **16**-1666, **19**-923, **19**-998, **19**-1001
Wiggin, C.J. **19**-66
Wiggins, G. appendixa-35
Wiglesworth, C. **19**-452
Wijkens, P. **10**-1436
Wijnen, J.W. **15**-2219
Wilbur, D.S. **15**-2436
Wilby, A.H. **15**-506
Wilcox, A.L. **10**-797
Wilcox, C.S. **15**-2111, **18**-729
Wilcox, Jr., C.F. **2**-358
Wild, D. **15**-2264
Wilder Jr., P. **18**-101
Wildt, H. **18**-908
Wilen, S.H. **3**-213, **4**-1, **4**-10, **4**-101, **4**-102, **4**-116, **4**-117, **4**-118, **4**-128, **4**-155, **4**-160, **4**-162, **4**-163, **4**-268, **4**-283, **4**-328, **4**-364, **4**-389, **4**-444, **10**-121
Wiles, R.A. **18**-452
Wiley, D.W. **15**-74
Wilhelm, E. **15**-1770
Wilhelm, R.S. **10**-1412, **10**-1429, **10**-1621, **15**-1150
Wilk, B.K. **10**-1947, **16**-1225, **16**-1621
Wilk, K.A. **17**-33, **17**-76
Wilke, G. **15**-829, **15**-2661
Wilke, J. **4**-492
Wilkens, H.J. **17**-408
Wilkerson, C.R. **16**-2107
Wilkins, C.L. **16**-1552
Wilkins, J.M. **12**-590
Wilkinson, B.L. **16**-1743
Wilkinson, D.E. **16**-1642
Wilkinson, F. **7**-13
Wilkinson, G. **2**-46, **12**-287, **14**-486, **15**-437, **15**-445, **18**-807
Will, B. **15**-1994
Willard, G.F. **17**-181
Willard, J.E. **14**-158
Willaredt, J. **8**-94
Willcott III, M.R. **18**-626
Wille, U. **15**-1365
Willem, R. **15**-2646
Willett, G.D. **2**-465
Willey, P.R. **14**-454
Willi, A.V. **6**-75, **8**-148, **11**-651, **11**-652
Willia, J.M.J. **17**-446
Williams Jr., J.M. **5**-145, **10**-566, **17**-350, **17**-356
Williams Jr., L.P. **18**-121
Williams Jr., V.Z. **18**-115, **18**-117
Williams, A. **9**-83, **16**-17, **16**-417, **16**-1674, **16**-2187, **16**-2276, **17**-487
Williams, A.D. **15**-1116
Williams, A.L. **15**-1374, **16**-986
Williams, A.R. **3**-220
Williams, C.M. **15**-1505, **19**-193
Williams, D. **15**-1814
Williams, D.B.G. **10**-687, **10**-974
Williams, D.J. **2**-298, **2**-342, **3**-194, **3**-196, **3**-197, **3**-220, **18**-460, **19**-51

Williams, D.L.H. **2**-444, **10**-549, **10**-777, **10**-783, **10**-784, **11**-39, **11**-155, **11**-158, **11**-580, **11**-609, **11**-611, **11**-614, **11**-620, **11**-622, **11**-623, **12**-202, **12**-203, **12**-204, **12**-733, **13**-34, **13**-80, **13**-783, **13**-784, **13**-858, **18**-788, **18**-943
Williams, D.R. **10**-1768, **15**-1233, **19**-1136
Williams, F. **5**-347
Williams, F.J. **10**-164, **18**-905
Williams, G.H. **11**-628, **13**-822, **14**-46, **14**-317, **14**-365
Williams, G.J. **19**-358, **19**-361
Williams, G.R. **2**-210
Williams, I.D. **15**-1975, **15**-2136
Williams, J. **8**-162
Williams, J.K. **15**-2399
Williams, J.M. **3**-59, **13**-289, **15**-474
Williams, J.M.J. **10**-933, **13**-396, **10**-923, **10**-933, **10**-1044, **10**-1535, **13**-395, **15**-530, **15**-955, **16**-116, **17**-1, **19**-116, **19**-660
Williams, K.B. **5**-101
Williams, K.J. **15**-271
Williams, L.M. **16**-877
Williams, M.J. **16**-310
Williams, N.H. **4**-355
Williams, P.H. **18**-396
Williams, R.E. **10**-186, **12**-50, **12**-356, **16**-1930, **16**-2122
Williams, R.H. **18**-481
Williams, R.J. **17**-130
Williams, R.M. **4**-137, **16**-1522
Williams, R.O. **15**-1511
Williams, R.V. **2**-308, **2**-318, **15**-2179, **18**-678, **18**-679
Williams, S. appendixa-1
Williams, S.M. **10**-974
Williams, T. **4**-211
Williams, T.J. **15**-2671, **15**-2676
Williams, V.A. **13**-397, **13**-506
Williams, W.G. **18**-75
Williamson, C. **16**-1496, **16**-1583
Williamson, D.G. **19**-344
Williamson, D.H. **15**-433
Williamson, J.S. **16**-331, **19**-1121
Williamson, K.L. **1**-36
Williard, P.G. **4**-244, **4**-255, **5**-180, **5**-200, **8**-216, **8**-228, **8**-229, **8**-230, **10**-361, **10**-824, **12**-421, **16**-489, **19**-227
Willis Jr., J.N. **4**-398
Willis Jr., W.W. **17**-295
Willis, A.C. **2**-266, **15**-2252, **15**-2276
Willis, B.J. **17**-525
Willis, C. **15**-512
Willis, C.R. **19**-1287, **19**-1395
Willis, D.M. **13**-817
Willis, J. **15**-1349
Willis, J.B. **10**-330
Willis, M.C. **10**-627, **15**-1033, **15**-1481, **16**-396
Willner, I. **2**-191, **2**-203, **2**-302, **2**-326
Wills, M. **15**-1959, **19**-989, **19**-1014
Willson, T.M. **16**-774
Willy, W.E. **4**-394, **10**-1107, **19**-891
Wilms, T.F.A. **7**-114
Wilsey, S. **18**-567
Wilsily, A. **15**-1170
Wilson Jr., R.B. **19**-282
Wilson, A.A. **10**-426
Wilson, A.C. **12**-538
Wilson, B. **8**-255
Wilson, C. **16**-410
Wilson, C.C. **3**-76
Wilson, C.L. **12**-26, **12**-27
Wilson, C.S. **16**-412
Wilson, C.V. **14**-467
Wilson, D. **15**-917
Wilson, D.R. **3**-163
Wilson, E.B. **3**-57, **4**-274
Wilson, E.R. **10**-1307
Wilson, F.X. **10**-1619
Wilson, H. **5**-408, **10**-392, **10**-439
Wilson, H.R. **17**-527
Wilson, J.D. **2**-107, **16**-1918
Wilson, J.G. **10**-1625
Wilson, J.M. **12**-697
Wilson, J.N. **15**-477
Wilson, J.S. **19**-1382
Wilson, J.Z. **10**-632
Wilson, K.R. **4**-97
Wilson, L.J. **15**-1580
Wilson, M. **19**-1608
Wilson, M.A. **15**-1708
Wilson, N.D.V. **10**-754
Wilson, P. **15**-1316
Wilson, P.W. **5**-370
Wilson, R. **16**-1439
Wilson, R.M. **5**-299, **7**-51, **7**-52
Wilson, S.E. **18**-899, **18**-904
Wilson, S.L. **14**-266
Wilson, S.R. **15**-2557, **18**-961
Wilson, T. **13**-420, **16**-774
Wilson, T.W. **16**-708
Wilson, V.P. **15**-166
Wilt, J.C. **10**-1541, **10**-916
Wilt, J.W. **15**-103, **14**-104, **18**-54, **18**-411
Wilterdink, R.J. **17**-524
Wilzbach, K.E. **4**-461
Wims, A.I. **19**-407
Winans, C.G. **2**-109
Winberg, K.J. **15**-1090
Winchester, W.R. **5**-161, **5**-162, **12**-387
Wind, R.A. **5**-233
Winemiller, M.D. **5**-191
Winer, A.M. **5**-289
Wingard, A.K. **17**-242
Wingert, H. **15**-2585, **18**-530, **18**-531
Wingstrand, E. **16**-1496
Winiarski, J. **13**-755
Winikov, E.H. **9**-37
Wink, D.J. **2**-282, **15**-880
Winkler, H.J.S. **3**-95, **4**-77
Winkler, J.D. **4**-244, **4**-255
Winkler, M. **5**-71
Winkler, T. **10**-1150, **15**-1775
Winn, C.L. **16**-807
Winnik, M.A. **6**-14, **10**-481, **18**-404
Winotai, C. **19**-505
Winstanley Jr., J. **4**-409
Winstein, S. **4**-360, **10**-63, **10**-72, **10**-80, **10**-116, **10**-118, **10**-119, **10**-136, **10**-143, **10**-144, **10**-169, **10**-171, **10**-187, **10**-229, **10**-353, **10**-450, **10**-458, **10**-461, **12**-8, **12**-34, **17**-11, **17**-74, **17**-81, **18**-15, **18**-76, **18**-103
Winter, A. H. **5**-442
Winter, J.E. **15**-1874
Winter, J.G. **11**-626
Winter, J.J.G. **15**-1816
Winter, J.N. **5**-311
Winter, M.J. **15**-2586
Winter, P. R. **5**-286
Winter, R.A.E. **17**-340, **17**-344
Winter, R.E.K. **18**-507
Winter, R.L. **14**-63
Winter, S.R. **10**-1985, **10**-1986
Winter, W. **5**-242
Winterfeldt, E. **15**-80, **15**-89, **19**-10
Winterman, D.R. **8**-96
Wintermute, R.D. **18**-127
Winum, J.-Y. **18**-221
Wipf, P. **9**-97, **10**-250, **15**-930, **15**-2199, **18**-698, **18**-730
Wipke, W.T. **18**-116, **18**-569
Wippel, H.G. **16**-1360
Wireko, F. **4**-146
Wirschun, W.G. **16**-1540
Wirth, T. **14**-161, **15**-1719, **15**-2100, **19**-188, **19**-532
Wirthwein, R. **13**-54
Wirtz, M.C. **13**-46
Wirz, J. **2**-362, **2**-435, **2**-438, **2**-445, **2**-468, **5**-440, **7**-23, **8**-64, **12**-83, **12**-93, **12**-97, **12**-160, **15**-211
Wise, L.D. **19**-1338
Wiseman, J.R. **4**-515, **4**-517, **10**-589, **10**-52
Wishnok, J.S. **18**-528
Wiskur, S.L. **10**-1889, **18**-227
Wisotsky, M.J. **5**-49, **8**-29
Wistrand, L. **13**-137
Wistrand, L.-G. **13**-760, **13**-812, **14**-290
Wistuba, E. **18**-35, **18**-407
Witham, C.A. **18**-275

Witherington, J. **10**-1619, **17**-367
Witholt, B. **19**-539, **19**-540, **19**-541, **19**-542
Witkop, B. **19**-1486
Witt, K.E. **19**-1692
Witt, O.N. **11**-37
Witte, K. **10**-225
Wittenberg, R. **11**-472, **16**-2091
Wittenberger, S.J. **16**-1740
Wittig, G. **4**-505, **5**-158, **8**-160, **10**-1350, **12**-442, **13**-847, **13**-851, **14**-403, **15**-2263, **15**-2545, **16**-1101, **16**-1311, **16**-1340, **17**-200, **17**-256, **18**-439
Wittman, M. **10**-883
Wittman, M.D. **19**-735
Wittmann, D.K. **10**-1692
Witulski, B. **15**-2606
Witz, M. **11**-311
Witzel, H. **5**-53, **10**-551
Wladislaw, B. **19**-1759
Wligus, C.P. **16**-109
Wlodarczak, L. **15**-1776
Wlostowska, J. **15**-2478
Wlostowski, M. **10**-1947
Wnuk, S.F. **10**-1469, **10**-1728
Wnuk, T.A. **10**-1010
Wo, S. **10**-1943
Wobser, S.D. **15**-311
Wodka, D. **16**-1899
Wodrich, M.D. **2**-43
Woell, J.B. **10**-2002, **10**-2003
Woerpel, K.A. **10**-1503, **12**-385, **15**-771, **16**-13
Woggon, W.-D. **19**-1036
Woggon, W. **19**-450
Wohl, J. **15**-1237
Wohl, R.A. **17**-411
Wohlhieter, G.E. **15**-1305
Wojciechowski, B.J. **19**-359
Wojciechowski, K. **10**-1666, **13**-757
Wojciechowski, M. **10**-75
Wojcik, J.M. **13**-634
Wojnarowski, W. **10**-335
Wojtczak, A. **19**-971
Wojtkowski, P.W. **10**-1758, **10**-1873
Wójtowicz, H. **19**-678
Wolber, G.J. **10**-242
Wolckenhauer, S.A. **15**-1040
Wold, S. **9**-29, **12**-63
Woldhuis, A.F. **11**-196
Wolf, A.D. **10**-201
Wolf, A.P. **14**-66, **18**-29, **18**-120, **18**-593
Wolf, C. **13**-205, **13**-587, **14**-294, **16**-549, **16**-1220, **16**-2022
Wolf, D.C. **18**-288
Wolf, J.F. **8**-252
Wolf, P. **15**-76
Wolf, S. **7**-101
Wolf, S.A. **15**-85
Wolf, W. **14**-376
Wolfarth, E.F. **18**-715
Wolfe Jr., J.R. **10**-99
Wolfe, J.F. **16**-1760, **16**-1824
Wolfe, J.P. **13**-210, **15**-346, **19**-279
Wolfe, S. **4**-297, **4**-378, **5**-126, **5**-127, **10**-378, **10**-387, **10**-1038, **10**-1226, **15**-1811, **16**-46, **19**-1765
Wölfel, G. **10**-898
Wolfenden, J.H. **11**-112
Wolff, C. **4**-94
Wolff, H. P. **4**-120
Wolff, M.A. **15**-683, **15**-686
Wolfinger, M.D. **17**-348
Wolford, L.T. **10**-1088
Wolford, R.K. **8**-258
Wolfrom, M.L. **19**-328
Wolfsberg, M. **4**-360, **6**-66
Wolfson, A. **19**-992
Wolinsky, J. **12**-172, **16**-1548, **19**-1566
Wolk, J.L. **10**-27, **10**-117, **10**-336
Wolkoff, P. **17**-304
Wolkowski, J.P. **13**-341
Wollenberg, R.H. **16**-1764
Wollweber, D. **5**-304
Wolman, Y. **8**-171, appendixa-1
Wolochowicz, I. **19**-1685
Wolovsky, R. **2**-300, **2**-301, **14**-331, **18**-881
Wolter, D. **14**-321
Wolter, M. **13**-240
Wolters, E.T.M. **16**-1954
Won, C.M. **11**-652
Wong, A. **9**-112
Wong, C.-M. **15**-331
Wong, C.-H. **16**-651
Wong, C. **16**-1624
Wong, C.-H. **10**-1746
Wong, C.H. **16**-1795
Wong, C.K. **14**-447, **19**-1572
Wong, C.M. **10**-1798, **16**-207, **19**-1343
Wong, C.T. **16**-1147
Wong, F.F. **16**-314
Wong, F.M. **19**-623
Wong, H. **11**-460, **19**-639
Wong, H.N.C. **2**-270, **2**-378, **3**-162, **4**-425, **4**-428, **5**-345, **15**-129, **17**-199, **18**-162, **18**-606, **18**-650
Wong, H.S. **10**-1526
Wong, K.-T. **12**-483
Wong, K.-Y. **15**-1899
Wong, M.-K. **15**-1891, **15**-1926, **15**-1933
Wong, M. **7**-74
Wong, M.W. **16**-1147
Wong, M.Y.H. **19**-959
Wong, N.R. **18**-554
Wong, O.A. **15**-1932, **15**-1943
Wong, R. **16**-428
Wong, S.C. **8**-136
Wong, T. **17**-199
Woo, E.P. **2**-320
Woo, J.C.S. **18**-766
Wood, D.E. **14**-55
Wood, F.K. **15**-1072
Wood, H.G. **4**-262
Wood, J.L. **3**-73, **14**-19, **15**-2059, **16**-316, **19**-1387
Wood, J.T. **11**-655
Wood, L.S. **5**-365
Wood, M.L. **18**-315
Wood, M.R. **12**-323
Wood, P.D. **5**-414
Wood, R.A. **13**-201
Wood, S.E. **18**-281
Wood, T.R. **16**-1991
Woodard, D.L. **11**-309, **12**-185
Woodard, R.W. **4**-22
Woodard, S.S. **15**-1970, **15**-1976
Woodburn, H.M. appendixa-1
Woodbury, R.P. **16**-2134, **19**-52
Woodcock, D.J. **17**-244, **18**-99
Woodcock, H.L. **5**-358
Woodford, B. **10**-1702, **16**-1066
Woodgate, P.D. **12**-169, **14**-473, **15**-1682, **15**-1708, **15**-1715, **15**-1733, **15**-1734, **15**-1759, **15**-1764, **19**-1415
Woodgate, S.D. **15**-1733
Woodling, R.E. **19**-1011
Woodnutt, D.J. **18**-956
Woodruff, R.A. **16**-1708
Woodward, G. **4**-63
Woodward, R.B. **15**-1819, **15**-2237, **15**-2297, **15**-2300, **15**-2311, **17**-358, **18**-424, **18**-509, **18**-511, **18**-559, **18**-565, **18**-659
Woodward, R.L. **15**-1481
Woodward, S. **8**-174, **10**-1002, **15**-1170, **15**-1823, **19**-1019
Woodworth, C.W. **15**-665
Woodworth, R.C. **15**-2491
Woody, R.W. **4**-118
Woolf, L.I. **17**-112, **17**-124
Woollins, J.D. **19**-1593
Woosley, J. **10**-831
Worakun, T. **10**-1311
Worden, S. **19**-1320
Workman, J.A. **18**-781
Workman, P.S. **16**-587
Worm, K. **11**-489
Worrall, J.M. **4**-385
Worrell, J.H. **10**-889
Worsch, D. **4**-169
Worthy, A.D. **15**-2161
Wothers, P.D. **4**-475
Wotiz, J.H. **13**-85
Wozniak, M. **13**-762
Wray, V. **4**-297, **10**-526
Wright, B.B. **5**-349
Wright, D.G. **17**-122
Wright, D.R. **17**-134
Wright, G.F. **2**-150

Wright, G.J. **9**-53, **11**-61, **11**-110
Wright, J.A. **15**-1549, **15**-1552
Wright, M.E. **10**-1969
Wrighton, M. **7**-58
Wristers, J. **18**-535
Wroble, R.R. **19**-1402
Wrobleski, A. **18**-325
Wroblewski, A.E. **4**-129, **4**-150, **15**-635
Wu, A. **14**-188, **14**-409, **16**-2116, **17**-172, **17**-173, **17**-174, **18**-118, **19**-1635, **19**-1703
Wu, B. **10**-1469, **12**-116, **15**-1587
Wu, C.-J. **15**-2616, **15**-2617
Wu, C.Y. **8**-36, **8**-38
Wu, D. **13**-223
Wu, D.K. **16**-1275
Wu, E.S.C. **17**-342
Wu, F. **13**-148
Wu, G. **3**-43, **4**-42, **10**-461, **10**-475
Wu, H.-P. **15**-641, **15**-643
Wu, H.-H. **16**-132
Wu, H.-L. **16**-666, **16**-746
Wu, H.-C. **19**-1543
Wu, H. **15**-365, **15**-2061, **16**-743, **16**-944, **16**-1201, **16**-1314, **19**-686, **19**-1252
Wu, J. **10**-1732, **15**-1022
Wu, J.-P. **10**-863
Wu, J.-S. **10**-932
Wu, J.-D. **16**-1115, **16**-303
Wu, J. X. **10**-1147
Wu, J. **9**-112, **10**-699, **10**-977, **10**-1224, **10**-1657, **10**-1732, **13**-321, **13**-416, **13**-512, **13**-579, **15**-1046, **15**-1170, **16**-341, **16**-746, **16**-1314, **16**-1371, **19**-1135
Wu, J.H. **15**-1119
Wu, J.X. **13**-121, **13**-277
Wu, J.Y. **11**-417, **15**-804
Wu, K.-H. **15**-2477, **16**-653
Wu, L.-Y. **15**-1055, **19**-1025
Wu, L.-L. **19**-1625
Wu, L. **10**-1223
Wu, M.-S. **15**-2597, **15**-2613
Wu, M.-J. **15**-545, **19**-724
Wu, M. **15**-1980, **16**-1498
Wu, M.H. **10**-696
Wu, M.J. **16**-1778
Wu, N. **13**-129
Wu, P.-J. **15**-1023
Wu, P.-Y. **16**-666, **16**-746
Wu, P. **15**-1440, **16**-1201, **18**-741
Wu, P.R. **19**-623
Wu, Q.-F. **4**-155
Wu, Q.-Q. **16**-209
Wu, Q. **13**-471, **15**-297
Wu, Q.Y.R. **19**-623
Wu, R. **16**-485
Wu, S.-H. **15**-531, **15**-610, **16**-591
Wu, S. **4**-185, **10**-1335, **10**-1343, **15**-286, **15**-641, **15**-1079, **17**-64, **19**-242, **19**-1017
Wu, T. **12**-627
Wu, T.R. **15**-1267, **15**-1274
Wu, W.-Y. **10**-1733
Wu, W.-Q. **13**-434
Wu, W.-X. **15**-66
Wu, W. **10**-1223, **13**-148, **15**-444, **15**-788, **16**-1206, **17**-6, **19**-623
Wu, X.-F. **12**-769
Wu, X.-Y. **15**-1933
Wu, X.-E. **19**-180
Wu, X. **11**-249, **11**-545, **13**-683, **16**-1085, **16**-1952, **19**-990, **19**-1034, **19**-1034, **19**-1036, **19**-1156, **19**-1262, **19**-1609, **19**-1612
Wu, Y. **3**-138, **10**-701, **10**-1479, **13**-244, **15**-1324, **16**-408, **18**-784, **19**-924
Wu, Y.-C. **16**-1778
Wu, Y.-D. **13**-434, **15**-1835, **15**-2315, **15**-2323, **16**-1082
Wu, Y.-g. **16**-1642
Wu, Y.-H. **16**-1422
Wu, Y.-J. **7**-128, **13**-197, **13**-356, **13**-503
Wu, Y.-T. **2**-403
Wu, Y.-W. **6**-84, **18**-62
Wu, Z.-W. **10**-932
Wu, Z.-L. **16**-666
Wu, Z. **4**-155, **10**-540, **13**-6, **13**-223, **13**-708, **13**-797, **15**-1924, **15**-1926, **16**-438, **16**-740
Wuchrer, M. **18**-843
Wudl, F. **2**-393
Wüest, H. **18**-438
Wulf, C.M. **18**-647
Wulff, W.D. **10**-164, **15**-2094, **15**-2651, **16**-989, **18**-388
Wulfman, D.S. **13**-769, **13**-775, **13**-778, **14**-390, **15**-2505, **17**-284
Wüllner, R. **18**-683
Wunderlich, D. **15**-755
Wunderlich, K. **10**-767
Würtele, C. **10**-840
Würthwein, E.-U. **4**-73, **16**-265
Würtz, S. **13**-605
Wurz, R.P. **15**-2339, **15**-2342
Wustrow, D.J. **19**-1338
Wuts, P.G.M. **10**-631, **10**-914, **16**-1874
Wyatt, J.L. **5**-298
Wyatt, P.A.H. **7**-18
Wyckoff, J.C. **14**-80, **14**-173
Wylie, W.A. **13**-20
Wyman, D.P. **14**-167
Wyman, W.E. **18**-307
Wyn-Jones, E. **4**-287
Wynberg, H. **4**-11, **4**-25, **4**-153, **4**-193, **11**-508, **14**-445, **15**-1911, **16**-2198, **16**-2201, **19**-1570
Wynn, T. **16**-648, **16**-1158, **16**-1173
Wynne, J.H. **16**-169
Wysocki, D.C. **2**-347

Xi, C. **10**-1911, **11**-127, **11**-138, **15**-838, **16**-2111
Xi, F. **19**-1176
Xi, P. **13**-129
Xi, Z. **15**-838, **15**-1575, **15**-1576
Xia, A.X. **15**-210
Xia, C.-G. **10**-973, **10**-1232, **13**-134, **15**-351, **15**-1387, **15**-1417, **15**-1424, **15**-1902, **15**-2061, **15**-418, **16**-1582, **16**-407
Xia, C. **10**-765, **15**-1980, **16**-1498, **19**-561
Xia, G. **16**-645, **16**-692, **19**-1657
Xia, J.-P. **16**-573
Xia, L. **2**-444
Xia, M. **10**-1894, **13**-419, **13**-574
Xia, Q.-H. **15**-1906
Xia, W.-J. **19**-83, **19**-1364
Xia, W. **12**-302, **16**-855
Xia, X. **10**-21
Xia, Y. **19**-722
Xian, M. **18**-965, **18**-966
Xiang, B. **5**-191, **15**-2510
Xiang, C.-L. **16**-565
Xiang, J. **10**-1921, **15**-1522
Xiang, S.-K. **10**-1607
Xianming, H. **10**-709
Xiao, J.-P. **19**-285
Xiao, J. **10**-1530, **12**-347, **13**-381, **13**-403, **13**-406, **13**-410, **13**-520, **13**-522, **15**-1610, **19**-990, **19**-1034, **19**-1036, **19**-1143, **19**-1145
Xiao, K.-J. **16**-469
Xiao, L. **10**-765, **10**-1362
Xiao, W.-J. **15**-1516, **15**-1518
Xiao, W. **16**-325
Xiao, X. **16**-897
Xiao, Y. **9**-127, **19**-1027
Xiaofeng, G. **2**-132
Xiaohui, Z. **10**-609
Xichun, F. **10**-709
Xidos, J.D. **15**-2247
Xie, C. **5**-307
Xie, D. **10**-855, **12**-286, **13**-436
Xie, F. **10**-1522
Xie, H. **13**-386, **15**-287, **15**-1106, **19**-234
Xie, J.-H. **15**-470, **15**-643, **16**-742, **16**-746, **19**-1014
Xie, J. **13**-206, **15**-956, **18**-110, **18**-166
Xie, L. **10**-1701, **12**-94
Xie, R.-G. **13**-222
Xie, R. **19**-1024
Xie, W. **16**-2076
Xie, X.-M. **16**-1433
Xie, Y.-X. **10**-1732, **12**-267, **12**-284, **13**-494, **13**-497, **13**-498,

13-502, **13**-588, **13**-591, **14**-357, **15**-1055, **15**-2596
Xie, Y.-Y. **19**-464
Xie, Y. **2**-279, **18**-538, **19**-168
Xin, B. **13**-497, **13**-500, **16**-2024, **16**-2026
Xin, L. **16**-572
Xin, X.-Q. **19**-140
Xin, Y. **10**-498, **16**-854
Xing, D. **19**-115, **19**-128
Xing, L. **15**-643
Xing, R. **16**-1201
Xing, Y.-L. **16**-53
Xing, Y. **19**-956
Xiong, H. **12**-627
Xiong, W. **16**-544
Xiong, Y. **10**-54, **13**-732, **16**-1497
Xiong, Z. **13**-697
Xiu, C.-G. **19**-491
Xodo, L.E. **4**-346
Xu, B. **18**-616
Xu, C.-Z. **19**-491
Xu, C. **10**-1379, **13**-197
Xu, D.-Q. **9**-137, **15**-1055
Xu, D. **10**-855, **13**-410, **15**-1793, **15**-1832, **15**-1843, **16**-1939, **19**-168
Xu, D.Q. **10**-611
Xu, F.-X. **15**-331
Xu, F. **15**-1113
Xu, G.-C. **18**-170
Xu, G. **13**-172
Xu, H.-J. **13**-148
Xu, H.-C. **15**-414
Xu, H. **15**-1055, **16**-786, **16**-1084, **16**-2022, **18**-495, **19**-1118
Xu, J.-M. **15**-297
Xu, J. **11**-452, **13**-106, **13**-218, **13**-386, **16**-452, **16**-544, **16**-670, **19**-971, **19**-1026, **19**-1046, **19**-1259, **19**-1261
Xu, K. **13**-503
Xu, L.-W. **4**-155, **10**-973, **10**-1232, **13**-134, **15**-351, **15**-418, **15**-1387, **15**-1417, **15**-1424, **15**-2061, **16**-165, **16**-1582
Xu, L. **10**-1530, **13**-148, **13**-403, **13**-410, **15**-2564, **19**-74, **19**-233, **19**-1611
Xu, M.-H. **16**-945, **19**-1670, **19**-1674
Xu, Q.-Y. **15**-1629
Xu, Q.-h. **19**-887
Xu, Q. **15**-1500, **15**-1501
Xu, R. **16**-571
Xu, W. **16**-2039, **15**-2199
Xu, X.-H. **19**-1625
Xu, X. **15**-370, **15**-1053, **15**-1747, **15**-2061, **15**-2119, **16**-589, **16**-814, **16**-1025, **19**-1026, **19**-1637
Xu, Y.-H. **13**-405, **15**-1922
Xu, Y.-J. **15**-1272
Xu, Y.-M. **16**-956
Xu, Y.-M. **16**-957
Xu, Y. **12**-179, **13**-503, **13**-564, **15**-1402, **16**-2012, **19**-163
Xu, Z.-B. **10**-599, **13**-168
Xu, Z.-Y. **9**-137, **10**-1213, **15**-1055
Xu, Z.-H. **16**-1597
Xu, Z.-Q. **16**-545
Xu, Z.-N. **19**-69, **19**-109
Xu, Z. **3**-138, **16**-544, **16**-670
Xu, Z.Y. **10**-611
Xue, F. **16**-546
Xue, L. **4**-362
Xue, P. **15**-2136
Xue, S. **18**-136, **18**-185, **18**-242
Xue, X. **10**-1141
Xue, Z.-Y. **15**-2114, **16**-413

Yabe, M. **15**-1457
Yabe, Y. **12**-263
Yablokov, V.A. **18**-406
Yabu, M. **16**-621
Yada, A. **13**-705
Yadav-Bhatnagar, N. **13**-227
Yadav, J. S. **16**-330
Yadav, J.C. **18**-699
Yadav, J.S. **9**-133., **10**-705, **10**-707, **10**-846, **10**-847, **10**-885, **10**-894, **10**-970, **10**-984, **10**-1003, **10**-1009, **10**-1069, **10**-1205, **10**-1266, **10**-1626, **10**-1653, **10**-1656, **11**-192, **11**-217, **11**-396, **11**-459, **12**-129, **13**-167, **13**-174, **13**-742, **14**-336, **15**-310, **15**-1058, **15**-138, **15**-1438, **15**-1456, **15**-1696, **15**-1736, **15**-2346, **16**-150, **16**-250, **16**-295, **16**-357, **16**-550, **16**-574, **16**-619, **16**-768, **16**-782, **16**-980, **16**-1234, **16**-1235, **16**-1555, **16**-1563, **16**-1635, **16**-1713, **16**-1717, **16**-1859, **16**-2034, **17**-370, **17**-401, **18**-328, **18**-642, **19**-294, **19**-992, **19**-1205, **19**-1244, **19**-1523, **19**-1532, **19**-1580, **19**-1592, **19**-1731
Yadav, L.D.S. **10**-642, **16**-2248, **18**-342, **18**-342
Yadav, V.K. **4**-142, **10**-1248, **11**-329, **15**-872, **16**-8
Yadov, J.S. **16**-1401
Yaeger, D.B. **15**-4, **15**-34
Yagasaki, H. **19**-993
Yager, W.A. **5**-431, **5**-365, **5**-430
Yaghmaie, F. **15**-486
Yagi, K. **15**-2638
Yagi, M. **19**-882
Yagihashi, F. **18**-364
Yagodin, V.G. **18**-718
Yaguchi, Y. **15**-1055
Yaguchi, Y. **15**-1712
Yagupolskii, L.M. **11**-453, **16**-442
Yahner, J.A. **16**-2155
Yajima, H. **4**-220
Yakabe, S. **15**-523
Yakaiah, T. **16**-627
Yakobson, G.G. **11**-352, **13**-81, **13**-90, **17**-310
Yakura, K. **16**-552
Yakura, T. **18**-386, **19**-259
Yakushina, L.M. **15**-294
Yalovskaya, A.I. **10**-1163
Yamabe, H. **11**-330
Yamabe, S. **10**-405, **15**-871, **15**-21, **15**-2405, **16**-455, **18**-71, **18**-365
Yamabe, T. **5**-120
Yamada, C. **5**-289
Yamada, H. **18**-523, **19**-1245
Yamada, J. **15**-1241, **16**-2033
Yamada, K.-i. **15**-1185, **15**-1204, **15**-139, **16**-405, **16**-892
Yamada, K. **10**-1195, **15**-871, **16**-1745
Yamada, M. **10**-726, **10**-1203, **15**-1546, **16**-836, **16**-1938, **16**-1949
Yamada, N. **10**-1943
Yamada, S. **4**-149, **11**-577, **12**-617, **12**-725, **13**-779, **16**-1794
Yamada, T. **12**-574, **15**-612, **15**-2046, **15**-2324, **19**-27, **19**-519, **19**-865, **19**-896
Yamada, Y. **10**-1968, **12**-227, **14**-306, **16**-2140, **19**-1037, **19**-1290
Yamada, Y.M.A. **10**-1781
Yamaga, T. **15**-656
Yamagami, M. **12**-752, **18**-944
Yamagami, T. **15**-894
Yamagata, K.-i. **15**-946
Yamagishi, F.G. **18**-422
Yamagishi, Y. **19**-995
Yamagiwa, N. **14**-297, **15**-406, **15**-1382, **15**-1405
Yamago, S. **15**-2163
Yamaguchi, A. **16**-1449
Yamaguchi, F. **4**-174
Yamaguchi, H. **3**-215, **15**-1106, **17**-373, **18**-899, **18**-902
Yamaguchi, J.-i. **16**-1816
Yamaguchi, J. **16**-395, **19**-281, **19**-515, **19**-517
Yamaguchi, K. **3**-195, **3**-207, **5**-167, **11**-418, **15**-1206, **15**-1890, **15**-2127, **15**-2136, **16**-239, **16**-2040, **19**-128, **19**-270, **19**-1654
Yamaguchi, M. **10**-856, **10**-1091, **10**-1925, **11**-328, **12**-424, **15**-384, **15**-650, **15**-816, **15**-1061, **15**-1112, **15**-1546, **16**-1506, **16**-1575, **16**-1576, **16**-1766, **16**-2082, **17**-207, **18**-358, **19**-864, **19**-1339, **19**-1398
Yamaguchi, R. **10**-934, **10**-943, **10**-1047, **10**-1585, **11**-347, **13**-750, **15**-590, **17**-179, **19**-667

Yamaguchi, S. **4**-109, **4**-210, **4**-1097, **15**-894, **16**-841
Yamaguchi, T. **10**-1585, **14**-11, **15**-1926, **19**-800, **19**-1034
Yamaguchi, Y. **5**-352, **16**-397, **16**-1578, **18**-274
Yamaji, M. **10**-740
Yamakaw, A. **16**-2081
Yamakawa, K. **16**-1276, **16**-1604, **18**-203
Yamakawa, Y. **15**-280
Yamaki, T. **15**-861
Yamamiya, Y. **10**-729
Yamamoto, A. **10**-1373, **10**-2008, **10**-2009, **10**-2011, **11**-342, **12**-289, **12**-727, **14**-327, **16**-397, **16**-612, **16**-704, **16**-1168, **18**-198, **19**-1744
Yamamoto, E. **16**-806
Yamamoto, G. **2**-353, **3**-51, **4**-528, **12**-359
Yamamoto, H. **10**-593, **10**-980, **10**-1098, **10**-1186, **10**-1325, **10**-1562, **10**-1602, **10**-1626, **10**-1741, **10**-1821, **11**-273, **11**-420, **11**-421, **12**-166, **12**-208, **12**-390, **12**-550, **14**-196, **14**-231, **14**-236, **15**-224, **15**-738, **15**-822, **15**-999, **15**-1251, **15**-1977, **15**-2189, **15**-2192, **15**-2252, **15**-2343, **15**-2570, **16**-132, **16**-502, **16**-585, **16**-622, **16**-645, **16**-652, **16**-654, **16**-692, **16**-771, **16**-780, **16**-865, **16**-885, **16**-1049, **16**-1074, **16**-1091, **16**-1094, **16**-1098, **16**-1142, **16**-1144, **16**-1172, **16**-1389, **16**-1490, **16**-1634, **16**-1778, **16**-1896, **16**-1915, **16**-2133, **17**-166, **17**-280, **17**-416, **18**-141, **18**-159, **18**-344, **18**-366, **18**-367, **19**-918, **19**-948, **19**-1235, **19**-1657
Yamamoto, I. **13**-352
Yamamoto, J. **18**-738, **18**-940, **19**-790
Yamamoto, K. **2**-76, **2**-332, **2**-359, **4**-82, **4**-489, **4**-491, **12**-565, **15**-786, **15**-871, **16**-1252, **19**-667
Yamamoto, M. **18**-238, **18**-500
Yamamoto, O. **18**-674
Yamamoto, R. **15**-1468
Yamamoto, S.-y. **16**-2004
Yamamoto, S. **10**-1448, **12**-329, **12**-496, **15**-1209
Yamamoto, T. **3**-134, **4**-238, **10**-1509, **10**-2008, **10**-2011, **12**-131, **12**-252, **12**-289, **13**-198, **16**-214, **16**-745
Yamamoto, Y. **10**-249, **10**-1003, **10**-1192, **10**-1326, **10**-1448, **10**-1586, **10**-1625, **13**-496, **14**-436, **15**-177
Yamamoto, Y. **15**-207, **15**-340, **15**-365, **15**-370, **15**-377, **15**-405, **15**-642, **15**-789, **15**-823, **15**-856, **15**-926, **15**-938, **15**-940, **15**-947, **15**-952, **15**-971, **15**-1164, **15**-1175, **15**-1206, **15**-1232, **15**-1241, **15**-1276, **15**-1411, **15**-1509, **15**-2377, **15**-2594, **15**-2596, **15**-2603, **15**-2610, **15**-2615, **15**-2629, **15**-2630, **15**-2640, **16**-460, **16**-607, **16**-617, **16**-905, **16**-912, **16**-950, **16**-951, **16**-1062, **16**-2033, **19**-532, **19**-725, **19**-870, **19**-982, **19**-1050, **19**-1322, **19**-1429, **19**-1656
Yamamura, G.-h. **16**-2004
Yamamura, K. **3**-106, **10**-1941
Yamamura, M. **10**-1341
Yamamura, S. **10**-1960, **19**-1414
Yamanaka, M. **4**-64, **14**-194, **15**-1027, **15**-1136, **15**-1152, **16**-400, **16**-937
Yamanaka, R. **19**-994
Yamanashi, M. **15**-865
Yamane, M. **15**-1479
Yamano, M. **10**-938
Yamanoi, Y. **13**-698, **13**-702
Yamaoka, M. **19**-1367
Yamaoka, Y. **15**-410, **10**-1888
Yamasaki, A. **11**-325
Yamasaki, H. **13**-698
Yamasaki, K. **5**-377, **15**-1072
Yamasaki, M. **15**-1012
Yamasaki, R. **10**-644
Yamasaki, S. **10**-1153, **10**-1154, **15**-1694, **15**-2030
Yamase, Y. **11**-437
Yamashina, N. **12**-566
Yamashita, A. **19**-1748
Yamashita, F. **15**-313, **15**-770
Yamashita, H. **15**-251
Yamashita, K. **11**-350, **15**-1577, **16**-1243
Yamashita, M. **10**-1389, **10**-1761, **10**-1809, **10**-1960, **10**-1962, **10**-1987, **11**-537, **12**-561, **12**-568, **13**-686, **19**-1034, **19**-1103, **19**-1585
Yamashita, T. **10**-1012
Yamashita, Y. **10**-930, **10**-975, **15**-2108, **15**-2327, **16**-1172
Yamataka, H. **5**-334, **6**-74, **10**-31, **10**-215, **10**-381, **16**-519, **16**-524, **16**-528, **16**-1346, **19**-958
Yamatake, T. **19**-504
Yamato, M. **4**-284, **5**-377
Yamauchi, A. **12**-754
Yamauchi, H. **19**-1245
Yamauchi, M. **15**-963, **19**-627
Yamauchi, S. **16**-448, **19**-895
Yamaura, Y. **12**-408
Yamawaki, J. **10**-184, **10**-1019, **16**-2162, **19**-107
Yamazaki, A. **10**-1911
Yamazaki, H. **10**-1831, **13**-684, **15**-1355, **15**-2446, **15**-2457, **19**-863, **19**-1293
Yamazaki, J. **14**-114
Yamazaki, O. **13**-326, **13**-327
Yamazaki, S. **15**-871, **15**-1895, **15**-1895, **15**-2405, **16**-455, **18**-365, **19**-268, **19**-275, **19**-281, **19**-404, **19**-612
Yamazaki, T. **10**-697, **10**-1641
Yamazoe, S. **15**-1468
Yambushev, F.D. **4**-45
Yamdagni, R. **8**-241, **8**-244
Yampolsky, I.V. **16**-2083, **16**-2084
Yamshita, Y. **16**-974
Yan, J. **4**-133, **10**-540, **12**-531, **13**-506, **14**-339, **19**-329
Yan, J.M. **11**-241
Yan, K. **19**-973
Yan, M. **13**-222, **15**-1204, **15**-1629
Yan, N. **15**-896
Yan, S. **5**-402, **12**-361, **16**-249, **16**-1201
Yan, T.-H. **16**-1074, **16**-1075, **16**-1422, **19**-1298
Yan, T.H. **16**-1421
Yan, W.-J. **16**-670
Yan, W. **16**-544
Yan, Y.-L. **12**-155, **15**-899, **15**-945
Yan, Y. **15**-1613
Yan, Z.-Y. **15**-1055, 1 **9**-1025
Yanada, K. **10**-850, **16**-1628, **17**-377
Yanada, R. **10**-850, **15**-962, **15**-963, **16**-1628, **17**-377
Yanagi, K. **10**-715
Yanagi, T. **13**-487
Yanagihara, H. **10**-2009
Yanagihara, K. **2**-332, **2**-359
Yanagihara, R. **3**-156, **11**-538
Yanagisawa, A. **10**-980, **10**-1325, **10**-1562, **10**-1626, **12**-449, **15**-1626, **16**-585, **16**-622, **16**-645, **16**-771, **16**-865, **16**-1049, **16**-1220
Yanagisawa, K. **10**-1341
Yanagisawa, Y. **19**-665
Yanagitsuru, S. **4**-203
Yanase, T. **13**-589
Yanchang, S. **2**-96
Yandovskii, V.N. **10**-1093, **18**-145
Yanella, J. **11**-258
Yáñez, O.M.O. **2**-88
Yang, B. **18**-548, **19**-1678
Yang, B.H. **13**-234, **19**-1462
Yang, B.Q. **19**-32
Yang, C.-H. **13**-500
Yang, C.-G. **15**-228, **15**-237
Yang, C.-T. **16**-1515
Yang, C.-f. **19**-1014
Yang, C. **10**-54, **13**-289, **15**-860, **19**-238
Yang, D.-H. **16**-68, **16**-78

Yang, D. **12**-155, **13**-386, **13**-630, **15**-899, **15**-945, **15**-1311, **15**-1926, **15**-1932, **15**-1939, **15**-2697, **16**-326, **16**-327., **19**-383
Yang, D.H. **7**-52, **7**-86, **16**-1556
Yang, F. **16**-132
Yang, G.-s. **10**-1476, **19**-1024
Yang, G. **4**-383, **14**-303, **16**-1206
Yang, H.-M. **4**-155
Yang, H.-C. **16**-1746
Yang, H.-j. **19**-33
Yang, H. **10**-228, **10**-1566, **11**-449, **11**-472, **19**-1655
Yang, J.-Y. **16**-565
Yang, J.-D. **19**-778
Yang, J. **15**-309, **15**-1079, **16**-897, **16**-1564, **19**-1289
Yang, J.W. **10**-1787, **15**-1834, **16**-394
Yang, K.-S. **16**-823
Yang, K. **15**-1677, **16**-46, **18**-856, **19**-1567
Yang, L.-M. **10**-1347, **13**-210, **13**-211, **13**-548
Yang, L. **5**-222, **11**-694, **15**-351, **15**-418, **15**-2061, **16**-1605, **19**-115, **19**-128
Yang, M.-S. **16**-165
Yang, M. **10**-976, **13**-470, **15**-2579
Yang, N.C. **7**-52, **16**-1556, **16**-2206, **16**-2207
Yang, P.-Y. **15**-562
Yang, P. **10**-1732
Yang, Q. **14**-469
Yang, S.-C. **10**-930
Yang, S.-D. **13**-517
Yang, S. **5**-70, **13**-720
Yang, S.H. **15**-2429, **13**-266, **17**-439
Yang, T.-H. **7**-55
Yang, T.-K. **15**-1210, **15**-1600, **16**-680, **19**-1024, **19**-1043
Yang, T. **13**-169
Yang, W.-L. **9**-137
Yang, X.-F. **15**-1492, **16**-546, **16**-596
Yang, X.-L. **19**-1073
Yang, X. **11**-127, **11**-138
Yang, Y.-l. **8**-127
Yang, Y.-H. **18**-616
Yang, Y. **4**-279, 1 **16**-1560, **16**-1968, **16**-2027
Yang, Z. **11**-463, **13**-599
Yang, Z.-Z. **4**-250
Yang, Z.-H. **16**-1084
Yang, Z. **10**-1469, **11**-460, **13**-512, **13**-585, **13**-665, **13**-697, **15**-245, **15**-1522, **16**-876, **16**-1084
Yanga, B. **10**-797
Yangand, J. **15**-1142
Yanigisawa, A. **16**-1172
Yanik, M.M. **8**-213
Yannoni, C.S. **2**-253, **2**-393, **5**-21, **5**-80, **10**-196, **10**-214, **11**-17
Yannoni, N. **5**-242
Yanovskaya, L.A. **15**-1032
Yany, F. **17**-421
Yao, C.-F. **13**-841, **15**-1220, **15**-1440, **15**-1444, **15**-1445
Yao, G. **5**-422, **16**-341
Yao, H.C. **12**-198
Yao, J. **13**-206
Yao, L.-Y. **15**-852
Yao, L. **18**-331
Yao, M.-L. **12**-294
Yao, P.-Y. **19**-720
Yao, Q. **18**-62, **18**-831, **18**-853, **18**-855
Yao, S. **15**-2336
Yao, T. **13**-428, **15**-239, **15**-2618
Yao, X. **15**-950
Yao, Z.-P. **19**-1217, **19**-1309
Yao, Z. **15**-509
Yaozeng, H. **2**-96
Yap, G.P.A. **4**-85, **14**-359, **15**-151, **15**-1095, **18**-632
Yasaka, S. **16**-538
Yashima, E. **4**-90
Yashkina, L.V. **16**-1518
Yashunskii, V.G. **2**-376
Yaskova, M.S. **11**-171
Yasman, Ya.B. **10**-559
Yasuda, K. **19**-103
Yasuda, M. **10**-624, **10**-1012, **10**-115, **10**-1154, **10**-1592, **10**-1594, **10**-1716, **10**-1726, **15**-1130, **16**-612, **16**-840, **16**-912, **18**-649, **19**-1085, **19**-1340
Yasuda, N. **16**-251, **16**-636
Yasuda, S. **10**-1374
Yasuda, Y. **16**-674
Yasue, K. **10**-980, **10**-1626, **16**-585, **16**-865
Yasuhara, F. **4**-109
Yasuhara, T. **12**-771, **16**-1873
Yasuhara, Y. **11**-532, **11**-533, **15**-127, **16**-899
Yasui, H. **10**-1365, **15**-154
Yasui, M. **18**-501
Yasukata, T. **18**-109
Yatagai, H. **10**-1326, **10**-1448, **14**-436
Yates Jr., J.T. **15**-485
Yates, B.F. **4**-290, **18**-414
Yates, B.L. **17**-494
Yates, J.B. **10**-1327
Yates, K. **2**-8, **8**-31, **8**-33, **8**-129, **8**-130, **8**-132, **12**-159, **15**-13, **15**-15, **15**-88, **15**-259, **15**-2300, **16**-1661, **16**-1664, **16**-1702, **16**-1703, **18**-512
Yato, M. **11**-504, **19**-1421, **19**-1446
Yats, L.D. **11**-639
Yatsugi, K.-i. **10**-471
Yatsugi, K. **10**-472
Yatsumonji, Y. **10**-1511
Yau, S.C. **19**-533
Yavari, I. **1**-94, **10**-214, **19**-1639
Yazaki, R. **15**-1122, **16**-1523
Yazawa, H. **15**-391
Yazawa, N. **13**-840
Yazdi, S.N. **13**-745
Yde, B. **16**-224, **16**-1920
Ye, C.-P. **15**-1906
Ye, C. **15**-1659
Ye, D. **19**-1304
Ye, H. **15**-2686
Ye, K.-Y. **16**-469
Ye, L. **12**-381
Ye, P. **13**-506, **19**-1299
Ye, Q. **5**-375, **5**-376
Ye, S. **10**-1224, **15**-2143, **16**-855, **19**-1262, **19**-1568
Ye, T. **12**-367, **12**-392, **15**-2497, **15**-2519
Ye, X.-R. **19**-140
Ye, Z. **13**-592, **13**-698, **15**-503
Yee, H. **19**-645
Yee, K.C. **17**-58
Yee, N.K. **13**-348, **15**-452, **16**-452, **16**-599, **16**-1507
Yeh, K.-L. **17**-189
Yeh, L.I. **12**-52
Yeh, M. **18**-568
Yeh, M.C.P. **10**-1437, **16**-473, **16**-2009
Yen, V.Q. **15**-1787
Yeom, C.-E. **15**-1394
Yeroushalmi, S. **2**-383, **5**-133
Yet, L. **16**-1522
Yeung, C.C. **13**-495
Yeung, E.S. **4**-129, **4**-150, **15**-635
Yeung, K.-S. **11**-463
Yeung, P.Y. **13**-291
Yeung, Y.-Y. **13**-604, **15**-1720, **15**-1741
Yi, B. **15**-643
Yi, C. **13**-588, **13**-591
Yi, K.Y. **17**-488
Yi, R. **10**-28
Yi, X.-H. **16**-559
Yijun, C. **16**-2221
Yin, D.-L. **12**-267
Yin, J.-J. **16**-1582
Yin, J. **10**-811, **10**-1146, **12**-298, **13**-530, **16**-1995, **19**-955
Yin, K. **14**-344
Yin, L. **10**-1487
Yin, P. **15**-338
Yin, W.-P. **11**-128
Yin, W. **11**-452, **14**-343
Yin, X.-x. **19**-1033
Yin, Y. **10**-591, **11**-137, **15**-256, **15**-1210
Ying, J. **15**-244
Ying, T. **16**-2039
Ying, Y. **14**-3
Yinglin, H. **10**-1041

Yip, C.-W. **15**-1997, **16**-658, **16**-746
Yip, R.W. **7**-57
Yip, W.-P. **15**-1809
Yip, Y.-C. **15**-1926
Yip, Y. **4**-428, **15**-129, **18**-67, **18**-162, **18**-606, **18**-615, **18**-650
Yli-Kauhaluoma, J. **15**-2222
Yliniemelä, A. **16**-1270
Yoakim, C. **10**-632, **10**-732
Yoda, H. **15**-1056, **16**-1085, **16**-1253
Yoder, R.A. **16**-965
Yoh, S. **10**-320
Yohitake, J. **12**-565
Yokayama, J.-i. **10**-1537
Yokoa, K. **10**-2004
Yokogi, M. **13**-531
Yokomichi, Y. **2**-178
Yokota, K. **15**-2607, **16**-2093
Yokota, M. **15**-595
Yokota, N. **15**-1061
Yokota, T. **13**-407, **15**-1521
Yokoya, S.-i. **16**-1362
Yokoyam, S. **16**-679
Yokoyama, H. **15**-2008
Yokoyama, K. **15**-2008
Yokoyama, M. **10**-738, **14**-386, **16**-426, **16**-1306, **16**-1837, **17**-476
Yokoyama, R. **19**-684
Yokoyama, S. **19**-1460
Yokoyama, T. **15**-1453, **18**-128, **19**-684
Yokoyama, Y. **4**-78, **16**-1051, **16**-1965
Yokozawa, T. **10**-1274
Yolacan, C. **16**-1592
Yomioka, K. **16**-900
Yonashiro, M. **10**-1696
Yoneda, E. **15**-1517, **15**-1525, **15**-1584, **15**-1585, **15**-1586
Yoneda, N. **10**-1102, **10**-1103, **10**-1144, **10**-1214, **10**-1976, **10**-1978, **13**-790, **13**-805, **15**-1646, **18**-408
Yoneda, R. **16**-1494
Yoneda, Y. **15**-1743
Yonekura, T. **2**-75
Yonemitsu, O. **12**-499, **19**-1294
Yonemitsu, T. **10**-614
Yonemura, K. **14**-269, **19**-1656
Yonemushi, Y. **16**-981
Yonetani, M. **3**-153
Yoneyama, Y. **2**-332, **2**-333, **2**-335, **2**-359
Yong, F.F. **13**-205
Yong, K. **19**-250
Yong, K.H. **10**-1338, **16**-468
Yong, L. **15**-2588
Yoo, B.R. **10**-1265
Yoo, B.W. **16**-2108, **19**-1313, **19**-1530, **19**-1531, **19**-1536, **19**-1581, **19**-1590, **19**-1591, **19**-1660
Yoo, E.J. **15**-1524
Yoo, E.S. **10**-1136
Yoo, H.Y. **18**-694, **18**-712
Yoo, K.H. **14**-76
Yoo, K.S. **13**-566
Yoo, M.-s. **10**-1764, **15**-1404
Yoo, S.H. **15**-2000
Yoo, W.-J. **12**-339, **14**-296
Yoon, C.-O.M. **19**-1308, **19**-966
Yoon, C.H. **13**-546, **13**-566, **17**-236
Yoon, C.M. **15**-521, **19**-676, **19**-966, **19**-1308, **19**-1313, **19**-1536, **19**-1581, **19**-1722
Yoon, D.C. **12**-191
Yoon, D.Y. **4**-305
Yoon, H.-J. **13**-150
Yoon, J.-Y. **15**-2671
Yoon, K.B. **10**-1111
Yoon, M.S. **19**-1091
Yoon, N.M. **15**-524, **16**-334, **16**-537, **16**-1639, **19**-847, **19**-851, **19**-854, **19**-855, **19**-856, **19**-858, **19**-1059, **19**-1093, **19**-1200, **19**-1286
Yoon, S.-K. **13**-627
Yoon, S.-H. **19**-1182
Yoon, T.P. **15**-2017, **15**-2412
Yoon, Y.-J. **16**-1640, **16**-1864
Yoon, Y.A. **15**-1556
Yorimitsu, H. **10**-1363, **10**-1365, **10**-1374, **10**-1378, **10**-1481, **10**-1486, **10**-1626, **10**-1715, **12**-526, **13**-457, **13**-461, **13**-465, **14**-12, **14**-17, **15**-154, **15**-308, **15**-317, **15**-394, **15**-890, **15**-901, **15**-904, **15**-942, **15**-1261, **15**-1297, **15**-1299, **15**-1344, **15**-1358, **15**-1360, **15**-1778, **15**-1779, **16**-466, **16**-739, **16**-869, **16**-1035, **17**-308
York, C. **16**-447, **16**-2066
Yorozu, K. **15**-1991
Yoshida, A. **19**-1367
Yoshida, E. **10**-834
Yoshida, H. **10**-1888, **14**-289
Yoshida, J.-i. **10**-1271, **10**-1343, **10**-1830, **10**-326, **14**-327, **15**-1542, **15**-2347
Yoshida, J. **10**-712, **14**-53, **16**-1492, **19**-327
Yoshida, K. **11**-630, **15**-452, **15**-1226, **15**-2401, **15**-2590, **16**-1096
Yoshida, M. **10**-315, **10**-758, **10**-1886, **11**-260, **12**-790, **13**-872, **14**-189, **15**-972, **15**-973, **15**-1402, **17**-389, **18**-427, **19**-1548
Yoshida, N. **19**-1760
Yoshida, S. **13**-698, **14**-224, **15**-1625
Yoshida, T. **4**-501, **17**-288, **18**-472, **18**-481
Yoshida, Y. **13**-840
Yoshida, Y. **16**-1143, **16**-2141
Yoshida, Z. **2**-228, **3**-66, **10**-1968, **14**-306, **15**-1724, **16**-2031, **18**-787
Yoshifuji, M. **12**-263, **12**-329, **13**-189, **15**-343
Yoshigami, R. **15**-1193
Yoshihara, N. **14**-289
Yoshii, F. **18**-385
Yoshikai, N. **10**-1409, **10**-1413, **10**-1535, **13**-344, **15**-1204
Yoshikawa, M. **13**-234
Yoshikawa, N. **16**-1090
Yoshikawa, S. **15**-2406
Yoshikoshi, A. **15**-1052, **15**-1125, **19**-864
Yoshimatsu, M. **16**-1166
Yoshimi, Y. **3**-31
Yoshimoto, M. **19**-1640
Yoshimoto, Y. **15**-844
Yoshimune, M. **10**-1272
Yoshimura, K. **11**-458
Yoshimura, M. **10**-496, **16**-352, **19**-1014
Yoshimura, N. **16**-621, **19**-282, **19**-1675
Yoshimura, T. **19**-1762
Yoshino, K. **14**-9
Yoshino, T. **10**-1531, **16**-1748
Yoshioka, A. **7**-62
Yoshioka, H. **10**-534, **13**-262, **15**-1670, **15**-1866
Yoshioka, M. **15**-1389, **15**-1623, **15**-1630
Yoshioka, N. **16**-1604
Yoshitake, S. **16**-1709
Yoshizane, K. **16**-640
Yoshizawa, K. **5**-120, **16**-1118, **16**-2136, **19**-1729
Yoshizawa, M. **9**-128
Yoskioka, K. **4**-171
Yost, J.M. **16**-1185
You, E. **13**-494, **13**-613
You, F. **15**-2262
You, H.-W. **16**-1852
You, J.-S. **13**-222, **16**-603
You, J. **13**-129, **13**-639, **15**-647, **16**-1240
You, L. **15**-877
You, S.-L. **4**-155, **11**-314
You, T. **10**-977
You, X.-Z. **4**-419
You, Z. **13**-697, **18**-777
Yougun, S. **19**-1349
Youn, G.J. **3**-196
Youn, S.W. **11**-323, **11**-406, **11**-408
Youn, Y.S. **10**-1072
Young Jr., J.E. **1**-79
Young, A.E. **12**-18
Young, A.R. **16**-1600

Young, B. **16**-2226, **16**-2228
Young, D. **12**-36, **12**-37, **16**-237
Young, D.D. **15**-2614
Young, D.G.J. **13**-377
Young, D.J. **13**-510, **16**-616
Young, D.W. **16**-1930, **19**-88, **19**-435
Young, F. **10**-1861
Young, F.R. **7**-70
Young, G.F. **2**-46
Young, J.-j. **10**-233
Young, L.B. **8**-23, **19**-597
Young, M.W. **17**-293
Young, P.R. **10**-558, **16**-234
Young, R.J. **19**-317
Young, R.M. **4**-443
Young, R.N. **5**-93, **5**-105, **16**-1840, **16**-2175
Young, T.C. **5**-157
Young, W.G. **10**-425, **10**-226, **10**-227, **10**-229, **10**-243, **10**-305, **12**-34, **17**-11
Young, W.R. **8**-78
Youngs, T.G.A. **9**-119
Yousaf, A. **11**-397
Yousaf, T.I. **12**-738, **16**-248
Yousefi, R. **15**-1720
Yousefian, S. **17**-284
Youshko, M.I. **16**-1950
Yousif, N.M. **16**-224
Youssef, A.K. **18**-591
Youssefyeh, R.D. **12**-318, **12**-316, **19**-363, **19**-363
Yovell, J. **10**-205
Yu, J.-Q. **10**-1887
Yu, B.M. **15**-1989
Yu, C.-M. **15**-1589, **16**-650
Yu, C. **18**-304
Yu, D. **1**-107
Yu, F. **15**-411
Yu, G.-A. **13**-594
Yu, G. **10**-1469, **11**-249
Yu, H.-h. **5**-234
Yu, H.-B. **16**-680
Yu, H. **15**-359, **15**-1933, **16**-202, **19**-976
Yu, J.-Q. **10**-1028, **11**-237, **11**-537, **15**-1423, **15**-1883, **19**-1543, **19**-566, **19**-869
Yu, J. **15**-150, **16**-1241
Yu, L. **13**-506
Yu, L.-T. **16**-1082
Yu, M. **15**-2255, **16**-999
Yu, N. **19**-115
Yu, R.T. **15**-2687
Yu, S. **13**-325, **13**-620, **15**-730
Yu, S.H. **11**-413, **12**-616, **16**-516
Yu, T.J. **7**-83
Yu, W.-Y. **13**-661, **15**-1891, **15**-1933, **19**-537, **19**-723
Yu, W. **10**-1725, **15**-176, **16**-1378, **19**-302
Yu, X.-Q. **13**-222, **13**-453, **19**-536
Yu, X. **15**-238, **16**-815, **16**-1327
Yu, Y.-H. **16**-855
Yu, Y. **12**-302, **12**-683, **16**-831, **16**-2090, **19**-1220
Yu, Z.-X. **15**-1028, **15**-2143, **15**-2697
Yu, Z. **3**-43, **11**-484, **15**-1010, **16**-868
Yu, Z.X. **15**-2699
Yuan, S. **16**-578
Yuan, W. **15**-2041
Yuan, Y.-C. **10**-932
Yuan, Y. **15**-1932, **15**-2330, **19**-792
Yuasa, Y. **10**-2008, **15**-1341
Yudha S., S. **15**-408
Yudilevich, J.A. **18**-574
Yudin, A.K. **10**-916, **10**-1001, **15**-158, **15**-2052, **15**-2054
Yue, H.-D. **9**-137, **15**-1055
Yue, L. **10**-701
Yue, T.-Y. **15**-596
Yue, X. **14**-93, **16**-1905
Yufit, D.S. **4**-460
Yuhara, M. **17**-329
Yuk, J.Y. **10**-606
Yukawa, Y. **10**-176, **17**-365, **18**-300
Yuki, Y. **10**-1381
Yukizaki, H. **10**-1588
Yulin, J. **10**-609
Yulin, J. **10**-724
Yum, E.K. **10**-1334, **10**-1335
Yun, C.-S. **13**-486, **13**-572
Yun, C. **12**-493
Yun, C.S. **13**-244
Yun, H. **13**-244
Yun, J. **15**-631
Yun, L. **13**-168
Yun, M. **11**-604, **15**-1489
Yun, Y.H. **4**-415
Yuncheng, Y. **10**-609, **10**-724
Yunes, R.A. **12**-750
Yura, T. **16**-1061
Yurchenko, A.G. **18**-354
Yur'ev, Yu.K. **15**-46
Yur'eva, N.M. **10**-791
Yurkovich, M.J. **13**-53
Yus, M. **5**-186, **10**-1721, **10**-1722, **12**-433, **12**-434, **12**-454, **12**-647, **13**-369, **13**-486, **15**-324, **15**-507, **15**-540, **15**-541, **15**-791, **15**-968, **16**-344, **16**-472, **16**-860, **16**-884, **16**-897, **16**-1526
Yusa, Y. **4**-64, **16**-716
Yusubov, M.S. **11**-289
Yuya, H. **3**-153
Yuyama, S. **15**-1193
Yuzhakov, G. **3**-69, **19**-348
Yuzhelevskii, Yu.A. **12**-321

Zabalov, M.V. **15**-1641
Zabawa, T.P. **15**-415
Zabicky, J. **2**-432, **2**-467, **4**-441, **5**-34, **5**-69, **5**-115, **5**-125, **8**-31, **8**-62, **10**-142, **10**-1020, **11**-372, **11**-625, **12**-84, **15**-129, **15**-427, **15**-663, **16**-106, **16**-365, **16**-1519, **16**-1693, **16**-1856, **16**-1866, **16**-1878, **16**-1881, **16**-1894, **16**-1937, **16**-1977, **17**-461, **18**-320, **18**-345, **19**-318, **19**-1472
Zaborsky, O.R. **16**-2272
Zabrowski, D.L. **19**-742
Zaccheria, F. **19**-1428
Zacchini. S. **5**-339
Zacharie, B. **15**-589
Zadel, G. **12**-564
Zaera, F. **15**-147, **15**-148, **15**-485
Zafiriou, O.C. **7**-58
Zagorsky, V.V. **12**-638
Zahalka, H.A. **17**-309, **19**-1432
Zahl, G. **18**-713
Zahler, R.E. **13**-45, **13**-77
Zahn, D. **16**-1680
Zahneisen, T. **5**-146
Záhorszky, U.I. **19**-1554, **19**-1556
Zahradník, R. **2**-210, **7**-5, **10**-363
Zaidi, S. **16**-1817
Zaidlewicz, M. **15**-680, **15**-712
Zaikov, G.E. **19**-331, **19**-344
Zair, T. **13**-409
Zaitsev, A.B. **15**-1828, **16**-553
Zaitseva, G.S. **15**-1641
Zajac Jr., W.W. **19**-310, **19**-729
Zajdel, W.J. **5**-131, **10**-1832
Zakarian, A. **18**-644
Zakharkin, L.I. **12**-504, **19**-1097, **19**-1099, **19**-1108
Zakharov, V.I. **15**-1413
Zakharov, V.P. **11**-525
Zaklika, K.A. **15**-2364
Zalán, E. **17**-407
Zalar, F.V. **12**-713
Zalatan, D.N. **15**-403, **15**-1105
Zalesov, V.S. **16**-2164
Zalewski, R.I. **8**-132
Zali-Boinee, H. **18**-353
Zalomaeva, O.V. **19**-260
Zaman, S. **18**-850
Zamani, R. **16**-337
Zamashchikov, V.V. **10**-215, **10**-294, **10**-455, **10**-456
Zambianchi, F. **19**-738
Zamboni, R. **15**-295
Zambrano, J.L. **19**-417
Zamir, D. **11**-571
Zammattio, F. **11**-258
Zamojski, A. **4**-120
Zanardi, E. **16**-1029
Zanardi, F. **16**-1029
Zanardi, G. **18**-73, **19**-1258
Zanatta, N. **9**-129
Zanda, M. **19**-1028
Zander, M. **2**-152
Zandomeneghi, M. **4**-66, **4**-159
Zanette, D. **10**-560
Zang, H.-J. **16**-1233

Zanger, M. **15**-1639, **16**-1356
Zani, L. **4**-161, **16**-887, **16**-893, **16**-903, **19**-1034
Zanini, M.L. **13**-379
Zanirato, P. **12**-541
Zank, G.A. **16**-218
Zanka, A. **11**-256, **19**-1072
Zanobini, F. **15**-278
Zanoni, B. **18**-203
Zanotti-Gerosa, A. **19**-1034
Zanotto, S.P. **16**-1738
Zaparucha, A. **15**-1114
Zapata, A. **17**-486
Zapf, A. **10**-1309, **11**-349, **11**-5, **13**-98, **13**-288, **13**-382, **13**-499, **3**-860
Zaporowski, L.F. **12**-78
Zappia, G. **13**-238
Zara, C.L. **12**-664
Zarakhani, N.G. **18**-352
Zard, S.Z. **14**-310, **14**-462, **14**-476, **15**-413, **15**-1300, **15**-1301, **16**-1598, **16**-1599, **17**-239, **19**-422, **19**-1237
Zare, R.N. **5**-353
Zarei, A. **11**-198
Zarei, A. **11**-455
Zaret, E.H. **14**-247
Zareyee, D. **19**-1587
Zaringhadam, P. **11**-659
Zarkadis, A.K. **5**-248, **11**-451
Zarkowsky, D.S. **10**-1146. **16**-1995
Zaro, J. **18**-428
Zarotti, P. **15**-1170
Zartler, E. R. **4**-133
Zass, E. **12**-35
Zaugg, H.E. **10**-360, **10**-1668, **11**-547, **16**-365, **16**-1962
Závada, J. **17**-8, **17**-16, **17**-20, **17**-23, **17**-24, **17**-26, **17**-27, **17**-28, **17**-31, **17**-32, **17**-100, **17**-261
Zavalij, P.Y. **3**-222
Zaveri, N.T. **11**-444
Zavitsas, A.A. **1**-97, **2**-42, **5**-253, **5**-282, **14**-74, **14**-283
Zawadzki, S. **10**-945, **19**-1263
Zawalski, R.C. **12**-753
Zbinden, H. **15**-487
Zbiral, E. **16**-1311
Zderic, S.A. **19**-1045
Zdravkova, M. **5**-276
Zdunek, L.Z. **8**-26
Zecchi, G. **15**-2103
Zechel, C. **16**-1936
Zechman, A.L. **15**-2475
Zecri, F.J. **16**-1367
Zee, O.P. **15**-2018
Zee, S. **15**-682
Zeegers-Huyskens, T. **3**-37
Zeeh, B. **10**-1711, **15**-2505, **18**-244
Zefirov, N.S. **1**-32, **4**-297, **4**-346, **4**-3, **4**-376, **4**-484, **10**-790, **10**-791, **10**-1683, **15**-10, **15**-21, **15**-46, **15**-279, **15**-1667, **15**-1700, **15**-1748, **15**-2003
Zefirov, Yu.V. **4**-520
Zegrocka, O. **19**-1125
Zehnder, M. **15**-67, **15**-790, **18**-515
Zeid, I. **17**-227
Zeidan, T.A. **5**-386, **18**-522
Zeifman, Yu.V. **16**-43
Zeiler, A.G. **17**-523, **17**-524
Zeilstra, J.J. **19**-1243
Zein, A. **13**-537
Zeiss, H. **3**-95
Zeitler, K. **16**-1591
Zeitz, H.-G. **14**-109
Zelenina, N.L. **17**-449
Zelle, R.E. **16**-1688
Zeller, J. **10**-151
Zeller, K. **18**-219, **18**-233
Zeltz, H.-G. **5**-255
Zemskov, S. **11**-308, **12**-111, **14**-151
Zeng, B.-B. **10**-1213
Zeng, B.-S. **19**-143
Zeng, F. **12**-306
Zeng, H. **15**-1266
Zeng, J. **19**-1683
Zeng, Q. **13**-234
Zeng, W. **15**-1887
Zeng, X. **10**-71, **15**-379
Zeni, G. **12**-300, **12**-301, **13**-375, **14**-362, **15**-943, **15**-1436
Zens, A.P. **4**-220
Zepp, R.G. **7**-52
Zerbetto, F. **3**-206
Zercher, C.K. **15**-2577, **18**-868
Zergenyi, J. **17**-459
Zerth, H.M. **16**-783, **16**-1778
Zetina-Rocha, C. **15**-1195
Zetterberg, K. **15**-341
Zevatskii, Y.E. **6**-9
Zewall, A.H. **6**-16
Zewge, D. **10**-1194, **13**-288
Zeynizaded, B. **15**-2659
Zeynizadeh, B. **10**-844
Zezza, C.A. **16**-1003
Zha, Z. **13**-388, **16**-589, **16**-612
Zhadonva, M.P. **16**-252
Zhan, B.-Z. **19**-128, **19**-129
Zhan, Z.-P. **15**-1345, **19**-830
Zhang, C. **15**-307
Zhang, A. **10**-1369, **12**-302, **13**-287, **15**-832, **16**-1991
Zhang, B. **12**-389
Zhang, C.-M. **15**-646
Zhang, C.-R. **19**-1616
Zhang, C. **11**-189, **11**-468, **15**-391, **15**-852, **15**-1903, **15**-1939
Zhang, D.-W. **19**-383
Zhang, D. Y. **5**-300
Zhang, D. **12**-510, **15**-893, **16**-1371, **16**-1605
Zhang, F. **12**-298
Zhang, F.-Y. **15**-1912, **16**-658
Zhang, F.J. **2**-300
Zhang, F.-M. **13**-179, **16**-270, **19**-1364, **19**-1649
Zhang, G.-l. **19**-33
Zhang, G.-L. **13**-222
Zhang, G.-W. **16**-1523
Zhang, G.-S. **16**-68, **16**-78, **16**-1778
Zhang, G.-Y. **16**-546
Zhang, G. **12**-381, **13**-496, **16**-1502, **16**-1503, **16**-1512, **16**-1515
Zhang, H.-C. **15**-2628, **15**-2635, **15**-2686, **19**-922
Zhang, H. **10**-1469, **10**-1905, **11**-694, **13**-205, **13**-428, **14**-343, **15**-2249, **16**-395, **16**-958, **16**-1432, **19**-763
Zhang, J.-R. **15**-1936
Zhang, J.-Y. **15**-607
Zhang, J.-Q. **16**-573
Zhang, J.-K. **16**-751
Zhang, J. **2**-141, **10**-869, **10**-1924, **12**-389, **13**-453, **13**-529, **13**-786, **15**-287, **15**-693, **16**-666, **19**-658, **19**-1058, **19**-1075
Zhang, K. **11**-264
Zhang, L. **10**-1732, **12**-355, **12**-381, **12**-445, **13**-522, **13**-579, **14**-303, **15**-867, **15**-1055, **15**-1085, **15**-2136, **16**-1084, **16**-2012
Zhang, L.H. **12**-179
Zhang, M.-B. **12**-284, **13**-588
Zhang, M.-H. **15**-2187
Zhang, M. **5**-400, **15**-607, **15**-1346, **15**-2479, **16**-103, **16**-2192
Zhang, O.Z. **13**-786
Zhang, P.-F. **16**-1333
Zhang, P. **15**-1046, **16**-2063
Zhang, Q. **10**-1548, **13**-494, **13**-564, **13**-785, **15**-2119, **16**-742, **16**-743, **16**-944, **19**-1046
Zhang, R. **13**-399, **15**-1883
Zhang, S.-L. **10**-1409, **13**-421
Zhang, S.-W. **15**-1525, **15**-1584, **15**-1585, **15**-1586, **19**-971
Zhang, S.-Y. **10**-1522, **15**-1846
Zhang, S. **11**-264, **12**-298, **12**-389, **13**-129, **13**-386, **13**-785, **13**-786, **15**-1829, **15**-2697, **19**-233, **19**-234, **19**-1611
Zhang, S.B. **15**-210
Zhang, T. **16**-625
Zhang, T.Y. **19**-726
Zhang, W. **10**-1522
Zhang, W.-C. **16**-476, **19**-1643
Zhang, W.-X. **10**-1243
Zhang, W. **4**-36, **12**-123, **13**-515, **15**-439, **15**-641, **15**-644, **15**-882,

15-1325, **15**-1977, **15**-1978, **15**-2045, **18**-821
Zhang, X.-D. **13**-591
Zhang, Y.-K. **5**-224, **10**-797
Zhang, X.-L. **15**-1832, **15**-1843
Zhang, X.-M. **1**-108, **1**-111, **1**-112, **5**-279, **8**-63
Zhang, X. **10**-821, **11**-694, **13**-100, **13**-319, **13**-491, **13**-630, **15**-227, **15**-239, **15**-452, **15**-457, **15**-594, **15**-811, **15**-1399. **15**-1613, **15**-1925, **15**-2000, **15**-2323, **16**-317, **16**-649, **16**-1057, **16**-2023, **16**-2256, **18**-773, **19**-44, **19**-1014, **19**-1017, **19**-1142, **19**-1255
Zhang, X.P. **15**-2516
Zhang, X.P. **16**-1434
Zhang, Y.-R. **19**-1262
Zhang, X.-X. **3**-120, **19**-1021
Zhang, Y. **10**-869
Zhang, Y. **4**-419, **7**-126, **10**-1051, **10**-1719, **11**-241, **11**-273, **11**-377, **11**-428, **11**-694, **12**-166, **12**-379
Zhang, Y. **12**-683, **12**-704, **13**-205, **13**-313, **13**-494, **13**-495, **13**-496, **13**-497, **13**-500, **13**-591, **13**-599, **14**-196, **14**-212, **14**-370, **14**-444, **15**-753, **15**-769, **15**-1826, **15**-2653, **16**-582, **16**-600, **16**-880, **16**-910, **16**-989, **16**-999, **16**-1026, **16**-1051, **16**-1718, **16**-1719, **16**-2024, **16**-2026, **16**-2039, **16**-2083, **16**-2102, **16**-2109, **16**-2307, **18**-388, **19**-184, **19**-202, **19**-502, **19**-622, **19**-722, **19**-1087, **19**-1252, **19**-1253, **19**-1365, **19**-1568, **19**-1569
Zhang, Z.-H. **16**-413
Zhang, Z.-B. **19**-1640, **19**-1683
Zhang, Z. **10**-1778, **10**-1780, **11**-460, **13**-292, **13**-388, **13**-785, **15**-206, **15**-250, **15**-416, **15**-882, **15**-883, **15**-1057, **15**-1179, **16**-1433, **16**-1821, **17**-220, **19**-715, **19**-1017, **19**-1124
Zhang, Z.J. **18**-808
Zhao, B. **15**-2041, **16**-1006
Zhao, C.-G. **15**-1933, **16**-1084, **16**-1220, **19**-230
Zhao, C.H. **16**-915
Zhao, C.-Q. **10**-793, **15**-395
Zhao, C.-Y. **4**-419
Zhao, C. **4**-114, **15**-2455, **15**-2567
Zhao, D. **13**-129, **13**-166, **16**-1150, **18**-767
Zhao, F. **13**-399
Zhao, G.-L. **15**-1402, **15**-2078
Zhao, G. **10**-1476, **13**-785, **15**-444, **16**-612, **16**-613, **16**-751, **16**-1206, **19**-1024, **19**-1033
Zhao, H. **10**-1628, **19**-1198
Zhao, J.-F. **15**-1023
Zhao, J. **11**-428, **13**-428, **15**-2608, **16**-854, **19**-722, **19**-1640
Zhao, K.-Q. **10**-1607
Zhao, K. **10**-583, **16**-1336, **19**-720
Zhao, L. **10**-602
Zhao, L.L. **13**-576
Zhao, M. **16**-625, **19**-647, **19**-650
Zhao, M.W. **10**-1146, **16**-1995
Zhao, P.-Q. **10**-1232, **10**-973
Zhao, P. **16**-1022, **17**-311, **19**-1087
Zhao, S.-W. **1**-117
Zhao, S.-H. **16**-794, **16**-797
Zhao, S. **15**-1587
Zhao, W.-G. **15**-764
Zhao, X. **1**-115, **4**-198, **10**-1141, **11**-484, **16**-868
Zhao, Y.-L. **13**-514
Zhao, Y. **5**-57, **7**-86, **10**-596, **10**-1905, **10**-1992, **11**-452, **13**-205, **14**-298, **16**-776, **16**-1364, **19**-224
Zhao, Y.J. **8**-146
Zhao, Z.-A. **11**-314
Zhao, Z. **19**-163
Zhdamarova, V.N. **13**-117
Zhdankin, V.V. **10**-790, **10**-791, **11**-289, **15**-10, **19**-783
Zhdanov, Y.A. **2**-431
Zhdanov, Yu.A. **18**-953
Zheng, B.-H. **10**-1719
Zheng, B. **12**-79
Zheng, C.Y. **15**-1650
Zheng, D.-H. **16**-1523
Zheng, F. **18**-93
Zheng, H. **8**-108, **16**-743
Zheng, J.-Z. **15**-307
Zheng, J.-C. **16**-1481, **16**-1597
Zheng, J. **16**-831, **19**-1032
Zheng, K. **15**-1024, **18**-510
Zheng, M. **15**-2187
Zheng, N. **11**-542
Zheng, O. **19**-55
Zheng, P. **18**-709, **19**-163
Zheng, Q.-G. **10**-725, **10**-900, **10**-1550, **11**-243, **16**-1230, **16**-1884, **19**-204
Zheng, T.-C. **10**-756
Zheng, W.-H. **10**-1719
Zheng, X. **10**-1904, **16**-1026, **16**-1963
Zheng, Y. **16**-582
Zheng, Z. **15**-453, **15**-643, **16**-1512
Zhmurova, I.N. **16**-1924, **19**-1259
Zhong, G. **15**-555, **16**-1082
Zhong, H.M. **10**-1082
Zhong, L. **15**-619
Zhong, P. **15**-315, **15**-467
Zhong, Q. **15**-2187
Zhong, Y.-L. **12**-759
Zhong, Y.-W. **19**-1670, **19**-1674
Zhong, Y.-L. **19**-599
Zhong, Y. **16**-893
Zhong, Z.-L. **3**-128
Zhong, Z. **8**-187
Zhou, B. **7**-56
Zhou, C.-Y. **16**-706, **16**-893, **16**-1560
Zhou, C. **15**-990, **15**-2519, **16**-1009
Zhou, D.-Y. **15**-1517, **15**-1595
Zhou, G. **16**-788, **16**-1185
Zhou, H. **10**-1627, **12**-759, **19**-952, **19**-957, **19**-1024
Zhou, J. **10**-1141
Zhou, J.-F. **16**-57
Zhou, J.-R. **16**-586
Zhou, J.-Y. **16**-591
Zhou, J. **10**-1470, **13**-450, **13**-533, **13**-591, **16**-1110, **16**-1543
Zhou, L.-L. **13**-576
Zhou, L. **12**-360, **13**-100, **13**-401, **15**-375, **15**-843, **15**-961, **15**-1720, **16**-744, **19**-1014, **19**-1041, **19**-1156, **19**-1582
Zhou, M.-M. **13**-388
Zhou, M. **16**-2062
Zhou, P. **13**-450
Zhou, Q.-L. **10**-1475, **10**-660, **15**-2045, **15**-470, **15**-643, **15**-646, **16**-1560, **16**-706, **16**-742, **16**-746, **16**-893, **16**-943, **19**-1014
Zhou, Q.J. **11**-489
Zhou, S.-Z. **11**-697
Zhou, S.-m. **12**-293
Zhou, S.-L. **15**-1387, **15**-1417, **15**-1424
Zhou, S.-z. **19**-1565
Zhou, S. **14**-303, **17**-472, **17**-473, **19**-1478
Zhou, T. **11**-185, **11**-528
Zhou, W.-J. **12**-262, **13**-497
Zhou, W. **12**-355, **15**-351, **15**-1971, **15**-2045, **19**-869
Zhou, X.-G. **19**-536
Zhou, X. **13**-100, **13**-223, **16**-1497
Zhou, Y.-F. **16**-545, **16**-670
Zhou, Y.-G. **10**-1243, **15**-559, **15**-562, **16**-317, **16**-1597
Zhou, Y.-M. **19**-140
Zhou, Y. **13**-388, **16**-734, **16**-1083, **19**-1055
Zhou, Z.-T. **19**-1014
Zhou, Z.-Y. **15**-1997, **15**-2509
Zhou, Z. **2**-101, **2**-122, **11**-90, **13**-198, **15**-932
Zhu, C. **10**-976, **16**-311, **16**-2200, **19**-1655
Zhu, C.Y. **4**-182
Zhu, D. **10**-1239, **13**-148, **16**-103, **19**-993
Zhu, F. **16**-129, **16**-776
Zhu, G. **15**-644, **15**-883
Zhu, H.J. **16**-667
Zhu, J.-L. **10**-1567, **16**-303

Zhu, J. **11**-460, **15**-441, **15**-619, **15**-1910, **16**-202, **16**-812, **16**-959, **19**-622
Zhu, L.-F. **16**-1433
Zhu, L. **10**-1905, **12**-628, **16**-1624
Zhu, M. **13**-397, **13**-506, **15**-2675
Zhu, N.-Y. **13**-386, **15**-899
Zhu, N. **15**-180
Zhu, Q.-M. **13**-494
Zhu, Q.-C. **19**-1141
Zhu, Q. **13**-512, **15**-1041
Zhu, S. **10**-1927
Zhu, S.-F. **10**-1475, **10**-660, **15**-643, **15**-646, **16**-1560, **16**-706, **16**-893
Zhu, S. **15**-1010, **16**-1462, **16**-1462
Zhu, W. **11**-222, **13**-205, **13**-591
Zhu, X.-Q. **15**-607
Zhu, X.-F. **16**-1357
Zhu, X. **13**-206, **13**-595
Zhu, Y.-Z. **13**-284, **13**-291, **16**-312
Zhu, Y. **3**-48, **12**-96, **19**-953
Zhu, Z. **5**-377, **5**-433, **10**-602, **10**-667, **19**-721
Zhuang, W. **10**-1141, **15**-1954, **16**-364
Zhulin, V.M. **14**-181
Zhun', I.V. **16**-2084
Zhuravel, M.A. **15**-2520
Zi, G.-F. **19**-1640
Zia-Ullah. **10**-1142
Zief, M. **4**-154, **4**-176
Ziegenbein, W. **10**-1793, **10**-1898, **12**-444, **16**-535, **17**-253
Zieger, H.E. **10**-1943
Ziegler, F.E. **18**-691, **18**-700, **18**-722
Ziegler, G.R. **16**-191
Ziegler, T. **15**-1617, **17**-394
Ziehn, K. **17**-485
Ziemer, B. **16**-1060
Ziemnicka-Merchant, B.T. **15**-2493
Zierke, T. **16**-755
Ziessel, R. **5**-305
Zijlstra, H. **3**-22
Zil'berman, E.N. **11**-560, **16**-98, **16**-119, **19**-1175
Zilkha, A. **3**-204
Ziller, J.W. **16**-13, **18**-816, **18**-884
Zim, D. **13**-189
Zimmer-Gasser, B. **4**-534
Zimmer, H. **19**-258
Zimmer, L.E. **15**-2563
Zimmerman, H.E. **1**-2, **2**-369, **7**-3, **12**-98, **15**-570, **15**-571, **15**-2303, **16**-1272, **17**-414, **18**-121, **18**-512, **18**-611, **18**-625, **18**-678, **18**-907, **18**-908, **18**-909, **18**-911, **18**-912, **18**-913, **18**-914, **18**-919, **18**-920, **18**-921
Zimmerman, J. **14**-45, **15**-1289, **15**-1290
Zimmerman, W.T. **17**-274
Zimmermann, A. **15**-2606
Zimmermann, C. **12**-639
Zimmermann, G. **2**-401, **4**-280, **14**-79
Zimmermann, H. **4**-39515-1255, **16**-1656, **18**-656
Zimmermann, K. **10**-883
Zimmt, M.B. **5**-398
Zink, J.I. **7**-14
Zinn, F.K. **15**-1151
Zinovyev, S. **13**-391
Zippel, M. **16**-1043, **17**-422
Zipse, H. **5**-213, **10**-348, **10**-397, **14**-16
Zirnstein, M.A. **8**-99, **8**-202
Ziurys, L.M. **8**-214
Ziyaei-Halimehjani, A. **16**-1224
Ziyaei, A. **15**-1450
Zlokazov, M.V. **15**-1600
Zmuda, H. **18**-795, **18**-799
Zoebisch, E.G. **2**-18
Zoghaib, W.M. **19**-915
Zohar, E. **15**-528
Zohdi, H.F. **18**-26
Zolfigol, M.A. **10**-664, **11**-134, **12**-732, **12**-739, **16**-80, **16**-2171, **19**-29, **19**-30, **19**-241
Zoli, L. **16**-849
Zollinger, H. **5**-69, **7**-5, **9**-64, **11**-7, **11**-9, **11**-10, **11**-29, **11**-108, **11**-162, **11**-163, **11**-164, **11**-165, **11**-167, **13**-29, **13**-30, **13**-34, **13**-36, **13**-37, **13**-38, **13**-770, **13**-789, **13**-836, **14**-391, **19**-1544
Zolopa, A.R. **10**-1872
Zoltewicz, J.A. **10**-675, **10**-879, **13**-1, **13**-4
Zon, G. **18**-903
Zondervan, C. **19**-470
Zonta, C. **3**-85
Zook, H.D. **5**-135, **10**-362, **10**-1712, **18**-189
Zopf, J.J. **2**-108
Zora, M. **18**-514, **18**-653, **18**-661
Zorc, B. **19**-210
Zordan, M. **16**-571
Zorkii, P.M. **4**-520
Zorzan, D. **11**-693, **13**-493
Zou, B. **13**-125, **16**-2076
Zou, G. **10**-1882
Zou, W. **16**-1084
Zou, Y. **13**-236, **19**-563
Zountsas, J. **4**-492
Zradni, F.-Z. **16**-1946
Zrinski, I. **2**-88
Zschunke, A. **18**-574
Zu, L. **15**-1106, **16**-815
Zubairi, Md.O. **19**-1088
Zubarev, V.E. **5**-221
Zuberbühler, A.D. **14**-223
Zuberi, S.S. **11**-311
Zubiani, G. **16**-484
Zubieta, J. **12**-425
Zucchi, C. **12**-332
Zucco, C. **2**-458, **11**-524, **12**-93, **12**-706, **13**-21
Zuckerman, J.J. **1**-18, **1**-95, **4**-273, **12**-1, **12**-409, **12**-577, **12**-587, **12**-623, **12**-644, **13**-743, **15**-909
Zuend, S.J. **10**-1769
Zuercher, W.J. **18**-887
Zuev, P.S. **5**-349, **5**-381, **15**-2537
Zueva, L.D. **18**-348
Zugravescu, I. **12**-442
Zuhl, A.M. **15**-1056
Zuidema, L.J. **14**-232
Zuika, I.V. **3**-55
Zuilhof, H. **5**-78
Zukerman-Schpector, J. **19**-568
Zuman, P. **6**-49, **6**-55, **6**-58, **6**-59
Zumpe, F.L. **10**-1542, **18**-737
Zundel, G. **3**-3
Zúñiga, N. **16**-2184
Zuo, G. **15**-2636
Zupan, M. **11**-309, **12**-114, **12**-130, **12**-133, **14**-157, **14**-187, **19**-666
Zupet, P. **12**-130
Zurawinski, R. **10**-865
Zürcher, C. **3**-205
Zurflüh, R. **19**-890
Zurita, E. **13**-517
Zuzukin, V. **16**-2210
Zvezdina, E.A. **16**-252
Zvolinskii, V.P. **11**-525
Zwanenburg, B. **6**-36, **15**-1951
Zweifel, G. **4**-199, **12**-465, **12**-573, **14**-424, **15**-516, **15**-520, **15**-684, **15**-726, **16**-463, **17**-325, **18**-278, **18**-280, **18**-453, **18**-478, **18**-483
Zweig, A. **18**-121
Zwick, W. **15**-1474
Zwierzak, A. **10**-924, **10**-945, **10**-1049, **10**-1076, **15**-412, **15**-2035, **19**-1263
Zwikker, J.W. **15**-577, **16**-1887
Zygmunt, J. **11**-618
Zyk, N.V. **15**-1667, **15**-2003
Zyranov, G.V. **12**-733
Zytowski, T. **15**-1303

SUBJECT INDEX

The vast use of transition metal catalysts led to limited citations of individual metals. In many cases, the term metal catalysis, or catalysts, metal is used as a heading, with several examples, often using different metals.

α-effects, and nucleophilicity, 431
$A^{1,3}$-strain, 182, 184
A2 mechanism, acetal hydrolysis, 456
ab initio calculations, 34, 233
  1,2-alkyl shifts in alkyne anions, 1337
  and acidity, 319
  and antiaromaticity, 66
  and cubyl carbocations, 383
  and nonclassical carbocations, 396
  and protonated of cyclopropanes, 881
  and S_N2 reactions, 377, 378
  carbocation stability, 862
  E2 mechanism, 1254
  Mukaiyama aldol reaction, 1152
  norbornyl carbocation, 404
  rate of cyclopropylcarbinyl radical rearrangement, 814
  transition state for radical hydrogen abstraction, 812
abnormal *Beckmann reaction*, 1359
abnormal *Beckmann rearrangement*, 1312, 1366
abnormal *Claisen rearrangement*, 1412
absolute aromaticity, 37
absolute configuration, 138
absolute configuration see enantiomers, chirality, stereogenic, chiral
  and biochemical methods, 141
  and circular dichroism, 143
  and GC, 142
  and *Mosher's acid* or *Mosher's ester*, 142
  and NMR, 142
  and optical comparison, 142
  and optical rotatory dispersion, 143
  and specific rotation, 143
  and the S_N2 reaction, 141
  and the steering wheel model, 140
  and universal NMR database, 143, 144
  Cahn-Ingold-Prelog system, 138–141
  D/L nomenclature, 138
  determination, 141
  Kishi's NMR method, 143, 144
  molar rotation, 143
  sequence rules, 138–141
absolute hardness, 332
  table, 333
absorbents, chiral, 156
absorption, and conjugation, 293
  differential, and diastereomers, 156
  differential, and resolution, 156
abstraction, and vinylic hydrogenation, 815
  by radicals, 694, 867
  by radicals, transition state, 808
  divalent atoms, 812
  from alkanes, by radicals, 813
  from alkenes, by radicals, 815
  of atoms by radicals, 808
  of atoms from radicals, 247
  of benzylic hydrogens, by radicals, 815
  of H, by radicals, and rearrangements, 1333
  by halogen radicals, 822
  by nitrenes, 259
  by radicals, ab initio study, 812
  by radicals, transition state, 812
  photochemical, 306
  radical, and stereoelectronic effects, 817
  by radicals, rate, 812
  selectivity by radicals, 813
  selectivity of bromine versus chlorine radicals, 822
  stereoselective, 817
acceleration, of the Diels-Alder reaction, 1022
acceptors, in the benzoin condensation, 1188
acenaphthylene, addition of DBr, 864
acenes, 57, 78
  zigzag, 78
acepentalenes, radical ions, 248
acetal formation, and drying agents, 1081
  and microwave irradiation, 1082
  azeotropic distillation, 1081
  in ionic liquids, 1082
  mechanism, 1082
acetaldehyde, and paraldehyde, 1240
  rational barrier, 178
acetals, acid catalyzed hydrolysis, 455
  alkoxymercuration of alkynes, 892
  and enol ethers, 1083
  and Lewis acids, 456
  and transacetalization, 1083
  as protecting groups, 1082
  base induced elimination to enol ethers, 1286
  chiral, 1082
  dimerization, 535
  formation of thioacetals, 478
  from alcohols and aldehydes or ketones, 1081
  from amides, 685
  from Grignard reagents, 534
  from ortho esters, 534
  from oxidation of hydroxy ethers, 831
  hydrolysis, 454

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.

© 2013 John Wiley & Sons, Inc. Published 2013 by John Wiley & Sons, Inc.

acetals, acid catalyzed hydrolysis (*Continued*)
hydrolysis, and Brønsted coefficient, 456
hydrolysis, and carbocations, 457
hydrolysis, and isotope labeling, 455
hydrolysis, and S_N1 mechanisms, 455
hydrolysis, rate determining step, 456
ketene silyl, with alkoxy ketones, 1153
ketene silyl, with imines, 1137, 1152
reduction of, 1537
transetherification, 465
with allylic silanes, 534
with organotrifluoroborates, 700
with silyl enol ethers, 534
acetanilides see anilines, acyl
acetates, allylic also see esters, allylic
as a base, 313
reaction with nucleophiles, 529
with boronic acids, Pd catalyst, 560
with Grignard reagents, 527
with keto acids, metal catalyzed, 856
acetates, enol also see enol
from ketenes with aldehydes or ketones, 892
acetates, homoallylic, 1126
metal, and acyloxylation, 835
propargylic, with dialkylzinc, 1121
acetic acid, cis conformation, 178
dimeric structure, 97
with alkenes, reactivity, 872
with Zn, reduction of conjugated systems, 916
acetic anhydride, and acyl fluoroborate, 1012
and dehydration of oximes to nitriles, 1311
and nitration of aromatic compounds, 593
conjugate addition, 968
acetoacetic acid synthesis, 548, 559
acetoacetic ester, and enol content, 90
enol content and solvent, 92
synthesis, 540
acetolysis also see solvolysis
of organomercury compounds, 659
acetone, tautomerism, and bromination, 285
acetoxy-ketones, from enols and ketones, 836
acetoxylation, of alkenes, 1012
acetoxy-sulfides, by Pummerer rearrangement, 1565
hydrolysis to aldehydes, 1565
acetyl carbocations, 215
acetyl hypofluorite, 608
acetylene see ethyne
acetylide ion, with alkyl halides, 561
with epoxides, 561
with sulfates, 561
with sulfonate esters, 561
acetylphenols, and Fries rearrangement, 636
aci form of nitro compounds, and tautomerism, 94
nitro compounds, 1079
nitro compounds, and the Nef reaction, 1079
acid catalysis, Friedel-Crafts alkylation, 610
addition of alkenes to alkenes, 931
addition of carboxylic acids to alkenes, 892
addition of water to carbonyls, 1075
aldol reaction, 1149
amide hydrolysis, 1199
esterification of carboxylic acids, with ethers, 1206
hydrocarboxylation of alkenes, 972
hydrolysis of amides, 1198
Knoevenagel reaction, 1157
Mannich reaction, 1101
rearrangement of hydrazobenzenes, 1415
acid catalysts, addition of water to alkenes, 885
alkenes with alcohols, 889
for the Schmidt reaction, 1363
hydration of allenes, 888
hydrocarboxylation, 973
of diketones, 1083
with aldehydes or ketones, 1149
acid derivatives, with amides, 1222
with organocerium reagents, 1230
with various organometallics reagents, 1231
acid solutions, and the tetrahedral mechanism, 1070
acid strength, 222, 313–318
and solvent, 320
crystallographic scale, 319
definition, 313
field effects, 334
Lewis acids, 331
mineral acids, 319
resonance effects, 336
acids, and diazotization, 789
as a proton donor, 312
catalysis, alcohol dehydration, 463
IUPAC terminology, 312
normal, definition, 323
phosphoric see phosphoric acid
sulfuric see sulfuric acid
superacid-SO_2, 210
Acid-Base Approach to Organic Chemistry, 1589
scid-base reactions, and elimination, 1271
carbanions + proton, 233
catalysis, 327
deprotonation by organometallics, 696
equilibrium, 312
formation of homoenolates, 226
acidic protons, and alkylation, 541
acidity also see acid strength
and benzyne reactions, 744
and carborane acids, 324
and carboxylic acids, 20
and conformation, 340
and electronegativity, 337
and entropy, 345
and F strain, 338
and face strain, 338
and five-membered rings, 59
and free energy, 345
and hybridization, 341
and hydrogen bonding, 98, 338
and indicators, 325
and ionic liquids, 324
and ionic strength, 346
and IR, 325
and Meldrum's acid, 340
and metalation, 697
and organolithium reagents, 232
and proton transfer, 323
and resonance, 337
and s-character, 341
and solvent effects, 320, 324, 327, 343–345
of solvents also see solvent acidity
and steric effects, 338
and the medium, 343
and the Periodic table, 337
gas phase, 344
Hammett acidity function, 325
-I effect, 336
inductive and field effects, 20
intrinsic, 344
kinetic, 222
of active methylene compounds, 539
of amides versus amines, 336
of benzoic acids, and substituents, 335
of cyclopentadiene, 59
of esters versus ethers, 336
of hydrocarbons, 222
of PCC, 1443
of phenalene, 56
of protons, and solvent acidity, 325

of β-hydrogens, and Zaitsev's rule, 1271
of β-hydrogens, in elimination reactions, 1271
pK_a of acid types, 314–318
protons in conjugated esters, ketones, nitriles, 549
protons α- to a heteroatom, 552
scales, and alcohols, 326
and amides, 326
and basic solvents, 326
and calorimetric measurements, 327
and carbon acids, 326
and indicators, 325
spectrophotometric measurement, 325
statistical effects, 338
substituent effects, 334
thermodynamic, 222
acids, also see Brønsted-Lowry acids
acids also see Lewis acids
acids also see solvent acidity
acids, acid strength, 314–318
activity of proton, 325
and hydrogen exchange, electrophilic aromatic substitution, 592
and keto-enol tautomerism, 665
and Michael addition, 948
and Michael reactions, 948
and organometallics, 695, 696
and pK_a, 314–318
aromatic, and decarboxylation, 719
Brønsted, addition of thiols to alkenes, 894
carbon, 319
carbon, and acidity scales, 326
carboxylic see carboxylic acids
conjugate, 312
conjugated, and decarboxylation, 719
conjugated, and reduction, 916
glycidic see glycidic
halogen, reactivity and halogenation, 825
hard, definition, 331
hardness, 331
inorganic, with anhydrides, 1211
inorganic, esters, hydrolysis, 453
Lewis see Lewis acids
Lewis, addition of thiols to alkenes, 894
protonation of carbanions, 221
proton-transfer reaction, 323
reaction with alkenes, 863
rearrangement of epoxides, 1343
soft, definition, 331
softness, 331
strength and structure, 334
strength, 313
strong, stability of carbocations, 210
sulfinic see sulfinic acids
sulfonic see sulfonic acids
sulfonyl, reduction with metals, 1252
superacids, 210, 319
and carbocation formation, 212
and carbocations, 210
triflimide, 888
type, table of pK_a, 314–318
very weak acids, 319
weak, deprotonation by metals, 698
with organometallics, 698
acoustic cavitation see cavitation
acrolein, canonical forms, 45
actinometer, and photochemical mechanism, 307
activated complex, 265
activated metals, 715
activating groups, and multiple substituents, 583
aromatic substitution, 578
for aromatic substitution, 741
in aromatic compounds, 576
in S_NAr reactions, 741, 742
activation energy, and ester hydrolysis, 1192
activation energy, Arrhenius, 284
enolate anions, 1146
activation entropy, 267
and ring-closing reactions, 268
and *Smiles rearrangement*, 801
and substitution reactions, 391
and the E^i reactions, 1279
activation hardness, 587
electrophilic aromatic substitution, 587
activation volume, and high pressure, 362
and reactivity, 362
activation, enthalpy, 267
free energy, 265
activation-strain model, 1275
active methylene compounds, acidity, 539
and diazo compounds, 677
and the *Hurtley reaction*, 779
and the *Knoevenagel reaction*, 1157
arylation, 778–780
coupling with allylic carbonates, 529
coupling with malonates, 780
coupling with organometallics, 780
dianions, 541
functional groups, 539
halogenation, 670
nitration, 677
with acyl halides, 1233
with alkyl halides, 538
with allylic esters, 528
with aryl halides, benzyne mechanism, 779
with aryldiazonium salts, 674
with dihalides, 541
with tosylazides, 678
activity, of radicals, 820
acyclic compounds, conformation, 175
acyclic molecules, and entropy, 265
acyl addition also see addition
acyl addition, 1141–1153
alkenes, 1122
alkynes with aldehydes or ketones, 1122
alkynes, 1122
allylic tin compounds, 1119
and the *Diels-Alder reaction*, 1027
and Ti complex, 1118
and ylids, 1179
enantioselectivity, dialkylzinc, 1120, 1121
enantioselectivity, Ti catalyst, 1120
Grignard reagents, 1107
hydrolysis, 1109
intramolecular, 971
Nozaki-Hiyama reaction, 1121
organoaluminum compounds, 1119
organochromium, enantioselectivity, 1121
organolithium reagents, 1110
organolithium reagents, enantioselectivity, 1110
organometallic reagents, 1117
organotin compounds, 1119
organotin compounds, enantioselectivity, 1119
organotitanium compounds, 1119
solvent free, 1114
syn or anti, 1068
water, 1076
with nucleophiles, 1067
with various metal salts, 1122
acyl anion equivalents, 549
and *Knoevenagel reaction*, 1160
acyl carbocations, 215
acyl carbon, substitution reactions, 420
acyl compounds, addition to alkenes or alkynes, 970
acyl fluorides see fluorides
acyl groups, electrofugal, 643
acyl halides see halides
O-acylhydroxamic acids see hydroxamic acids
acyl radicals see radicals
acyl silanes, 1155

acyl substitution, with organometallic reagents, 1231
acylals, and *Étard reaction*, 1479
  and silanes, 1084
  formation of, reagents, 1084
  formation, and microwaves, 1084
  from aldehydes with anhydrides, 1084
  hydrolysis to aldehydes, 1479
acylamidation, of alkenes, 1012
O-acylation see acylation, *O*-acylation
acylation, C versus O, 688
  Friedel-Crafts, 602, 643
  Friedel-Crafts see *Friedel-Crafts*
  O-acylation, and enolate anions, 1233
  O-acylation, and Friedel-Crafts acylation, 622
  O-acylation, with acyl halides, 1233
  of alcohols, 1207
  alkenes, 685, 992
  of amides, 1222
  of amides, by amides, 1221
  of amines, 1215
  of amines, and Merrifield synthesis, 1218
  of amines, ionic liquids, 1215
  of amines, microwaves, 1215
  of amines, polymer-bound, 1215
  of amines, reagents for, 1217
  of amines, with esters, 1219
  of aryl halides, 689
  of carboxylic acids, 1209
  of carboxylic dianions, 1237
  of conjugated compounds, 968
  of dienes, 685
  of diketone dianions, 1237
  of dithianes, 1236
  of enamines, 550, 551
  of enolate anions, 688
  of heterocycles, 845
  with acyl halides, 1232
  with nitriles, 632
acylazides see azides
acylcyanation, of imines, 1184
acylium ions, 621, 624
acylium ions, and the Schmidt reaction, 1364
  from carboxylic acids, 1364
  with alkenes, 685
  with nitriles and alkenes, 1012
acyloin condensation and surface reaction at Na, 1561
  and catenanes, 1561
  and chlorotrimethylsilane, 1560
  and Dieckmann condensation, 1560
  and surface area of metal, 1561
  and ultrasound, 1561
  importance of K in Na, 1561
  mechanism, 1561
  with trimethylsilyl chloride, 1561
acyloin ester condensation, 1560
acyloins also see hydroxy ketones
  and benzoin condensation, 1188
  and the benzoin condensation, 1188
  by the acyloin ester condensation, 1560
  preparation of enol ethers, 687
  reductive coupling of esters, 1560
  trapping with trimethylsilyl chloride, 1561
acyloxy compounds, 796
acyloxy ketones, 1012
acyloxy radials, 246
acyloxylation, 835
  and Markovnikov's rule, 1012
  of alkenes, 1012
  of alkynes, 1012
  of enols, 836
  of ketones, 836
  radical, 836
  with metal acetates, 835
acyloxymercuration, 892
acylperoxides see peroxides
acylthiazolidinethiones, chiral, 1155
Adam's catalyst, 920
adamantane, 822
adamantanes, and chirality, 129
  and strain, 199
adamantyl carbocations, 217, 1328
addition, exo, and bicyclic alkenes, 878
addition compounds, 104
1,3-addition reactions, dipolar, alkyl azides, 1009, 1010
1,4-addition reactions, to dienes, 884
addition reactions, acyl, 1067
  and I strain, 351
  and reactivity, 351
  and strain, 351
  metals, 1116–1123
addition reactions, alkenes versus alkynes, 873
  and alkenes and ionization potential, 873
  and alkenes, activating substituents, 872
  and alkynes, halonium ions, 873
  and allenes, 874
  and electrostatic potentials, 875
  and inversion of configuration, 875
  and Markovnikov's rule, 874
  and radicals, 867
  anti see anti
  conjugate, and resonance, 870
  conjugate, definition, 866
  conjugate, of radicals, 870
  conjugate, of thiols, 895
  conjugate, radical, rate constants, 870
  conjugate, to enynes, 870
  conjugated see Michael addition
  dipolar, [1,3]-, 1014–1020
  dipolar, [1,3]- see [3+2]-cycloaddition
  electronic effects, 872
addition reactions, electrophilic, 263
  and dienes, 870
  and stereochemistry, 860
  and the S_N1 mechanism, 860
  cyclic intermediates, 861
  mechanism, 859
  simultaneous addition, 861
  termolecular addition, 861
addition reactions, free-radical, 263
  HX to alkenes or alkynes, 884
  intramolecular, of radicals see radical cyclization
  IUPAC nomenclature, 369
addition reactions, nucleophilic, 263
  and carbonyls, 1068
  and the tetrahedral mechanism, 1068
  mechanism, 865
addition reactions, of alkynes, and UV, 872
  orientation, 874, 877
  pericyclic, 263
addition reactions, radical, 874, 876, 910
  and steric effects, 875
  and the Felkin-Anh model, 871
  mechanism, 867
  to alkenes, 247
  to alkenes, intramolecular, 868
  with alkenes, 815
addition reactions, reactivity of substrates, 872
  reactivity, 871, 872
  simultaneous, 263
  syn see syn
  termolecular, mechanism, 861
  to alkenes, 263
  to alkenes, and strain, 351
  to alkenes, and the Cieplack effect, 878
  to alkenes, four-center mechanism, 869
  to alkenes, nitrenes, 259
  to alkynes, and π-orbitals, 873
  to cyclopropanes, 879
  to dienes, 869
  to isocyanides, 1246
  to norbornenes, stereochemistry, 878
addition-elimination mechanism see mechanism

addition-elimination mechanism, 685, 741, 784, 1196, 1197
and alkylation of aromatic compounds, 785
and oxidation-reduction, 1436
and the Heck reaction, 766, 767
Bucherer reaction, 756
hydrolysis of carbamates, 1197
metal hydride, 663
additives, chiral, 1181
chiral, and conjugate addition, 947
chiral, and Michael addition, 947
epoxidation of alkenes, 1002
AD-mix-α, and asymmetric dihydroxylation, 996
AD-mix-β, and asymmetric dihydroxylation, 996
Ag catalyst, cyclobutane ring openings, 1424
vinylcyclopropane rearrangement, 1399
and diazo compounds, 692
aggregates, and dialkylamide bases, 341
and enolate anions, 342
and HMPA, 341
lithium compounds, 695
organolithium reagents, 229, 697, 1110
aggregation state, enolate anions, 232
ab initio study, enolate anions, 233
tert-butyllithium, solvent effects, 229
organocuprates, 950
organolithium reagents, 232
phenyllithium, 232
AIBN (azobis(isobutyronitrile)), 804
aldehydes with chlorine, 829
and addition of silanes to alkenes, 930
and allyltin coupling reactions, 525
and coupling with allylic silanes, 511
and radical conjugate addition, 959
and radical cyclization with silanes, 963
and radical cyclization, 961
and radical elimination, 1296
and radical halogenation, 826
and reduction of alkyl halides, 1532
and reduction of thiocarbonates, 1538
and seleno esters, 964, 965
and sulfoxide elimination, 1296
and the Schmidt reaction, 1364
carbonylation of amines, 568
conjugated acids with nitric acid, 838
coupling alkanes and alkynes, 561
decomposition, 804
formation of radicals, 804
halides with oximes, 1189
lactone formation, 566
metal catalyzed carbonylation, 975
NBS, amines and aldehydes, 837
vinyl carboxylic acids and nitric acid, 838
with silanes, 1538
with silanes, reduction, 1543
air, and triethylborane, 797
and zeolite, oxidation of alcohols, 1451
with thioketones, 1088
Al compounds see organoaluminum
Al, vinylic compounds, 523
alanes, alkynyl, conjugate addition, 954
and reductive cleavage of enamines, 1547
conjugate addition, 954
reducing agents, 1509
reduction of aldehydes or ketones, 1509
reduction of enamines, 1547
trialkyl, conjugate addition, 954
vinyl, dimerization, 850
vinyl, from alkynes, 927
alanine, 136
alcohol deoxygenation, mechanism, 1535
alcohol-alkynes, and hydrogen bonding, 103
alcohols, acid catalyzed addition to nitriles, 1085, 1239
alcohols, acid catalyzed dehydration, E1, mechanism, 1284
alcohols, acylation, 1201, 1207
alcohols, addition to aldehydes or ketones, 1081
to alkenes, 970
to carbonyls, 1081
to isocyanates, 1085
to ketenes, 892
alcohols, alkenyl, 1166
alcohols, alkyl azides, and *Mitsunobu reaction*, 1364
alcohols, alkyl halides and In or Ir or Ru catalyst, 460
alcohols, alkylation of amines, 483, 485
with Me_3Al, 533
alcohols, allenic, with In compounds, 533
alcohols, allylic esters and Pd catalyst, 460
alcohols, allylic with aziridines, 538
and allylic silanes with aldehydes, 1125
and asymmetric epoxidation, 1005
and semipinacol rearrangement, 1343
and *Sharpless asymmetric epoxidation*, 1004
and the *Baylis-Hillman reaction*, 1127
base induced elimination of epoxides, enantioselectivity, 1287
by allylic oxidation with selenium dioxide, 1470, 1471
by oxidation of alkenes, 1470, 1471
by reduction of conjugated carbonyls, 1504
by the *Prins reaction*, 1184
coupling and rearrangement, 532
coupling with arylboronic acids, 532
formation of organometallics, 1126
from allylic hydrocarbons, 1470, 1471
from allylic sulfones, 1415
halogenation, 503
isomerization to enols, 663
isomerization with metal catalysts, 1357
oxidation to carboxylic esters, 1484
oxidation with Cr reagents, 1443
oxidation with MnO_2, 1445
PPh_3 and CCl_4, 503
reduction, and rearrangement, 1535
to allylic amines, Pd catalyst, 485
with alkynes, 938
with boranes, 923
with dialylzinc and Pd catalyst, 1117
with *Grignard reagents*, 533
with imines, 1138
with organocuprates, 533
with Re catalyst, 1357
with sulfur ylids, 1179
alcohols, and acidity scales, 326
and alkoxymercuration, 891
and boron-to-carbon rearrangement, 1375
and carbonylation of alkyl halides, 566
and carbonylation of amines, 731

alcohols, and acidity scales (*Continued*)
and carbonylation of aryl halides, 781
and carbonylation, 974
and formation of carbocations, 210
and *Friedel-Crafts alkylation*, 610
and phase transfer, 501
and *Swern oxidation*, 1447
and the *Koch-Haaf reaction*, 566
and the *Koch-Haaf reaction*, 972
and the *Mitsunobu reaction*, 1203
and the *Pinner synthesis*, 1086
and the *Ritter reaction*, 1239
and the *Schotten-Baumann procedure*, 1200
and the S_Ni mechanism, 409
and transesterification, 1206
and transetherification, 464
anti-Markovnikov preparation via hydroboration, 1375
as solvents, 909
base-catalyzed addition to alkynes, 891
alcohols, benzylic, and atropisomers, 131
halogenating agents, 503
oxidation with MnO_2, 1445
oxidation, and microwaves, 1451
alcohols, biooxidation, 1451
alcohols, by *anti-Markovnikov* addition to alkenes, 886
by *Cannizzaro reaction*, 1562, 1563
by enantioselective hydroboration, 924
by hydrolysis of borates, 1509
by *Meerwein-Ponndorf-Verley reduction*, 1507
by oxidation of bora-1,3-dioxolanes, 1375
by oxidation of boranes, 923, 1375
by oxidation of hydrocarbons, 1469
by oxidation of hydrocarbons, enantioselectivity, 1470
by oxidation of hydrocarbons, reagents for, 1470
by oxymercuration, 885, 886
by reduction of aldehydes or ketones, 1503–1515
by reduction of amides, 1544
by reduction of boranes, 1377
by reduction of carboxylic acids, 1515
by reduction of carboxylic esters, 1506
by reduction of carboxylic esters, reagents, 1516
by reduction of epoxides, reagents, 1502
by reduction with *Grignard reagents*, 1111
by *Tamao-Fleming oxidation*, 468
by the *Barbier reaction*, 1108
by the *Bouveault-Blanc procedure*, 1506
Alcohols, carbonylation with alkyl halides to give esters, 565
carbonylation, 566
catalytic hydrogenation, 1534
chiral homoallylic, 537
chiral, with *Grignard reagents*, 1110
chiral, with ketenes, 892
chiral, with organolithium reagents, 1110
chromium(VI) oxidation, mechanism, 1444
concentration and equilibria, 1202
conjugate addition, 967
conversion to aniline derivatives, 485
conversion to sulfonate esters, and reduction, 1535
alcohols, coupling, 532
alcohols, coupling,
with arylboronic acids, 889
with $LiAlH_2$ and $TiCl_3$, 532
with organometallics, 532
alcohols, Cr(VI) oxidation, mechanism, 1444
cyclic, from diene- aldehydes, 1123
cycloalkyl, from cycloalkyl amines and nitrous acid, 1345
cyclobutyl, from cyclopropylcarbinyl amines, 1345
cyclodehydration, 616
cyclopropyl propargylic, rearrangement, 1345
cyclopropylcarbinyl, from cyclobutyl amines, 1345
cyclopropylcarbinyl, FVP, 1399
cyclopropylcarbinyl, halogenation, 503
alcohols, dehydration, 463
acid catalyzed, 1282–1285
and carbocations, 463
and *Hofmann's rule*, 1283
and *Mitsunobu reaction*, 464
and supercritical carbon dioxide, 364
and *Zaitsev's rule*, 1283
dehydrating agents, 1283
formation of alkenes, 664
in supercritical carbon dioxide, 364
with metal oxides, 1283
alcohols, diene, rearrangement, 1396
alcohols, dihydroxylation, reagents, 1534
enzymatic oxidation, 1451
epoxy, rearrangement, 1344
esterification of aldehydes, 1485
esterification also see esterification
for amides, and organometallics, 1228
formation of amines, 485
formation of azides, 561
formation of enol ethers, 465
from addition of organometallics to aldehydes or ketones, 1114
alcohols, from aldehydes or ketones, 1141–1153
from aldehydes, 615
from alkenes, 885, 1375
from alkylboranes, 700
from amides and *Grignard reagents*, 1228
from amines, 474
from anhydrides and *Grignard reagents*, 1228
from anhydrides, and organometallics, 1228
from boranes and carbon monoxide, 1376
from carboxylic acids, 1515
from carboxylic esters and *Grignard reagents*, 1228
from carboxylic esters and organometallics, 1228
from carboxylic esters, *Bouveault-Blanc procedure*, 1516
from diazoketones, 454
from dienes or trienes, 1376
from epoxides, 535, 1502
from esters, 1516
from ethers, 504, 505
from ethers, by *Wittig rearrangement*, 1373, 1374
from *Grignard reactions*, 535, 1107–1114
from Grignard reagents, and oxygen, 699
from halomethyl ethers, 1376
from hydrocarbons and ozone, 1469
from hydroperoxides, 1539
from inorganic esters, 453
from ketones, 615
from organolithium reagents, 535
from peroxides, 1540

alcohols, *Grignard reagents*, with aldehydes or ketones, 1107–1114
alcohols, halo, with $LiAlH_4$-$TiCl_3$, 1306
α-halo, 1107
halogenating agents, 502
halogenation, rearrangement, 501
homoallyic, 1116, 1123, 1185, 1285
alcohols, homoallylic, allylic organometallics, 1115
chiral, from epoxides, 537
from alkenes and chloral, 1186
from allylic silanes and aldehydes, 1180
pyrolysis, 1314
with aldehydes, 1186
alcohols, homopropargylic, 1123
hydrolysis of esters, 556
hydroxyalkylation of aromatic compounds, 615
α-hydroxylation of allylic compounds, 1472
α-hydroxylation of benzylic compounds, 1472
in esterification reactions, 1202–1206
indirect reduction to hydrocarbons, 1535
insertion by carbenes, 692
intramolecular addition of alkenes, 890
metal catalyzed coupling with allyl silanes, 533
metal catalyzed dehydration, 1283
metal catalyzed oxidation with oxygen, metals for, 1446
metal catalyzed oxidation with TEMPO, 1448
Moffatt oxidation, 1448
Oppenauer oxidation, 1447
alcohols, oxidation, by catalytic dehydrogenation, 1450
in supercritical CO_2, 1442
to acyl fluorides, 1484
to aldehydes but not acids, reagents, 1443
to aldehydes or ketones, 1442–1452
to aldehydes, 831
to carboxylic acids, 831, 1483
to carboxylic acids, reagents for, 1483
to cyclic ethers, 830
to ketones, reagents for, 1446, 1447
with air and zeolite, 1451
with alternative hypervalent iodine reagents, 1450
with *Bobbitt's reagent*, 1449
with *Collins reagent*, 1443
with *Dess-Martin periodinane*, 1449
with dichromate, 1442
with DMSO and DCC, 1448
with DMSO and oxalyl chloride, 1447
with DMSO and sulfur trioxide, 1448
with DMSO and trifluoroacetic anhydride, 1448
with DMSO reagents, 1447
with *Fremy's salt*, 1452
with hypervalent iodine, 1449
with *Jones reagent*, 1442
with manganese dioxide, 1445
with miscellaneous reagents, 1451
with Oxone, 1452
with periodate, 1452
with potassium permanganate, 1445
with TEMPO, co-reagents, 1448
with TEMPO in water, 1449
with TPAP, 1446
with trimethylsilyl chromate, 1443
and Cr(IV), 1444
and cyclodextrin, 1451
and *Grubb's catalyst*, 1445
and NBS, 1451
and Oxone, 1450
and phase transfer, 1445
DDQ and ultrasound, 1452
in ionic liquids, 365
microwave irradiation, 1446
radical mechanism, 1445
alcohols, oxidative coupling with amines, 494
alcohols, oxidizing reagents for making cyclic ethers, 831
alcohols, oxymercuration see alkoxymercuration
alcohols, permanganate oxidation, and ultrasound, 1445
photochemical addition to alkenes, 891
photochemistry, 292
PPh_3 and CCl_4, 502
alcohols, propargyl, acid catalyzed rearrangement, 1357
base induced rearrangement, 1357, 1358
Friedel-Crafts alkylation, 612
isomerization with metal catalysts, 1358
Meyer-Schuster rearrangement, 1357
formation of allenes, 664
with boronic acids, 1305
alcohols, protection as ethers, 460
protonolysis and carbocation formation, 219
radical dimerization, 839
reaction with aldehydes or ketones, compatible functional groups, 1082
reaction with organotitanium reagents, 533
reaction with phosgene, 1086
reaction with sulfinyl halides, 480
reaction with thiols, 477
reagents for deoxygenation, 1535
reagents utilized with DMSO, for oxidation, 1448
reduction of acyl halides, 1544
reduction of hydroperoxides, 1539
reduction to hydrocarbons, reagents, 1534
reductive alkylation of aldehydes, 1084
solvent free oxidation, 1442
solvolysis, 1330
structural variation of chromates for oxidation, 1444
supercritical, as a solvent, 1542
supercritical, reduction of ketones, 1542
TEMPO oxidation, in ionic liquids, 1448, 1449
vinylcyclopropyl, sigmatropic shifts, 1395
Alcohols, with acyl halides and Zn, 1201
with acyl halides, 1200
with acyl halides, S_N1 or SN2 mechanism, 1200
with acyl halides, tetrahedral mechanism, 1200
with acyl hydrazides, 1209
with aldehydes or ketones and HX, 1106
alcohols, with aldehydes, 1084
with alkenes and hydrazoic acid, 1364
with alkenes, 889
with alkenes, enantioselectivity, 889
with alkenes, *Markovnikov's rule*, 889
with alkenes, regioselectivity, 889
with alkyl halides, 460
with alkynes, 889
with allenes, formation of tetrahydrofurans, 890
with amides, 494
with anhydrides, 1201
with anhydrides, catalysts for, 1201
with anhydrides, microwave irradiation, 1202
with aziridines, 466
with borohydride, 1511
with boron trichloride, 702

alcohols, with aldehydes (*Continued*)
with boron trioxide, 702
with carbon disulfide, 1086
with carboxylic acids and DCC, 1205
with carboxylic acids, 1202–1206
with carboxylic acids, acid catalyzed, 1202
with carboxylic acids, equilibrium, 1202
with cyanogen chloride, 1086
with DAST, 501
with diazomethane, 462
with DMF, 1208
with enol ethers, 891
with epoxides, 465
with halogens and alkenes, 984
with halogens, 986
with HBr or HI, 504
with hydrazoic acid, 485
with hydrogen sulfide, 476
with imides, 494
with inorganic acids, 473
with isothiocyanates, 1085
with ketenes, 892, 1353
with *Lawesson's reagent*, 476
with lead tetraacetate, 830
with metal halides, 502
with *Michael type alkenes*, 891
with mineral acids, 500
with NaOH and CS_2, 1289
with onium salts, 467
with oxidizing agents and ylids, 1166
with polymer supported oxidizing agents, 1443
with PPh_3 and iodine, 502
with sulfonamides, 1250
with sulfonyl halides, 1250
with thionyl chloride, 409, 500
with trifluoroborates, 462
alcoholysis, metal catalyzed, 891
of alkenes, 891
of amides, 1208
of anhydrides, enantioselectivity, 1202
of cyclic anhydrides, 1202
of nitriles, 1085
aldehyde-alkenes, and radical cyclization, 964
aldehyde-alkenes, cyclization, 1123
aldehyde-carboxylic acid, intramolecular reaction, 1155
aldehydes, acetal formation, 1081
aldehydes, acid catalyzed addition of aldehydes, 1240
rearrangement, 1348
aldehydes, addition of alcohols, 1081
of allylic boranes, 1124
of amides, 1099
of dialkylzinc reagents, 1115
of diazomethane, 1355
of *Grignard reagents*, mechanism, 1111, 1112
of organolithium reagents, mechanism, 1113
of organometallics, 1114–1125
of thiols, 1087
of water, 1075
to alkenes, 970
to alkenes, in ionic liquids, 972
aldehydes, alkylation, 542
aldehydes, alkylation-reduction, 1114
aldehydes, amphiprotic properties, 665
aldehydes, and 9-BBN, 923
and autoxidation, 832
and bisulfite addition product, 1090
and carbanions, 234
and Claisen condensation, 1154
and Collman's reagent, 564
and enolate anion formation, 1113
and formation of aminals, 1091, 1092
and hemiaminals, 1090
and insertion, 692
and *Peterson alkenylation*, 1162
and reagents for hydrolysis of C=N compounds, 1077, 1078
and tautomerism, 89
and the aldol reaction, 1141–1153
and the *Baylis-Hillman reaction*, 1127
and the benzoin condensation, 1187
and *the Cannizzaro reaction*, 1563
and the *Claisen-Schmidt reaction*, 1144, 1145
and the *Dakin reaction*, 1370
and the *Knoevenagel reaction*, 1157
and the *Mannich reaction*, 1100
and *the McMurry reaction*, 1559
and the *Mukaiyama aldol reaction*, 1151–1153
and the *Paterno-Büchi reaction*, 1243
and the *Perkin reaction*, 1161
and the *Reformatsky reaction*, 1129
and the *Stetter reaction*, 971
and the *Tischenko reaction*, 1564
and *Tollens' reaction*, 1164
and Umpolung, 553
aldehydes, aryl, and the *Gatterman reaction*, 626
and iminium salts, 627
and reverse *Gatterman-Koch reaction*, 643
benzoin condensation, 1187
by benzylic CH oxidation, 1479
by α-CH oxidation of methyl aromatic compounds, 1479
decarbonylation, 643
formation of hydrazones, 1093
from aromatic compounds, 625
reagents, for benzylic oxidation, 1479
with ammonia and metal peroxides, 837
aldehydes, as dienophiles, 1037
aldehydes, azine formation, 1092
aldehydes, borane reduction reagents, 1509
aldehydes, by acid treatment of *Reissert compounds*, 1519
by aldol condensation with ketones, 1144
by base cleavage of acyl sulfonylhydrazides, 1519
by Dibal reduction of esters, 1518
by DMSO-type oxidation of alcohols, 1448
by hydrolysis of acylals, 1479
by hydrolysis of alkoxides, 1511
by hydrolysis of C=N compounds, 1077
by hydrolysis of enol ethers, 887
by hydrolysis of imines, 1482
by hydrolysis of *Schiff bases*, 1077
by *Krönke reaction* with benzylic halides, 1482
by *McFadden-Sevens reduction*, 1519
by *Oppenauer oxidation*, 1447
by oxidation of alcohols, 1442–1452
by oxidation of alcohols, reagents, for, 1446, 1447
by oxidation of alkenes, 1487–1489
by oxidation of alkenes, reagents for, 1489
by oxidation of alkyl halides, 1481
by oxidation of amines, 1482
by oxidative cleavage of diols, 1456
by ozonolysis of alkenes, 1459
by pyrolysis of allylic ethers, 1315
by pyrolysis of enol ethers, 1286
by pyrolysis of homoallylic alcohols, 1314
by reduction of acyl halides, reagents, 1517

by reduction of anhydrides, 1518
by reduction of boranes, 1377
by reduction of carboxylic acids, reagents, 1518
by reduction of carboxylic esters, reagents, 1518
by reduction of imidazoles, 1519
by reduction of nitriles, reagents, 1523
by reduction of ortho esters, 1537
by *Rosenmund reduction*, 1517
by *Stephen reduction*, 1523
by the aliphatic *Vilsmeier reaction*, 685
by the *Barton reaction*, 1427
by the *Étard reaction*, 1479
by the *Kornblum reaction*, 1481
by the *Nef reaction*, 1079
by the *Sommelet reaction*, 1482
by the *Sonn-Müller method*, 1520
by the *Wacker process*, 1488
by *Vilsmeier-Haack reaction*, 625
aldehydes, catalytic hydrogenation, 1506
chemoselective reducing agents, 1505
chiral, 1147
condensation with esters, 1153, 1154
condensation see aldol
aldehydes, conjugated see conjugated compounds
aldehydes, conjugate addition, and microwaves, 969
aldehydes, conjugated, and metathesis, 1420
and organocuprates, 952
and organolithium reagents, 952, 1109
by aldol reaction, 1141–1153
E/Z-isomerization with thiourea, 882
from allyl allene ethers, 1409
from vinyl silanes, 708
reagents for conjugate reduction, 917
reagents for reduction of alkenes, 919
reduction, and microwaves, 919
with boranes, 957
with *Grignard reagents*, 1109
aldehydes, coupling to carboxylic esters, reagents, 1564
cyclization, 971
cycloaddition to alkenes, 1243
decarbonylation with *Wilkinson's catalyst*, 856, 857
decarbonylation, 303, 1300, 1333
dehydrogenation, 1441
deprotonation in the benzoin condensation, 1188
electrophilicity, 1152
enantioselective acyl addition see acyl addition
enol content, 90
enzymatic reductions, 1510
fluorination, 669
aldehydes, formation of cyanoamines, 486
enolate anions, 1143
ketones, 688, 689
nitriles, reagents for, 1095, 1096
oxocarbenium ions, 1348
silyl enol ethers, 687
aldehydes, *Friedel-Crafts cyclization*, 617
aldehydes, from acyl halides, 564, 1518
from alcohols, 1370
from aldehydes, 1518
from alkyl halides, 565
from alkynes and hydroboration, 925
from allylic ethers, 1374
from amides, 1519
from amines, 1483
from boronic acids and organolithium reagents, 1377
from chloroform, 627
from chloroiminium salts, 1523
from cycloaddition of singlet oxygen to alkenes, 1040
from dihalides, 452
from enol borinates, 957
from enol ethers, 1286
from enols, 719
from epoxides, 1343
from esters, 1518
from formic acid, 708
from glycidic acids, 719
from glycidic esters, 1162
from *Grignard reagents*, 782
from halo amides, 1360
from homoallylic alcohols, 1315
from hydrocarbons, 709
from iminium salts, 1312
from metallated imines, 1248
from methyl groups, 1428
from nitroso compounds, 1428
from organolithium reagents, 782
from organometallics, 708
from oxazines, 556
from sulfonic anhydrides, 626
from sulfoxides, 553
from thiazoles, 557
from thiazolines, 557
from vinylic compounds, 453
from Weinreb amides, 1520
aldehydes, α-halogenation of, 829
aldehydes, halogenation, enantioselectivity, 669
homologation of, 1355
hydration of, 1075
hydrolysis of acetoxy sulfides, 1565
hydrolysis of enol ethers, 1167
aldehydes, in the *Henry reaction*, 1156
in the *Nozaki-Hiyama reaction*, 1121
in the *Paterno-Büchi reaction*, 1049
in the *Pictet-Spengler reaction*, 618
in the *Prins reaction*, 1013
in the *Reimer-Tiemann reaction*, 627
aldehydes, intramolecular addition to conjugate esters, 1123
iodination of, 669
Lewis acid arylated addition of allylic silanes, 1125
$LiAlH_4$ reduction, mechanism, 1508
mechanism of hydration, 1076
Meerwein-Ponndorf-Verley reduction, 1507
aldehydes, metal catalyzed addition to alkenes, 970
addition of haloesters, 1129
cycloaddition with ketenes, 1242
decarbonylation, 856
decarbonylation, mechanism, 857
aldehydes, Meyers aldehyde synthesis, 556
more reactive than ketones, 1069
aldehydes, oxidation, of alcohols, 831
to carboxylic acids, 1445, 1484–1487
to carboxylic acids, mechanism, 1486
to carboxylic acids, reagents for, 1485
to carboxylic esters, 1484, 1485
with chromic acid, mechanism, 1486
with permanganate, mechanism, 1487
aldehydes, oxygen and alkenes, 1006
aldehydes, photochemical [2+2]-cycloaddition with alkenes, 1049
photochemical addition to alkenes, 972
photochemistry, 293
protecting groups, 1088
protection of, 457

aldehydes, photochemical [2+2]-cycloaddition with alkenes (*Continued*)
radical addition to alkenes, mechanism, 972
reaction with alcohols, compatible functional groups, 1082
reaction with amines, 1090
reaction with anhydrides, 1084
reaction with base, 1143
aldehydes, reduction, in the *Cannizzaro reaction*, 1509, 1562, 1563
in ionic liquids, 1512
to alcohols, 1503–1515
to methyl, reagents for, 1541
versus ketones, 1505
with alanes, 1509
with aluminum isopropoxide, 1507
with ammonium formates, 1510
with baker's yeast, 1510
with boranes, 1508
with enzymes, 1512
with hydrides, 1503
with metals, 1507
with silanes, 1509
with sodium in ethanol, 1506
with sodium in ethanol, mechanism, 1506
with tin hydrides, 1509
aldehydes, reductive alkylation with alcohols, 1084
aldehydes, reductive amination, 1096–1099
aldehydes, reductive coupling to alkenes, reagents, 1558
aldehydes, reductive coupling to diols, reagents, 1555
aldehydes, reductive dimerization, 1085
aldehydes, steric hindrance and reduction, 1505
structural requirements and the Wittig reaction, 1166
tautomerism sugars, 94
tautomerism, 665
trimerization of, 1240
vinylation of, 545
aldehydes, with acylperoxides, 835
with alcohols and HX, 1106
with alcohols, 1084
with aldehydes, 1240
with alkenes or alkynes, 1122
with alkyne anions, 1114
with alkyne anions, enantioselectivity, 1115
with alkynes and amines, 1135
with alkynes, 1122
with allenes, 1122, 1123, 1185
with allyl silanes, 1099
with allylic boronates, 1124
with allylic silanes, 1180
with allylic silanes, and transition metals, 1125
with allylic trihalosilanes, 1126
with allyltin compounds, 1118
with amides, 495
with amides, Ba catalyst, 1155
with amines and hydrogen, 1096–1099
with amines, 551, 618, 1090, 1096, 1189, 1486
with an acid catalyst, 1149
with anhydrides, 1161
with aromatic compounds, 615
with aryl halides, 1123
with aziridines, 467
with bis(*Grignard*) reagents, 1109
with boranes, transition metal catalysts, 1124
with boron stabilized carbons, 688
with boronic acids, 1124
with boronic acids, enantioselectivity, 1124
with carbonates, 1236
with chiral amides, 1120
with chiral boranes, 1125
with conjugated compounds, 1127
with conjugated compounds, 1181
with conjugated esters, and the Stetter reaction, 1123
with conjugated ketones, and radicals, 1188
with cyanide ion, 1182, 1187
with cyanide, and conjugate addition, 969
with diazoalkanes, 1059, 1177
with diazoesters, 688
with diazomethane, 1177
with diazomethane, formation of ketones, 694
with dienes, 1123
with dihalocarbenes, 1177
aldehydes, with enamines, 1145
with enolate anions, 232, 1141–1153
with enolate anions see aldol
with *Grignard reagents*, 1107–1114
with halo esters, 1161
with HCN, 1180
with homoallylic alcohols, 1186
with hydrazines, 1092
with hydrazones, 1138
with hydroxylamine and formic acid, 1095
with hydroxylamine, 1094
with imines, 1558
with imino esters, 541
with indoles, 1123
with iodine, and ammonia, 837
with isocyanides and carboxylic acids, 1247
with ketimines, 1122
with ketones, 1164
with LDA, 1143
with lithioamides, 1110
with lithio-silanes, 1162
aldehydes, with MeLi and CH_2I_2, 1110
with NBS, radical halogenation, 829
with nitro compounds, 1156
with nitronates, 1157
with organoaluminum or organotitanium, 1119
with organochromium compounds, 1121
with organocuprates, 1122
with organolithium reagents, 1108, 1160
with organometallics, 153
with organometallics, enantioseelctivity, 1117
with phenylhydrazine, 1412
with phosphonate esters, 1123, 1170
with phosphorus ylids, 1165
with polymer bound borates, 1124
with potassium cyanide, 1187, 1188
with silyl enol ethers, and chiral boranes, 1148
with sodium azide, 1223
with sodium bisulfite, 1090
with sulfonamides, 1100
with sulfur ylids, 1175–1177
with thiobenzilic acid, 1320
with thioesters, 1155
with TMSCN, and amine N-oxides, 1181
with TMSCN, and lithium perchlorate, 1181
with TMSCN, solvent free, 1181
with transition metals, and acyl radicals, 805
with trifluoroborates, 1125
with various metal salts, 1122
with vinyl acetate, 1356
with ylids, 1165–1173
aldehydes, *Wolff-Kishner reduction*, 1540
aldimines see imines
aldol condensation, 1141–1153
acid catalyzed, 1149
and alkoxide bases, 1144
and asymmetric synthesis, 154
and chiral auxiliaries, 1147, 1148
and chiral bases, 1147
and chiral catalysts, 1148
and chiral ligands, 1148

and dehydration of products, 1283
and dihalides, 452
and enolate anions, 543
and enolization, 1146
and hydroformylation, 979
and mixed aggregate bases, 1146
and SET mechanism, 1141
and the *Cannizzaro reaction*, 1563
and the *Michael reaction*, 1146
and the *Robinson annulation*, 1150
and the *Tischenko reaction*, 1564
bis(aldol), 1145
chelation stabilized products, 1145
chiral reaction partners, 1147
crossed, regioselectivity, 1145
definition, 1143
diamine protonic acid catalysts, 1148
diastereoselectivity, 1145, 1146
directed, 1149
double aldol, 1144
enantioselectivity, 1147–1149
enzyme mediated, 1144
equilibrium, 1143
in aqueous media, 1148
in ionic liquids, 1143
aldol condensation, intramolecular, 1149
acid catalyzed, 1149
and entropy, 1149
and Robinson annulation, 1150
enantioselectivity, 1149
regioselectivity, 1150
with diketones, 1150
Aldol condensation, isomerization of aldol products, 1147
mechanism of acid catalyzed reaction, 1149
mechanism, 1143
mechanism, computational study, 1146
mixed, 1144
mixed, and the *Tollens' reaction*, 1164
aldol condensation, Mukaiyama, 1148
aldol condensation, nitro, enantioselectivity, 1156, 1157
aldol condensation, organocatalysts, 1147
retro, 718, 1143
scope, 1144, 1145
self condensation, 1144
side reactions, 544
solvent effects, 1143, 1144
solventless, 366
stereoselectivity and amide bases, 1146
stereoselectivity, 1146, 1147
structural variants and chirality, 1148
syn/anti isomers, 1146, 1147
transition metal catalysts, 1145
transition state geometry, 1145
transition state, 1145
vinylogous, chiral, 1148
vinylogous, enantioselectivity, 1148
vinylogy, 1143, 1144
with chiral organobases, 1147
isomerization, 1147
aldol, *Mukaiyama*, 1151–1153
catalysts for, 1151, 1152
enantioselectivity, 1153
in water, 1152
intramolecular, 1152
metal salts as catalysts, 1151, 1152
substrates for, 1152
aldols, 1143
and atropisomers, 132
dehydration, 1283
homo-, 1160
aldol-type reactions, 1142
aldoximines see oximes
Aldrich Library of Spectra, 1583
algorithm, dielectric screening effects, 437
alkali fusion, 747
alkaloids, atropisomers, 132
alkane cleavage, and steric factors, 726
alkane metathesis, 1421
alkanes, addition to alkenes, 928
addition to alkenes, and *Friedel-Crafts reactions*, 927
and bond angle, 25
and conformations, 178
and gauche conformations, 178
and guest-host interactions, 113
and photochemistry, 292
and photosensitization, 839
and superacids, 690
anti-Markovnikov amination, 898
by addition of alkanes to alkenes, 927
by coupling of alkanes, 839
by decyanation of nitriles, 726
by hydrogenation of thioethers, 851
by radical addition to alkenes, 960
by reductive cleavage of cyclopropanes, 920
cleavage by hydrogenation, 726
cleavage, mechanism, 726
coupling alcohols with organometallics, 532
dehydrogenation to alkynes, 1442
deuterium exchange, 906
diazosilyl, with ketones, 1175
formation of carbocations, 492
from aldehydes, 856, 857
from alkyl halides, 520
from *Grignard reagents*, 699
from metal sulfonates, 530
from organocuprates, 520
alkanes, halogenation, 821–826
halogenation, and UV, 821
hydrogen abstraction by radicals, 813
hydrogenation of thiols, 851
insertion by nitrenes, 679
metal catalyzed addition to alkenes, 928
nitration mechanism, 677
nitration, 676
nitration, and N-hydroxysuccinimide, 677
nitration, and radicals, 677
organometallics with alkyl halides, 523–526
oxygen insertion, 1472
radical coupling, 839
trialkyl, metal catalyzed addition to alkynes, 941
via coupling reactions, 690
with Lewis acids, 1341
with radicals, 811–813
Wurtz reaction, 513
alkene metathesis, 1417–1423
and microwaves, 1420
compatible functional groups, 1419
enantioselectivity, 1420
formation of cyclic dienes, 1421
metallocenes, 1422
polymer bound catalysts, 1420
ring opening, 1420
synthetic importance, 1419
alkene migration, and the Heck reaction, 765
alkene-aldehydes, by [2,3]-*Wittig rearrangement*, 1414
by *Claisen rearrangement*, 1408, 1409
cyclization, 1123
intramolecular addition, 1123
via *oxy-Cope rearrangement*, 1401
alkene-amides, cyclization, 1013
alkene-amines, formation of cyclic amines, 482
alkene-boranes see boranes
alkene-boranes see boranes, vinyl
alkene-bromine complex, 983
alkene-carboxylic acids, and halolactamization, 986, 987
and halolactonization, 986, 987
and iodolactonization, 986

alkene-carboxylic acids, and halolactamization (*Continued*)
by *Claisen rearrangement*, 1409
cyclization, 1013
from lactones, 1288
halogenation, 986, 987
alkene-dienes, carbonylation, 976
alkene-diketones, by *Claisen rearrangement*, 1408
alkenes from dithianes, 554
alkenes also see cycloadditions
alkenes also see Diels-Alder
alkenes, [2+2]-cycloaddition reactions, 1041
with alkynes, 1047
with cyclopropanes, 1044
with ketenes, MO, 1045, 1046
alkenes, acid catalyzed, addition of alkenes, 931–935
addition of formaldehyde, 1184
dehydration of alcohols, 1282–1285
hydration, 873
alkenes, activating substituents for addition reaction, 872
alkenes, acylamidation, 1012
acylation, 685
acyloxylation with palladium acetate, 836
acyloxylation, 1012
alkenes, addition, cyclic mechanism, 869
alkenes, addition, four-center mechanism, 869
alkenes, addition, of acyl compounds, 970
of alcohols, 970
of aldehydes, 970
of aldehydes, in ionic liquids, 972
of alkanes, in ionic liquids, 928
of alkyl halides, Friedel-Crafts catalysts, 991
of amides, 897
of amines, 970, 1008
of aminonitrenes, 1010
of anions, 233, 865
of azido groups, 1009
of bromine, stereoselectivity, 862
of carbamates, 900
of carbenes, 250, 254, 1051
of carbenes, and steric hindrance, 1053
of carboxylic acids, 892
of carboxylic esters, 970
of DBr, 864
of fluorine, 982
of *Grignard reagents*, 926
of halo-amines, 988
of haloamines, in ionic liquids, 989
of haloazide, 990
of halocarbamates, 901
of HBr, 864
of HBr, with peroxides, 960
of HCl, 864
of HCN, 980
of HX, 864
of hydrazines, 897
of hydrogen sulfide, 894
of hydroxylamines, 897
of iodine azide, 990
of iodo azide, mechanism, 990
of isothiocyanates, 988
of nitrenes, 259
of nitrosyl halides, 989
of nitryl chloride, 989
of organolithium reagents, 936
of organometallics compounds, 938
of polyhalo compounds, 991
of protons, 863
of radicals, 247, 867, 960, 970
of selenols (RSeH), 895
of sulfonic acids, 893
of sulfonyl halides, 987
of thiols, 893
of thiols, mechanism, 895
of water, 864
to alkanes, 927
to carbocations, 220
alkenes, addition reactions, 263
and the *Cieplack effect*, 878
alkenes, alkoxy carbonylation of, 974
alkenes, alkoxymercuration of, 891
alkenes, allylic oxidation with selenium dioxide, mechanism, 1470
alkenes, amidation of, 900
alkenes, amination of, 491, 679, 896
and hydroboration, 899
Markovnikov's rule, 897
metal catalyzed, 679
alkenes, amino-carbonylation of, 974
alkenes, aminomercuration of, 899, 1009
alkenes, aminosulfenylation of, 1012
alkenes, and amide bases with ammonium salts, 1292
and anisotropy, 51
and *Birch reduction*, 909
and *Bredt's rule*, 1269, 1270
and carbene rearrangements, 1337
and carbene transfer, 1051
and carbocation formation, 875
and carbonylation, 974
and complex formation, 107
and E/Z nomenclature, 163
and formation of bis(selenenyl) compounds, 1006
and *Friedel-Crafts acylation*, 685
and *Friedel-Crafts alkylation*, 609
and *Hofmann's rule*, 1271
and homoconjugation, 43
and *Julia-Colonna epoxidation*, enantioselectivity, 1004
and kinetic resolution, 158
and *Markovnikov's rule*, 874
and metal catalyzed diazoalkane reactions, 1051
and nanoparticles, 910
and neighboring groups, 396, 397
and nitric acid, 676
and NMR, 51
and PES, 14
and prototropic rearrangement, 662
and radical addition, generation of radicals, 960
and radical addition, of aldehydes, mechanism, 972
and radical addition, rate of reaction, 961
and radical addition, stereoselectivity, 868
and radical-induced addition of polyhalo compounds, 991
and reversible addition of radicals, 869
and ring current, 51
and sigmatropic migration of hydrogen, 1392
and the *Baeyer test*, 994
and the *Simmons-Smith* procedure, 1057
and the *Stetter reaction*, 971
and *Weitz-Scheffer epoxidation*, 1000
and X-ray crystallography, 206
and *Zaitsev's rule*, 662, 1271
alkenes, animation, and temperature effects, 896
alkenes, anti addition, 864
alkenes, *anti-Bredt*, by the *Wittig reaction*, 1168
anti-dihydroxylation, 994
anti-Markovnikov addition, 875
anti-Markovnikov addition, of boranes, 923
anti-Markovnikov addition, of radicals, 960
anti-Markovnikov addition, of water, 886
aryl, electrocyclic ring closure reactions, 1390
aryl, from alkenes, 762
alkenes, arylation, 762, 794
arylation also see Heck reaction
and regiochemistry, 764
metal catalyzed, 762–768

with organometallics, 762
alkenes, as bases, 322
as radical precursors, 963
asymmetric epoxidation, with manganese salen complexes, 1004
azidomercuration of, 902
aziridination, enantioselective, 1011
aziridination, in ionic liquids, 1011
aziridination, organocatalysts, 1011
baker's yeast reduction, enantioselectivity, 912
base induced elimination, of alkyl halides, 1296
base induced elimination, of alkyl halides, suitable bases, 1297
bicyclic, exo addition, 878
bicyclic, strain, 203
bis(thiocyanato), 988
bridgehead, 204
bromination of, reagents for, 983
alkenes, by addition of alkenes to alkynes, 931–935
by addition of organometallics to alkynes, 940
by base indeed elimination of halo sulfones, 1302
by bis(decarboxylation) of dicarboxylic acids, 1468
by cleavage of cyclic thionocarbonates, 1301
by *Cope elimination*, 1292
by decarbonylation of aldehydes, 1300
by decomposition of inorganic esters, 1289
by dehydration of alcohols, 664
by dehydrogenation, 1441
by dehydrohalogenation, 1296
by dehydrohalogenation, suitable bases, 1296
by deoxygenation of diols, 1301
by desulfurization of thiophenes, 852
by dimeric metathesis, 1421
by dimerization of carbenes, 255
by E^i reactions, 1279
alkenes, by elimination, of epoxides, 1286
of boranes, 1299
of dihalides, reagents for, 1304
of epoxides, reagents for, 1287
of hydroxy acids, 1308
alkenes, by fragmentation of amines, 1307
alkenes, by fragmentation of halo ethers, 1307
alkenes, by *Grob fragmentation*, 1307
by *Hofmann degradation*, 1290
by *Hofmann elimination*, 1271
by hydroboration of alkynes, 911
by hydrogenation of alkynes, 905
by metal catalyzed dehydration of alcohols, 1283
by metal catalyzed elimination of carboxylic acids, 1288
by oxidation coupling of alkyl halides, 1495
by *Peterson alkenylation*, 1162
by protonation of vinylboranes, 1379
alkenes, by pyrolysis, of allylic ethers, 1315
of amine oxides, 1292
of ammonium salts, 1290
of enol ethers, 1286
of esters, 1288
of esters, mechanism, 1288
of homoallylic alcohols, 1314
of sulfones, 1295
of sulfoxides, 1295
of xanthate esters, 1288
of β-lactones, 1309
alkenes, by radical elimination of bis(xanthates), 1301
by rearrangement of carbenes, 1051
by reduction of thiiranes, 1502
by reduction of vinyl halides, 1534
by reduction, of alkynes, 912
by reduction, of propargyl halides, 1533
by reductive coupling of ketones and aldehydes, reagents, 1558
by the *Bamford-Stevens reaction*, 1294
by the *Boord reaction*, 1306
by the *Chugaev reaction*, 1288
by the *Corey-Winter reaction*, 1301
by the ene reaction, 941–943
by the *McMurry reaction*, 1559
by the *Ramberg-Bäcklund reaction*, 1302
by the *Shapiro reaction*, 1293
by the *silyl-Wittig reaction*, 1162
by the *Wittig reaction*, 1165
by the *Wittig-Horner reaction*, 1170
by twofold extrusion, 1319, 1320
alkenes, C=C migration and hydrogenation, 909
captodative, 164
carbene addition, enantioselectivity, 1054
carbene addition, rate constant, 1052
carbonylation of, 974
catalytic hydrogenation of, 902–909
CH oxidation with hypervalent iodine, 1473
chlorination of, reagents for, 983
cis, from LDA and aziridino hydrazones, 1294
cleavage with superacids, 725
alkenes, conjugated, and *Birch reduction*, 915
reduction of, reagents for, 916
reduction with metal hydrides, 916
reduction with metals in ammonia, 912
alkenes, conversion, to alkynes, 1300
to trialkylboranes, 558
alkenes, coupling reactions, 935
with alkenes, 933
with alkyl groups, 684
with alkynes, 561
with carbocations, 690
with heteroaryl halides, 763
metal catalysts, 932
alkenes, crowded, and strain, 206
alkenes, cyanation of, 689
alkenes, cyclic, addition of deuterated carboxylic acids, 878
and *Bredt's rule*, 203
and the *Hofmann rule*, 1291
by *McMurry coupling*, 1559
by the *Story synthesis*, 1319
epoxidation of, and stereochemistry, 877
from cyclic sulfides, 1303
from enynes, 933, 934
oxidative cleavage, 1464
via the *Wittig reaction*, 1172
alkenes, cyclization, from organolithium reagents, 937
alkenes, cycloaddition, with aldehydes or ketones, 1243
with alkenes, 1040–1051
with dienes, 1020–1039
with norbornadienes, 1027
alkenes, cyclopropanation of, 1053
definition of regioselectivity, 874
diacetamidation of, 1009
diacetoxylation of, 997
dialkoxylation of, 995
diamination of, 1008
diboration of, 997
dihalo, base induced elimination to alkynes, 1298

alkenes, cyclopropanation of (*Continued*)
dihalo, with DMF, 686
dihydroxylation with metal acetates, 997
alkenes, dihydroxylation, 992–997
catalysts for, 993
enantioselectivity, 995
in ionic liquids, 365, 993
regioselectivity, 995
with lipases, 997
alkenes, dimerization with metals, 931
alkenes, electron donating groups, and the *Diels-Alder*, 1021
alkenes, electron withdrawing groups and the *Diels-Alder*, 1021
alkenes, electronic effects, *Diels-Alder reaction*, 1021
alkenes, enantioselective epoxidation, catalysts, 1003
alkenes, enantioselective reduction, 912
alkenes, epoxidation, 998–1006
alternative methods, 1000
and additives, 1002
co-reagents with peroxides, 999
enantioselectivity, 1000, 1001, 1004
in ionic liquids, 1000
kinetics, 999
metal catalysts with peroxides, 999, 1000
reagents for, 998, 999
stereochemistry of, 878
with Chloramine-M, 1002
with dioxiranes, 1001
with ketones and Oxone, 1001
with sodium hypochlorite, 1004
alkenes, erythro/threo addition, 860
E-selectivity, in the *Wittig reaction*, 1171
ester addition, *anti-Markovnikov*, 975
η-complexes, 908
exocyclic, 1167
fluorination, reagents for, 982
Alkenes, formation of, dihalides, 1304
diols, 992–997
lactones, 1013
less stable, and the *Wittig reaction*, 1167
ozonides, 1459
thiiranes, 1006
and Hofmann's rule, 1281
alkenes, formylation, 685
alkenes, *Friedel-Crafts alkylation*, 610
alkenes, *Friedel-Crafts alkylation*, and *Markovnikov's rule*, 614
alkenes, from acyl halides, 1300
from aldehydes or ketones, 924, 1165
from aldehydes or ketones, methods, 1175
from aldehydes, 554, 1059
from alkanes, 1441
from alkenes, 902–909, 1417
from alkenes, by metathesis, 1417
from alkenes, by sigmatropic migration, 1392
from alkenyl boranes, 1377
from alkyl halides, 515, 1297
from allenes, 911
from allylic acetates, 527
from allylic silanes, 510
from amine oxides, 1292
from ammonium salts, 1290
from aziridines, 1304
from aziridines, and nitrous acid, 1304
from base elimination, of ethers, 1285
from boranes, 1299
from carbenes, 255, 256
from cyclic ethers, 1285
from cyclobutanes, 1423
from diazo compounds, 1294, 1295
from diazoalkanes, 256, 1059
from dicarboxylic acids, 1468
from dienes, 869
from diols, 1301
from enamines, 923
from enol ethers, 1286
from episulfides, 1286
from episulfides, reagents for, 1288
from episulfones, 1302
from episulfoxides, 1288
from epoxides, stereochemistry, 1286
from epoxides, with sulfur ylids, 1287
from ethers, 1285
from halo amines, 1307
from halo ethers, 1306
from halo sulfones, 1302
from halohydrins, 1306
from homoallylic alcohols, 1315
from hydroxy-silanes, 1162
from ketones, 923
from lithio-silanes, 1162
from nitrogen ylids, 1292
from oxathiolanones, 1319, 1320
from phosphorus ylids, 1165
from propargylic acetates and Grignard reagents, 527
from radicals, 246
from selenoxides, 554, 1296
from sulfenes, 1299
from sulfonate esters, 1289
from sulfonyl halides, 1299
from thiiranes, 1288
from Ti carbenoids, 1175
from tosylates, 1289
from vinylboranes, NaOH and iodine, 1377
from xanthate esters, 1289
alkenes, ha halogenation of, and π-complexes, 863
alkenes, halo see halides, vinyl
alkenes, haloacylation of, 992
and the Vilsmeir reaction, 992
mechanism, 992
alkenes, halogenation of, 883
and bridged ions, 982
and isotopic labeling, 863
and radical initiators, 982
and UV light, 982
in ionic liquids, 983
mechanism, 982
regioselectivity, 822
the *Prins reaction*, 991
tolerable functional groups, 983
alkenes, halohydrin formation, and Markovnikov's rule, 985
ionic liquids, 985
alkenes, homoallylic, 396
hydration of, 885
hydration of, and Markovnikov's rule, 885
hydration of, rate, 873
alkenes, hydroamination of, enantioselectivity, 1007
Markovnikov's rule, 897
alkenes, hydroboration of, 874, 909, 920–926
and hydration, 886
in the presence of alkynes, 925
stereochemistry, 878
alkenes, hydrocarboxylation of, 972, 973
hydroformylation of, regioselective, 980
hydrogen abstraction by radicals, 815
hydrometalation of, 926
hydrosilation of, 928
hydroxylation of, 885
hydroxysulfenylation of, 1006
hydrozirconation of, 926
alkenes, in the *Heck reaction*, 763–768, 793
in the *Jacobsen reaction*, 646
in the *Koch reaction*, 972
in the Koch-Haaf reaction, 972
in the *Paterno-Büchi reaction*, 1049
in the *Paterno-Büchi reaction*, 1243
in the *Prins reaction*, 1184
in the *Waits-Scheffer epoxidation*, 1003
in the *Woodward modification* of the *Prevost reaction*, 994

alkenes, intramolecular, addition of alcohols, 890
addition of radicals, 868
Grignard addition, 936
Heck reaction, 763
alkenes, iodination of, 823
iodoacetyl addition, 986
ionization potential, and addition reactions, 873
alkenes, isomerization of, E/Z isomers, 881
metal catalysts for, 882
positional isomers, 881
via boranes, 664
and supercritical CO_2, 766
alkenes, *Jacobsen-Katsuki epoxidation* of, 1005
alkenes, lactam formation from, 1013
lactonization of, 1013
lactonization of, and ultrasound, 1013
alkenes, Lewis acid catalyzed addition, of acyl halides, 992
of alkyl halides, 990
of silanes, 929
alkenes, mechanism, halohydrin formation, 985
alkenes, *Meerwein arylation*, 794
alkenes, metal catalyzed, addition, of alkanes, 928
of alkenes, 931
of alkynes, 931
of aromatic compounds, 939
of diazoacetates, 1010
of Grignard reagents, 936
of imides, 901
of phosphines, 899
of silanes, 928
to aldehydes, 971
alkenes, metal catalyzed, addition, to arenes, 939
amination, 896, 897
carbonylation, 973, 975
carboxylation, 978
cyclization to allenes, 934
decarbonylation of acyl halides, 1300
hydration, 886
hydroamination, 1007
hydroformylation, 979
with aryldiazonium salts, 793
alkenes, metal induced, elimination of halo ethers, 1306
alkenes, metal mediated, elimination of dihalides, 1304
alkenes, metal-mediated, addition to nitriles, 1239
alkenes, *Michael type*, addition of amines, 896
addition of hydrazoic acid, 901
and addition of thiols, 895
with alcohols, 891
with diaryl sulfimides, 1010
alkenes, mixed halogenation of, 983
molecular orbitals, 1031
nitration of, and nitronium salts, 677
nitroso-halogenation of, 989
orbital overlap in [2+2]-cycloaddition, 1044
alkenes, oxidation of, in the *Wacker process*, 1488
oxidation of, to aldehydes or ketones, 1487–1489
α-oxidation, to conjugated ketones, 1477
oxidation of, with RuO_4, 1471
oxidation to, aldehydes or ketones, reagents for, 1489
oxidation to, allylic alcohols, 1470, 1471
alkenes, oxidative cleavage of, 1459, 1460, 1463–1465
Barbier-Wieland procedure, 1464
mechanism, 1464, 1465
with the *Lemieux-von Rudloff reagent*, 1463
alkenes, oxidative decarboxylation, of carboxylic acids, 1467
alkenes, oxyamination of, 1007
alkenes, oxymercuration of, 874, 885, 886
alkenes, ozonolysis of, 1459–1463
and 1,3-dipolar addition, 1460, 1462
and isotope labeling, 1462
and rearrangement, 1460
Criegee mechanism, 1460–1462
mechanism, 1460–1462
regiochemistry of ozonide formation, 1460, 1461
to aldehydes or ketones, 1459
alkenes, perdeuteration of, 661
peroxide epoxidation, and microwaves, 10001000
peroxyacid epoxidation of, mechanism, 999
alkenes, photochemical [2+2]-cycloaddition, with aldehydes, 1049
alkenes, photochemical [2+2]-cycloaddition, with ketones, 1049
alkenes, photochemical addition, of alcohols, 891
of aldehydes, 972
of thiols, 895
alkenes, photochemical isomerization of, 304
alkenes, photochemical isomerization of, E/Z, 882
alkenes, photochemistry of, 293, 552
and geometry, 305
photoisomerization of, 304, 882
photooxygenated, 1006
photooxygenation of, with singlet oxygen, 1005
polyhalo, 884
protonolysis of, to from carbocations, 219
push-pull, 164
radical halogenation of, 826
radical halogenation of, mechanism, 824
alkenes, reaction, with peroxides, 999
with protons, 863
alkenes, reactivity, in alkene metathesis, 1420
in catalytic hydrogenation, 904
in diazo transfer reactions, 1054
in metal catalyzed hydroformylation, 979
in the *Diels-Alder reaction*, 1021
with bromine, 872
with HCN, 980
with mixed halogens, 983
alkenes, reagents, for oxidative cleavage, 1463, 1464
alkenes, reagents, to prepare halohydrins, 985
alkenes, rearrangements, 661
and carbocations, 662
and π-allyl complexes, 663
metal catalyzed, 663
photochemical, 663
alkenes, reducing agents, 909
alkenes, reduction, and CIDNP, 910
by hydroboration, 910
to alkanes, 909
with diimide, and the mechanism, 910
with lithium aluminum hydride-metal salts, 917
with samarium iodide and triamines, 910
with silanes, 917
with sodium borohydride-metal salts, 917
alkenes, regioselectivity, in the Heck reaction, 765
resolution of, 174
selectivity, in catalytic hydrogenation, 904
Sharpless asymmetric dihydroxylation, 996
Sharpless asymmetric epoxidation of, 1004
Sharpless asymmetric epoxidation of, structural limitation, 1004
Shi epoxidation of, 1002

alkenes, stability of, and heat of combustion, 1270
and hyperconjugation, 1270
and *Zaitsev's rule*, 1270
alkenes, stereochemistry of elimination reactions, 1273
alkenes, stereochemistry of, and hydrogenation, 906
alkenes, stereoselective addition, of boranes, 922
alkenes, steric factors, and catalytic hydrogenation, 904
alkenes, structure, and addition reactions, 871
and asymmetric epoxidation, 1005
and dihydroxylation, 997
and ozonolysis, 1459
and the *Prins reaction*, 1186
alkenes, substituted, and the *Heck reaction*, 763
alkenes, substitution and the *Heck reaction*, 764
alkenes, symmetrical, and diimide reduction, 910
alkenes, syn addition of bromine, 864
alkenes, thermodynamic stability, 664, 1167, 1271
and metathesis, 1417
alkenes, thermodynamically more stable, 664
alkenes, twisted, 206
alkenes, unsymmetrical, by *McMurry coupling*, 1559
alkenes, unsymmetrical, from ketones with low valent titanium, 1559
alkenes, versus alkynes, in addition reactions, 873
alkenes, versus alkynes, in ozonolysis, 1460
alkenes, via *Tebbe's reagent*, 1174
alkenes, with 9-BBN, 922
with acids, 863
with acids, dimerization, 931
with acids, HX, 883
with acids, reactivity, 872
with acyl halides, 684
with acylium ions, 685
with alcohols and alkoxy-amination, 1008
with alcohols, 889
with alcohols, and hydrazoic acid, 1364
with alcohols, and *Markovnikov's rule*, 889
with alcohols, enantioselectivity, 889
with alcohols, regioselectivity, 889
with aldehydes and oxygen, 1006
with aldehydes or ketones, 1122
with alkenes, 931–935
with alkenes, temperature and pressure effects, 927
with alkyl azides, 1009
with alkynes, 931–935
with allylic carbocations, 212
with amides, 900
with amines, temperature and pressure, 896
with amines and thiols, 1012
with anilines, 897
with aromatic compounds, 609, 610
with aromatic hydrocarbons, 939
with aryl disulfides, and metal salts, 1006
with aryldiazonium salts, 794
with aziridines, 1018
with boranes, 558, 700, 920–926, 1299
with boranes, steric effects, 921
with bromamines, 1011
with bromine, 828
with bromine, and peroxides, 1336
with bromine, reactivity in methanol, 872
with carbenes, stereochemistry, 878
with carbenoids, 1057
with carbocations, 859
with catecholborane, 702, 959
with CCl_4, to form trihalides, 452
with chiral dioxiranes, 1002
with Chloramine-T, 1007, 1011
with chloroformates, 992
with chloronium ions, 863
with chlorosulfonyl isocyanate, 1245
with chlorosulfonyl isocyanate, and microwaves, 1245
with D_2, 908, 909
alkenes, with diimide, 909
with disdiamylborane, 922
with diselenides, 1007
with disulfides, 1007
with *Grignard reagents*, 1109
with *Grignard reagents*, and oxygen, 936
with halogens, 828
with halogens, and carbocations, 863
with HBr, 876
with HBr, and peroxides, 883
with HCl, 322
with HX, and phase transfer catalysts, 884
with hydrazoic acid, 901
with hydrogen peroxide, and formic acid, 994
with hypervalent iodine compounds, 985
with hypohalous acids, 984
with imido-selenium compounds, 679
with iodoesters, 991
with iodolactones, 991
with ketones, intramolecular reaction, 939
with malonate derivatives, 960
with manganese acetate, 1013
with mcpba, 998
with mercuric acetate, 885
alkenes, with metal hydrides, 926
with metals and alcohols, 909
with nitriles and acylium ions, 1012
with organocuprates, 937
with organolithium reagents, 937
with organolithium reagents, and ammonium salts, 1291
with organomanganese compounds, 938
with organometallic compounds, 936–940
with osmium tetroxide, 992, 993
with oxygen, 886
with oxygen, reactivity and structure, 834
with permanganate, 993
with peroxides, 883
with peroxyacids, 998, 1488
with peroxyacids, stereochemistry, 878
with phenols, 889
with phosphine oxides, 899
with phosphites, 900
with photosensitized oxygen, 833, 834
with polyhydrogen fluoride-pyridine, 883
with potassium permanganate, 992
with radicals, 806, 810, 815
with radicals, 879
with radicals, *Baldwin's rules*, 868
with silyl halides, and DMSO, 988
with silylphosphines, 899
with silylthiols, 894
with singlet oxygen, 833, 1006
with singlet oxygen, mechanism, 834
with sulfinylimines, 1136
with sulfonamides, 900
with sulfonyl halides, 988
with the *Petasis reagent*, 1174
with thiiranium ions, 1012
with thiocarbonates, 894, 970
with thiols, 894, 1006
with thiophenol, 894

with thiourea, metal catalyzed formation of thiiranes, 1006
with tosylaziridines, 1011
with tosylimines, metal catalysts, 1136
with trialkylsilanes and acids, 909
with trialkylsilyl halides, 884
with trichloroamine, 491
with trichloroisocyanuric acid, 884
with trimethyelenmethane, 1019
with triplet oxygen, 833
with water, 885
alkenes, Z-selectivity, in the *Wittig reaction*, 1171
alkene-silanes see silanes, vinyl
alkene-silanes, cyclization, 930
alkene-triflamides, cyclization, 900
alkoxide bases, and ester enolate anions, 1236
and the aldol reaction, 1144
with halo esters, 1161
with halo sulfones, 1177
alkoxides, and 1,3-elimination, 1307
and *Grob fragmentation*, 1307
and LIDAKOR, 1287
and reduction of aldehydes or ketones, 1508
and the *Grignard reaction*, 1107
cleavage, 654, 718
from ketones or aldehydes, 233
gas phase cleavage, 223
hydrolysis, 1511
metal catalyzed reaction with aryl halides, 748
metal, syn elimination by Ei mechanism, 1285
metal, thermolysis of alkenes, 1285
thermal cleavage, 721
thermal cleavage, mechanisms, 722
with alkyl halides, 459
with alkyl sulfates, 462
with dihalides, 460
with inorganic esters, 462
alkoxy radicals, 254, 804, 817
alkoxy-amination, of alkenes, 1008
alkoxy-carbonylation, of alkenes, 974
alkoxymercuration, and *Markovnikov's rule*, 891
alkoxymercuration, of alkenes, 891
alkyl azides see azides
alkyl chlorides see halides
alkyl groups, activating for electrophilic aromatic substitution, 580
alkyl groups, and transannular rearrangement, 1333
alkyl halides see halides, alkyl
alkyl nitrites, 675
alkyl sulfates see sulfates
alkylating reagents, *Friedel-Crafts alkylation*, 611
O-alkylation see alkylation, *O*-alkylation
alkylation, α to carboxylic acids, 557
alkylation, α- to heteroatoms, 555
alkylation, α to N in amines, 555
alkylation, α to terminal triple bond, 561
alkylation, and radicals, 445
and substitution, 373
and the acetoacetic acid synthesis, 540
and the cyanoacetic esters synthesis, 541
and the malonic ester synthesis, 540
and the *Morita-Baylis-Hillman reaction*, 1129
and trialkylboranes, 558
alkylation, at carbon, enolate anions, 447
alkylation, at oxygen, enolate anions, 447
alkylation, by *Hiyama coupling*, 545
by *Ziegler alkylation*, 785
alkylation, double, 539
enantioselective, 544
exhaustive, and amines, 482
metal catalyzed, of enol carbonates, 545
alkylation, *O*-alkylation, 449
and amide formation, 493
and enolate anions, 539
enolate anions, 447
nitronic esters, 448
phenoxide ions, 448
alkylation, of hydrazones, 548
of active methylene compounds, 539
of aldehydes, 542
alkynes, 561, 940, 1379
of allylic amine carbanions, 556
of allylic ether carbanions, 555
of amides, 494
of amines, 481, 487
of amines, and the *Delépine reaction*, 483
of amines, metal catalyzed, 483
of amines, with alcohols, 483
of amino acids, 1097
of aromatic compounds, 784–787
of aromatic compounds, and organometallics, 785
of aromatic nitro compounds, 786
of boronates, 558
of boronic acids, 558
of carboxylic acid salts, 552
of carboxylic esters, 542
of conjugated compounds, 949
of cyanide ion, 563
of cyclic carbamates, 493
of dimethylhydrazones, 548
of dithianes, 552–556
of dithioacetals, 552–556
of dithioketals, 552–556
of enol carbonates, 545
of enols, and Lewis acids, 544
of formamidines, 555
of heterocycles, 482, 786
of hydroperoxide anions, 472
of hydroxynitriles, 549
of imides, 494
of imines, 548, 1099
of inorganic esters, 462
alkylation, of ketones, 542
of ketones, *Stork enamine reaction*, 550
of keto-sulfones, 540, 548
of keto-sulfoxides, 540, 548
of lactams, 493
of lactones, 543
of N,2-pyrrolidinones, 445
of nitriles, 542
of oxazines, 556
of oxazolidin-2-ones, 493
of oximes, 475
of phosphines, 483
of pyridine, and organometallics, 785
of pyrrole, 482
of pyrrole, and organometallics, 785
of pyrrole, in ionic liquids, 482
of quinoline, photochemical, 845
of silyl enol ethers, 544
of sulfonamides, 495
of sulfones, 554
of sulfonic acid salts, 480
of sulfonic esters, 554
of thioethers, 554
of vinyl sulfides, 554
alkylation, on Montmorillonite clay, 445
alkylation, photochemical, of heterocycles, 845
alkylation, radical, of aromatic compounds, 843
of aromatic compounds, and CIDNP, 844
of aromatic compounds, mechanism, 843
of heterocycles, 845
alkylation, reductive, 1096–1099
replacement of amino, 787
alkylation, with dianions, 448, 541
with diazo compounds, 462
with enamine salts, 550

alkylation, with enolate anions, 232, 447, 539, 542, 547, 548
enantioselective, 546
and chiral additives, 546
and chiral oxazolidinones, 546
and phase transfer, 543
chiral bases, 546
metal catalyzed, 544
solvents, 544
with naphthoxide, 449
alkylboranes see boranes
alkylboronic acids see boronic acids
alkylchloroaluminum amides, formation of amidines, 1104
alkylcopper-magnesium bromide (*Normant reagent*), 940
alkylidene carbenes, 252
alkylidene cyclohexanes, and a chiral axis, 140
alkylidene lactams, from ynamides, 900
alkylidene malonic acid derivatives, conjugate addition, 952
alkylideneoxetanes, 1243
alkylmagnesium fluorides, 714
alkylnitrites with acids, 789
alkylsilane, with malonates, 930
alkyltrifluoroborates, with aryl halides, 768
alkyne acids, cyclization, 1013
alkyne allene from alkynes, 934
alkyne amines, hydration, 888
alkyne anions, 648
alkyne anions also see acetylides
ab initio study of 1,2-alkyl shifts, 1337
and *Favorskii reaction*, 1114
and the *Nef reaction*, 1158
and the *Knoevenagel reaction*, 1158
with aldehydes and ketones, 1114
with aldehydes or ketones, enantioselectivity, 1115
alkyne anions, metal, and Stephens-Castro coupling, 775
with aryl halides, 775–778
with aryl halides also see Stephens-Castro
with boranes, 1377
alkyne compounds, and nucleophilic substitution, 419
alkyne thioethers, hydration, 888
alkyne, silyl, halogenation, 706
alkyne-alcohols, dehydration, 1284
from alleneboranes and aldehydes, 924
hydration, 891
alkyne-boranes see boranes
alkyne-carboxylic acids, formation of lactones, 893
alkyne-esters, from metalated alkynes, 700
alkyne-ethers, hydration, 888
alkyne-ketones, by carbonylation of alkynes and aryl halides, 782
by *Eschenmoser-Tanabe ring cleavage*, 1309
conjugate addition, of boranes, and boron trifluoride, 959
from amides and alkynylboranes, 1231
from epoxy hydrazones, 1309
alkynes, [2+2]-cycloaddition, 1041, 1047
with alkenes, 1047
with cyclopropanes, 1044
alkynes, [3+2]-cycloaddition, 1018, 1019
alkynes, acid catalyzed isomerization, 665
acyl addition, and the *Barbier reaction*, 1115
acyloxylation of, 1012
alkynes, addition reactions, 561
and *Markovnikov's rule*, 884
and UV light, 873
and π-orbitals, 873
formation of halonium ions, 873
of acids HX, 884
of acyl compounds, 970
of aziridines, 1018
of HCN, 981
of HX, 865
of hypohalous acids, 986
of *Normant reagents*, 940
of organocuprates, 941
of organolithium reagents, 936
of organometallic compounds, 938
of silanes, intramolecular, 929
of sulfonic acids, 893
of sulfonyl halides, 988
via boranes, 1379
alkynes, α-alkylation, 561
alkynes, and alkene isomerization, 887
and formation of enol esters, 893
and *Friedel-Crafts alkylation*, 610
and hydrogen bonding, 101
and proton transfer, 324
and the *Fritsch-Buttenberg-Wiechell rearrangement*, 1298
and the *Glaser reaction*, 841
alkynes, β anti-elimination, 1257
alkynes, anti-*Markovnikov hydration*, 887
alkynes, antimony, with acyl halides, 1227
alkynes, as neighboring groups, 396
baker's yeast reduction, enantioselectivity, 912
base-catalyzed addition of alcohols, 891
bis addition of organometallics, 940
alkynes, by alkyne alkylation, 561
by base induced elimination of dihalides, 1297
by dehydrogenation of alkenes, 1442
by dehydrohalogenation, 1297
by E2 reactions, 1257
by hydroboration, enantioselectivity, 1379
by oxidative coupling of dihalotoluenes, 1495
by pyrolysis of acyl phosphorus ylids, 1293
by pyrolysis of bis(ammonium) salts, 1291
by the Wittig-Horner reaction, 1170
alkynes, carbonylation reactions, 974
with aryl halides, 782
alkynes, catalytic hydrogenation of, 905, 912
and stereoselectivity, 906
alkynes, complex with mercuric salts, 888
alkynes, conjugate addition, 954
conversion to ketals, 890
copper mediated coupling, 840
alkynes, coupling, and *Sonogashira coupling*, 842
to give diynes, 842
with alkanes, 561
with arylpyridinium salts, 777
with organosamarium compounds, 562
with silanes, 562
alkynes, cross coupling, 934
cross metathesis, 1422
cyclic poly-ynes, 841
cyclization of, 935
cycloaddition with dienes, 1021
cyclopropyl, and radicals, 240
alkynes, cyclotrimerization, 1059
metal catalysts and metal catalyzed, 1060
alkynes, diamination of, 1009
dihydroxylation of, 997, 1471
dimerization, metal catalyzed, 933
ene reaction of, 943
formation of bridged ions, 874
formation of vinylic carbocations, 865
alkynes, from aldehydes, 1168

from alkenes, 1300
from alkyl halides, 561
Alkynes, from alkyl halides, with a Co catalyst, 1297
from alkynes, by metathesis, 1422
from aryl halides, 775–778
from aryl halides see Stephens-Castro
from boranes, 1300, 1379
from boranes, and metal alkyne anions, 1377
from dihalosulfones, 1303
from enol phosphates or enol triflates, 1286
from metal alkyne anions, 775–778
from metal alkyne anions also see Stephens-Castro
from nitrenes and alkenes, 1010
from nitriles, 775
from thiirene dioxides, 1303
from vinyl halides, 412
alkynes, halo see haloalkynes
coupling reactions, 562
with boranes, 1379
alkynes, halogenation, 706, 984
alkynes, hydration, 887
and metal catalysts, 887
and tautomerism, 887
alkynes, hydration, metal free, 888
rate determining step, 889
alkynes, hydroamination of, 898
alkynes, hydroarylation of, 937
alkynes, hydroboration of, 925
and reduction to alkenes, 911
in the presence of alkenes, 925
alkynes, hydrocarboxylation of, 973
alkynes, hydroformylation of, 979
with the Lindlar catalyst, 905
alkynes, hydrometallation of, 927
alkynes, hydrosilation of, 929
alkynes, in the *Sonogashira coupling*, 776
in the *Cadiot-Chodkeiwicz reaction*, 841
in the *Eglinton reaction*, 840
in the *Hay reaction*, 841
in the *Heck reaction*, 765
in the *Stephens-Castro coupling* reaction, 775
in the *Stille coupling*, 682
alkynes, internal coupling, 935
intramolecular coupling, 934
intramolecular *Grignard* addition, 936
Lewis acid catalyzed, addition of silanes, 929
Lewis-acid catalyzed, addition of alkyl halides, 991
lithiation of, 695
lithio see lithioalkynes
lithio, Pd catalyzed coupling, 516
mercuric catalyzed hydration, mechanism, 888
alkynes, metal catalyzed, addition, of amides, 901
of arylboronic acids, 940, 941
of Grignard reagents, 936
of imides, 901
of phosphines, 899
of trialkylboranes, 941
to alkenes, 931
alkynes, metal catalyzed, amination, 898
carbonylation, 975
carboxylation with carbon dioxide, 893
conjugate addition, 954
coupling to alkynes, 933
coupling with triarylstilbines, 777
coupling with vinyl halides, 934
coupling, 840
cyclotrimerization, 1060
hydration, 887
hydroformylation, 979
alkynes, metal mediated, coupling with alkyl halides, 561
addition of HCN, 981
coupling, 933
alkynes, metalated, coupling reactions, 561
alkynes, metallated, with boranes, 1379
alkynes, metalation of, 695, 697
alkynes, metathesis, 1422
alkynes, methylthio, metal catalyzed coupling with arylboronic acids, 778
alkynes, *Michael reactions*, 948
alkynes, *Michael type*, and addition of thiols, 895
alkynes, mixed halogenation, 984
alkynes, oxidation, to diketones, 1489
to diketones, reagents, 1489
alkynes, oxidative cleavage, 1464
alkynes, Pd catalyzed, cross coupling, 561
alkynes, peroxymercuration of, 892
alkynes, phosphino, 707
alkynes, propargylic, CH oxidation, 1477
dehalogenation, 1305
alkynes, radical addition, 961
alkynes, reaction, with dialkylaluminum reagents, 927
with haloboranes, 851
with organometallics, 927
alkynes, rearrangement, to allenes, 664
alkynes, reduction, with Dibal, 911, 912
with metals in ammonia, 911
with sodium in ammonia, 1064
alkynes, reductive coupling, 933
alkynes, seleno, hydration, 887
alkynes, silyl, alkylation, 561
as a protecting group, 842
metal catalyzed coupling with aryl halides, 777
alkynes, tetramerization of, 1059
alkynes, trimerization of, 1059
alkynes, versus alkenes, catalytic hydrogenation, 905
in addition reactions, 873
in ozonolysis, 1460
alkynes, with alcohols, 889
with aldehydes and amines, 1135
with aldehydes or ketones, 1122
with alkenes, 931–935
with alkyl halides, 991
with alkylboronic acids, 684
with alkynes, 931–935
with allenes, 935
with allylic alcohols, 938
with allylic halides, 940
with allylizinc reagents, 938
with amines and Pd catalyst, 910
with amines, 896
with amines, intramolecular, 898
with amines, metal catalyzed, 898
with aryl halides, 775, 776, 939
with aryl halides also see Sonogashira
with arylboronic acids, 941
with aziridines, 1018
with boranes, 1377
with bromine, 862
with bromonium ions, 862
with carbamates, 562, 707
with carbenes, 1055
with catecholborane, 705
with chloroformates, 1228
with diesters, 939
with epoxides, 536
with ethers, microwave irradiation, 928
with *Grignard reagents*, 648, 696
alkynes, with imines, 1133
with In reagents, 938
with iodo azide, 990
with iodonium salts, 778
with isocyanides, 1061
with isonitriles, uranium complex, 1141
with metals, 698

alkynes, with imines (*Continued*)
with nitrile enolate anions, 939
with nitryl chloride, 989
with organolithium reagents, 937
with organometallic compounds, 938
with organozinc compounds, 940
with phosphine oxides, 899
with propargyl acetates, 935
with *Schwartz's reagent*, 933
with silanes, metal catalyzed, 562, 929
with siloxanes, 912, 929
with silyl enol ethers, 931, 939
with sulfonic acids, 894
with sulfonyl halides, 988
with sulfur monochloride, 1006
with thiols tolerable functional groups, 894
with thiols, 894
with thiols, metal catalyzed, 895
with thiols, photochemical, 894
with thiols, substituent effects, 894
with tosylimines, 1134
with trialkylsilyl halides, 884
with trichloroiocyanuric acid, 706
with triflimide, 888
with vinyltellurium, 939
alkynones, 663
allene tin compounds, with aryl halides, 767
allene-alcohols, carbonylation, 978
allene-alcohols, tautomerization, 412
allene-alkenes, carbonylation, 975
allene-amines, 898
allene-carboxylic acids, cyclization to butenolides, 893
allene-epoxides, 1004
allene-esters, cyclization to butenolides, 893
allenes, [2+2]-cycloaddition, 1041, 1043, 1045
with alkenes, 1041
with alkynes, 1042
allenes, addition of chloroformates, 992
allenes, and addition reactions, 874
and alkyne isomerization, 664
and atropisomers, 132
and *Cahn-Ingold-Prelog system*, 140
and chirality, 130, 132
and cumulative double bonds, 132
and formation of allylic carbocations, 876
and formation of conjugated ketones, 412
and *Markovnikov's rule*, 876
and *Meyer-Schuster rearrangement*, 412
and mirror planes, 132
and rearrangement of alkynes, 664
and rearrangement of en-ynes, 664
and the *Heck reaction*, 765
and the *Simmons-Smith procedure*, 1058
allenes, as neighboring groups, 396
by rearrangement of cyclopropenes, 1055
catalytic hydrogenation of, 905, 912
allenes, chiral, 522, 663
cyclic, 203
enantioselectivity, 663
ene reaction, 943
epoxidation, with oxaziridinium salts, 1002
allenes, from carbon dioxide and phosphorus ylids, 1173
from cyclopropylidenoids, 1305
from *Grignard reagents*, 517, 527
from *Grignard reagents*, and propargyl halides, 517
from ketones, 1188
from organocuprates, 521, 527
from propargyl esters, 527
from propargyl halides, 517
from propargylic alcohols, 664
from propargylic alcohols, with boronic acids, 1305
from propargylic ethers, 534
allenes, halogenation of, 984
hybridization, 132
hydration of, 888
hydroamination of, 898
hydroamination of, intramolecular, 898
in the *Nazarov cyclization*, 946
allenes, metal catalyzed, addition of amides, 901
amination, 898
cyclization with alkenes, 934
allenes, neighboring groups, 396
orientation of addition, 877
rearrangement, 664
allenes, reduction, 911, 912
with Dibal, 912
with sodium and ammonia, 911
allenes, via allylic rearrangement, 412
allenes, with alcohols, formation of tetrahydrofurans, 890
with aldehydes or ketones, 1122
with aldehydes, 1123, 1185
with alkynes, 935
with amines, 896, 898, 978
with amines, intramolecular, 898
with chlorosulfonyl isocyanate, 1245
with 1,5-dienes, *Cope rearrangement*, 1402
with electrophiles, 876
with halo azide, 990
with ketones, 1123
with organomanganese compounds, 938
with radicals, 877
allophanates, from carbamates, 1085
allowed reactions, in Hückel systems, 1033
Möbius systems, 1033
alloxans, dialkyl, with Oxone, 1002
allyl carbanion, and resonance, 40
allyl cation, and resonance, 40
π-allyl complexes, and acylation of dienes, 685
and hydroformylation, 979
and rearrangement of alkenes, 663
mechanism, 663
with metals, 106
allyl halides see halides
allyl radicals, and resonance, 40
electron diffraction, 238
allylamines, with aryl halides, 753
allylation, decarboxylative, metal catalyzed, 856
allylgallium reagents, 526
allyl lithium reagents, sulfur stabilized, 232
allyl lithium, 106
π-allyl nickel, complexes, coupling reactions, 514
π-allyl palladium, and allylic esters, 528
complex, 42
allyl tin also see organotin
allyl tin see tin
allylic acetate also see esters, allylic
allylic alcohols see alcohols
allylic carbanions, 223, 556, 657, 662, 662, 870
and LDA, 1020
canonical forms, 223
allylic carbocations see carbocations
allylic carbonates see carbonates
allylic CH, benzyoxylation, 1471
allylic compounds, ambident substrates, 450
and autoxidation, 832
α-hydroxylation, 1472
with oxygen, 834
allylic halogenation, radical, 826

allylic oxidation of alkenes, with selenium dioxide, mechanism, 1470
of alkenes, 1470, 1471
Sharpless method and selenium dioxide, 1471
allylic phosphonates see phosphonates
allylic radicals see radicals
allylic rearrangements also see rearrangements
allylic rearrangements, 539, 657, 658
and metal complexes, 663
and propargyl systems, 412
and SNi′, 411
formation of allenes, 412
halogenation, 827
nucleophilic, 663
S_N2', 410
with allylic alcohols, 532
with vinyl epoxides, 537
Wurtz reaction, 514
allylic silanes see silanes
allylic substrates, and S_N1 reactions, 420
all and S_N2 rate of reaction, 420
and substitution reactions, 420
allylic α-hydroxylation, 1472
Alpine-Borane (B-(3-pinanyl)-9-borabicyclo[3..1]nonanes)
Alpine-Borane, and reduction, 1514
alternant hydrocarbons, 63
electrophilic aromatic substitution, 585
energy levels, 64
odd and even, 64
topological polarization, 65
alternating axis of symmetry, 125
alumina, 445
and acetoacetic ester synthesis, 540
and acyl halides with alcohols, 1200
and chlorination of lactams, 731
and conversion of aldehydes to nitriles, 1095
and dehydration of alcohols, 1282
and dehydration of oximes to nitriles, 1311
and *Diels Alder reactions*, 1023
and elimination of alcohols to alkenes, 1285
and elimination of ethers to alkenes, 1285
and *Meerwein-Ponndorf-Verley reduction*, 1507
and reduction of nitro compounds, 1525
and sodium borohydride, 1504
and Suzuki-Miyaura coupling, 771
as a catalyst, 476, 1200
aluminum alkoxides, and *Oppenauer oxidation*, 1447
aluminum amalgam, sulfoxide reduction, 540
aluminum compounds, and *Meerwein-Ponndorf-Verley reduction*, 1507
hydrolysis of, 699
aluminum cyanides, with ketones, 1181
aluminum hydride also see hydrides
aluminum hydride, with carboxylic acids, 1515
aluminum hydride, lithium see lithium aluminum hydride
aluminum hydride, sodium see sodium borohydride
aluminum isopropoxides, reduction of carbonyls, 1507
aluminum, dialkyl, with alkynes, 927
aluminum-free *Meerwein-Ponndorf-Verley reduction*, 1507
Amberlyst 15, 467
and acetal cleavage, 456
and halogenation of epoxides, 506
halogenation of alcohols, 501
imines with ketene silyl acetals, 1137
ambident nucleophiles see nucleophiles
ambident substrates see substrates
American Chemical Society: ASAP papers, 1570
amidation, and carbenes, 837
aromatic compounds, 600
of alkenes, 900
of aromatic compounds, 630
oxidative, 837
oxidative, and epoxides, 838
amidazines, bases, 322
amide bases, 482
and enolate anion formation, 687
and stereoselectivity in the aldol reaction, 1146
and *Stevens' rearrangement*, 1371
and the aldol reaction, 1144
and the *Chichibabin reaction*, 787
and the *Haller-Bauer reaction*, 725
and transamination, 487
chiral, 668
halogenation of carboxylic acids, 673
magnesium, 687
polymer bound, 1143
with alkyl halides, 493
with ammonium salts, 1292
with aryl halides, 493, 751
with benzylic ammonium salts, 798
with epoxides, 489
with ketones, 680
amide esters, by the *Passerini reaction*, 1247
amide forming reagents, 1217
amide hydrolysis, acid catalyzed, 1199
base catalyzed, 1199
IUPAC mechanism, 1198, 1200
kinetics, 1198
MO studies, 1198
rate constants, 1199
rate, 348
amide-esters, from isocyanides, 1246
amides also see formamides
amides, acidity, 336
acylation, 1222
acylation, by amides, 1221
acyloxy see amide-esters
addition to aldehydes, 1099
addition to alkenes, 897, 1013
alcoholysis, 1208
alkylation, 494
alkylation-reduction, 1114
allylic, isomerization to enamides, 882
amides, and acidity scales, 326
and catenanes, 118
and conformation, 179
and electron delocalization, 90
and enantiomeric excess, 160, 161
and *Hofmann rearrangement*, 1360
and hydrogen bonding, 98, 103
and isomers, 164
and N-ylids, 225
and proton transfer, 324
and pyramidal inversion, 127, 128
and resonance, 179
and the *Claisen condensation*, 1154
and the *Haller-Bauer reaction*, 725
and the *Mannich reaction*, 631
and the *Sonn-Müller method* to prepare aldehydes, 1523
and the *von Braun reaction*, 1313
and the *Wittig reaction*, 199
and the zip reaction, 1222
and transamidation, 1212
amides, aryl, from aromatic compounds, 630
amides, arylation of, 755

amides, and enolate condensations, 544
as a base, 1371
with heterocycles, 787
with imines, 548
amides, azidination of, 678
azido, 678
aziridinyl, vinylcyclopropane rearrangement, 1399
amides, by amidation of alkenes, 900
by carbene insertion, 692
by carbonylation of alkynes, 978
by carbonylation of amines, 567
by carbonylation of imines, 709
by carbonylation, 631, 1223
by *Chapman rearrangement*, 1428
by hydration of alkynes, 888
by hydrolysis of isocyanates, 1361
by hydrolysis of nitriles, 1080, 1081
by metal catalyzed carbonylation of dienes, 973
by α-oxidation of cyclic amines, 1477
by α-oxidation of lactams, 1477
by pyrolysis of ammonium carboxylates, 1216
by rearrangement, of *O*-tosyl oximes, 1312
by rearrangement, of oximes, 1365
by solid-phase synthesis, 1218
by the *Gatterman amide synthesis*, 629
by the *Ritter reaction*, 1239
by the *Willgerodt reaction*, 1566
amides, chiral, and azodicarboxylates, 679
amides, conjugate addition, enantioselectivity, 966
amides, conjugated, and conjugate addition, 952
coupling to give dimeric diamides, 839
from allylic amines, 731
radical coupling, 838
amides, conversion to amides, 626
amides, dealkylation, reagents, 1554
amides, dehydration, 1284
with PCl_5, 1313
and *Swern oxidation*, 1313
to isonitriles, 1314
to isonitriles, reagents for, 1314
to nitriles, 1313
to nitriles, reagents for, 1313
amides, dialkyl, aggregates, 341
and chelation, 342
and halogenation of carboxylic acids, 673
and HMPA, 341
as bases, 341
as bases, in the aldol reaction, 1146
amides, diallyl, in the ene reaction, 942
amides, diazotization of, 1200
amides, enol content, 91
amides, enol form, 1239
and dehydration to nitriles, 1313
amides, exchange with carboxylic acids, 1210
fluorination, 730
formation of, and microwave irradiation, 631
amides, from acyl halides, with amines or ammonia, 1213
from aldehydes, 495
from aldehydes, with amines, 1486
from aldehydes, with ammonia, 837
from alkenes, and nitriles, 1239
from alkyl halides, 493
from amide bases, 493
from amides, 755, 1554
from amides, and aldehydes, 837
from amides, and amines, 1212
from amines, 555, 1477
from ammonium salts, with amides, 1221
from anhydrides, with ammonia or amines, 1214
from aryl amines, 754
from aryl halides, 493
from azides, 1218
from carboxylic acids, and the *Burgess reagent*, 1216
from carboxylic acids, by dehydrating agents, 1217
from DMF, 631
from esters, and electrochemistry, 1220
from esters, with ammonia or amines, 1219
from *Grignard reagents*, and isocyanates, 1139, 1140
from hydrocarbons, 838
from imino esters, 1428
from isocyanates, 630, 1141
from ketenes, with amines, 1100
from ketones, 725, 1363, 1566
from nitrenes, 679
from nitriles, 838, 1080
from nitriles, with alcohols, 1239
from organoboranes, 709
from oximes, 1325, 1365
from sulfonamides, 1222
from sulfonate esters, 493
from thioamides, 1087
amides, halo, photolysis of, 1427
amides, hydration of alkyne amines, 888
amides, hydrolysis, 1197–1200
and twisted bonds, 1197
isotopic labeling, 1199
mechanism, 1198–1200
nucleophilic catalysis, 1198
amides, in *Friedel-Crafts cyclizations*, 617
in *Friedel-Crafts reactions*, 631
in the *Mitsunobu reaction*, 494
amides, keto-enol tautomerism, 91
amides, lithiation, 696
amides, lithium, with aldehydes, 1110
amides, metal catalysis, 630
amides, metal catalyzed, addition of amines to nitriles, 1104
addition to alkynes, 901
addition to allenes, 901
amides, methoxy methyl see Weinreb amides
amides, N-halo, rearrangement, 640
nitroso, rearrangement, 796
nucleophilic strength, 493
oxazolidinone, with alcohols, 1209
radical coupling, 840
reaction with halogens, 1361
reaction with hydroxide, 348
reagents for reduction, 1545
amides, reduction, to aldehydes, reagents, 1518
to amines, reagents, 1544
with *Hantzsch esters*, 1545
with LiH_2NBH_3, 1544
with metals and silanes, 1545
with silanes, 1545
amides, reductive cleavage, 1554
amides, sodium also see sodium amide
amides, spirocyclic, 600
torsional barrier, 180
twisted, 199
via oxidative coupling of alcohols and amines, 494
amides, *Weinreb* see *Weinreb amides*
amides, with alcohols, 494, 1208
with aldehydes, 495
with aldehydes, Ba catalyst, 1155
with alkenes, 900
with alkynylboranes, 1231
with amine salts, 1222
with amines, 1212
with anhydrides, 1197, 1198, 1223
with aryl halides, 755
with carboxylic acids, 1218
with *Caro's acid*, 1087
with diazo compounds, 495

with diazonium salts, 1198
with Dibal, 1519
with *Grignard reagents*, 1229
with hypohalites, 1360
with LDA, 1155
with $LiAlH_4$, 1519, 1544
with nitrous acid, 1198
with oxalyl chloride, 1223
with PCl_5, 1429
with peroxides, 1198
with phosgene, 1314
with phosphorus pentachloride, 1429
with sulfonyl azides, 678
with sulfurization reagents, 1212
with triflic anhydride, 1208
with trimethyloxonium salts, 1209
amidines, by addition of amines to nitriles, 1104
by addition of ammonia to nitriles, 1104
from imidates, 1220
amidocuprates, 966
amidomethylation, 631
amidomethylation, aromatic compounds, 631
amidyl radicals, 965
aminals, and enamine formation, 1092
formation, 1091, 1092
amination, and sulfamate esters, 679
and triazoles, 787
electrochemical, 838
metal catalyzed, 707
amination, of alkenes, 679, 896
and hydroboration, 899
Markovnikov's rule, 897
metal catalyzed, 679
temperature effects, 896
amination, of alkynes, metal catalyzed, 898
amination, of allenes, 898
intramolecular, 898
metal catalyzed, 898
amination, of allylic CH, 1475
of aromatic compounds, 599
of aromatic compounds, and σ-substitution, 599
of CH, of hydrocarbons, 1475
of *Grignard reagents*, 706, 754
of heterocycles, 787
of heterocycles, vicarious substitution, 787
of organolithium reagents, 754
of organometallics, 706
of pyridine, 787
of quinoline, 787
amination, reductive also see reductive
amination, reductive, 1096–1099
metal catalysts, 1097
reagents, 1097, 1098
amine alcohols, form amine halides, 1356
amine halides, with water, 1356
amine leaving groups, in *Mannich bases*, 433
amine oxides, and *Cope elimination*, 1292
and *Meisenheimer rearrangement* to oximes, 1373
and resonance, 49
and the *Boekelheide reaction*, 1373
and ylids, 49
by oxidation of amines, reagents, 1492
pyrolysis to alkenes, 1292
reduction to amines, reagents, 1549
with aldehydes and TMSCN, 1181
amine salts, resolution, 156
with amides, 1222
amine-Claisen rearrangement, 1410, 1411
amines, α-alkylation, 555
amines, α-hydroxylation, with *Pseudomonas oleovoran*, 1476
amines, α-hydroxylation, with *Sphingomonas* sp HXN-200, 1476
amines, α-oxidation to amides, 1477
amines, acidity, 336
amines, acylation, 1215
and aminoboranes, 1218
and the *Merrifield synthesis*, 1218
and the *Schotten-Baumann procedure*, 1213
ionic liquids, 1215
microwaves, 1215
of amines with esters, catalysts for, 1220
polymer-bound, 1215
with esters, 1219
with esters, and microwaves, 1220
amines, addition of, *Grignard reagents* to imines, 1133
organolithium reagents to imines, 1133
organometallics, in ionic liquids, 1135
amines, addition to, alkenes, 970, 1008
isocyanates, 1103
isothiocyanates, 1103
nitriles, 1104
amines, alkylation, 481, 487
by the *Delépine reaction*, 483
metal catalyzed, 483
with alcohols, 483, 485
amines, allylic, and the *Claisen rearrangement*, 1410
carbanions, alkylation of, 556
CH amination, 1475
formation of conjugated amides, 731
from aldehydes and sulfonamides, 1129
from allylic alcohols, Pd catalyst, 485
from allylic carbonates, Pd catalyst, 484
isomerization, 882
amines, amination of alkenes, 896
amines, amination of alkenes, Markovnikov's rule, 897
amines, and carbamate formation, 470
and carbonylation, 974
and cleavage of methyl ethers, 486
and differential hydration, 343
and formation of alcohols, 474
and formation of carbamates, 555
and formation of formamidines, 555
and formation of onium salts, 331
and formation of phosphoramides, 555
and formation of *Schiff bases*, 1091
and leaving groups, 433
and metal catalyzed amination of alkynes, 898
and *Michael addition*, 965
and phase transfer catalysts, 483
and proton transfer, 324
and pyramidal inversion, 127, 128
and racemization, 129
and resonance, 337
and the *Gabriel synthesis*, 482
and the *Hofmann-Löffler reaction*, 1426
and the *Ing-Manske procedure*, 494
and transamidation, 1212
amines, anilines see aniline
amines, anilines, nitration, 594
amines, aromatic see anilines
amines, aromatic, deamination, 1550
methylation, 612
with alkyl nitrites, 606
with epoxides, 488
amines, aryl also see anilines

amines, aryl, and the *Bucherer reaction*, 756
from aryl phosphates, 756
rearrangement with organolithium reagents, 1624
amines, arylation, and microwaves, 752
with arylboronic acids, 754
amines, as leaving groups, 1258
as ligands, 41
as solvents, 909
amines, basicity of, 320
amines, bicyclic, by amination of alkenes, 897
bridgehead, and chirality, 129
amines, by base induced rearrangement of ammonium salts, 1371
by catalytic hydrogenation of nitriles, 1522
by CH oxidation of hydrocarbons, 1475
by dealkylation of amines, 1553
by Hofmann rearrangement, 1360
by hydrogenation of enamines, 898, 905
by hydrolysis of cyanamides, 1081
by hydrolysis of isocyanates, 1360
by metal reduction of hydroxylamines, 1526
by metal reduction of nitro compounds, mechanism, 1525
by oxidation of CH, 1475
by reduction of amides, 1544
by reduction of amides, reagents, 1518, 1544
by reduction of amine oxides, reagents, 1548
by reduction of azides, reagents, 1529
by reduction of azo compounds, 1530, 1554
by reduction of azoxy compounds, 1554
by reduction of C=N compounds, 1520
by reduction of diazonium salts, 1530
by reduction of enamines, 1521
by reduction of hydrazo compounds, 1554
by reduction of hydrazones, 1520, 1528
by reduction of imines, enantioselectivity, 1521
by reduction of imines, reagents, 1520
by reduction of isocyanates, 1530
by reduction of isothiocyanates, 1530
amines, by reduction of nitriles, reagents, 1522
by reduction of nitrilium ions, 1523
by reduction of nitro compounds, reagents, 1524–1526
by reduction of nitro compounds, with metals in acid, 1524
by reduction of nitroso compounds, 1530
by reduction of oximes reagents, 1521, 1527
by reduction of quaternary ammonium salts, 1548
by reduction of *Schiff bases*, 1520
by reduction of semicarbazones, 1528
by reduction of sulfonamides, 1547
by reduction, of iminium salts, 1520
by reductive alkylation, 1096–1099
by silane reduction of amides, 1545
by *Stevens' rearrangement*, 1371
by the *Buchwald-Hartwig reaction*, 752
by the *Gabriel synthesis*, 494
by the *Katritzky pyrylium-pyridinium method*, 480
amines, carbamoyl, 1212
amines, carbonylation, 567, 568, 730
and electrolysis, 731
with alcohols, 731
amines, chiral, 548, 1244
and *Mannich reactions*, 1102, 1103
from formamidines, 555
organolithium reagents with imines, 1134
amines, chloro, from amines, 729
amines, conjugate addition, 965
and transition metals, 965
enantioselectivity, 969
solvent free, 966
to thiolactams, 966
amines, cyanation of, 689
amines, cyclic, aminyl-radical cyclization, 484
by conjugate addition of amines, 966
by reduction of imides, 1545
by reduction of lactams, 1545
by S_N2' reaction, 483
cleavage with cyanogen bromide, 509
from alkene-amines, 482
from diols, 486
from halo-amines, 482
from haloamines, 1426
hydroxylation, 1476
α-oxidation to lactams, 1477
α-oxidation to lactams, reagents, 1477
ring expansion via Steven's rearrangement, 1371
ring expansion, and carbonylation, 731
von Braun reaction, 509
amines, cycloalkyl, with nitrous acid, 1345
amines, dealkylation reagents, 1553, 1554
amines, deamination, 1543
indirect methods, 1547
reagents, 1547
stereochemistry, 1548
amines, dehydrogenation nitriles, reagents for, 1454
amines, demethylation, 477
amines, diaryl, 599, 754
amines, diazotization, 1327, 1345
and rearrangements, 1327
with alkyl nitrites, 792
amines, dicarbonyl, as nucleophiles, 447
ditosyl, with halide ions, 509
energy barrier to pyramidal inversion, 127, 128
exhaustive alkylation, 482
fluorination, 730
formation of amides, 555
formation, by metal catalysis, 481
amines, from acyl halides, 1363
from addition of amines to alkenes, 896
from addition of ammonia to alkenes, 896
from alcohols, 485
from alkenes, 491
from alkyl halides, 485
from amides, 1519
from amides, with Grignard rearrangements, 1229
from amine oxides, 1373
from amines, 1371, 1454, 1553
from amino ethers, 534
from aminoboranes, 483
from ammonium salts, 1371
from azides, 706, 1529
from aziridines, 538
from boronic acids, 484
from carbamates, 1198
from carbocations, 492
from cyanohydrins, 561
from diazo compounds, 487
from enamine alkylation, 556
from ethers, 485

from *Grignard reagents*, 531, 534
from halides, catalyst, 484
from hydrolysis of isocyanates, 1362
from hydroxylamines, 1527
from imines, 1134, 1454
from isocyanates, 1362, 1363
from isocyanides, 493
from nitro compounds, 1524
from nitroso compounds, 1526, 1527
from organometallics, 538, 706
from oxetanes, 493
from oximes, reagents, 1527
from phosphonium salts, 560
from trichloroamine, 491
amines, gas phase basicity, 343
amines, halo, and *Grob fragmentation*, 1307
amines, halo, fragmentation, 1307
from amines, 729
with acid, 1427
amines, homoallylic, 1136, 1137
amines, hydrogenolysis, 1547
amines, hydrolysis of isocyanates, 1363
Amines, hydroxylation via enzymes, 1476
amines, in the *Bruylants reaction*, 531
in *the Hinsberg test*, 1251
in *the interrupted Nazarov*, 947
in the *Mannich reaction*, 1101–1103
in the *Mentshutkin reaction*, 481
in the *Mitsunobu reaction*, 485
in the *Pictet-Spengler reaction*, 618
in the *Staudinger reaction*, 1529
in the *von Braun reaction*, 509
amines, intramolecular arylation, 754
amines, metal catalyzed, addition to nitriles, 1104
amination of allenes, 898
animation of alkenes, 896, 897
arylation, 753
arylation, and ionic liquids, 752
arylation, and microwaves, 752
arylation, and S_NAr mechanism, 754
arylation, mechanism, 752
carbonylation, 730
conjugate addition, 966
coupling to diamines, 1558
reaction with aryl halides, 599
amines, metal mediated, arylation, 754
amines, metal reduction, of nitro compounds, 1526
amines, migration, 1356
naphthyl, from naphthols, 756
N-arylation, 751
N-Boc, metal catalyzed lithiation, 555
nitrosation, 727, 728
nitrosation, mechanism, 728
organometallic compounds with imines, 1133–1138
amines, oxidation, 1455
of manganese dioxide, 1455
reagents for, 1483
to amine oxides, reagents, 1492
to hydroxylamine with Caro's acid, 1490
to hydroxylamines, reagents for, 1491
to imines, 1482
to ketones or aldehydes, 1482
to nitriles, 1453, 1454
to nitro compounds, reagents, 1491
to nitrones, 1455
with Chloramine-T and O_2, 1477
with TPAP, 1483
amines, oxidative coupling with alcohols, 494
amines, photochemistry, 292
propargylic, 1133
propargylic, with CuI and Pd catalyst, 1305
amines, reaction, with aldehydes or ketones, 1090
with aromatic compounds, 631
with KOH, 474
with nitrous acid, 219
amines, reactivity differences with halides, 481
amines, reagents, for acylation, 1217
amines, reagents, for reductive alkylation of aldehydes or ketones, 1097
amines, reduction, of azides, 561
of imides, 1545
of oximes with borane, 1521
of oximes, reagents, 1527
to amines, reagents, 1520
to hydrocarbons, reagents, 1547
amines, reductive amination, with aldehydes or ketones, 1096–1099
amines, reductive cleavage, 1553
amines, replacement, by an alkyl group, 787
with alkyl, 793
amines, secondary, from primary amines, 754
silyl, with aryl halides, 752
silylalkyl, 484
substitution, of aryl halides, 734
substitution, of aryl halides, base catalysis, 734
amines, with acyl halides, 1213, 1299
with acyl halides, ketene formation, 1042
with acyl halides, to give ketenes, 1298
with aldehydes and alkynes, 1135
with aldehydes or ketones, 551, 1090, 1096
with aldehydes, 618, 1189, 1486
with aldehydes, NBS-AIBN, 837
with alkenes, and thiols, 1012
with alkenes, *Markovnikov's rule*, 897
with alkenes, temperature and pressure, 896
with alkyl halides and hexamethylenetetramine, 483
with alkyl halides, 481
with alkynes, 896
with alkynes, and a Pd catalyst, 910
with alkynes, intramolecular, 898
with alkynes, metal catalyzed, 898
with allenes, 896, 898, 978
with allenes, intramolecular, 898
with amides, 1212
with anhydrides, 1215
with anhydrides, mechanism, 1215
with aryl halides, and Pd catalyst, 752
with aryl halides, and the Goldberg reaction, 753
with aryl halides, replacement of alkyl groups, 751
with aryl triflates, 751
with aziridines, 491
with benzyl chloroformate, 1214
with boron trifluoride, 1222
with bromoacetophenone, 421
with calcium, reduction of aromatic compounds, 915
with carbon dioxide, 731
with carbon disulfide, 1104
with carbonates, 1215, 1220
with carboxylic acids and DCC, 1217
with carboxylic esters, mechanism, 1220
with chloroform, 492
with chloroformates, 1214
with CS_2, 1104
with cyanamide, 483
with cyanogen bromide, 509
with cyclic anhydrides, 1215
with cyclopropane, 492
with diazo compounds, 487
with diazoesters, 1058

amines, with acyl halides (*Continued*)
with diazomethane, 487
with dienes, 896
with diketones, 1091
with dimethyl(methylthio) sulfonium salts, 1012
with epoxides, 488
with epoxides, microwaves, 488
with esters, 1219
with esters and enzymes, 1220
with esters, IUPAC mechanism, 1221
with formaldehyde, 631
with formic acid and iodine, 1213
with guanidine, 494
with *Hünig's base*, 1440
with hydrazine, 494
with hypohalites, 729
with hyponitrites, 793
with ketenes, 1100, 1353
amines, with lactams, high pressure, 1222
with Lewis acids, 492
with lithium, reduction of aromatic compounds, 915
with lithium, reductive cleavage of carboxylic esters, 1538
with *Mannich bases*, 487
with microwave irradiation, 481
with Na or Li, 909
with nitrites, 1483
with nitro-ketones, 725
with nitronium salts, 728
with nitrous acid, 434, 727, 1346
with nitrous acid, and pH, 789
with nitrous acid, kinetics, 789
with nitrous acid, mechanism, 790
with onium salts, 731
with organocuprates, 707
with organolithium reagents, 687, 1373
with oxetanes, 490
with phosgene, 1213
with phosphites, 1105
with pyrylium ions, 1091
with *Sanger's reagent*, 752
with sulfonamides, 1222
with sulfonyl halides to give sulfenes, 1299
with sulfonyl halides, 1251, 1299
with sulfonyl halides, formation of sulfenes, 1249
with *tert*-butoxy anhydride, 1214
with thiiranes, 490
with thiophosgene, 1214
with tricarbonates, 731
with trifluoroarylboronates, 754
with β-lactones, and angle strain, 1221
aminium radical ions, 599
aminium salts, and vinylcyclopropane rearrangement, 1400
amino acid surrogates, 548
amino acids, 676
and chirality, 136
and the *Dakin-West reaction*, 722
and the semipinacol rearrangement, 1343
by the *Sorenson method*, 541
conversion to lactams, 1216
decarboxylation, 721
diazotization, 508
from acyl halides, 679
from azido acids, 678
N-alkylation, 1097
with nitrous acid, rearrangement, 1343
amino acids-boric acid, and resolution, 173
amino alcohols see hydroxyamines
amino alcohols, and cyclodextrin, 489
and semipinacol rearrangement, 1343
and formation of aziridines, 560
and microwave irradiation, 488
coupling ketones with *O*-methyl oximes, 1558
enantioselective formation, 489
from amines, 490
from amino acids, 1515
from azide-alcohols, 490
from azido-alcohols, 489
from epoxides, 488, 490
from epoxides, and amide bases, 489
from lactams, 1230
from oxetanes, 490
protonation and fragmentation, 1308
solvent free preparation, 488
with lithium perchlorate in ethers, 489
with nitrous acid, 1346
amino cyclase I, enzyme, 1220
amino esters, cyclization to lactams, 1220
diazoesters with amines, 1058
alkoxy-amination of alkenes, 1008
amino ethers, from alcohols, 466
from aziridines, 466
amino ketones, and *Michael addition*, 1230
by rearrangement of *O*-tosyl imines, 1358
by the *Mannich reaction*, 1100–1103
by the *Neber rearrangement*, 1359
elimination, 1101
from *Eschenmoser's salt*, 1102
amino nitriles, 1182
and cyanohydrins, 1182
and the *Strecker synthesis*, 1182
and the *Bruylants reaction*, 531
with *Grignard reagents*, 531
amino thioethers, from aziridines, 466
amino thiols, from epoxides, 490
aminoalkylation, heteroaromatic compounds, 753
of aromatic compounds, 631
aminoboranes, conversion to amines, 483
with carboxylic acids, 1218
aminoborohydride, reduction of amides, 1544
aminocarbenes, 252
aminocarbonylation, 782, 974
of alkenes, 974
aminochlorination, 988, 989
amino-Cope rearrangement, 1401
aminohalogenation, 988, 989
aminohydroxylation, and $(DHQ)_2PHAL$, 1007, 1008
enantioselectivity, 1007
of alkenes, 1007
Sharpless asymmetric, 1007
aminomercuration, of alkenes, 899, 1009
aminomethyl aromatic compounds, 798
aminomethylation, of aryl halides, 632
aminonitrenes, addition to alkenes, 1010
amino-organocuprates, 951
aminophenols, from oximes, 800
from the *Bamberger rearrangement*, 800
aminopyridine, halogenation, 606
aminosulfenylation, of alkenes, 1012
aminoxyl radicals, 241
aminyl radicals, 965
aminyl-radical cyclization, 484
ammonia, addition to cyanamide, 1104
addition to nitriles, 1104
amination of alkenes, 896
and formation of enolate anions, 547
and pyramidal inversion, 127, 128
and sodium, reduction of alkynes, 911
and the *Bucherer reaction*, 756
as a solvent, 739, 740, 747, 778, 1292
bond angles, 6

impurities, and the *Birch reduction*, 914
liquid, and enolate alkylation, 544
supercritical, 364
with acyl halides, 1213
with aldehydes or ketones, 1090
with alkyl halides, 481
with anhydrides, 1214
with carboxylic acids, 1216
with conjugated ketones, 547
with epoxides, 488
with esters, 1219
with metals, and decyanation, 726
with metals, and formation of enolate anions, 778
with metals, cleavage of cyclopropanes, 920
with metals, reduction of alkynes, 911
with sulfonyl halides, 1251
ammonium carboxylates, from carboxylic acids, 1216
ammonium chloride, with Fe, 1554
ammonium formate see formate
ammonium formate, Pd-C, reduction of heterocycles, 916
ammonium ketones, and *Robinson annulation*, 1150
ammonium salts, alkyl rearrangement, 640
allylic, rearrangement, 1414
and amide hydrolysis, 1197
and amination of alkenes, 897
and esterification, 1203
and formation of aldehydes, 886
and *Hofmann degradation*, 1290
and *Hofmann's rule*, 1271
and indirect hydration, 886
and phase transfer catalysis, 442
and *Stevens' rearrangement*, 798, 1371
and syn-elimination, 1258
and the *Hofmann-Martius reaction*, 640
and the *Knoevenagel reaction*, 1158
base induced rearrangement, 1371
benzylic, and *Sommelet-Hauser rearrangement*, 798
benzylic, rearrangement, 798
chiral catalyst, 1245
chiral, 779, 1182
chiral, with HCN, 1183
cleavage, 470
dealkylation, 487
demethylation, 477
formation of nitrogen ylids, 1292
from amines and alkyl halides, 482
from amines, 727
halo, photolysis, 1427
halo, rearrangement, 1427
heating, formation of alkyl halides, 509
pyrolysis to alkenes, 1290
quaternary, and *Emde reduction*, 1548
quaternary, and out-in isomers, 168
quaternary, polymer bound, 1003
quaternary, thermal stability, 443
rearrangement, 799
tetraalkyl, reduction to amines, 1548
with amide bases, 1292
with amides, 1221
with $LiAlH_4$, 1548
with organolithium reagents, 697, 1291
with organolithium reagents, Ei mechanism, 1292
amphiprotic properties, 665
anchimeric assistance, and cyclopropyl groups, 398
and S_N2 reactions, 391
in cyclopropane ring opening, 1389
in migrating group in rearrangements, 1326
solvolysis, 396, 397
angelic acid, 656
angle dihedral see dihedral angle
angle strain, and cyclobutanes, 195
β-lactones with amines, 1221
angles, bond see bond angles
angles, bond, and bicyclo[1.1.0] butane, 195
and cyclopropane, 194
and cyclopropene, 201
and prismane, 198
and steric strain, 192
and twisted alkenes, 206
methane, 8
angles, dihedral, and conformation, 178
angles, torsion, and conformations, 175
and molecular mechanics, 190
and specific rotation, 125
dihaloethanes, 177
angular momentum, and intersystem crossing, 298
angular polyacenes, 57
anhydride, acetic, with DMSO, 1566
anhydride, triflic, with amides and alcohols, 1208
anhydride, trifluoroacetic, and DMSO, for oxidation of alcohols, 1448
anhydrides, alcoholysis, 1201
and microwave irradiation, 1202
enantioselectivity, 1202
anhydrides, and dehydration of alcohols, 1284
and *Friedel-Crafts acylation*, 621, 623
and nitration of anilines, 594
and the *Gomberg-Bachmann reaction*, 796
by addition of carboxylic acids to ketene, 893
tert- butoxy, with amines, 1214
by dehydration, of carboxylic acids, 1210
carboxylic sulfonic, 622
anhydrides, cyclic, alcoholysis, 1202
and Friedel-Crafts acylation, 624
from dicarboxylic acids, 1202, 1210
with amines, 1215
anhydrides, formation of acyl azides, 497
anhydrides, from acyl halides and carboxylate salts, 1209
from acyl peroxides, 835
from aldehydes, 835
from carboxylic acids, 1210
from carboxylic acids, with enol esters, 1210
from epoxides, 536
from phosgene and carboxylate salts, 1210
hydrolysis, 1190
and pyridine, 1190
mechanism, 1190
nucleophilic catalysis, 1190
of imines, 1518
in the *Perkin reaction*, 1161
anhydrides, mixed, 622, 623, 848
Friedel-Crafts acylation, 623
from acyl halides and carboxylate salts, 1209
with amines, 1215
with DMAP, 1204
anhydrides, of phosphoric acid, 1211
of sulfonic acids, 1211
organic-inorganic, hydrolysis, 1202
organic-inorganic, mixed, from anhydrides, 1211
reaction, with aldehydes, 1084
reaction, with sulfoxides, 1565
reduction, to aldehydes, 1518
reduction, to lactones, reagents, 1544
sulfonic, and *Friedel-Crafts acylation*, 622

anhydrides, of phosphoric acid (*Continued*)
sulfonic, and the *Vilsmeier-Haack reaction*, 626
trichloroacetic, 1084
trifluoro, with cyanoboranes, 1376, 1377
anhydrides, with alcohols, 1201
with alcohols, catalysts for, 1201
with aldehydes, 1161
with amides, 1197, 1198, 1223
with amines, 1215
with amines, mechanism, 1215
with ammonia or amines, 1214
with carboxylic acids, 722
with carboxylic acids, and DCC, 1210
with DCC, and carboxylic acids, 1217
with ethers, 471
with *Grignard reagents*, 1229
with hydrogen peroxide, 472
with inorganic acids, 1211
with organometallics, 1229
with organometallics, enantioselectivity, 1229
with phosphorus ylids, 1173
with sulfonamides, 1215
aniline derivatives, from alcohols, 485
from aryl halides, 752
aniline, ammonium salts, photolysis, 641
and resonance, 45
canonical forms, 45
derivatives, formation of aryl azides, 497
electron density potential map, 45
meta nitration, 594
nitration under acidic conditions, 594
with CS_2, 1105
anilines, acyl, halogenation, 640
and the *Orton rearrangement*, 640
anilines, ammonium salts, and rearrangement, 640
and the *Hofmann-Martius reaction*, 640
metal mediated rearrangement, 640
anilines, and alkyl nitrites, 847
and *Boyland-Sims oxidation*, 634
and formation of aryl halides, 847
and *Friedel-Crafts alkylation*, 612
and hydroxylation reactions, 634
and the *Fischer-Hepp rearrangement*, 639
and the *Hofmann-Martius reaction*, 640
and the *Mannich reaction*, 1101
and the *Mills reaction*, 793
and the *Reilly-Hickenbottom rearrangement*, 641
and thionitrites, 847
anilines, conjugate addition, 966
anilines, deamination, by reduction of diazonium salts, 1550
diazotization, 788
diazotization, mechanism, 790
anilines, from amines and aryl triflates, 751
from amines, 604, 751–755
from aromatic compounds, 598
from aryl halides, 751–755
from diazo compounds, 1521
from *Grignard reagents*, 754
from hydrazoic acid, 598
from N-nitroamines, 638
from organolithium reagents, 754
from oximes, 800
anilines, halogenation, 606
anilines, halogenation, and Lewis acids, 604
anilines, nitration of, 594
anilines, N-nitro, rearrangements, and radicals, 638
anilines, N-nitroso, rearrangement, 639
anilines, oxidation, to azo compounds, 1455
to nitroso compounds, 1490
with Caro's acid, mechanism, 1490
anilines, pK_a, 338
replacement of amino with alkyl, 787, 793
ring closure, with aldehydes or ketones, 1091
anilines, with alkenes, 897
with aryl nitroso compounds, 793
with azo compounds, 639
with *Caro's acid*, 1490
with hyponitrites and allyl halides, 793
anion relay chemistry, 553
1,3-anionic cycloadditions
anionic cleavage, 718
anionic ligands, and oxidation of alcohols, 1445
anionic oxy-Cope rearrangement, 1401
anionic Snieckus-Fries rearrangement, 637
anions, addition to alkenes, 865
addition to conjugated carbonyls, 866
aryl, 1550
N-nitro, rearrangements, isotopic labeling, 638
anisotropy, and alkenes, 51
and aromatic compounds, 51
and cyclophanes, 51
magnetic, and NMR, 17
annellation, 57
and cyclopentadiene, 59
and strain, 48
Annual Reports in Organic Synthesis, 1586
Annual Reports on the Progress of Chemistry, 1585
annulation, Robinson see Robinson
annulene, and aromaticity, 72
annuleneones, 79
annulenes, 47
annulenes, and alkyne coupling, 840
and antiaromaticity, 69, 79
and aromaticity, 65, 71–75, 78
and *Hartree-Fock* calculations, 72
and HPLC, 82
and Hückel's rule, 72
and Möbius aromaticity, 81, 82
and NMR, 72-, 75, 78, 79, 81
and planarity, 73, 74
and the *Eglinton reaction*, 840
and X-ray crystallography, 75, 80
annulenes, aromatic substitution, 73, 75
aromaticity, 74, 75
atropic, 80
bond alternation, 80
bond angles, 72
bond distance, 75, 80
bridged, 80
conformational mobility, 79, 80
conformations, 72
definition of, 65
diatropic, 73, 76
heat of combustion, 81
N and O analogs, 73
planarity of, 81
strain energy, 73
annulenes,
annulenium cations, 82
anomeric effect, 186, 187
and 2nd row heteroatoms, 188
and hyperconjugation, 187
and parallel dipoles, 187
and solvation, 187
radicals, 243
antarafacial migration, in sigmatropic rearrangement, 1392, 1393
antarafacial overlap, 1035
antarafacial rearrangements, configuration of migrating groups, 1396, 1397
antarafacial, migration, 1392

anthracene compounds, as hosts, 115
anthracene derivatives, Bradsher reaction, 617
anthracene, alkylation of, with organometallics, 785
and resonance, 46
catalytic hydrogenation, 913
electrophilic aromatic substitution, 584
resonance energy, 56
anti addition, 860
and alkenes, 864
anti- Markovnikov, hydration of alkenes, 886
anti nomenclature, 149
antiaromatic compounds, and bond distance, 53
antiaromatic systems, and ring current, 53
antiaromaticity, 67
ab initio calculations, 66
and annulenes, 69, 79
and dipleiadiene, 81
and indacene, 79
and methanoannulenes, 79
and NMR, 69, 81
and paratropic compounds, 81
and stability, 67
for cyclobutadiene, 37
MO calculations, 66
of cyclazines, 79
of cyclobutadienes, 67
of cycloheptatrienyl anions, 71
of oxirenes, 1003
antibodies, and *Michael reactions*, 947
antibodies, catalytic, and epoxidation, 1000
antibody catalyzed *oxy-Cope rearrangement*, 1401
antibody-catalyzed [3+2] cycloadditions, 1017
antibonding orbitals, 4, 5
and S_NAr reactions, 743
of allylic carbocations, 39
anti-Bredt alkenes, by the *Wittig reaction*, 1168
anticlinal conformation, 177
anti-Markovnikov addition, for alkene amination and hydroboration, 899
and aminomercuration, 899
for HBr, peroxides, and alkenes, 883
and hydration of alkynes, 887
and Lewis acid catalyzed, silanes to alkenes, 929, 930
and Lewis acid catalyzed, silanes to alkynes, 929, 930
for borane addition to alkenes, 923
of cyanide, 981
for phosphines and alkynes, metal catalysts, 899
for radicals to alkenes, 960
for silanes to alkenes, 930
for thiols to alkenes, 894
for water to alkenes, 886
Anti-Markovnikov orientation, 875
and amination of alkynes, 898
and hydroboration, 705, 1375
and *Schwartz's reagent*, 981
for esters with alkenes, 975
antimony compounds, with aziridines, 687
antimony pentafluoride and FSO_3H, 320
and cation stability, 210
antimony, and optical activity, 129
antioxidants, and autoxidation, 832
antiperiplanar conformation, 177
antipodes, 123
apparent 1,3-hydride shift, 1332
aprotic solvents, 437
and enolate anions, 687, 1143
aqueous media, and the aldol reaction, 1148
and the *Heck reaction*, 764
and the *Strecker synthesis*, 1182
Ar matrix, trapping carbenes, 1354
Arbuzov reaction, 1170
arenes, see aromatic compounds
arenes, allylic, isomerization, 882
by Friedel-Crafts acylation, 613
by *Friedel-Crafts alkylation*, 609
metal catalyzed addition to alkenes, 939
side chain halogenation, 605
arenium ion mechanism, 569, 570, 572
and mercuration of aromatic compounds, 785
rate, 571
arenium ions, 212, 570
arenium ions, +I and –I effects, 577
ab initio study, 573
and activating groups, 576
and aromaticity, 570
and carbocations, 570
and deuterium ions, 571
and encounter complex, 575
and equilibrium, 577
and Lewis acids, 575
and nitration, 597
and nitronium ions, 575
and radicals, 596
and resonance, 570
and steric hindrance and deprotonation, 572
and the E1 mechanism, 569
and the *Hammond postulate*, 576
and σ-complexes, 570
arenium ions, canonical forms, 585, 591
deactivating groups, 576
destabilization, 577
destabilizing groups, 578
field effects, 577
from radicals, 590
ipso position, 582
isolation, 572
isotope effects, 571, 572
kinetics versus thermodynamic control, 576
mechanism, evidence for, 571–575
partition factor, 571
partitioning effects, 571
reaction with nucleophiles, 582
stability, 574
stabilization, 577
stabilizing groups, 578
stable solutions, 573
substituted, resonance, 577
argon and nitrogen, fluorination of alkenes, 982
argon matrix, 202
and carbenes, 251
argon, as a guest, 114
Arndt-Eistert synthesis, 1238, 1352–1354
and Wolff rearrangement, 1353
enantioselectivity, 1353
aromatic amines, with alkyl nitrites, 606
aromatic carbocation, 736
aromatic carboxylic acids see carboxylic acids
aromatic chameleons, 63
aromatic character, 51
aromatic compounds, acenes, 57
activation groups, 576
acyloxylation, 836
addition of carbenes, 1056
addition of *Grignard reagents*, 955
alkyl substituents also see benzylic
alkylation, 784–787
amidation, 600
amidomethylation, 631
amination with trichloroamine, 599
amination, 599
amination, and haloamines, 599
aminoalkylation, 631
aminomethyl, 798
and anisotropy, 51, 52
and annellation, 57
and aromaticity, 50, 54
and *Benkeser reduction*, 915
and benzylic hydrogens, with radicals, 815
and *Birch reduction*, 914
and cyclodehydration, 616

aromatic compounds, acenes (*Continued*)
and deactivating groups, 576
and DEAD, 600
and decarbonylation, 643
and electron donor-acceptor complexes, 104
and field effects, 21
and formation of aldehydes, 625
and formation of anilines, 598
and formation of biaryls, 620
and formation of nitriles, 633
and formation of thioethers, 632
and geared molecules, 205
and hydrogen exchange, 592
and MO calculations, 33, 34
and radical alkylation, 843
and radical arylation, 844
and resonance, 33, 34, 46
and restricted rotation, 206
and *retro-diols -Alder reactions*, 1310
and strain, 204
and the *Baker-Nathan effect*, 86
and the *Dakin reaction*, 1466
and the *Duff reaction*, 628
and the *Gatterman amide synthesis*, 629
and the *Gatterman-Koch reaction*, 627
and the *Gomberg-Bachmann reaction*, 795
and the *Haworth reaction*, 623
and the *Mills-Nixon effect*, 48
and the *Schiemann reaction*, 608, 792
and the *Wurtz-Fittig reaction*, 513
and thermal extrusion of carbon monoxide, 1310
and π-π-interactions, 104
aromatic compounds, aromatic character, 51
aromatization of six-membered rings, 1437
aromatic compounds, arylation, 784–787, 795
and radicals, 795, 796
mechanism, 795, 796
with aryllead tricarboxylates, 844
aromatic compounds, bond alternation, 48
bromination, 664
aromatic compounds, by *Bergman cyclization*, 1386
by coupling with aryl halides, 844
by cyclotrimerization of alkynes, 1059
by cyclotrimerization, 1061
by decarboxylation, 644
by dihydroxylation of phenols, 1536
by electrocyclic ring closure, 1390
by *Friedel-Crafts alkylation*, 609
by photochemical coupling with aryl halides, 844
by reduction of diazonium salts, 1550
by reduction of diazonium salts, reagents, 1549
by reduction of phenols, 1535
by reversal of *Friedel-Crafts alkylation*, 641
aromatic compounds, canonical forms, 56
catalytic hydrogenation, 912, 913
chlorination, 580, 664
cyanation, 633
deactivated, amination, 599
deactivated, bromination, 606
deuteration, 592
dihydroxylation, 998
directed ortho metalation, 784
distorted, 47
electrolysis, formation of phenols, 635
electronic effects, and Birch reduction, 914
fluorination, 608, 792
formylation, 625
Friedel Crafts acylation, 602
Friedel-Crafts acylation, and reduction, 613
aromatic compounds, from alcohols, 610
from alkenes, 609
from alkyl halides, 609
from aromatic compounds, 843
from aryl ethers, 646
from aryl halides, 647
from aryl ketones, 642
from aryl organometallics, 648
from arylsulfonic acid, 646
from en-diynes, 1386
from organometallics with aryl halides, 523–526
fused ring, 48
fused, and bond distance, 55
fused, and carbanions, 224
aromatic compounds, halogenation, 603
and haloamines, 604
and ionic liquids, 604
and Lewis acids, 606
and NBS, 604
temperature dependence, 607
aromatic compounds, hydroxyalkylation, 615
aromatic compounds, hydroxylation, 634, 830
and the *Elbs reaction*, 634
with potassium persulfate, 634
with *Udenfriend's reagent*, 830
aromatic compounds, iodination, 607
and oxidizing agents, 607
aromatic compounds, lithiation, 784–787
mercuration, 785
metal catalyzed addition to alkenes, 939
metal catalyzed hydrogen exchange, 592
metalation, 635, 784–787
methyl see methyl aromatic
nitrating reagents, 594
aromatic compounds, nitration, 576, 593, 664
and arylboronic acids, 596
with nitronium ion, 595
aromatic compounds, nitro, from N-nitroanilines, 638
aromatic compounds, nitroso, 639
aromatic compounds, ortho-meta-para substitution, 576
aromatic compounds, oxidation, of side chains, alkyl group reactivity, 1466
with *Fremy's salt*, 1453
with phthalocyanines, 1453
aromatic compounds, oxidative cleavage, reagents, 1465
phenylenes, 48
polycyclic, and FVP, 1391
reaction with alkenes, 609
reaction with alkyl halides, 609
reaction with amines, 631
reaction with nitrenes, 1011
reactivity with radicals, 818
aromatic compounds, reactivity, 576, 587, 588
aromatic compounds, reduction, with lithium and ammonia, 913
with metals and ammonia, 913
with potassium and ammonia, 913
with sodium and ammonia, 913
aromatic compounds, replacement of nitro with alkyl, 797
ring expansions, 1011
six-membered rings, 54
strained, 48
strained, and rotation barrier, 205
sulfonation, 600
sulfonation, mechanism, 601
thioalkylation, 632
tormented, 48
tritiation, 593
twisted, 48
UV and IR, and strain, 204
aromatic compounds, with acyl halides, 621, 642
with acyl peroxides, 843

with aldehydes, 615
with alkanes, 610
with aryl organometallics, 620
with aryldiazonium salts, 794
with calcium and amines, 915
with carbocations, 642
with DMSO, 632
with *Fenton's reagent*, 830
with formaldehyde, 619
with hydrazoic acid, 598
with ketones, 615
with lithium and amines, 915
with mercury fulminate, 633
with metals and amines, 915
with methoxyacetyl chloride, 619
with nitrate esters, 593
with nitriles, 632
with nitronium salts, 595
with organolithium reagents, 784–787
with peroxyacids, 634
with phenonium ions, 399
with phosgene, 629
with polyphosphoric acid, 602
with *Pseudomonas putida*, 998
with radicals, mechanism, 809
with sulfonyl halides, 602
with sulfoxides, 632
with sulfur trioxide, 601
with sulfuric acid, 600
with trichloroacetonitrile, 633
aromatic diazonium salts see diazonium salts
aromatic ethers, reductive cleavage, 1537
aromatic groups, β, and neighboring groups, 402
aromatic halogenation, photochemistry, 604
reactivity of halogens, 603
aromatic hydrocarbons, alternant, electrocyclic rearrangement, 1391
oxidation to quinones, 1764
with alkenes, 939
aromatic index see aromaticity index
aromatic rings, and elimination, 1270
as neighboring groups, 398–400
bond distance, 37
aromatic sextet, 51, 54
and benzene, 33
and heterocycles, 57
aromatic side chains, oxidation, reagents, 1466
aromatic sulfonation see sulfonation
aromatic π-cloud, 32
aromaticity index, 58–59
and fulvalenes, 63
and heterocycles, 58
aromaticity, 50
aromaticity, absolute, 37
aromaticity, and absolute hardness, 59
and annellation, 57
and annulenes, 47, 65, 71, 72, 74, 75, 78
and arenium ions, 570
and aromatic compounds, 50, 54
and arynes, 738
and azaannulenes, 73, 74
and *Bader's electron delocalization index*, 59
and *Baird's theory*, 63
and benzenoid hydrocarbons, 53
and benzoannulenes, 75
and benzynes, 738
and bond alternation, 60
and bond distances, 66
and bond order, 59
and calicene, 63
and chemical shift, 51
and circuit resonance energy, 53
and cyclobutadiene, 65
and cyclodecapentaene, 65
and cycloheptatrienyl anion, 71
and cyclooctatetraene, 65, 71
and cyclopentadienide ion, 57, 58
and cyclopentadienyl cation, 69
and cyclophanes, 47
and cyclopropenyl anion, 69
and diamagnetic ring current, 51, 53, 66
and diatropic, 51
and distortion, 47
and fulvalenes, 63
and furan, 57, 58
and heptalene, 62
and heteroaromatic compounds, 54, 58
and *Hückel's rule*, 65, 70
and *Hund's rule*, 66
and hybridization, 48
and hyperconjugation, 86
and isotope labeling, 60
and methanoannulenes, 73, 74
and molecular refraction, 59
and naphthalene, 57
and nitrogen heterocycles, 54
aromaticity, and NMR, 51, 74, 75
and paramagnetic ring current, 53
and partial bond fixation, 55
and phenalene, 56
and phenanthrene, 55
and planarity, 66, 76
and polyacenes, 57
and pyrenes, 75
and pyridine, 54
and pyrrole, 57, 58
and resonance energy, 58
and ring current, 51
and symmetry, 66
and the conjugated-circuit model, 53
and the hardness model, 54
and the *Herndon model*, 53
and the *Hess-Schaad model*, 53
and the pyrylium ion, 54
and the SCF method, 54
and the tropylium ion, 62
and thiophene, 57, 58
and triphenylene, 57
aromaticity, annulenes, 73
aromatic character, 51
aromatic sextet, 54
azulene, 63
bishomoaromatic, 83
C-, 88
fullerenes, 84
fused ring aromatic compounds, 59
heptalene, 63
heterocycles, 58
homoaromatic compounds, 83, 84
local, 59
mesoionic compounds, 82
Möbius, 81, 82
nonaromatic systems, 66
of benzene, 37
parameters, 66
pentalene, 63
phenacenes, 78
relative, for benzene, 36
spherical, 84
spherical, homoaromaticity, 84
squaric acid dianion, 82
superaromatic compounds, 78
sydnones, 82
the cyclopropenyl cation, 66, 67
trihomoaromatic, 83
tropone, 60
Y, 38
aromatization, and metal catalysts, 1438
and selenium or sulfur, 1438
by *Bergman cyclization*, 1386
by chloranil, 1439
by DDQ, 1439
by reaction with quinones, 1439
by reaction with quinones, mechanism, 1439
of enamines, 1439
of six-membered rings, 1437
reagents for, 1439
to form heterocycles, 1439
Arrhenius activation energy, 284
arsenic, and optical activity, 129
arsine ylids, 1169
arsines, and ylid formation, 1169
arsonium ylids, with tosylimines, 1177
aryl anions, 1550
aryl boranes, acyl addition, 1124
aryl carbocations see carbocations

aryl diazonium salts, and the *Heck reaction*, 763
aryl groups, activating for electrophilic aromatic substitution, 580
and radical rearrangement, 1334
migration and radical delocalization, 1335
migration in carbocations, 1342
transition state of rearrangement, 1335
aryl halides, and hyperconjugation, 44
and resonance, 44
dehalogenation, reagents for, 647
aryl nitro compounds, with fluoride ion, 797
aryl organometallics, protonation, 572
aryl radicals, 790, 818, 1550
aryl radicals also see radicals
arylation reactions, and sonochemistry, 309
arylation, and esters, 779
and the *Heck reaction*, 763–768
and the malonic ester synthesis, 616
free radical, 620
intramolecular, 844
Meerwein, 794
of active methylene compounds, 778–780
of alkenes, 762, 794
of amides, 755
of amines, 751
of amines, and microwaves, 752
of amines, intramolecular, 754
of aromatic compounds, 784–787, 795
of enolate anions, 778–780
of enolate anions, photochemical, 780
of haloalkynes, metal catalyzed, 561
of lactams, 755
of oximes, metal catalyzed, 848
of silanes, metal catalyzed, 783
of urea, 755
radical, of aromatic compounds, 844
sulfonamides, 493
arylazides see azides
arylbismuth compounds, 753
arylboronic acids see boronic acids
and aromatic sulfonation, 603
Friedel-Crafts acylation, 624
Pd catalyzed coupling, 620
with alkynes, 941
aryldiazonium salts, fluorination of, 792
preparation, 791
aryllithium compounds, directed ortho metalation, 517
metal halogen exchange, 516
preparation of arylsilanes, 511
aryllithium see organolithium, aryl
arylmercury compounds, 526
arylpalladium salts, 526
arylphosphonium salts, coupling, 755
arylpyridinium salts, coupling with alkynes, 777
arylsiloxanes, 784
arylthallium compounds, arylation reactions, 845
conversion to aryl cyanides, 786
conversion to aryl esters, 786
to fluorides, 786
conversion to nitro compounds, 786
conversion to phenols, 786
aryltrifluoroborates, Friedel-Crafts alkylation, 616
arylzinc compounds, and Negishi coupling, 524
arynes, and aromaticity, 738
and IR, 738, 739
and nonaromatic rings, 739
definition, 738
hetarynes, 739
in the *Diels-Alder reaction*, 738
Pauling resonance energy, 739
regioselectivity in formation, 743, 744
substrate structure and substitution, 743
ASAP papers, 1570
ascorbic acid, and *Udenfriend's reagent*, 830
A-S_E2 mechanism, 456, 457, 863
aspartic acid, specific rotation, 125
asymmetric [3,3]-sigmatropic rearrangement, 1403
asymmetric atoms see chiral, stereogenic
asymmetric *aza-Michael reaction*, 966
asymmetric boranes, 924
asymmetric catalysts, hydrogenation, 918, 919
asymmetric catalytic hydrogenation, 1512
asymmetric dihydroxylation, 995, 996
asymmetric dihydroxylation, *Sharpless*, 996
asymmetric epoxidation see epoxidation
asymmetric *Heck reaction*, 766
asymmetric hydroformylation, 980
asymmetric hydrogen bonds, 99
asymmetric induction, 153
asymmetric induction also see enantioselectivity
asymmetric induction, coupling with allylic carbonates, 529
asymmetric reactions also see enantioselectivity
asymmetric reduction, of prochiral ketones, 1511–1515
asymmetric synthesis, 149–154
asymmetry synthesis also see synthesis
ate complexes, 330, 331
and *Fries rearrangement*, 636
ethers with borane, 921
onium salts, 331
with organolithium reagents, and reduction of alkyl halides, 1533
atom transfer also see hydrogen transfer
atom transfer, of radicals, 806, 867
atomic orbitals, 7
atomic orbitals, overlap of, 4
atomization, heat of, 27, 28
atomization, heat of also see heat of atomization
atoms stereogenic also see stereogenic, chiral
atoms, chiral also see chiral, stereogenic
atropic, annulenes, 80
atropisomerism, and *Friedel-Crafts coupling*, 616
and thioamides, 164
and benzylic alcohols, 131
and conformations, 180
and equilibrium constants, 132
and metal complexes, 132
and pyrroles, 131
and restricted rotation, 132
and sulfoxides, 131
atropisomers, isolation of, 132
atropisomers, with a chiral axis, 140
with biphenyls, 131
with alkaloids, 132
with allenes, 132
with biaryls, 131, 773
with BINAP, 131
with calixarenes, 133
with spiranes, 133
attacking reagent, definition, 261
Au catalyst, alcohols with alkenes, 889
alkylation of amines, 485
and diazo compounds, 692
cyclization of alkyne acids, 1013
cyclization of carbamates, 901
halogenation of alkenes, 982
hydration of alkynes, 887
isomerization of allylic acetates, 1357
Sonogashira coupling, 777
sulfonic acids with alkynes, 894
Au/Ag catalyst, and Friedel-Crafts cyclization, 618
Austin Model, 34

autoxidation formation of hydroperoxides, 832
and antioxidants, 832
and radicals, 833
initiation steps with oxygen, 833
mechanism, 833
of aldehydes, 832
of allylic and benzylic hydrogens, 832
with oxygen, 832
with singlet oxygen, 833
auxiliaries, chiral, and Mukaiyama aldol reaction, 1153
auxiliaries, *Evans*, and enolate alkylation, 546
auxochrome, 293
axial substitutents, in chair conformations, 181
axillaries, chiral, and the aldol reaction, 1147, 1148
axis of symmetry, and chirality, 125
axis, chiral, and helicenes, 140
and alkylidene cyclohexanes, 140
and annulenes, 140
and atropisomers, 140
and cyclophanes, 140
and metallocenes, 140
and molecular propellers, 140
and R/S nomenclature, 140
azaadamantanone, and strain, 199
and Wittig reaction, 199
azaannulenes, 73
aza-Baylis-Hillman reaction, 1128, 1137
enantioselectivity, 1137
aza-Bergman cyclization, 1387
aza-Brook rearrangement, 1431
azabullvalenes, 1405
aza-Claisen rearrangements, and trichloroacetimidates, 1411
metal catalysts, 1410
aza-Cope rearrangements, 1401, 1410
enantioselectivity, 1401
metal catalyzed, 1410
azacrown ethers also see ethers, azacrown
azacrown ethers, 109
photoisomerization, 305
aza-Diels-Alder reactions, 1038
in ionic liquids, 1038
azadienes, chiral, 1038
in the *Diels-Alder reaction*, 1038
azadodecahedranes, 198
aza-ene reaction, 943
azaferrocene, as a catalyst, 1353
aza-Henry reaction, 1157
aza-Michael reaction, 965
and DBU catalyst, 966
enantioselectivity, 966
and microwave irradiation, 966
azapagodanes, synthesis, 198
aza-Payne rearrangement, 467
aza-Wacker process, 1489
aza-Wittig rearrangement, 1375
aza-Wittig reaction, 1173
azeotropes, and formation of borate esters, 702
azeotropic distillation, and acetal or ketal formation, 1081
and enamine formation, 1091, 1092
and esterification of acids, 1202, 1203
and formation of imines, 1091
azetidines, from amines and ditosylates, 483
from lactams, 1166
azide carboxylic acids, reduction and cyclization, 1217
azide ions, and inversion, 389
and rate of ionization, 388
as a leaving group, 706
with epoxides, 489, 490
with epoxides, Mitsunobu, 489
azide-alcohols, cyclization to aziridines, 496
azide-amides, 678
azide-amines, from silylazides, 491
azides, acyl, 1323
and the Curtius rearrangement, 1361
decomposition, 1323
from acyl halides, 496, 497
from aldehydes, 1223
from anhydrides, 497
from esters, 497
from nitrous acid and hydrazines, 1361
azides, acyl, in the Curtius reaction, 497
thermolysis to isocyanates, 1361
addition to alkenes, 1009
azides, alkyl, acid catalyzed ring expansion, 1362
addition to alkenes, 1009
and phase transfer catalysis, 496
and ultrasound, 496
by addition of hydrazoic acid to *Michael-type alkenes*, 901
by the *Mitsunobu reaction*, with alcohols, 1364
from alcohols, alkenes, and hydrazoic acid, 1364
in [3+2]-cycloaddition reactions, 1017
in 1,3-dipolar addition reactions, 1009, 1010
in the metal catalyzed *Schmidt reaction*, 1364
pyrolysis to imines, 1362
with haloalkylboranes, 707
azides, and formation of nitrenes, 258
and the *Dess-Martin periodinane*, 497
and the *Staudinger reaction*, 1529
and triazenes, 707
azides, aryl, from alkyl nitrites, 496
from aniline derivatives, 497
ring expansion, 1362
with haloalkylboranes, 707
azides, carbonylation, 730
conjugate addition, 967
azides, from alkyl halides, 496
from benzotriazoles, 497
from benzylic alcohols, 561
from boronic acids, 496
from hydrazines, 727
from reactions of azide ion, 496
azides, halo, by addition of haloazide to alkenes, 990
reduction, 990
with alkenes, 990
with allenes, 990
with $LiAlH_4$, 990
azides, in [3+2]-cycloaddition reactions, 1015, 1018
metal catalyzed reaction with epoxides, 489
metal, with epoxides, 496
polymer supported, 1053
polymer supported, diazo transfer reagents, 1054
azides, reduction of, 706
reduction to amines, 561
reduction to amines, reagents, 1529
reduction, and amidation of alkenes, 901
azides, silyl, with epoxides, 489
azides, sulfonyl, and diazo-transfer reactions, 678
reduction to sulfonamides, 1530
with active methylene compounds, 678
with amides, 678
azides, tosyl, with organolithium reagents, 706
azides, with aldehydes, 1223
with alkynes, 990
with carboxylic acids, 1218
with CO, 730
with *Grignard reagents*, 754
with iodosobenzene, 1009
with organometallics, 706, 1229
azidomercuration, of alkenes, 902
azines, from aldehydes and ketones, 1092
azinic acids, 94
azirenes, as intermediates in the *Neber rearrangement*, 276, 1359

aziridination, and ring expansion of aromatic compounds, 1011
enantioselectivity, 678
of alkenes, enantioselectivity, 1011
of alkenes, in ionic liquids, 1011
of alkenes, organocatalysts, 1011
of amides, 678
versus diazo-transfer, 678
aziridines, acyl, rearrangement, 1399
addition to alkynes, 1018
and Chloramine-T, 1011
and leaving groups, 432
and the tetrahedral mechanism, 415
as ambident substrates, 450
asymmetric, from alkenes, 1011
aziridines, by extrusion of nitrogen from triazolines, 1316, 1317
by extrusion of sulfur dioxide from sultams, 1319
by reduction of oximes, 1528
by thermolysis of triazolines, 1009, 1010
aziridines, carbonylation, 1245
aziridines, chiral, from reduction of azirines, 1011
conformational stability, 127
enantioselective preparation, 497
enantioselective ring opening, 467
aziridines, from alkene-amines, 483
from alkenes and chloramine-T, 1011
from alkenes, 1009, 1010
from allene-amides, 901
from amino-alcohols, 560
from azide-alcohols, 496
from diazoacetates and imines, 1010
from epoxides, 490
from haloamines, 482
from imines and sulfur ylids, 1177
from imines, 1139, 1177
from iodo azides, 990
from nitrenes and alkenes, 1010
from oximes, 1528
from photolysis of triazolines, 1009, 1010
from sulfimides and electron deficient alkenes, 1010
aziridines, halogenation of, 507
metal catalyzed ring opening, 491
opening by nucleophiles, 538
ring opening to dipoles, 1018
ring opening with metal catalysts, 467
tosyl, 990
tosyl, pinacol rearrangement, 1344
via nucleophilic substitution, 415
via Te ylids, 1177
vinyl, [1.5]-hydrogen shifts, 1395
aziridines, with alcohols, 466
with aldehydes, 467
with alkenes or alkynes, 1018
with allylic alcohols, 538
with amines, 491
with antimony compounds, 687
with borates, 560
with CO_2, 731
with *Grignard reagents*, 538
with mcpba, 1304
with nitrous acid, 1304
with organocuprates, 538
with organolithium reagents, 1019
with organometallics, 538
with TBAF (tetrabutylammonium fluoride), 538
aziridinium salts, and migration of amino groups, 1357
from amine-halides, 1357
with bromide ion, 507
with water, 1357
azirines, from alkynes, 1010
metal catalyzed [4+2]-cycloaddition, 1037
stability, 1010
with water, 1359
azo compounds also see AIBN
azo compounds, 598, 674, 675, 795
azo compounds, and aryl triazenes, 597
and E/Z nomenclature, 163
and electrophilic aromatic substitution, 597
and formation of carbocations, 1547
and loss of nitrogen, 1455
and radicals, 245
and the *Mills reaction*, 793
azo compounds, aryl, from aryl triazenes, 639
azo compounds, by oxidation of amines, 1455
by oxidation of anilines, 1455
by oxidation of arylhydrazines, 1454
by oxidation of hydrazines, reagents, 1455
by reduction of azoxy compounds, reagents, 1549
by reduction of nitro compounds, reagents, 1562
by *Wallach rearrangement*, 1429
azo compounds, decomposition to radicals, 804
azo compounds, E/Z isomerization, 598
azo compounds, E/Z isomers, 305
azo compounds, from anilines, 793
from aryl nitroso compounds, 793
from aryldiazonium salts, 796
from azoxy compounds, 1429
azo compounds, in the *Diels-Alder reaction*, 1037
oxidation to azoxy compounds, 1492
photochemistry, 1391
photoisomerization, 305
reduction to amines, 1530, 1554
reductive alkylation, 1099
water soluble, 804
with aromatic compounds, 795
azo dyes, 597
azobenzenes, by reduction of nitro compounds, 1525
metal catalyzed coupling, 598
azobis compounds, radical initiators, 960
azobis(isobutyronitrile) see AIBN
azo-Cope rearrangement, 1411
azodicarboxylates, 469
alkylation of amides, 494
amines from alcohols, 485
and chiral amides, 679
diethyl see DEAD
with diols, 461
azoles, metal catalyzed coupling with aryl halides, 760
azomethine imines, [3+2]-cycloaddition, 1015
azonine, 73
azopyridines, and esterification, 1203
azoxy compounds, 729
azoxy compounds, acid catalyzed rearrangement to azo compounds, 1429
and ESR, 729
and radicals, 729
and the *Wallach rearrangement*, 1429
by oxidation of amines, 1455
by oxidation of azo compounds, 1492
by reduction of nitro compounds, 1561
by reduction of nitro compounds, reagents, 1562
from alkyl diazotates, 498
from alkyl halides, 498
from nitroso compounds, 728, 1562
from oximes, 728

in [3+2]-cycloaddition reactions, 1015
reduction to amines, 1554
reduction to azo compounds, reagents, 1549
with $LiAlH_4$, 1554
azoxybenzenes, by reduction of nitro compounds, 1525
azulene dianion, 63
azulene, and aromaticity, 63
and fluorescence, 298
and MO calculations, 63
dipole moment, 63
nonalternant hydrocarbon, 63
stability, 63
and carbocations, 213
formylation, 626
radical cations, 249
azulenyl nitrones, and radicals, 236

B strain see strain
B to O rearrangement, 1375
B-(3-pinanyl)-9-borabicyclo [3.3.1]nonane see Alpine-Borane
Bacilllus megaterium, and carboxylation, 630
α-hydroxylation, 1472
with O_2, CH oxidation, 1472
back donation, and carbocations, 861, 888
backside attack, and S_N2, 374, 650
and substitution, 374
bacterial monooxygenase, oxidation of thioethers, 1494
Bader's electron delocalization index, 59
Baeyer strain, 192, 193
Baeyer Villiger reaction, and the *Dakin reaction*, 1467
and epoxidation, 1004
enantioselectivity, 1369
Baeyer-Villiger rearrangement, 1368
and enolizable diketones, 1370
anti versus gauche migration, 1369
aryl migration, 1370
enzymatic, 1369
ionic liquids, 1369
isotope effects, 1370
mechanism, 1370
metal catalyzed, 1369
migratory aptitude, 1369
solventless, 1369
Baird's theory, 63
bakelite polymers, 616
baker's yeast, reduction of aldehydes or ketones, 1510, 1512
reduction of nitro compounds, 1525
reduction of azides, 1529
reduction of conjugated nitro compounds, 919
reduction of oximes, 1527
enantioselective reduction of alkenes, 912
enantioselective reduction of alkynes, 912
Baker-Nathan effect, and hyperconjugation, 86
Baker-Nathan order, and aromatic substitution, 580
and substitution reactions, 423
$B_{AL}2$ mechanism, 462
Baldwin's rules, and enolate anions, 271
and radical addition to alkenes, 868
and radical cyclization, 876, 961, 962
for ring closure, 270–271
ball milling, oxidative amidation, 837
Balz-Schiemann reaction see *Schiemann reaction*
Bamberger rearrangement, 800
mechanism, 800
Bamford-Stevens reaction, 1294
formation of diazo compounds, 1294
mechanism, 1294, 1295
solvent effects, 1294
suitable bases, 1294
banana bonds, and cyclopropane, 194
barbaralane, and *Cope rearrangements*, 1405
Barbier reaction, 1108
and alkyne acyl addition, 1115
and In metal, 1115
and the *Grignard reaction*, 1108
compatible metals, 1109
retro-, 1109
Barbier-Wieland procedure, oxidative cleavage of alkenes, 1464
barbituric acid, 1223
barralene, 1425, 81
and chirality, 135
barrier, energy, to rotation, 165
barrier, intrinsic, 273, 274
barrier, rotation, biphenyls, 130
in acetaldehyde, 178
Barton reaction, 1427
and nitroso compounds, 1428
H-abstraction transition state, 1428
mechanism, 1427, 1428
Barton-McCombie reaction, 1538
base, Hünig's see Hünig's base
base-acid reactions, and elimination, 1271
base-catalyzed, 328
acylation of alcohols, 1200
amide hydrolysis, 1199
amination of alkenes, 897
amine substitution of aryl halides, 734
and arenium ions partition factor, 572
and the *Marcus equation*, 328
coupling aryl halides with active methylene compounds, 779
hydrolysis of amides, 1198
Mannich reaction, 1101
reactions, 328
rearrangements, *O*-tosyl imines to amino ketones, 1359
base-cleavage, of keto esters, 723
of ketones, 723, 724
of ketones, steric effects, 725
base-free *Heck reactions*, 763
base-free *Suzuki-Miyaura coupling*, 774
base-induced addition of amides to aldehydes, 1099
dehydrogenation, 1442
elimination of alkyl halides, 1296
elimination of alkyl halides, suitable bases, 1297
elimination, 1254–1260
elimination, of ethers, 1285
enolate anions, 1146
halogenation, of alkanes, 823
base strength, 313
and E2 reactions, 1272
and E2C reactions, 1269
and ester enolate anions, 1154
and field effects, 334
and hydrogen bonding, 320
and pK, table, 321
and proton sponges, 339
and solvent effects, 322
and the *Claisen condensation*, 1154, 1235
E2 and E1, 1267
elimination versus substitution, 1276
in elimination reactions, 1274
superbases, 322
table, 338, 339
bases, alkenes, 322
alkoxide, and the aldol reaction, 1144
alkoxide, with halo esters, 1161
amide, 482
amide also see amide bases
amidinazines, 322
bases, and active methylene compounds, 539
and coupling of aromatic compounds and aryldiazonium salts, 794
and formation of phosphorus ylids, 1165
and hydrogen exchange, 661

bases, and active methylene compounds (*Continued*)
and hydrogen exchange, aromatic substitution, 592
and keto-enol tautomerism, 665
and pK, 322
and pK, table, 321
and rearrangement of alkynes, 664
and rearrangement of double bonds, 661
and the haloform reaction, 724
and the *Stetter reaction*, 971
bases, as proton acceptor, 312
bases, base strength, 321
and solvents, 322
table, 338
bases, catalysis of the halogen dance, 647
chiral, and enolate alkylation, 546
chiral, and the aldol reaction, 1147
conjugate, 312
conjugate, and leaving groups, 1262
bases, dialkyl amides, 342, 1287
and the aldol reaction, 1144, 1146
bases, enolate anions, 342
formamidines, 322
Grignard reagents, 322
hard, definition, 331
hardness, 331
Hünig's base, 1440
in the *Henry reaction*, 1156
in the *Perkin reaction*, 1161
in the *Wittig reaction*, 1165
IUPAC terminology, 312
bases, LDA, 342, 544
Lewis see Lewis bases
LHMDS, 544
LTMP, 544
Mannich, 1100
bases, non ionic, 1207, 1297
organolithium reagents, 322
organometallics, 322
phenoxides, 1164
phosphazene, 1286, 1401
pK, table, 321
proton sponges, 322, 339
proton-transfer reactions, 323
quinilino-quinolines, 322
reaction with phosphonium salts, 1165
required for generation of enolate anions, 543
sodium amide, 1371
soft, definition, 331
softness, 331
bases, strength, 313
strength, and structure, 334
suitable for E2 reactions, 1274
suitable for elimination reactions, 1276
suitable for the *Sevens rearrangement*, 1371
bases, superbases, 322
bases, with ammonium halides, 1292
with dialkylamino halides, 1307
with DMSO, 786
with episulfides, 1286
with epoxides, 1286
with phosphonium salts, 1166
with silyl enol ethers, 544
basicity, and ambident nucleophiles, 448
and differential hydration, 343
and electronegativity, 337
and hydrogen bonding, 320
and hydrogen bonding, 98
and ionic strength, 346
and leaving groups, 432
and nucleophilicity, 427
and proton affinity, 320
and solvent effects, 343, 344
and steric effects, 338
and the medium, 343
gas phase, 343
in THF and water, 320
of amines, 320
of aromatic compounds, 663
of organolithium reagents versus Grignard reagents, 1109
of pyrrole versus pyridine, 58
solution versus gas phase, 343, 344
table, 321
versus nucleophilicity, and elimination, 1276
basis sets, for Möbius-Hückel method, 1032
basketane, 1424
bathochromic shift, 293
bay region, phenanthrene, 56
Bayer test, and dihydroxylation of alkenes, 994
Baylis-Hillman reaction, 1127
and chiral auxiliaries, 1128
and chiral catalysts, 1128
and DABCO, 1127, 1128
ionic liquids, 1127
and microwaves, 1127
and PEG, 1127
and the *Rauhut-Currier cyclization*, 1128
and sulfolanes, 1127
and ultrasound, 1127
and ureas, 1128
Baylis-Hillman reaction, aza-, 1128, 1137
enantioselectivity, 1137
Baylis-Hillman reaction, double, 1137
enantioselectivity, 1128, 1137
functional group compatibility, 1128
in aqueous media, 1127
intramolecular, 1128
ionic liquids, 1127
mechanism, 1127
metal mediated, 1128
sila-, 1128
9-BBN, 922
and conjugate addition, 957, 958
carbonylation, 1377
reduction of lactams, 1545
with alkenes, 922
Beckmann rearrangement, 1312, 1325, 1359, 1365
Beckmann rearrangement, abnormal, 1312, 1359, 1366
and oxidation of oximes, 1455
and the *Ritter reaction*, 1367
and *Vilsmeier-Haack reaction*, 626
in ionic liquids, 1366
in supercritical water, 1366
mechanism, 1366, 1367
migratory aptitude, 1366
migratory aptitudes of groups, 1328
nitrilium ions, 1367
photochemical, 1367
reagents for, 1365
second order, 1312
solventless, 1366
stereochemistry of migrating groups, 1325
Beilstein CrossFire, replaced by *Reaxys*, 1580
Beilstein, 1578–1580
Beilstein, divisions, 1579, 1580
Beilstein, Ergzänzungswerks, 1579
Beilstein, *Handbuch der Organischen Chemie*, 1578
Beilstein, supplements, 1579
belt cyclophanes, 47
belts, molecular, 118
Benkeser reduction, 915
bent benzene rings, and strain, 206
bent bonds, and cyclopropane, 194
benzamide, hydrolysis, 1073
benzanthracenes, 48
benzene derivatives, and Dewar benzenes, 1387
by cyclotrimerization, 1061
benzene oxide, from oxepin, 1406
benzene, addition of carbenes or methylene, 1056
benzene, alkyl, gas phase protonation, 575
benzene, and bond order, 34
and carbocations, 570
and delocalization, 37
and HMO theory, 36

and metal complexes, 106
and NMR, 51
and resonance, 32, 33
and ring current, 51, 52
and the aromatic sextet, 51
and the diene-cyclobutene interconversion, 1387
aromatic sextet, 33
aromaticity, 37
as a solvent, 714
bent, 206
boat conformation, 48
bond energy, 35
delocalization, and MO, 35
delocalization, and valence bond theory, 35
electrostatic potential map, 32
heat of atomization, 35
heat of hydrogenation, 36
hexaisopropyl, 205
in electrophilic aromatic substitution reactions, 588
molecular orbitals (MO), 33
orientation in substitution, 576
planarity of, 46, 47
protonation of, 580
reactivity, 576
relative aromaticity, 36
resonance energy, 35, 36, 56
substituted, UV spectra of, table, 294
valence isomers of, 1051
benzenechromium tricarbonyl, 106
benzenediazonium chloride, bond distances, 789
benzenediazonium tetrafluoroborate, 795
benzenediazonium also see diazonium
benzeneonium ions, electron potential map, 573
spectral analysis, 573
benzeneseleninyl chloride, chlorination, 826
benzenoid hydrocarbons, and aromaticity, 53
benzenonium ions, 573
and chemical shift, 573
and NMR, 573
benzhydrol, reduction to benzpinacol, 306
benzidine rearrangement, 635, 1415
and [5,5]-sigmatropic rearrangement, 1416
disproportionation, 1415
isotope labeling, 1416
kinetics, 1416
mechanism, 1415, 1416
rate determining step, 1416
benzil, 1113
benzil-benzylic acid rearrangement, 1350
benzil-benzylic acid rearrangements, mechanism, 1350
benzo[*a*]pentalene, by rearrangement of biphenylene, 1391
benzoannulenes, and aromaticity, 75
benzocorannulene, 85
benzocyclobutane derivatives, and bond distance, 24
benzocyclobutenes, 48
by extrusion of sulfur dioxide, 1318
electrocyclic ring opening, 1380
ring current, 49
benzocyclohepatrienyl anion, 71
benzocyclopropene, 48
and strain, 201
benzofuranone, 667
benzofurans, from alkynes, 891
in *Friedel-Crafts cyclization*, 617
metal catalyzed cleavage, 535
benzoic acid, meta-chloro, peroxy see mcpba
benzoic acids, field effects, 335
pK_a, 335
substituent effects, 335
substituents and pK_a, 334
benzoin condensation, 1187
aldehyde deprotonation, 1188
and acyloins, 1188
and addition of HCN to carbonyls, 1181
donor-acceptor atoms, 1187
donors and acceptors, 1188
enantioselectivity, 1188
mechanism, 1187
mixed, 1188
benzoins see hydroxy ketones
benzophenone, and cross conjugation, 42
as a radical inhibitor, 807
benzotriazoles, acyl, acylating reagent, 1232
conversion to azides, 497
with enamines, 551
benzoxazine, tautomerism, 94
benzoylation, benzene, rate and product distribution, 588
rate and product distribution, 588
benzoylnorephedrine, and rearrangement, 351
benzpinacol, from benzhydrol, 306
benzvalene, 1406
benzyl chloroformate see chloroformate
benzylic carbanions, 223, 556
canonical forms, 223
energy levels, 64
benzylic carbocations, 213
canonical forms, 213
energy levels, 64
benzylic CH oxidation, to aldehydes, 1479
benzylic compounds, and autoxidation, 832
and the *Étard reaction*, 1479
α-hydroxylation, 1472
benzylic halogenation, radical, 826
benzylic hydrogenation, with radicals, 815
benzylic radicals, 238, 815
energy levels, 64
benzylic substrates, and S_N2 rate of reaction, 420
and substitution reactions, 420
benzylic α-hydroxylation, 1472
benzyloxylation, allylic CH, 1471
benzyne, 736
as an intermediate, 747
definition, 737
formation, reactivity of halides, 738
fused ring, 739
in the *Diels-Alder reaction*, 276
benzyne, mechanism, 737–739, 743, 751
and cine substitution, 738
and coupling aryl halides with active methylene compounds, 779
and *Grignard reagents* with aryl halides, 761
and isotope labeling, 737
reactions, and acidity, 744
reactions, and carbanion stability, 744
reactions, and field effects, 744
reactivity order of halides, 738
regioselectivity, 738
benzynes also see arynes
benzynes, and aromaticity, 738
and arynes, 738
and E1cB reactions, 1265
and mechanism, 276
as intermediates, 276
in [2+2]-cycloaddition reactions, 1041
in the *Diels-Alder reaction*, 1021
Bergman cyclization, 1386
and Cope rearrangement, 1404
Bergman cyclization, aza-, 1387
betaine-lithium halide intermediate, in the *Wittig reaction*, 1172
betaine-lithium halides, 1168
betaines, and the Wittig reaction, 1168
from phosphines and epoxides, 1169
with NCS, 1172
X-ray structure, 1168
betweenanenes, and strain, 202
BF_3 see boron trifluoride

Bi catalyst, silanes with aldehydes and carbamates, 1099
Bi, and alkylation of lactams, 493
biadamantylidene, 199
biaryls, and atropisomers, 131
  and *Birch reduction*, 914
  and chirality, 130
  and *Friedel-Crafts reaction*s, 619
  and hydroxylation of aromatic compounds, 830
  and iodine, 1390
  and Lewis acids, 619
  and *Suzuki-Miyaura coupling*, 772
  and symmetry, 131
  and the *Cahn-Ingold-Prelog system*, 140
  and the *Gomberg-Bachmann reaction*, 795
  and the *Heck reaction*, 768
  and the *Scholl reaction*, 619
  and the *Suzuki reaction*, 889
  and the *Ullmann reaction*, 768
biaryls, atropisomers, 773
biaryls, by Pd catalyzed coupling of aryl iodides, 511
  by *Ullmann biaryl synthesis*, 748
biaryls, conformations, 180
  coupling, reagents, for, 760, 761
  diamino, by benzidine rearrangement, 1415
  diamino, from hydrazobenzene, 1415
  dimerization of organometallics, 850
  Friedel-Crafts acylation, 625
biaryls, from aromatic compounds, 619, 620, 794, 844
  from aryl halides, 759, 768, 783, 844
  from aryl halides, under radical conditions, 850
  from aryl organometallics, 620
  from aryl radicals, 809
  from arylborinates, 620
  from arylboronic acids, 770
  from aryldiazonium salts and aryltrifluoroborates, 794
  from aryldiazonium salts, 794, 796
  from arylmagnesium compounds, 761
  from arylsulfonic acids, 770
  from nickel complexes and aryl halides, 769
  from trifluoroborates and aryl halides, 775
biaryls, heteroaryl, 760
  hypervalent aryliodine derivatives, 621
  in ionic liquids, 760, 761
  metal catalyzed coupling of *Grignard reagents*, 849
  metal catalyzed formation, 760–762
  noncatalyzed coupling, 760
  photochemical methods, 762
  photochemistry, 1390
  unsymmetrical, preparation of, 759
bicarbenes, 252
bicyclic alkenes, and *Bredt's rule*, 203
bicyclic bridged compounds, 167
bicyclic compounds, and [2+2]-cycloaddition, 1044
  and Bredt's rule, 720
  and decarboxylation, 720
  and S_N1 reactions, 382
  by the *Wurtz reaction*, 514
bicyclo[5.1.0]octadiene, Cope rearrangement, 1404
bicyclobutanes, rearrangement to dienes, 1424
bicyclobutonium ion, 406
bicycloheptadienes, photochemistry, 305
bifluorenylidene, rearrangement, 1391
bifurcated hydrogen bond, 99
Bijvoet, and X-ray analysis, 139, 142
bimolecular substitution see substitution, S_N2
BINAP [2,2′-bis (diphenylphosphino)-1,1′-binaphthyl]
  and atropisomers, 131
  and enantioselectivity, 958
  and reduction of ketones, 1512
binapthols, chiral, 155
BINOL, and alkyne acyl addition, 1115
  and formation of amino-alcohols, 489
  as a catalyst, 1115
biocatalysts, carbonyls with cyanide, 1181
  for the *Henry reaction*, 1156
  for reduction of aldehydes or ketones, 1512
biochemical deracemization, 159
biooxidation, of alcohols, 1451
biosynthesis, cholesterol, 932
  squalene to lanostereol, 932
  steroids, 931
biphenyl, activation energy of rotation, 130
biphenyl, and complex formation, 112
biphenylene, 692
  rearrangement of, 1391
biphenylenediol, and hydrogen bonds, 99
biphenylenes, and [2+2]-cycloaddition, 1041
  pyrolysis and diradicals, 1391
biphenyls, and atropisomers, 131
  and chirality, 130
  and isomerization, 645
  barrier to rotation, 176
  rotation barrier, 130
biradicals, and DNP, 238
  and Norrish Type II cleavage, 303
  and the *Diels-Alder reaction*, 1030
  in the *Bergman cyclization*, 1386
  lifetime, 245
Birch reduction, 249, 909
  and electron transfer, 1435
  and impurities in ammonia, 914
  and reduction of alkenes, 912
  canonical forms, 915
  electronic effects on the substrate, 914
  of aromatic compounds, 914
  of aromatic compounds, mechanism, 914
  of conjugated alkenes, 915
  of heteroaromatic compounds, 914
bis(aldol) condensation, 1145
bis(alkoxides), metal mediated formation of alkenes, 1301
bis(amides), from addition of amides to aldehydes, 1099
  from hydroxyamides, 1099
  from the *Ugi reaction*, 1247
bis(amino)fluorenes, as proton sponges, 339
bis(amino)naphthalenes, as proton sponges, 339
bis(amino)phenanthrenes, as proton sponges, 339
bis(ammonium salts) and Hofmann degradation, 1291
bis(decarboxylation), of dicarboxylic acids, 1468
  of dicarboxylic acids, mechanism, 1469
bis(dimethylamino)naphthalene, 322
2,2′-bis(diphenylphosphino)-1,1′-binaphthyl see BINAP
bis(*Grignard*) reagents, 1109
  with esters, 1228
bis(imines) from aldehydes and imines, 1558
2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide see Lawesson's reagent
bis(oxazolines), and chiral catalysts, 951

bis(phosphines), as chiral ligands in catalytic hydrogenation, 904
as a chiral catalyst, 919
bis(phosphoranes), and out-in isomers, 169
bis(quaternary)ammonium salts, 443
bis(selenenyl) compounds, from alkenes, 1006
bis(thocyanato)alkenes, 988
bis(xanthates) radical elimination, 1301
Bischler-Napieralski reaction, 617
in ionic liquids, 618
bisecting bonds, and conformations, 178
bisecting conformation, 179
bishomoaromatic compounds, 83
bishomocubane, 1424
bismuth compounds, and acetal cleavage, 456
bisulfite, sodium see sodium
bisulfites addition products, 1090
Blaise reaction, 1131
blocking groups, and ketones, 546
for enolate anions, 546
boat conformation, 180
and benzene, 48
cycloheptatrienyl cations, 60
Bobbitt's reagent, and oxidation of alcohols, 1449
Boekelheide reaction, 1373
boiling point elevation, and Grignard reagents, 230
boiling points, and Beilstein, 1578
and hydrogen bonding, 101
and transesterification, 1206
bond alternation, 80
and phenylenes, 48
annulenes, 80
pentalene derivatives, 63
tropone and tropolone, 60
bond angle also see angle
bond angles, 25
bond angles, and conformation, 188
and E2 reactions, 1257
and hybridization, 25
and ionization of alkyl halides, 350
and lone pairs, 27
and orbitals, 25
and p character, 26, 27
and radical hydrogen abstraction, 817
and resonance, 45
and s character, 26
and stability, 45
and strained molecules, 26
bond angles, in annulenes, 72
in carbenes, 251
in carbocations, 350
bond angles, MO calculations, 35
bond angles, of alkanes, 25
of alkyl halides, 25
of BF_3, 8
of carbon tetrachloride, 25
of cyclooctatetraene, 71
of cyclopropenyl cations, 67
of ethylene, 9
of methane, 8
of nitrogen, 6
of O, S, N compounds, 26
of organic compounds, table, 26
of oxygen, 6
of water, 6
bond angles, solvent effects, 6
bond angles, tables, 21
bond cleavage, and mechanism, 261
heterolytic, 261
bond dissociation energy also see energy
bond dissociation energy, and radical halogenation, 825
C-D bond, 285
C-H, and radical reactivity, 813
radicals and reactivity, 819, 820
bond distance, 21
bond distance, and antiaromaticity, 53
and aromaticity, 66
and bond energy, 30
and bond type, table, 22
and cross conjugation, 43
and delocalization, 37, 53
and electron diffraction, 22
and hybridization, 23, 24, 38
and hyperconjugation, 46, 87
and microwave spectroscopy, 22
and molecular mechanics, 190
and orbitals, 22
and π-bonds, 25
and resonance, 45
and s character, 24
and spectroscopy, 22
and stability, 45
and strain, 206
and X-ray diffraction, 21
and X-ray, 23
bond distance, C–D, 24
C–Si, 22
in annulenes, 74, 75, 80
in aromatic rings, 37
in benzenediazonium chloride, 789
in benzocyclobutane derivatives, 24
in benzocylobutene, 49
in bridged compounds, 207
in butadiene, 38
in fused aromatic compounds, 55
in sp^3 carbon compounds, table, 22
MO calculations, 35
tables, 21
bond elongation, and hyperconjugation, 88
bond energy, 27, 96
bond energy, and atom abstraction by radicals, 812
and bond distance, 30
and bond length, 30
and bond type, 30
and bond type, table, 29
and dissociation energy, 27
and double bonds, 30
and electronegativity, 16, 28
and electronic effects, 30
and heat of atomization, 27
and heat of combustion, 27
and hybridization, 29, 30
and hydrogen bonding, 29
and ionic configuration, 30
and keto-enol tautomerism, 90
and orbital interactions, 30
and *Pauli repulsion*, 30
and radicals, 30
and ring strain, 30
and s character, 28, 30
and solvents, 30
and steric factors, 28
and the periodic table, 30
bond energy, bond types, 29
in diatomic molecules, 27
bond energy, of benzene, 35
of hydrocarbons, 28
of hydrogen bonds, 97
of isobutane, 28
of isopentane, 28
of methane, 28
of organic compounds, 30
of propane, 28
bond energy, solvent effects, 29
bond fixation, 69
and PES, 69
in aromatic rings, 55
bond length see bond distance
bond length, and bond energy, 30
and electrophilic aromatic substitution, 586
and s character, 30
of alkenes, 10
bond moments, 18
bond order, and cross conjugation, 42
and MO, of butadiene, 38
and NMR, 55
and resonance, 31
and the aromaticity index, 59
bond order, of benzene, 34
of cyclopentadienide ion, 59
of naphthalene, 55
bond order, ring, 59
valence, 915
bond polarization, 16
bond resonance energy, 59

bond rotation, and kinetics, 283
and the E2 reaction, 1256
in carbenes, 250
in carbocations, 863
in catalytic hydrogenation, 908
in dienes, 1021
in radicals, 244
restricted, 164
bond strength, and periodic table, 30
bond switching, and the *Stone-Wales rearrangement*, 1391
bond type, and bond distance, 22
and bond energy, 30
and bond energy, table, 29
and tautomerism, 89
bonding, charge-transfer, 107, 109
covalent, 3
dipole induced, 109
electrons, 31
in ferrocene, 61
in metallocenes, 61
localized chemical, 3
maximum coordination number, 9
orbitals, 4, 5
orbitals, allylic carbocation, 39
P-P, 169
bonds, and electronic structure, 15
and formal charge, 15
annelated, 48, 49
banana, and cyclopropane, 194
bent, and cyclopropane, 194
C≡N triple bond, 10
C-D, bond dissociation energy, 285
coordinate covalent, 15
delocalized, 37
double bond in ethylene, 9
double bond to O or N, 10
double bonds to S, O, Si, 11
energy and wavelength, 295
in fused ring aromatic compounds, 48, 49
in ylids, 49
ionic, and electronegativity, 18
long bonds, 23
metallocenes, 106
multiple, 9, 11
multiple, and PES, 13
organometallic, 228
PES and methane, 13
π-bonds, and bond distance, 25
and resonance, 44
nonadjacent, stabilization of carbanions, 226
bonds, polar-covalent, and organometallics, 228
polarized, 16
$\sigma-$bonds, and resonance, 33
as neighboring groups, 402
migration, and dyotropic rearrangement, 1430, 1431
migration, and sigmatropic rearrangement, 1392
neighboring group participation, 394
participation, and cyclopropylmethyl groups, 404, 405
rearrangements, metal catalyzed, 1423
bonds, Si=N double bond, 11
bonds, triple, 10
bonds, triple bond in ethyne, 10
triple bonds to O or N, 10
bonds, twisted, and amide hydrolysis, 1197
Boord reaction, 1306
metals used, 1306
with magnesium, 1306
9-borabicyclo[3.3.1]nonane see 9-BBN
borane-amine complex, with aryl halides, 752
borane-dimethyl sulfide complex, 1547
borane-dimethyl sulfide, 702
borane-THF, reaction with alkenes, 921
boranes, acyloxy, from carboxylic acids, and catecholborane, 1222
boranes, addition to alkenes, steric effects, 921
boranes, alkenyl, coupling reactions, 559
from alkynes, 1377
with aryl halides, 559
with NaOH and iodine, 1377
with vinyl halides, 559
boranes, alkyl, and alkene isomerization, 664
carbonylation with imines, 709
conversion of alcohols, 700
coupling to alkyl halides with Ni catalyst, 526
from alkenes, 700
from *Grignard reagents*, 712
halogenation, and radicals, 705
oxidation, mechanism, 701
silver mediated coupling, 989
thermal stability, 664
with ammonia and hypochlorite, 707
with basic hydrogen peroxide, 700
with chloramine, 707
with hydroxylamine-O-sulfonic acid, 707
boranes, alkyne, enantioselectivity, 1379
protonation, 1380
with amides, 1231
with iodine, 1379
organoboranes, allylic addition to aldehydes or ketones, 1124
and acyl addition, 1124
metal catalyzed epoxide opening, 537
with lactams, 1231
boranes, amino, conversion to amines, 483
boranes, and alkyne formation, 1300
and alkynes, reduction to alkenes, 911
and borneol, 1125
and boron-carbon rearrangement, 1375
and chain elongation, 957
and ether solvents, 921
and functional groups, 923
and H.C. Brown, 558
and *Markovnikov's rule*, 921
and Pd catalyzed coupling with aryl halides, 702
and radical cyclization, 959, 963
and radicals, 805, 960
and reduction of enamines, 1547
boranes, *anti-Markovnikov* addition to alkenes, 923
boranes, aryl, chiral, acyl addition, 1124
aryl, coupling, 851
as catalysts, 1520
asymmetric, 924
ate complexes with ethers, 921
carbonylation, 1377
chiral allylic, 1125
chiral boranes, 924
chiral, 924
boranes, conjugate addition, 957
and galvinoxyl, 959
and oxygen, 957
and peroxide, 957
boranes, coupling reactions, 558
boranes, cyano see cyanoboranes
boranes, cyclic, from dienes, 925
boranes, dimers, 921
diols, 701
boranes, elimination to alkenes, 1299
and Zaitsev's rule, 1299
equilibrium, 1299
boranes, enol, 151
exposure to oxygen, 805
formation of aldehydes, 1377
boranes, from alkenes, 558
from boranes, 1358
boranes, halo, addition to aldehydes or ketones, 1124
amination, enantioselectivity, 707
with alkynes, 851
boranes, haloalkyl, with azides, 707
boranes, isomerization, 1358

boranes, isomerization, equilibrium, 1358
metallated alkynes, 1379
migration of boron, 1358
monochloro, with alkenes, 923
boranes, oxidation of, 701, 923
oxidation, stereochemistry, 701
oxidation, to alcohols, 923
oxidation, with hydrogen peroxide and NaOH, 923
oxidation, with perborate, 701
oxidation, with trimethylamine oxide, 701
photochemical isomerization, 664
protonolysis with carboxylic acids, 911
radical coupling, mechanism, 851
radical initiator, 960
boranes, reaction with oxygen, 699
boranes, reaction with oxygen, and radicals, 964
boranes, reagents for reduction, 1509
boranes, reduction, enantioselectivity, 1509
of aldehydes or ketones, 1508
of azo compounds, 1554
of carboxylic acids, 1515
of nitriles, 1522
of oximes, 1521
reagents, 1522
with hydride reagents, 1377
with lithium borohydride, 1377
boranes, reference acid, for bases, 339
sulfurated, with Grignard rearrangements, 712
synthetic transformations, 923
thermal isomerization, 1299
thermolysis, 1358
boranes, trialkyl, alkylation, 558
exposure to air, 797
preparation from alkenes, 558
with halogens, 704
with haloketones, 548
boranes, vinyl also see boranes, alkenyl
boranes, vinyl, conjugate addition, 958
dimerization, 851
from alkynes, 925
halogenation, 705
oxidation with peroxide to give ketones, 1380
stereochemistry, 705
boranes, vinyl, with iodide and hydroxide, 1377
boranes, with aldehydes, enantioselectivity, 1125
with aldehydes, transition metal catalysts, 1124
with alkenes, 558, 700, 920–926, 1299
with alkynes, 1377
with allylic alcohols, 923
with aryl halides, 774
with carbon monoxide, 1375
with chiral additives, and reduction, 1513
with CO, 1376, 1377
with CO, mechanism, 1376
with cyanide ion, 1376
with dianions of carboxylic acids, 1377
with diazo compounds, 559
with dihalo nitriles, 558
with epoxides, enantioselectivity, 506
with haloketones, 558
with haloketones, mechanism, 559
with halomethyl ethers, 1376
with ICl, 705
with iodine and NaOH, 1377
with iodoboranes, 1379
with mercuric chloride, 1377
with metal alkyne anions, 1379
with oxygen, mechanism, 805
with silanes, 1538
with thioketones, 1231
with transition metals, 957
with trihalo esters, 558
with tri-tert-butoxyaluminum hydride, 1377
borates, acyl addition, 1124
addition to aldehydes, 1124
borates, alkyl, from alcohols, 702
from boron trichloride, 702
with *Grignard reagents*, 701
borates, alkyl-alkynyl, coupling, 851
and reduction of nitro compounds, 1528
aryl, and *Suzuki-Miyaura* coupling, 774
by reduction of aldehydes or ketones with boranes, 1509
conjugate addition, 958
borates, enol, and the aldol reaction, 1146
borates, from boron trioxide, 702
from organometallics, 701
hydrolysis to alcohols, 1509
polymer bound, with aldehydes, 1124
reducing agents, 1522
borates, trifluoro see trifluoroborates
borates, with alcohols, 701
with aziridines, 560
with epoxides, 560
with organolithium reagents, 953
borderline mechanism, and substitution, 388
boric acid, catalyst, 966
from alkylborane oxidation, 700
boric acid-amino acids, and resolution, 173
boric anhydride, with keto esters, 721
borinates, and decarboxylation, 721
aryl, formation of biaryls, 620
aryl, with aromatic compounds, 620
borinates, enol also see enol
borinates, enol,
and enolate anions, 547, 1146
and the aldol reaction, 1146, 1147
and the *Ireland-Claisen rearrangement*, 1410
from conjugate addition of boranes, 957
halogenation, 672
hydrolysis, 957
borneol, with boranes, 1125
boron-to-carbon rearrangements, and reduction of boranes, 1377
Borodin, Alexander, 854
borohydride exchange resin, and reduction of alkyl halides, 1532
and reduction of alkynes, 911
and reduction of nitro compounds, 1525
borohydride, dimethylamino, lithium, reduction of nitriles, 1522
borohydride, sodium, and microwaves, 1504
and reduction of acyl halides, 1544
and reduction of aldehydes or ketones, 1503
and reduction of carboxylic esters to alcohols, 1516
and reduction of epoxides, 1502
and reduction of imines, 1520
functional group reactivity, 1505
in acid, reduction of alcohols, 1535
on alumina, 1504
reduction of carbonyls, and disproportionation, 1511
reduction of conjugated carbonyls, 1504
reduction of nitrilium ions, 1523
with alcohols, 1511
with boronic acids, reduction of carboxylic acids, 1515
with chiral additives, 1513
with Lewis acids, reduction of ethers, 1543
borohydride, tetraalkylammonium, reduction of carboxylic acids, 1515

borohydride, triethyl, lithium, and reduction of amides, 1545
and reduction of epoxides, 1502
and reduction of tosylates, 1537
borohydride, tri-sec-butyl, lithium see L-Selectride
borohydride, tri-sec-butyl, potassium see K-Selectride
boron ate complexes, and coupling reactions, 515
boron compounds, and ester condensation reactions, 1234
chiral, reducing agents, 1527
conjugate addition, 955
boron trichloride, with alcohols, 702
boron triflate, and asymmetric aldol reactions, 1148
boron trifluoride, and conjugate addition of boranes to alkyne-ketones, 959
and conversion of alkenes to alcohols, 452
and orbitals, 8
electronic structure, 15
with alkynyl epoxides, 1305
with amines, and amides, 1222
with tosylaziridines, 1304
boron trioxide, with alcohols, 702
boron, electronic configuration, 8
boron, migration in organoboranes, 1358
boronate esters, conjugate addition, 958
boronates, 560
addition to imines, 1136
alkylation, 558
alkynyl, homocoupling, 843
allylic with aldehydes, 1124
oxidation, 1376
vinyl, ene reaction, 943
vinyl, with organolithium reagents, 533
with nitrones, 1136
boronic acids, 560
boronic acids, addition of imines, 1136
boronic acids, alkyl, in the *Stille coupling*, 683
metal-mediated coupling, 524
with alkynes, 684
with vinyl halides, 683
boronic acids, alkylation, 558
boronic acids, alkynyl, in the Sonogashira coupling, 778
boronic acids, and arylation of amines, 754
and formation of amides, 1217
and polymerization, 702
boronic acids, aryl, and halide exchange, 757
and nitration of aromatic compounds, 596
coupling, 771
hydrolysis to form phenols, 746
in the *Suzuki-Miyaura coupling*, 770, 774
metal catalyzed, addition o to alkynes, 940
metal catalyzed, addition to alkynes, 941
metal catalyzed, coupling with methylthioalkynes, 778
metal catalyzed, cyclization of dienes, 940
metal catalyzed, reaction with arylsulfonic acids, 770
metal mediated, reaction with thiols, 750
oxidation, 746
with acyl halides, 774
with alkyl halides, 889
with aryl halides, 770–775
with sulfonyl halides, 1252
as a catalyst, 1216
boronic acids, carbonylation, of aryl halides, 782
carbonylation, with conjugated ketones, 978
catalysts for conversion of carboxylic acids to amides, 1216
boronic acids, conjugate addition, 955, 958
boronic acids, conversion of alcohols to esters, 1485
conversion to amines, 484
conversion to azides, 496
coupling, with alcohols, 770
coupling, with allylic alcohols, 532
fluorination, 705
boronic acids, from borates, 701
from *Grignard reagents*, 701
from organometallics, 701
from trifluoroborates, 701
boronic acids, homocoupling, 770
boronic acids, in the *Suzuki-Miyaura coupling*, 560, 701
boronic acids, metal catalyzed coupling, 701
addition to aldehydes, 1124
coupling to allene and allylic halides, 935
formation of, 701
boronic acids, oxidation of, 702
problems with isolation, 702
boronic acids, vinyl, halogenation, 705
stereochemistry, 705
with aryl halides, 890
boronic acids, with acyl halides, 1225, 1226
with acyl halides, Pd catalyst, 1226
with aldehydes, enantioselectivity, 1124
with alkyl halides, 772
with allylic acetates, Pd catalysts, 560
with carbamoyl halides, 1226
with carboxylic acids, 1131
with carboxylic acids, metal catalyzed, 1131
with diazonium salts, 772, 793
with epoxides, 560
with imines, enantioselectivity, 1136
with isocyanates, 1140
with metals, conjugate addition, 958
with nitriles, 1140
with O_2, and a Pd catalyst, 1485
with propargylic alcohols, 1305
with thioesters, 1231
boronic esters, alkynyl, cyclotrimerization, 1062
carbonylation, 708
for reduction, 1509
from catecholborane and alkenes, 702
preparation, nonaqueous workup, 702
vinyl, from vinyl *Grignard reagents*, 702
with organolithium reagents, 1377
boron-to-carbon rearrangement, 1375
boron-to-carbon rearrangements, and formation of aldehydes, 1377
boroxines, and *Suzuki-Miyaura coupling*, 774
bosons, 123
Bouveault reaction, 1229
Bouveault-Blanc procedure, 1506
reduction of esters to alcohols, 1516
bowl-shaped hydrocarbons, 85
bowl-to-bowl inversion, 84
Boyland-Sims oxidation, 634
Bradsher reaction, 617
BrCl, with alkenes, 983
Bredt, anti- see *anti-Bredt*
Bredt's rule, and pyrolytic elimination, 1281
and bicyclic alkenes, 203
and cyclic alkenes, 203
and decarboxylation, 720
and elimination reactions, 1269, 1270
and enol formation, 720
definition, 203
bridged annulenes see annulenes
bridged bromine radicals, and ESR, 869

bridged carbocations, 395
bridged intermediates, radicals, and bromine, 868
bridged ions, from alkynes, 874
bridged radicals, 811
bridged radicals see radicals
bridged systems, IUPAC names, 195
bridgehead alkenes, 204
bridgehead atoms, and chirality, 129
bridgehead carbocations, 217, 382
bridgehead carbons, and electrophilic substitution, 651
and S_N1 reactions, 382
and S_N2, 376, 424
bridgehead diazonium ions, 598
bridgehead hydrogens, reactivity with radicals, 817
bridgehead radicals, 243
British Abstracts, 1578
bromamine-T and $RuCl_3$, 1492
and oxidation of amines to amine oxides, 1492
bromides see halogens
bromides, acyl see halides, acyl
bromides, acyl, from aldehydes, 829
bromides, alkyl, and *Grignard reagents*, 231
rates of solvolysis, 419
from phenols, 757
bromination, 822
bromination, and *Markovnikov's rule*, 875
bromination, aromatic, and the *Sandmeyer reaction*, 605
bromination, by the *Wohl Ziegler reaction*, 826
of alkenes, 862
of alkenes, reagents for, 983
of alkynes, 862
of aromatic compounds, 603, 664
of aromatic compounds, and NBS, 604
of benzene, rate and product distribution, 588
of toluene, rate and product distribution, 588
reagents, for alkenes, 983
with NBS, 826
bromine-alkene complex, 983
bromine radicals, 808
bromine, addition to alkenes, activating substituents, 872
stereoselectivity, 862
cyclic intermediates, 870
bromine, and acetone, and mechanism, 285
and conversion of alcohols to esters, 1485
and substitution, 652
and the *Hell-Volhard-Zelenskii reaction*, 673
bromine, from NBS, 827, 828
halogenation of aromatic compounds, 605
syn addition to alkenes, 864
bromine, with alkenes, 828, 982
with alkenes, and peroxide, 1336
with alkenes, reactivity in methanol, 872
with alkenes, reactivity of alkenes, 872
with alkynes, 862
with aromatic compounds, 603
with cyclobutane, 195
with cyclopropane, 194
with heptalene, 62
with phenanthrene, 56
with sodium hydroxide, and Hofmann rearrangement, 1360
with UV light, 982
bromite, sodium see sodium
bromoacetophenone, with amines, 421
bromoacids, 136
bromoalkynes, with imidazole, 562
bromoamine, with alkenes, 1011
bromoform, flash photolysis, 252
with *Grignard reagents*, 717
bromonium ions, 606, 860, 879, 983
and halohydrin formation, 985
and neighboring group mechanism, 392
from alkenes, 828, 862
with alkynes, 862
bromonium radical, 811
bromothiophene, 755
Brønsted acidity, and Lewis acidity, 338
Brønsted acids, 313–318
and pinacol rearrangements, 1342
diamine, and asymmetric aldol reactions, 1148
Brønsted bases, 320–322
Brønsted catalysis equation, 328
Brønsted coefficient, and acetal hydrolysis, 456
Brønsted equation, and equilibrium constants, 329
and free energy, 328
and *Marcus equation*, 329
and mechanism, 1269
Brønsted plot, and nucleophilicity, 430
and S_N2, 379
Brønsted relation, 356
Brønsted theory, 312
Brønsted α, 329
Brønsted-Lowry acids, and decarbonylation of aryl aldehydes, 643
and Friedel-Crafts acylation, 622
and Friedel-Crafts alkylation, 610
and rearrangement of alkenes, 664
halogenation of aromatic compounds, 607
rearrangement of N-nitroaniline, 638
Brook rearrangement, 553, 1431
and dithianes, 1432
aza-, 1431
homo-, 1431
reverse, 1431
synthetic applications, 1432
brosylates, and solvolysis, 385, 396
leaving groups, 432, 433
Brown $\sigma*$ values, electrophilic aromatic substitution, 588
Brown, H.C., and hydroboration, 558
brucine, and resolution, 155
Bruylants reaction, 531
and iminium ions, 532
BSA, and the *Tsuji-Trost reaction*, 528
bubbles, and ultrasound, 445
Bucherer reaction, 746, 756
Buchwald-Hartwig cross coupling reaction, 752
buckminsterfullerene, 84
buckybowls, 84
buffers, and elimination, 1263
bullvalene, 1406
and *Cope rearrangement*, 1405
tautomeric forms, 1405
Bunnett-Olsen equation, and solvent acidity, 326, 327
Bunte salts, formation of disulfides, 479
from alkyl halides, 479
hydrolysis, 476
Burgess reagent, and conversion of carboxylic acids to amides, 1216
and dehydration of amide to nitriles, 1313
and dehydration of oximes to nitriles, 1311
structure, 1311
butadiene, and cross conjugation, 42
and delocalization, 37
bond distance, 38
delocalization, 38
electrostatic potential map, 37
energy of, 37, 38
heat of atomization, 38
hybridization, 38

butadiene, and cross conjugation (*Continued*)
MO bond orders, 38
orbitals of, 37, 38
resonance energy, 37, 38
with HCl, 870
butadiene-cyclobutene, and orbital symmetry, 1388
butadiyne, 39
butane, and conformations, 176–178
gauche conformations, 178
butenolides, and *Claisen rearrangement-Conia reaction*, 1409
from allene-carboxylic acids, 893
butyllithium also see organolithiums
butyllithium, and dithianes, 553
with dimethylhydrazones, 548
with phosphoranes, 1172
with thioanisole, 554
tert-butyllithium, solvents and aggregation state, 229
butyllithium-TMEDA, 784

Cadiot-Chodkeiwicz reaction, 841
mechanism, 842
cage compounds, 113
and urea, 155
Cahn-Ingold-Prelog rules, and absolute configuration, 138–141
and alkenes, 163
and diastereomers, 148
and diastereotopic hydrogen atoms, 172
and E/Z isomers, 163
and enantiotopic hydrogen atoms, 172
R/S nomenclature, 138–141
calcium ions, and crown ethers, 111
calcium peroxide diperoxohydrate, 833
calcium, in amines, reduction of aromatic compounds, 915
calculations, ab initio, and Lewis base strength, 330
and nitrenes, 258
and nonclassical carbocations, 396
norbornyl carbocation, 404
calculations, acidity, ab initio, 319
calculations, and conformations, 174
and isotope effects, 286
and prismane, 198
azaannulenes, 74
carbocation stability, 215
Möbius aromaticity, 81
strain energy, 193
wave mechanical, 4
calicene, and aromaticity, 63
calixarene-proton complex, 110
calixarenes, 110
and atropisomers, 133
and chirality, 135
and suppression of dediazoniation, 1550
catalysts for enolate alkylation, 548
chiral, and phosphine oxides, 155
enantiopure, 110
calixresorcarenes, NMR, 51
C-alkylation, enolate anions, 447
of enols, 544
calorimetric measurements, 327
and acidity scales, 327
calorimetric methods, and kinetics, 282
calorimetry, picosecond optical grating, 1056
Cambridge structural database, and hydrogen bonding, 98
camphene, from isoborneol, 1338
camphor, 167
Cannizzaro reaction, 1562, 1563
and dihalides, 452
and diions, 1563
and hydride transfer, 1435
and organobases, 1563
and reduction of aldehydes, 1509
and the aldol reaction, 1563
and *Tollens' condensation*, 1563
crossed, 1563
crossed, and the *Tollen's condensation*, 1563
crossed, and the *Tollens' reaction*, 1164
in D_2O, 1564
mechanism, 1563
tetrahedral intermediate, 1564
canonical forms also see resonance
canonical forms, 31, 43
+M and –M effects, 348
and 1,3-dipoles, 1014, 1016
and aromatic compounds, 56
and aromatic rings, 55
and heteroatom stabilized carbocations, 215
and hyperconjugation, 46, 86, 87
and nucleophilic aromatic substitution, 733
and the *Birch reduction*, 915
and vinyl chloride, 40
canonical forms, of acrolein, 45
of diazonium salts, 788
of 4-chloronitrobenzene, 586
of allylic carbanions, 223
of allylic carbocation, 409
of aniline, 45
of arenium ions, 585, 591
of aryldiazonium salts, 788
of benzylic carbanions, 223
of benzylic carbocations, 213
of cyclopentadienide ion, 58
of denralenes, 43
of enolate anions, 92
canonical forms, of acrolein, 45
of ethylene, 44
of fluorene carbanions, 656
of molecules, 6
of naphthalene, 55
of nitro compounds, 94
of N-ylids, 225
of phenanthrene, 56
of pyrrole, 58
of triphenylmethyl radical, 238
capped cyclodextrins, 117
caprolactams, conformation, 189
captodative effect, 69
and esr, 240
and radicals, 239, 240
caranylboranes, 924
carbalkoxylation, of heterocycles, 846
carbamates, addition to alkenes, 900
and ortho metalation, 784
and oxyamination, 1007
and the *Knoevenagel reaction*, 1160
tert-butoxy, stability, 1214
by carbonylation of amines, with alcohols, 731
by electrolytic carbonylation of amines, 731
by *Hofmann rearrangement*, 1360
by insertion of nitrenes, 680
conjugate addition, 966, 967
carbamates, cyclic, alkylation, 493
from alkene-carbamates, 901
from isocyanates and oxetanes, 1085
via Hofmann rearrangement, 1361
carbamates, from alcohols with isocyanates, 1085
from alcohols, 731
from amines, 470, 555
from aryl halides, 754
from carbonates and amines, 1220
from carbonates, 1215
from chloroformates and amines, 1214
from cyanogen chloride and alcohols, 1086
from isocyanates, 498
from keto esters, 1476
carbamates, hydrolysis, 1198
addition-elimination mechanism, 1197
mechanism, 1196, 1197

in the *Suzuki-Miyaura reaction*, 771
carbamates, lithiated allylic, 1160
lithiation, 555
metal catalyzed conjugate addition, 966
reaction with isocyanates, 1085
torsional barrier, 180
with aldehydes or ketones, enantioselectivity, 1160
with alkynes, 562, 707
with allylic silanes, 1099
with NBS and DBU, 1361
carbamic acids, by hydrolysis of isocyanates, 1085
carbamoyl chloride, 629
carbamoyl amines, 1212
carbamoyl lactams, in the *Friedel-Crafts acylation*, 621
carbamoyl nitrenes, 680
carbanion intermediates, and Wolff-Kishner reduction, 1542
carbanion ion pairs, and E1cB reactions, 1267
carbanion mechanism, 866
and E1cB reactions, 1262
carbanionic character, and E2 reaction, 1266
carbanions, 208
addition to cations, 865
carbanions, allylic, 223, 657, 657, 662, 662, 870
and [3+2]-cycloaddition, 1020
and [3+2]-cycloaddition, mechanism, 1020
carbanions, and conjugation, 223
and cyclopropyl stabilization, 224
and field effects, 225
and fused aromatic compounds, 224
and homoenolates, 226
and hybridization, 227
and isoinversion, 656
and isoracemization, 655
and organomagnesium compounds, 222
and organometallic compounds, 221
and pyramidal inversion, 227
and racemization, 226
and rearrangement, 234
and resonance stabilization, 227
and resonance, 654
and retention of configuration, 227
and spectroscopic analysis, 224
and substitution at vinyl carbon, 414
and UV, 662
and vicarious nucleophilic substitution of hydrogen, 786
and X-ray crystallography, 224
carbanions, aromatic, 226
carbanions, aryl, and NMR, 915
benzylic, 223
boron stabilized, with aldehydes, 688
chiral, 227
conducted tour mechanism, 656
conjugated to heteroatoms, 224
definition, 221
diphenylmethyl, 223
dithianes, acylation of, 1236
fate of, 233
fluorene, 656
formation of a stable salt, 224
carbanions, from alkenes, 233
from cleavage of alkoxides, 718
from DMSO, 786
from radicals, 248
carbanions, generation of, 233
hydrogen exchange, 655
Knoevenagel, with allylic esters, 528
lifetime, 866
methyl, 227
methylsulfinyl, 786, 1086
methylsulfonyl, with esters, 1236
Na or K, 228
nitrile, 224
oscillation, 227
overlap with d orbitals, 225
oxidation to radicals, 234
protonation of, 221
pyramidal, and racemization, 654
pyramidal, and the S_E1 mechanism, 654
rate of isotope exchange, 655
Rb or Cs, 229
carbanions, reaction with a proton, 233
resonance stabilized, 223, 657
solvation, 227
solvation, by leaving groups, 655
carbanions, stability, 222, 223
and benzyne reactions, 744
and hybridization, 225
and hyperconjugation, 225
and lone electron pairs, 225
and s character, 222, 225
and transmetallation, 712
carbanions, stabilization, and the counterion, 226
by fluorine, 696
by nonadjacent π-bonds, 226
by S or P, 225, 228
by sulfonyl, 225
carbanions, stabilizing groups, 226, 720
stereochemistry, solvent effects, 655
strain and stability, 225
structure and stability, 227
triphenylmethyl, 223
via decarboxylation, 233
via deprotonation, 233
vinyl, 227
vinyl and configurational stability, 228
carbanions, with aldehydes, 234
with alkyl halides, 234
with allylic halides, 515
with aryl nitro compounds, 786
with electrophiles, 233
with ketones, 234
carbazoles, in the *Diels-Alder reaction*, 1022
preparation, 630
carbene addition, 1010
mechanism, 1055
carbene complexes, by diazo transfer reactions, 1054
metal, 1017
carbene insertion, 691
amides, 692
and ultrasound, 692
intramolecular, 692
ring expansion, 692
carbene rearrangements, 1337
carbene rearrangements alsosee rearrangements
carbene to carbene rearrangement, 1354
carbene transfer, 1051
carbenes, 208, 249–257, 1051
carbenes, acyl, rearrangement to ketenes, 256
carbenes, addition, of imines, 254
of pyrroles, 1056
to alkenes, 250, 254, 1051
to alkenes, and steric hindrance, 1053
to alkenes, enantioselectivity, 1054
to alkenes, rate constants, 1052
to aromatic compounds, 1056
to benzene, 1056
to dienes, 1053
to indoles, 1056
carbenes, addition, ring expansion and strain, 1057
carbenes, alkyl, rearrangement, 691
alkylidene, 252
allylic, and rearrangement, 691
amino, 252
carbenes, and [1+2]-cycloaddition, 1051
and amidation, 837
and bond angles, 251
and chiral ligands, 1122
and CIDNP, 694
and cleavage of diazoalkanes, 463
and diazoalkanes, 463
and diradicals, 1055

carbenes, and [1+2]-cycloaddition (*Continued*)
and elimination, 257
and EPR, 251
and formylation, 627, 628
and hemicarcerands, 252
and *Hund's rule*, 250
and hydrogen abstraction, 693
and IR, 251
and IUPAC mechanisms, 435
and leaving groups, 435
and nitrogen extrusion reactions, 1317
and nonbonded electrons, 250
and radicals, 245, 693
and resonance, 693
and sonochemistry, 309
and spin trapping, 251
and stereochemistry, 251
and substitution, 257
and syn addition, 1055
and synthesis, 255
and the *Reimer-Tiemann reaction*, 627, 628
and the *Simmons-Smith procedure*, 1051
and *Wolff rearrangement*, 256
and X-ray crystallography, 255
and ylids, 693
carbenes, as catalysts, 967, 1181
carbenes, bicarbenes, 252
chiral, 252
coupling, 255
cyclopropane rearrangements, 256
decay, singlet to triplet, 250
decomposition of diazoalkanes, 254
definition, 249
diaryl, 251
diboron, 252
dichloro, 252
dichlorocarbene, 249
dichloromethylene, 249, 252
dihalo, with aldehydes or ketones, 1177
dimerization, 255
direct insertion, 694
electrochemical generation, 253
electronic effects of substituents, 1055
electrophilic, 1055
fate of, 253
Fischer carbene complexes, 1017
Fischer carbenes, 1054
formyl, lifetime, 254
fragmentation, 257
fragmentation, to radicals, 257
free, 1053
carbenes, from alkyl halides, 253
from carboxylate ions, 253
from cyclopropane dihalides, 1347
from cyclopropane photolysis, 253
from diazirines, 254
from diazomethane, 250, 253
from ketenes, 253
carbenes, generation by ultrasound, 691
generation of, 253
geometry, 252
halo, 1052
carbenes, heterocyclic, 967
and cyclotrimerization, 1061
catalyst for *Claisen rearrangement*, 1408
organocatalysts, 1108
carbenes, imidazolium complex, and alkyl halide coupling, 518
carbenes, in an argon matrix, 251
carbenes, insertion reactions, 254, 255, 1051
enantioselectivity, 692
into O-H, 692
isotopic labeling, 693
mechanism, 693
metal catalyzed, 692
carbenes, ipso attack, 628
carbenes, isolation of, 249
carbenes, metal, 1053, 1244, 1423
carbenes, metal also see metal carbenes
cyclotrimerization, formation of heterocycles, 1063
carbenes, metal complexes, 1053
carbenes, methylene, 249, 252
octylidenes, 252
oxychloro, 257
reaction with diazoalkanes, 256
carbenes, reactivity, 255, 691
carbenes, rearrangement, 256, 257, 1051
and ketones, 1353
carbenes, silyl, 252
carbenes, singlet, 250, 1055
and insertion, 694
decay to triplet state, 250
solvent effects, 254, 255
stability, 249, 255
stable, 255
structural types, 1051
structure, 249
substituent effects, 1055
transient grating spectroscopy, 254
trapping in a matrix, 249
trapping in an Ar matrix, 1354
carbenes, triplet, 250, 257, 1055
and insertion, 694
persistent, 251
carbenes, vinyl, 252
with alkynes, 1055
with ketenes, 1053
with thioketones, 1178
carbenium ions, chloro-, 1106
carbenoids, 1051, 1055
and diazoalkanes, 463
and insertion, 694
and ring expansion, 1347
chiral, 252
definition, 254
elimination reactions, 254
formation of, 1051, 1052
homologation, 691
mechanism of formation, 1052
reactions, 1057
carbocations also see oxocarbenium ions
carbocations, 208, 1069
carbocations, acetyl, 215
carbocations, acyl, 215
and *Friedel-Crafts acylation*, 624
and Lewis acids, 625
from acyl halides, 624
stability of, 215
carbocations, adamantyl, 217, 1328
addition of alkenes, 220
alkene neighboring groups, 396
alkynyl, isotopic labeling, 415
alkynyl, stability, 415
carbocations, allylic, 39, 212, 213, 657, 877
and [3+2]-cycloaddition, 1020
and cyclopropyl carbocations, 1346
and ion pairs, 410
and rearrangement, 420
and resonance, 420, 869
canonical forms, 409
from addition to dienes, 869
from allenes, 876
from cyclopropanes, 1389
from cyclopropyl halides, 423
HOMO, 1389
protonation, 1390
carbocations, and absolute configuration, 396
and acetal hydrolysis, 457
and acid catalyzed dehydration of alcohols, 1284
and addition of alkyl halides to alkenes, 991
and addition to cyclopropanes, 880
and alcohol addition to alkenes, 889
and alcohol dehydration, 463
and alkene rearrangement, 662
and alkyl halides, 211, 381
and allylic rearrangement, 409
and arenium ions, 212, 570
and aromatic compounds, 642
and azulenes, 213
and benzene, 570
and bond angles, 350
and bond rotation, 861, 863

and carbonylation of alkyl halides with alcohols, 566
and chair conformations, 216
and charge distribution, 212
and chemical shifts, 217
and cleavage of ketones, 725
and conjugated dienes, 212
and conjugation, 212
and cyclobutane ring opening, 1424
and cyclopropyl groups, 213
and cyclopropylmethyl groups, 404, 405
and *Demyanov rearrangement*, 1345
and diazonium salts, 434, 690
and double hyperconjugation, 212
and E1 mechanism, 1261
and electrophilic substitution, 659
and electrophilicity, 379
and elimination transition state, 1274
and ESCA, 407
and ester hydrolysis, 1196
and formation of double bonds, 220
and *Friedel-Crafts* alkyl substrates, 613
and *Friedel-Crafts alkylation*, 613, 1323
and *Friedel-Crafts reactions*, 927
and halohydrin formation, 985
and homoconjugation, 212
and hydration of alkenes, 885
and hydride extraction, 1435
and hydrocarboxylation, 973
and hyperconjugation, 86, 211, 212, 217, 287, 420
and insertion, 690
and ion pairs, 210
and IR, 209, 216
carbocations, and Lewis acids, 642
and *Markovnikov's rule*, 874
and NMR, 209, 214, 216–218, 398, 401
and nonclassical carbocations, 404
and norbornyl compounds, 382
and PES, 216
and phenonium ions, 399
and pK, 215
and planarity, 382
and polyene cyclization, 932
and Raman spectroscopy, 216
and rearrangement, 690, 885, 1322
and rearrangement, of alkenes, 664
and resonance, 219, 420, 875
and reverse *Friedel-Crafts alkylation*, 642
and ring expansion, 1345
and S_N1 mechanisms, 1323
and S_N1 reactions, 379, 382
and solvolysis of alkyl halides, 287
and spectroscopic analysis, 216
and *Stieglitz rearrangement*, 1368
and strain, 398
and superacids, 210, 379, 407, 725, 1390
and the counterion, 209
and the gegenion, 209
and the *Hammond postulate*, 418, 875
and the *Hofmann Martius reaction*, 641
and the *Lederer-Manasse reaction*, 616
and the pinacol rearrangement, 1343
and the *Prins reaction*, 1184
and UV light, 382
and *Wagner-Meerwein rearrangement*, 1338–1342
and Zaitsev's rule, 1338, 1339
carbocations, aromatic, 736
carbocations, aryl, 736
and arylation of aromatic compounds, 796
and the *Gomberg-Bachmann reaction*, 796
and tritium decay, 416
carbocations, back donation, 861, 888
benzylic, 213
benzylic, canonical forms, 213
bicyclobutonium, 406
bridged, 395
bridgehead, 217, 382
tert-butyl, 661
tert-butyl, X-ray, 211
calculations of stability, 215
canonical forms, 215
carbonyl, exo attack, 1339
chiral, in [4+3]-cycloadditions, 1064
carbocations, conjugation, to cyclobutanes, 214
to cyclopropanes, 214
to heteroatoms, 214
carbocations, coupling, with alkenes, 690
carbocations, cubyl, 383
cyclobutyl, 214, 1345
cyclopropenyl, 66, 67
cyclopropyl, and ring opening, 1389
carbocations, cyclopropylcarbinyl, 395, 1345
[1,2]-sigmatropic hydrogen shift, 1345
and *Demyanov rearrangement*, 1345
carbocations, cyclopropylmethyl, 213
cyclopropylmethyl, and NMR, 406
degenerate, 1324
destabilizing groups, 421
detection of, 382
deuterium labeling, and rearrangements, 1327
dications, 213
direction of rearrangement, 1323
dissociation energy, table, 216
dodecahedral, 217
equilibration of, 407
fate of, 218
carbocations, formation of, on zeolites, 215
carbocations, formation, formation, by ionization of alkyl halides, 218
of a stable salt, 224
carbocations, from alcohols, 210, 219
alkanes, 492, 725, 1341
from alkenes, 219
from alkyl diazonium compounds, 219
from amines, 219
from anions and nitrous acid, 219
from azo compounds, 1547
from bicyclic compounds, rearrangements, 1331
from diazo compounds, 1327
from isoborneol, 1338
from radicals, 248
generation of, 218
geometrical structure and migratory aptitudes, 1331
halogens with alkenes, 863
halonium ions and substituent effects, 864
heteroatom stabilized, 214, 219
carbocations, homoallylic, 395
in superacids, 661, 1332
in-out isomerism, 102
isolable, 421
long range rearrangements, 1331
loss of a proton, 220
memory effect, 1331
methoxymethyl, 214
methyl, X-ray, 209
migration of aryl groups, 1342
multiple, 1, 2-shifts, 1340
neopentyl, rearrangement, 1326
nomenclature, 208

carbocations, nonclassical, 218, 394, 1340, 1340
ab initio calculations, 396
and 1,3-*Wagner-Meerwein rearrangement*, 1340
and cyclobutyl groups, 405
and cyclopropylmethyl, 404, 405
and delocalization, 395
and laser Raman, 404
and NMR, 396, 398, 404, 1340
and norbornyl systems, 395
and nortricyclane, 404
and rearrangement, 404
and solvolysis, 396, 397
and stability, 403
and X-ray electron spectroscopy, 404
arguments against, 396, 397, 403
controversy, 1340
cyclopropylcarbinyl, 395
in superacids, 1340
π route, 395
σ route, 395
carbocations, norbornadienyl, and NMR, 396
carbocations, norbornyl, ab initio calculations, 404
and NMR, 404
classical argument, 403
in stable solutions, 403
stability, 404
carbocations, on Zeolite Y, 215
open, and halonium ions, 864
oxygen stabilized, 618
tert-pentyl, rearrangement of, 1324
phenyl, 215
photochemical generation, 382
planar, 383
primary, and the S_N1 mechanism, 419
propargyl, 213
propeller shaped, 217
rate of reaction with nucleophiles, 427
reaction with nitriles, 1239
reaction with nucleophiles, 220
rearrangements, 210, 220, 566, 726, 889, 928
sequential 1,2-shifts, 1332
silyl, 219
carbocations, stability, 215, 874, 875
ab initio molecular orbital calculation, 862
and cleavage of alkanes, 726
and direction of rearrangement, 1323
and NMR, 1324
and pinacol rearrangement, 1343
and selectivity, 588
and solvolysis, 383
and X-ray crystallography, 209
in strong acids, 210
open versus bridged, 862
carbocations, stabilization, 861
by cyclopropyl groups, 395
by oxygen, 1184
carbocations, stabilizing groups, and migratory aptitudes, 1329
and rearrangements, 1329
carbocations, stable, 213, 690
carbocations, stable solutions of, 210
carbocations, stereochemistry, 217
of elimination, 1274
carbocations, structure, and delocalization, 211
and NMR, 1390
carbocations, substituent effects, 218
tervalent, 661
thiacarbenium ions, 219
triarylmethyl, 217
trications, 213
trihomobarrelyl, 217
triphenylmethyl, 213, 217
trityl, 213
twisted, 1331
carbocations, α-substitution, 420
carbocations, vinyl, 215, 415, 865
and p orbitals, 415
and tritium-decay, 416
from alkynes, 865
stabilizing groups, 415
carbocations, with alkenes, 859
with water, 1184
X-ray crystallography, 209
carbodiimides also see DCC
by dehydration of ureas, 1314
from isocyanates and phosphine oxides, 1241
from ureas, 1314
oligomeric, 1241
polymer supported, 1217
with alcohols and NBS or NIS, 503
carbohydrates, and cyclodextrins, 116
and osazones, 1093
and sonochemistry, 309
carbolines, iodination, 607
carbon 14, 1327, 1329
and cyclopentadienide ion, 58
carbon acids, 319
carbon-carbon bond, and bond rotation, 250
carbon dioxide, addition of amines, 1105
as a guest, 114
as a leaving group, 644, 1210, 1238, 1242, 1309, 1310, 1318, 1319
critical temperature, 363
electrofugal activity, 644
extrusion from lactones, 1318
formation of carboxylate salts, 629
from decarboxylation, 644
metal catalyzed carboxylation of alkynes, 893
organolithium reagents and dienes, 978
carbon dioxide, supercritical, alkene isomerization and *the Heck reaction*, 766
alkene metathesis, 1420
and alcohol dehydration, 364
and carbonylation, 364
and catalysis, 363
and nucleophilicity, 442
and polymers, 364
and reactivity, 363
and S_N2, 437
and *Stille coupling*, 682
and substitution reactions, 442
and *Suzuki-Miyaura coupling*, 771
and synthesis, 364
and the *Diels Alder reactions*, 1023
and the *Glaser reaction*, 841
and the *Heck reaction*, 764, 766
aryl halides with amines, 751
as a solvent, 841, 1510
enzyme reductions, 1510
formation of carbamates, 731
metal catalyzed carbonylation, 975
nitrile oxide cycloaddition, 1016
oxidation of alcohols, 1442
carbon dioxide, thermal extrusion from lactones, 1310
carbon dioxide, with amides, 731
with amines, 731
with aromatic compounds, 629
with aryl halides, 1132
with aziridines, 731
with *Grignard reagents*, 1132
with organolithium reagents, 708, 1132
with organometallic reagents, 1132
with organometallics, 708
with phosphorus ylids, 1173
with ylids, 1173
carbon disulfide, and *Friedel-Crafts acylation*, 622
base catalyzed addition to ketones, 1164
with alcohols, 1086
with alcohols and NaOH, 1289
with amines or anilines, 1105
with amines, 1104
with dihalides, 478
with *Grignard reagents*, 1132
with hydroxylamine, 1527

with organolithium reagents, 1132
carbon leaving groups, 718
carbon migrations, [1,j]-sigmatropic, 1396
carbon monoxide, amines with alkynes, 978
aminocarbonylation, 975
and alcohols, 566
and coupling reactions, 536
and halo ketones, 567
and hydrocarboxylation, 973, 974
and hydrogenation of dienes, 905
and metal catalyzed carbonylation, 975
and metal catalyzed hydroformylation of alkenes, 979
and the *Heck reaction*, 767
and the *Koch reaction*, 972
as a leaving group, 1309, 1317
carbonylation of alkyl halides, 565
carbonylation of amines, 730
carbonylation reactions, 974
extrusion from lactones, 1310
extrusion from cyclobutanone, 1317
hydrocarboxylation, 972
preparation of divinyl ketones, 565
surrogates, 781
thermal extrusion from ketones, 1309
water and alkenes, 972
carbon monoxide, with allene-alkenes, 975
with aryl halides and alcohols, 781
with azides, 730
with boranes, 1375, 1376, 1377
with epoxides, 471
with *Grignard reagents*, 708
carbon [3+2]-cycloaddition, 1019
carbon NMR see NMR
carbon nucleophiles, 510, 758
carbon tetrachloride, and bond angle, 25
and dipole moment, 19
with organolithium reagents, 716
carbon tetrahalides see halides
Carbon-13 NMR Spectra, 1583
carbon-14 labeling, 277, 615, 737, 1113, 1348, 1372
carbonate ester salts, 1086
carbonate esters, 1086
carbonates, allylic, and the *Tsuji-Trost reaction*, 528
coupling, asymmetric induction, 529
coupling, with active methylene compounds, 530
coupling, with enolate anions, 529
metal catalyzed, coupling, 529
Pd catalyst, with amines, 484
with vinyl silanes, 511
carbonates, and amines, 1220
and resonance, 40
cyclic, carbonylation of allene alcohols, 893
dialkyl, from alkyl halides, 470
enol, alkylation, 545
from alcohols, 470
from alkyl halides, 470
from haloformic acids, 1086
from phosgene and alcohols, 1086
in Suzuki-Miyaura coupling, 771
metal, with ketones, 1164
methyl magnesium, with ketones, 1163
methylmagnesium, indirect carboxylation, 1163
propargylic, 477
with aldehydes, 1236
with amines, 1215
with ketones, 1236
carbon-H hydrogen bonding, 101
carbonium ions see carbocations
carbon-metal bonds, 221
carbons, MS of, 209
carbonyl carbon, and HSAB, 430
and nucleophilicity, 430
nucleophilicity order, 430
carbonyl compounds, conjugated, addition of organometallics, 949–956
carbonyl compounds, acyl addition, 1067
conjugated, addition of vinylsilanes, 930
cyanation, 689
α-hydroxylation, reagents, 1473
in the *Diels-Alder reaction*, 1037
metal catalyzed addition of organotin compounds, 1118, 1119
pK_a, of an α-proton, 542
reactivity in the tetrahedral mechanism, 1074
structural compatibility with organometallics, 1115
carbonyl ene reaction, 943
carbonyl nitrenes, insertion, 680
carbonyl oxides, [3+2]-cycloaddition, 1015
and ozonolysis, 1460
syn/anti isomers, 1463
carbonyl ylids, [3+2]-cycloaddition, 1015
carbonyl, and bonding, 11
carbonyl, conjugated with alkyl halides, 1129
carbonyl, metal mediated, 709
carbonyl, pK_a of α-proton, 542
carbonylation, and alcohols, 974
and alkenes, 974
and amines, 974
and conjugated ketones, 978
and formation of amides, 631, 730, 1223
and formation of aryl carboxylic acids, 629
and formation of ureas, 730
and *Friedel-Crafts acylation*, 625
and *Grignard reactions*, 1111
and metal catalysts, of alkenes, 973
and supercritical carbon dioxide, 364
and the *Pauson-Khand reaction*, 976
carbonylation, aryl halides with alcohols, 781
microwave irradiation, 781
carbonylation, double, 536, 568
carbonylation, intramolecular, with aryl halides, 781
carbonylation, metal catalyzed, 972, 973
and AIBN, 975
and *Stille coupling*, 975
in supercritical carbon dioxide, 975
dienes, 976
carbonylation, of 9-BBN, 1377
of alcohols, 566
of alkene-dienes, 976
of alkenes, 975
of alkyl halides, 567
of alkyl halides, metal catalyzed, 566
of alkyl halides, metal mediated, 564
of alkynes, 974
of alkynes, metal catalyzed, 893
of allene alcohols, 893
of amines, 567, 568
of aryl halides, with organometallics, 782
of azides, 730
of aziridines, 1245
of boranes, 1377
of boronic esters, 708
of diazonium salts, metal catalyzed, 848
of imines, 978
of organometallics, 564, 708
of vinylmercury compounds, 709
carbonylation, reactions, and metal complexes, 567
carbonylation, *Reppe*, 973

carbonylative cross coupling, 525
carbonyldiimidazole, and acylation of amines, 1218
and esterification, 1205, 1206
formation of amides, 1217
carbonyls, addition of alcohols, 1081
addition of water, 1075
addition of water, mechanism, 1076
and *Cram's rule*, 1068
approach of nucleophiles, 1071, 1072
catalysis of nucleophilic attack, by nucleophiles, 1073
conjugated and reactivity, 1069
conjugated, addition of anions, 866
directionality of approach of nucleophiles, 1072
facial selectivity, 1068
formation of stereoisomers, 1067.1068
fragmentation of halo ethers, 1307
nucleophilic addition, 1068
oxygen reacts as a base, 1069
α stereogenic center, 667
trajectory of nucleophilic approach, 1071, 1072
with hydrogen sulfide, 1087
with *Lawesson's reagent*, 1089
carbophilic addition, 1067
carborane acids, 324
carboxylate anions, aryl, rearrangements, 645
by reduction of esters, 1538
decarboxylation, 719
formation of carbenes, 253
rearrangements, and *Henkel reactions*, 645
resonance, 644
carboxylate salts, alkylation, 552
and lactone formation, 469
and organolithium reagents, 1131
and the *Kolbe reaction*, 853
diamines, 552
from aromatic compounds, 629
radical coupling, 853
with acyl halides, 1209
with aryl halides, 749
with cyanogen bromide, 1241
with cyanogen bromide, mechanisms, 1242
with LDA, 1237
with organolithium reagents, 1229
with $SOCl_2$, 1210
carboxylates, ammonium, from carboxylic acids and ammonia, 1216
ammonium, pyrolysis, 1216
lead, chiral, 1456
radioactive, 277
carboxylation, by enzymes, 630
enzymatic, in supercritical carbon dioxide, 630
indirect, 1163
ketones, 1163
of alkenes, metal catalyzed, 978
of phenoxide, 630
vinyllithium compounds, 656
with *Bacillus megaterium*, 630
carboxylic acid-alcohols see hydroxy acids
carboxylic acid-aldehydes, intramolecular reaction, 1155
carboxylic acid-azides, reduction and cyclization, 1217
carboxylic acid-ketones, 1163
carboxylic acids also see dicarboxylic acids
carboxylic acids, acidity, 20
carboxylic acids, acylation, 1209
acylation, with aminoboranes, 1218
addition, to alkenes, 892
alkene, by pyrolysis of lactones, 1288
α-alkylation, 557
alkyl halides with $NaNO_2$, 566
alkylation with diazo compounds, 471
carboxylic acids, and ethers, 1206
and field effects, 20
and free energy, 345
and hydrogen bonding, 97
and inductive effects, 20
and ionization, 345
and resonance effects of pK_a, 336
and tautomerism, 95
and the *Dakin-West reaction*, 722
and the *Japp-Klingemann reaction*, 675
and the *Koch reaction*, 972
and the *Koch-Haaf reaction*, 972
and the *Kolbe-Schmidt reaction*, 629
and the *Mitsunobu reaction*, 1203
and the *Schmidt reaction*, 1363
and the *Wolff rearrangement*, 1353
carboxylic acids, anhydrides and decarboxylation, 722
aromatic, and the *Hammett equation*, 352
aryl, and the *von Richter rearrangement*, 797
aryl, by oxidation of aromatic side chains, 1465
aryl, from aryl nitro compounds, 797
aryl, ortho alkylation, 552
as nucleophiles, 1189
benzoic see benzoic acid
bromo, 136
carboxylic acids, by carbonylation of alkenes, 973
by cleavage of ketone esters, 723
by hydrolysis, of anhydrides, 1190
by hydrolysis, of carboxylic esters, 1190–1197
by hydrolysis, of ketenes, 1354
by hydrolysis, of nitriles, 1080
by oxidation, of alcohols, 831, 1443, 1483
reagents for, 1483
carboxylic acids, by oxidation, of aldehydes with chromic acid, mechanism, 1486
with permanganate, mechanism, 1487
of aldehydes, 1443, 1484–1487
of aldehydes, mechanism, 1486
of aldehydes, reagents for, 1485
of boranes, 925
of enol ethers, 1489
carboxylic acids, by oxidative cleavage, of alkenes, 1463
of alkynes, 1464
of ethers, 1484
carboxylic acids, by pyrolysis, of esters, 1288
by pyrolysis, of esters, mechanism, 1288
by the *Arndt-Eistert synthesis*, 1352–1354
by the *Barbier-Wieland procedure*, 1464
by the *Willgerodt reaction*, 1566
carboxylic acids, by-products of epoxidation, 998
chain extension, 1353
cleavage of methyl ketones, 724
carboxylic acids, conjugated, by the *Doebner modification*, 1158
by the *Perkin reaction*, 1161
decarboxylation, 720
formation of vinyl nitro compounds, 838
from alkynes, 973
hydrogenation in ionic liquids, 919
with NBS and lithium acetate, 856
with nitric acids and AIBN, 838
carboxylic acids, conversion to dithiocarboxylic esters, 1089
carboxylic acids, conversion to hydroperoxides, 472

carboxylic acids, decarboxylation, 718, 1238
mechanism, 1238
carboxylic acids, dehydrating agents, 1284
dehydration, 1210, 1284
dehydrative acylation, 622
derivatives, aldol-like reactions, 1153–1155
deuterated, addition to cyclic alkenes, 878
carboxylic acids, dianions, with boranes, 1378
with esters, 1237
carboxylic acids, dilithiated, 699
carboxylic acids, esterification also see esterification
carboxylic acids, esterification, 1202–1206
carboxylic acids, esterification, and azeotropic distillation, 1202, 1203
and excess alcohols, 1202
and microwave irradiation, 1203
and steric hindrance, 349
catalysts, 1203
carboxylic acids, esters see carboxylate esters
carboxylic acids, exchange, with acyl halides, 1224
with amides, 1210
with esters, 1210
carboxylic acids, field effects, and pK_a, 334
carboxylic acids, formation, of hydrazones, 675
carboxylic acids, from diazoketones, 1352
from acyl halides, 1353
from acyl halides, and ethers, 1201
from acyl peroxides, 700
from alkyl halides, 566, 941
from amides, 1197
from anhydrides and alcohols, 1201
from aromatic compounds, 629
from boranes, and acid dianions, 1377
from carbon dioxide, and phosphorus ylids, 1173
from cleavage of diketones, 723
from diazonium salts, 848
from esters, 1190
from *Grignard reagents*, 700
from ketenes, 1353
carboxylic acids, from ketones, 675, 723, 724, 1566
from malonic esters synthesis, 540
from nitriles, 563
from nitro compounds, 797
from organometallic reagents, 568
from organometallics, and carbon dioxide, 1132
from oxazolines, 557
from peroxyacids, and alkenes, 998
from primary alcohols with Jones reagent, 1443
from tetracarbonylferrates, 567
from the haloform reaction, 724
carboxylic acids, gas phase pyrolysis, 1288
carboxylic acids, halo, 508
lactone formation, 269
with aldehydes or ketones, 1161
carboxylic acids, halogenation, 672
and amide bases, 673
electrolysis, 673
carboxylic acids, hydroboration, and reduction of alkenes, 911
hydrocarboxylation of alkenes, 972
hydrolysis of acyl halides, 1189
hydrolysis of amides, 1197–1200
in *Friedel-Crafts acylation*, 621
in the *Hell-Volhard-Zelenskii reaction*, 673
metal catalyzed elimination, 1288
oxidation, to peroxyacids, 1487
oxidation, with hydrogen peroxide, 1487
oxidative decarboxylation to alkenes, 1467
oxidative decarboxylation to alkenes, 1467
oxidative decarboxylation, mechanism, 1468
photochemistry, esterification, 1203
photolysis, 854
pK_a, table, 335
preparation of *Weinreb amides*, 1217
prochiral, dehydrohalogenation, 1298
propargyl, from alkynes, 1133
carboxylic acids, pyrolysis see decarboxylation
carboxylic acids, pyrolysis, Ei mechanism, 1288
carboxylic acids, pyrolysis, with thorium oxide, 1238
carboxylic acids, radical alkylation, of heterocycles, 845
carboxylic acids, radical coupling, 840
carboxylic acids, reagents, for conversion to alkyl halides, 855
carboxylic acids, reduction, of hydrocarbons, 1546
to alcohols, 1515
to aldehydes, reagents, 1518
with borane, 1515
carboxylic acids, reductive cleavage, of esters, 1538
reversible esterification, 1202
salts, see carboxylate salts
structural limitations of decarboxylation, 719
structure, and decarboxylation, 719
vinyl, with NBS, 856
carboxylic acids, with alcohols and DCC, 1205
with alcohols, 1202–1206
with alcohols, acid catalyzed, 1202
with alcohols, equilibrium, 1202
with alkyne-boranes, 1379, 1380
with aluminum hydride, 1515
with amides, 1218
with amines and DCC, 1217
with aminoboranes, 1218
with ammonia, 1216
with anhydrides, 722
with azides, 1218
with boronic acids, 1131
with boronic acids, metal catalyzed, 1131
with cyanuric fluoride, 1224
with DCC and H_2O_2, 473
with enol esters, 1210
with halogenating reagents, 1223
with hydrazoic acid, 1363
with imidazole, 1216
with imines, 1244
with inorganic acid halides, 1224
with isocyanides and carbonyls, 1247
with isocyanides, 1246
with *Lawesson's reagent*, 1211
with Li and amines, 1518
with *Mukaiyama's reagents*, 1284
with organolithium reagents, 1131, 1229
with phosphoramides, 1218
with pyridine, 845
with quinolines, 845
with sulfonamides, 1218
with the *Burgess reagent*, 1216
with thiols, 1206
with trichloroisocyanuric acid, 1216
with triphenylphosphine and carbon tetrachloride, 1224
carboxylic anhydrides, 688
carboxylic anhydrides also see anhydrides

carboxylic esters also see esters
carboxylic esters, acetoacetic, and alkylation, 540
carboxylic esters, α-acetoxylation of ketones, 1475
acidity of γ-protons, 549
acidity, 336
addition to alkenes, 970
carboxylic esters, allylic also see carbonates, allylic
and π-allyl palladium, 528
coupling with enolate anions, 528
coupling with lactones, 528
coupling with organometallics, 527
isomerization, 1357
metal mediated coupling, 527
with active methylene compounds, 610
with aryl halides, 528
with enolate anions, 530
with keto acids, metal catalyzed, 856
with *Knoevenagel carbanions*, 528
carboxylic esters, alkylation, 542
carboxylic esters, amines and enzymes, 1220
carboxylic esters, and acylation of amines, microwaves, 1220
and DBU, 470
and dimethyl carbonate, 470
and DMF acetals, 470
and E^i reactions, 1280
and formation of acyl azides, 497
and *Friedel-Crafts alkylation*, 611
and silyl ketene acetals, 1152
and S_N2 reactions, 437
and the *Baylis-Hillman reactions*, 1127
and the *Claisen condensation*, 1154, 1234
and the *Hunsdiecker reaction*, 855
and the *Katritzky pyrylium-pyridinium method*, 470
and the *Pinner synthesis*, 1086
and the *Reformatsky reaction*, 1131
and the *Schotten-Baumann procedure*, 1200
and the *Stobbe condensation*, 1154
carboxylic esters, aryl, by carbonylation, 781
arylation, 779
as acylating reagents, 1236
base catalyzed condensation, 1234
basic hydrolysis, and isotope labeling, 1071, 1072
basic hydrolysis, tetrahedral mechanism, 1071
Bouveault-Blanc procedure, 1506
carboxylic esters, by acyloxymercuration, 892
by carbonylation of alkenes, 975
by carbonylation of aryl halides, 781
by cleavage of keto esters, 723
by *Favorskii rearrangement*, 1350
by hydration, of alkynes, 888
by hydrolysis, of imino esters, 1085
by oxidation, of aldehydes, 1484, 1485
by oxidation, of allylic alcohols, 1484
by the *Mitsunobu reaction*, 469
by the *Tischenko reaction*, 1564
by transesterification, 1206
carboxylic esters, carbonylation, of alcohols and alkyl halides, 565
of alkyl halides and alcohols, 564
carboxylic esters, catalysts for hydrolysis, 1191
α-CH oxidation of ethers, 1478
chloroformates, with silanes, 1539
carboxylic esters, cleavage, 477
with NaCN-HMPA, 564
with Zn and acetic acid, 470
carboxylic esters, condensation, with aldehydes or ketones, 1153, 1154
carboxylic esters, conjugated, 1, 4-addition of alcohols, 891
from boronic esters, 708
from organomercury compounds, 709
intramolecular addition of an aldehyde, 1123
photolysis, 882
proton acidity, 549
with the *Petasis reagent*, 1174
with tosylimines, 1137
carboxylic esters, demethylation, 477
diazo, with ketones, 1175
dihalo, with boranes, 558
dithiocarboxylic, with organocuprates, 1132, 1133
elimination, and oxalates, 1289
enol content, 90
carboxylic esters, enol, 1200
and transesterification, 1208
from alkynes, 893
hydrolysis, 1197
hydrolysis, mechanism, 1197
with carboxylic acids, 1210
with ketones, 545
carboxylic esters, enolate anions, and *O*-acylation, 1233
carboxylic esters, epoxidation, formation of glycidic esters, 1003
exchange, with carboxylic acids, 1210
formation by S_N2 reactions, 468
formation of glycidic esters, 1003
formation with microwave irradiation, 469
carboxylic esters, from acyl halides, and alcohols, 1200
from acyl halides, with ketones, 1084
from acyl hydrazides, 1209
from acyl peroxides, 835
from acyl tosylates, 471
from alcohols, and boronic acids, 1485
from aldehydes, 1484, 1485, 1564
from aldehydes, reagents, 1564
from alkenes, with carboxylic acids, 892
from alkyl halides, 468, 566
from amides. with alcohols, 1208
from anhydrides, 471
from anhydrides, with alcohols, 1201
from aryl halides, 748, 749
from arylthallium compounds, 786
from carboxylate salts, 468
from carboxylic acids, with alcohols, 1202–1206
from chloroformates and *Grignard reagents*, 1226
from diazo compounds, with acids, 471
from diazomethane, with acids, 471
from ethers, 471
from *Grignard reagents*, with chloroformates, 1227
from halo ketones, 1350
from hydrocarbons, 835
from ketenes, 892, 1083
from ketones, with peroxy acids, 1368
from methyl ketones, 724
from organometallics, 703
from oxazolidinone amides, 1209
from oxazolidinone amides, 1209
from oxonium salts, 470
from tetracarbonyl ferrates, 567
from trihalides, 452
from vinylorganometallics, 708

carboxylic esters, gem-diacetates, 1469
glycidic, from conjugated esters, 1003
carboxylic esters, halo, with aldehydes or ketones, 1161
with alkoxide bases, 1161
with hexamethyldisilazide, 1161
with imines, 1162
carboxylic esters, heteroaryl, by carbonylation, 781
from aryl halides, 781
carboxylic esters, homologation, 1232
hydration of alkyne ethers, 888
carboxylic esters, hydrolysis, 556, 1190–1197
activation energy, 1192
and microwave irradiation, 1191, 1192
and carbocations, 1196
and freezing point depression, 1195
and isotopic labeling, 1195, 1196
and microwave irradiation, 1192
and molecular dynamics, 1192
and nucleophiles, 1191
and phase transfer, 1192
and retention of configuration, 1195
and silica gel, 1191, 1192
and solubility effects, 1192
and steric hindrance, 1191
and ultrasound, 1192
enantioselectivity, 1192
enzymatic, 1191
equilibrium, 1190
IUPAC mechanism, 1192–1197
mechanism, 356, 1192–1197
rate constants, 356
rates, 350
S_N1 and S_N2 mechanisms, 1195
tetrahedral mechanism, 1192–1197
transition states, 1196
with enzymes, 1192
carboxylic esters, hydrostannation, 919
hydroxy, 1154
α-hydroxylation, 1752
carboxylic esters, imino see imino esters
carboxylic esters, intermediates, and oxidation-reduction, 1435
iodo, with alkenes, 991
keto, with low valent titanium, 1559
malonic see malonate
malonic, alkylation, 540
metal, and dihydroxylation of alkenes, 997
nitrophenyl, leaving group, 1219
carboxylic esters, of carboxylic acids see carboxylic esters
carboxylic esters, phenolic, 636, 1201, 1203, 1209
propargylic, 1228
pyrolysis, 1288
pyrolysis, mechanism, 1288
radical coupling, 840
reagents for reduction, 1516
rearrangement, 635
carboxylic esters, reduction, radical mechanism, 1539
to aldehydes, 1518
with Dibal, 1518
with tributyltin hydride, 918
reductive acylation, of ketones, 1084
reductive cleavage, to hydrocarbons, 1538
reductive cleavage, with lithium in amines, 1538
reductive coupling, to acyloins, 1560
solvent effects, in alkylation reactions, 468
solvolysis of, and NMR, 382
steric hindrance to formation of, 349
sulfenylation, 681
carboxylic esters, to alcohols, *Bouveault-Blanc procedure*, 1516
to alcohols, reagents, 1516
to aldehydes, reagents, 1518
to ethers, reagents, 1543
to methyl compounds, 1546
carboxylic esters, via CH oxidation, 1472
carboxylic esters, vinyl also see vinyl
carboxylic esters, vinyl, and transesterification, 1207
hydrolysis, 1192
hydrolysis, by esterases, 1192
with aldehydes, 1356
carboxylic esters, with aldehydes, Stetter reaction, 1123
with amines or ammonia, 1219
with amines, IUPAC mechanism, 1221
with amines, mechanism, 1220
with amines, rate determining step, 1220, 1221
with carbon nucleophiles, 1236
with carboxylic acid dianions, 1237
with dimagnesium compounds, 1228
with dimethyl sulfate, 470
with *Grignard reagents*, 1229
with ketones, 1155, 1236
with LDA, 1154, 1234
with Lewis acids, 636
with metal carbenes, 1174
with Mo peroxide, α-hydroxylation of enolate anions, 1473
with MoOPH, α-hydroxylation of enolate anions, 1473
with nitriles, 1236
with organometallics, 1229
with silanes, 1517
with sodium in ethanol, 1506
with the *Petasis reagent*, 1174
with trimethylphosphate, 470
with trimethylsilyl sulfides and AlCl3, 1211
carboxylic ester-thioethers, 1006
carboxylic salts, from carboxylic esters, 508
carboxylic sulfonic anhydrides, 622
carbynes, 252
carcerands, 115
carcerands, and cyclopentadiene, 68
carciplex, 115
Caro's acid, conversion of thioamides to amides, 1087
oxidation of amines to hydroxylamines, 1490
oxidation of amines to amine oxides, 1492
oxidation of anilines to nitroso compounds, 1490
oxidation of anilines, mechanism, 1490
with thioamides, 1087
C-aromaticity, 88
Carroll rearrangement, enantioselectivity, 1409
carvone, photochemical [2+2]-cycloaddition, 1048
photochemistry, 1049
carvonecamphor, by photochemical [2+2]-cycloaddition, 1048
from carvone, 1049
CAS Online, replaced by *SciFinder*, 1574
CAS Registry Number, 1594
CAS Registry, 1578, 1594
CASSI, 1600
catalysis, acid or base, and ester hydrolysis, 1190
catalysis, acid, epoxide alcoholysis, 465
of acetals, 455
of epoxides, 458
catalysis, acid-base, 327
catalysis, alcohols and diazo compounds, 463
and *Brønsted catalysis equation*, 328
and free energy, 277
and mechanism, 277

catalysis, alcohols and diazo compounds (*Continued*)
and supercritical carbon dioxide, 363
and the *Diels-Alder reaction*, 1022
catalysis, base, 328
and oxime formation, 1095
and the Marcus equation, 328
coupling aryl halides and active methylene compounds, 779
catalysis, general acid, 328, 456
catalysis, general, 328
catalysis, Lewis acid, sulfonyl halides with halo esters, 524
catalysis, metal, amine alkylation, 483
arylation of sulfonamides, 493
aziridine ring opening, 491
cleavage of ethers, 505
coupling with *Grignard reagents*, 520
halogenation of epoxides, 507
organometallics coupling, 523–526
vinyl ester formation, 469
catalysis, micellar, and *Williamson reaction*, 460
catalysis, nucleophilic, 1190
catalysis, phase transfer see phase transfer
catalysis, specific acid, 328
catalyst free, thiols with vinyl ethers, 894
catalysts, alumina, 1200
ammonium salts, 1245
and hydrogenation of alkynes, 905
asymmetric, and synthesis, 153
azaferrocene, 1353
BINOL, 1115
biocatalysts, 1181
boranes, 1520
boric acid, 966
boronic acids, 1216
carbenes, 967
catalysts, chiral, 340, 966, 1102, 1103, 1152, 1181, 1242, 1369
catalysts, chiral, and bis (oxazolines), 951
and conjugate addition of carbamates, 966
and dihydroxylation of alkenes, 995, 996
and *Friedel-Crafts alkylation*, 611, 612
and heteroatom *Diels-Alder reactions*, 1038
and hydrogenation, 153
and *Mannich reactions*, 1102, 1103
and *Michael reactions*, 947
and reduction, 1513
and the aldol reaction, 1147
and the *aza-Michael reactions*, 966
and the *Baylis-Hillman reaction*, 1128
and the *Diels-Alder reaction*, 1026
and the *Mukaiyama aldol reaction*, 1153
and the *Prins reaction*, 1186
and the *Suzuki-Miyaura reaction*, 773
bis(phosphines), 919
phosphoric acids, 1136
thioureas, in the *Pictet-Spengler reaction*, 618
transition metal, 1153, 1182
trimethylsilyl cyanide, and cyanohydrin formation, 1181
catalysts, Cinchona alkaloids, 1102, 1157, 1245
DBU, 966
definition, 277
dendrimers, 1245
dendritic, and transfer hydrogenation, 912
diamine protonic acids, for the aldol reaction, 1148
ferrous chloride and $S_{RN}1$, 417
flavin, 997
for acylation of amines, 1215
for acylation of amines, with esters, 1220
for alcoholysis of anhydrides, 1201
for alkene metathesis, 1418, 1419, 1421
for carboxylic acid esterification, 1203
for cyanohydrin formation from trimethylsilyl cyanide, 1181
for *Dieckmann condensation*, 1235
for enantioselective epoxidation of alkenes, 1003
for epoxidation, 1003
for *Friedel-Crafts acylation*, 622
for *Friedel-Crafts reactions*, with phosgene, 629
for *Friedel-Crafts*, addition of alkyl halides to alkenes, 991
for *Grignard coupling*, 761
for hydrogenation, 902
for hydrolysis of carboxylic esters, 1191
for photochemical [2+2]-cycloaddition, 1043
for the *Tischenko reaction*, 1564
for transesterification, 1207
from dihydroxylation of alkenes, 993
heterocyclic carbenes, 1181, 1408
catalysts, heterogeneous, and hydrogenation, 902
particle sites, 907
surface sites, 907, 908
catalysts, homogeneous, 903
hydrogenation, 902
types, 904
catalysts, hydrogen ion, and the tetrahedral mechanism, 1070
hydrogenation, soluble, 902
imidazolidones, 1025
imidazolium salts, 1187
in heteroatom *Diels-Alder reactions*, 1038
in the *Mukaiyama aldol reaction*, 1151, 1152
iodine, 1208
Lewis acids, 1185
Lindlar, and hydrogenation of alkynes, 905
MABR, 1119
catalysts, metal, and epoxide alcoholysis, 466
and *Cope rearrangement*, 1402
and the *Heck reaction*, 763–768
catalysts, chiral, 1183
coupling with silanes, 511
epoxides and amines, 489
for cyclotrimerization of alkynes, 1060
for dehydrogenation of alcohols, 1450
formation of cyclic amines, 560
with acyl halides, 1300
catalysts, Mn complex, 1005
optically active, 123
organo- also see organocatalysts
organo, chiral, 1183
organocatalysts, 1181
oxazolidines, 947
Pd, 41, 42
phase-transfer, 945, 1238
phosphamide, 1152
phosphines, 944
phosphoramides, 1143
polymer bound, 1420
proazaphosphatranes, 1126
Pybox, 1102
pyridine, 1200, 1202
quinidine, 1242
quinuclidine, 1128
recyclable, for alkene metathesis, 1420
sulfonamides, 1152
thiazolium salts, 971, 1188
Ti, acyl addition, 1120
TPAP oxidation, 1445

catalysts, transition metal, 1181
and *Claisen rearrangements*, 1410
and *Grignard reagents* with imines, 1133
and the *Mukaiyama aldol reaction*, 1151, 1152
with allyltin compounds, 1118
catalysts, triphase, 445
catalysts, *Wilkinson's*, 41
catalytic *Claisen rearrangement*, 1408
catalytic dehydrogenation, of alcohols, 1450
catalytic hydrogenation see hydrogenation
catalytic *Sakurai reactions*, 956
catalytic *Wagner-Meerwein rearrangements*, 1340
catechol, oxidation with $KMnO_4$, 1453
catecholborane, 701
and conjugate addition, 959
with alkenes, 959
with alkynes, 705, 925
with chiral additives, in reductions, 1513
catenanes, 118, 120
and acyloin condensation, 1561
and chirality, 135
and daisy chains, 118
and mass spectrometry, 119
and molecular necklaces, 118
and π-π interactions, 119
cyclic, 118
diastereomers, 119
doubly interlocking, 119
enantiomer separation by HPLC, 120
enantiomers, 120
heteroatom, 119
interlocked, 119
rotation of units, 119
synthesis of, 119
topological stereoisomers, 119
via acyloin condensation, 1561
cathecolborane, 805, 924
cation affinity, 427
cationic *Diels-Alder reaction*, 1022
cation-molecule pair, 387
cation-π-interactions, 104
cationotropic rearrangements, 1321
cations, alternant hydrocarbons, 64
annulenium, 82
radical, 810, 814
reaction with carbanions, 865
role in hydride reductions, 1511
separataion with crwon ethers, 109
cavitands, 110
cavitation noise, and acoustic cavitation, 307
cavitation, 307
and sonochemistry, 307
acoustic, and cavitation noise, 307
and sonochemistry, 307
and ultrasound, 445
C-calculation, phenoxide ions, 448
CD see circular dichroism
CD, chiral molecular in achiral solvents, 145
cedranediolborane, 702
cell length, and specific rotation, 124
Cellosolve, 466
center of symmetry, and chirality, 125
centrohexacyclines, and strain, 198
ceric ammonium nitrate, and acetal cleavage, 456
and nitration of aromatic compounds, 593
cesium alkyls, 229
cesium aryls, 229
cesium fluoride, as a base, 482
cesium hydroxide, as a base, 481
chain elongation, and boranes, 957
(CH)n compounds, and Cope rearrangement, 1406
α-CH oxidation, of cyclic ethers to lactones, 1478
of ethers to carboxylic esters, 1478
of ketones, with selenium dioxide, mechanism, 1478
of lactams to imides, 1478
of methyl aromatic compounds, 1479
and the *Étard reaction*, 1479
chain extension, by the *Vilsmeir-Haack reaction*, 626
chain mechanism, metathesis, 1423
chain reactions, and radicals, 806
and SET mechanism, 389
IUPAC mechanism, 808
chair conformations, 180
and divinylcyclobutane rearrangements, 1403
chair transition state, *Claisen rearrangement*, 1407
chair-to-chair interconversion, 181
channel-type complexes, 117
Chapman rearrangement, 1428
mechanism, 1429
charge dispersal, elimination versus substitution, 1277
charge distribution, in conjugated carbocations, 212
charge separation, and hyperconjugation, 88
and resonance, 44
charge transfer, bonding, 107, 109
complexes, 104
complexes, UV, and solvents, 441
spectra, 104
spectrum, 653
Charton's ν values, 360
chelation, and aldol products, 1145
dialkylamide bases, 342
cheletropic reactions, cyclic sulfones, 1303
Chemical Abstracts Service Source Index (*CASSI*), 1600
Chemical Abstracts, 1574–1583, 1594
and patents, 1576
and *SciFinder*, 1569, 1575
collective indexes, 1577
index guide, 1576–1578
indexes, 1576
Registry number, 1578
superceded by *SciFinder*, 1576
chemical induced dynamic electron polarization see CIDEP
chemical properties, and Beilstein, 1578
chemical shift, 17
alkenes, 51
and annulenes, 78, 79, 81
and antiaromaticity, 69
and benzenonium ion, 573
and carbocations, 217
and conformations, 174
and cyclobutadiene, 68
and electronegativity, 17
and hydrogen bonding, 100
and paramagnetic ring current, 53
and ring current, 51, 52
homoaromatic compounds, 83
chemically induced dynamic nuclear polarization see CIDNP
Chemisches Zentralblatt, 1578
chemoselective reducing agents, for aldehydes rather than ketones, 1505
chemoselective reducing agents, for ketones rather than aldehydes, 1505
chemoselectivity, definition, 1504
in the reduction of alkyl halides, 1533
Chemtracts: Organic Chemistry, 1586
Chichibabin reaction, and mechanism, 787
chiral absorbents, 156
chiral acetals, 1082
chiral additives, 1181
and *Cinchona* alkaloids, 966
and conjugate addition, 947
and dihydroxylation of alkenes, 995, 996

chiral additives (*Continued*)
and enolate alkylation, 546
and *Michael addition*, 947
and *Michael reactions*, 947
and resolution, 158
and the *Claisen reaction*, 1155
and the *Mukaiyama aldol reaction*, 1153
and the *Mukaiyama aldol*, 1153
diazoborolidines, 1155
in reduction, 1513
metal catalyzed cyclopropanation, 1054
proline, 1474
sparteine, 1110
with lithium aluminum hydride, 1513
with sodium borohydride, 1513
chiral Al complex, 616
chiral aldehydes, 1147
chiral allenes, 522, 663
chiral allylic boranes, 1125
chiral amides, with aldehydes, 1120
chiral amines also see amines
chiral amines, 1244
with ketones, 549
chiral ammonium salts, 1182
as catalysts, 1245
chiral atoms also see stereogenic
chiral atoms, and optical activity and symmetry, 126
definition, 126
chiral auxiliaries, and asymmetric synthesis, 151, 152
and *Mannich reactions*, 1102, 1103
and the aldol reaction, 1147, 1148
and the *Baylis-Hillman reaction*, 1128
and the *Diels-Alder reaction*, 1026
and the *Mukaiyama aldol reaction*, 1153
definition, 151
chiral azadienes, 1038
chiral bases, and enolate allylation, 546
and the aldol reaction, 1147
chiral benzylic cations, 610
chiral binapthols, 155
chiral bis(hydroxyamides), 1005
chiral boranes, 924
chiral boron compounds, reducing agents, 1527
chiral carbanions, 227
chiral carbenoids, 252
chiral compound, cyclooctatetraene, 134
chiral compounds also see chirality
chiral compounds also see diastereomers
chiral compounds also see enantiomers
chiral compounds, adamantanes, 129
chiral compounds, and allenes, 132
and axis of symmetry, 125
and biaryls or biphenyls, 130
and *Cram's rule*, 150
and diastereomers, 146
and diastereotopic faces, 172
and diastereotopic, 171
and different rate of reaction, 123
and enantiomeric excess, 160
and enantiotopic faces, 172
and epimers, 147
and *Fischer projections*, 136
and GC, 161
and HPLC, 161
and kinetic resolution, 156
and molar rotation, 143
and NMR, 160
and optical purity, 160, 161
and orsional diastereomers, 132
and paracyclophanes, 134
and polarizability, 126
and prochiral centers, 171
and racemates, 124
and restricted rotation, 134
and specific rotation, 143
and symmetry, 123, 125
and synthesis, 149–154
and the 2^n rule, 147
and the *Cahn-Ingold-Prelog rules*, 138–141
and the chiral pool, 149
and the *Cornforth model*, 151
and the *Felkin-Anh model*, 151
chiral compounds, atropisomers, 131
chemical reactions, 141
cyclooctene, 134
cyclophanes, 134
D/L nomenclature, 138
erythro/threo, 149
from achiral compounds, 151
fulgide, 134
glyceraldehyde, 137
helical, 133
helicene or heptalene, 133
meso form, 147
metallocenes, 134
nitroxide radicals, 243
pseudoasymmetric carbon, 147
resolution of, 129
spiranes, 134
stereoselective synthesis, 150
syn/anti, 149
with Lewis acids, 340
with multiple stereogenic atoms, 146
chiral crown ethers, 109, 157
chiral dialkylamide bases, 1298
chiral diamines, 1103, 1137
chiral dienophiles, 1026
chiral diols, 1082
chiral dioxiranes, 1002
chiral enols, 1147
chiral *Grignard reagents*, 716
chiral hydrazines, with ketones, 549
chiral hydroperoxides, 1001
chiral imines, 966, 1103
chiral iminium salts, 1002
and epoxidation, 1000
chiral ionic liquids, 365, 954
chiral ketones, 1147
chiral lanthanide shift reagents, 161
chiral lead carboxylates, 1456
chiral Lewis acidity, 340
chiral Lewis acids, 1026
and the *Diels-Alder reaction*, 1026
chiral ligands, 697, 1134, 1137, 1149, 1153
and dihydroxylation, 996, 997
and enolate alkylation, 544
and insertion reactions, 693
and reduction, 1513
and *Sharpless asymmetric dihydroxylation*, 996
and the aldol reaction, 1148
for the Suzuki-Miyaura coupling, 773
imidazolinyl carbenes, 1122
in catalytic hydrogenation, 904
with organozinc compounds, 953
chiral *Lossen rearrangement*, 1363
chiral metal catalysts, 1183
chiral molecules, 122
and stereogenic atoms, 126
chiral organocatalysts, 967, 1147, 1181, 1183
chiral oxaziridines, α-hydroxylation, 1474
chiral Pd complex, 1369, 1409
chiral phosphine ligands, 780
chiral phosphine oxides, 1492
chiral phosphines, 904
chiral phosphoric acid catalyst, 1136
chiral poisoning, in asymmetric catalysis, 904
chiral pool, and synthesis, 149
chiral quaternary ammonium salts, 779
chiral reactions see enantioselectivity
chiral reagents, for reduction of ketones, 1511–1515
chiral recognition, and diastereomers, 156
and resolution, 156
chiral rotaxanes, 120

chiral selenium ylids, 1176
chiral solvating agents, for NMR, 161
chiral solvents, and NMR, 161
chiral sulfur reagents, 1494
chiral sulfur ylids, 1176
chiral sulfur, 541
chiral templates, conjugate addition of *Grignard reagents*, 952
chiral thioureas, 1103
chiral transition metal catalysts, 1182
chiral transition metal complexes, 1148
chiral transition metals, and reducing agents, 1514
chirality, and bond rotation, 228
chirality transfer, and [2,3]-*Wittig rearrangement*, 1414
chirality also see chiral compounds
chirality also see enantiomers
chirality, adamantanes, 129
chirality, and a *Möbius strip* compound, 135
and absolute configuration, 137
and allenes, 130, 132
and asymmetric induction, 153
and axis of symmetry, 125
and barrelene, 135
and bridgehead atoms, 129
and calixarenes, 135
and carbanions, 228
and catenanes, 135
and center of symmetry, 125
and circularly polarized light, 145
and crown ethers, 135
and cumulenes, 133
and diastereomers, 146
and enantiomers, 122
and enantioselective reactions, 153
and epimers, 147
and helical shapes, 133
and heptahelicene, 134
and hydrocarbons, 135
and isotopes, 135
and meso compounds, 147
and metallocenes, 134
and methylenecyclohexanes, 133
and mirror plane, 125
and molar rotation, 143
and molecular knots, 135
chirality, and optical activity, 122
and paracyclophanes, 134
and pentahelicene, 134
and phosphates, 127
and phosphorus, 169
and plane of symmetry, 125, 126
and plane polarized light, 145
and polarizability, 126
and pyramidal inversions, 127, 128
and quadrivalent stereogenic atoms, 126
and resolution, 124
and restricted rotation, 134
and rotaxanes, 135
and specific rotation, 143
and spiranes, 133
and substituted cyclohexanes, 184
and sulfones, 127
and superimposability, 122, 126
and symmetry, 135
and tervalent stereogenic atoms, 127
and the 2^n rule, 147
and the *Cahn-Ingold-Prelog rules*, 138–141
and trans-cyclooctene, 134
and triarylamines, 135
and twisting, 133
chirality, asymmetric reduction, 152
CD in achiral solvents, 145
D/L nomenclature, 138
definition of, 122
helical, 133
helical, and cyclophanes, 134
induced chirality in achiral solvents, 146
perpendicular dissymmetric planes, 130
torsional diastereomers, 132
truxilic acid, 125
Chiraphos, catalytic hydrogenation, 904
chloral hydrate, 1076
chloramines, and halogenation of aromatic compounds, 605
from amines, 729
with organoboranes, 707
chloramine-M, epoxidation of alkenes, 1002
chloramine-T, and formation of aziridines, 1011
and NBS, 1011
and sodium iodide, 792
aziridine formation, 1011
formation of aziridines from alkenes, 990
formation of chlorohydrins, 985
with alkenes, 1007
with O_2, oxidation of amines, 1477
with pyridinium bromide perbromide, 990
chloranil: (2,3,5,6-tetrachloro-1, 4-benzoquinone), 1439
chloranil, and aromatization, 1439
chloride ion, from PCl_6^-, 1106
chlorides see halogens
chlorides, acyl see halides, acyl
chlorides, acyl, from aldehydes, 829
chlorides, alkyl see halides
chlorides, alkyl, and Grignard reagents, 231
chlorides, aryl, deactivated, catalysts for coupling, 771
chlorides, aryl, from aryl iodides, 757
chlorides, from alcohols, 501
chlorides, vinyl see vinyl chloride
chlorination reagents, for alkenes, 983
chlorination, 822
chlorination, allylic, 827
and bezeneseleninyl chloride, 826
and cyclodextrin, 581
aromatic compounds, 580, 603, 664
of alcohols, 409
of alkenes, reagents for, 983
of benzene, rate and product distribution, 588
of malic acid, 375
of toluene, rate and product distribution, 588
radical, and dichlorine monoxide, 827
chlorine radicals, 804
chlorine trifluoride, and fluorine radicals, 822
chlorine, and water, oxidation of thiols, 1493
halogenation of aromatic compounds, 605
in water, 985
with alkenes, 982
with aromatic compounds, 603
with UV light, 982
chlorites, epoxidation, 1000
chloroamines, formation of formamides, 492
chlorocarbenium ions, 1106
chlorocholestenol, 148
chlorochromate, pyridinium see PCC
chlorocyclopropanone, 171
chloroform, and proton transfer, 324
hydrolysis of, 453
in the *Reimer-Tiemann reaction*, 627
with amines, 492
with phenoxides, 627
chloroformamides, from amines, 1213
chloroformates, addition to allenes, 992
benzyl, with amines, 1214
S_Ni decomposition, 409
with alkenes, 992

chloroformates, addition to allenes (*Continued*)
with *Grignard reagents*, 1226, 1227
with silanes, 1539
with terminal alkynes, 1228
chlorofumaric acid, and asymmetric synthesis, 153
chloroiminium salts, with *Grignard reagents*, 1138
chloromalic acid, and asymmetric synthesis, 153
chloromethylamides, 632
chloromethylation, and the *Friedel-Crafts reaction*, 619
chloronium ions, and halohydrin formation, 985
with alkenes, 863
chloroperoxybenzoic acid, meta, oxidation of sulfides see mcpba
chlorophosphates, and nitrile formation, 1096
chloropyridinium salts, and lactonization, 1204
chlorosulfates, from alkenes with chlorine and sulfur trioxide, 986
chlorosulfenation, 837
chlorosulfonyl isocyanates see isocyanate
chlorosulfuric acid, formation of aryl sulfonyl halides, 602
chlorothioformates, with amines, 1251
chlorotrimethylsilane, and the acyloin condensation, 1560
with enolate anions, 686
chlorotriphenylmethane, ionization, 213
chlorotris(triphenylphosphine) rhodium (*Wilkinson's catalyst*), 903
cholest-6-en-3-one, 351
cholesterol, biosynthesis, 932
cholic acid, and resolution, 157
as a host, 115
chromate, trimethylsilyl, oxidation of alcohols, 1443
chromates, structural variation for oxidation of alcohols, 1444
chromatographic absorbents, and *Diels Alder reactions*, 1022
chromatography, and resolution, 156
chromic acid, and oxidation of alcohols, 1442
oxidation of hydrocarbons, 1470
chromic chloride, with $LiAlH_4$, 1121
chromium (IV), and oxidation of alcohols, 1444
chromium (VI), oxidation of alcohols, mechanism, 1444
and oxidation of alcohols, 1442–1445
oxidation of hydrocarbons, 1470
chromium complexes, 41
Fischer carbene complexes, 1062
chromium compounds, oxidation of alcohols to carboxylic acids, 1483
chromium hexacarbonyl, 41
chromium oxide, on silica gel, 1442
chromium reagents, and oxidative cleavage of alkenes, 1463, 1464
and oxidative cleavage of cyclic ketones, 1458
chromium trioxide, oxidation of aromatic hydrocarbons, 1480
chromium, oxidation states, 1444
chromophore absorption, 293
chromophore, definition, 291, 293
chromotropic spin traps, 236
chromyl chloride, and the Étard reaction, 1479
chromyl chloride, CH oxidation of aryl methyl, 1479
Chugaev reaction, 1288
and isotope effects, 1289
Ei mechanism, 1289
CIDEP (chemically induced dynamic electron polarization), 237
CIDNP (chemically induced dynamic nuclear polarization)
and NMR, 237
and aryl radicals, 810
and carbenes, 694
and *Grignard reagents*, 715
and hydrogen-metal exchange, 717
and intermediates, 276
and radical rearrangements, 1335
and radicals, 236, 237, 390
and SET mechanism, 390
and the *photo-Fries rearrangement*, 637
and the *Steven's rearrangement*, 1372
organolithium compounds with alkyl halides, 520
radical alkylation of aromatic compounds, 844
reduction of alkenes, 910
Cieplack effect, and addition to alkenes, 878
Cinchona alkaloids, and dihydroxylation, 996
and epoxidation, 1001
and *Grob fragmentation*, 1307
and phase transfer catalysts, 1003
and Sharpless aminohydroxylation, 1007
and sulfinic esters, 473
as a chiral catalyst, 1102, 1245
as a chiral additive, 966
as phase transfer catalysts, 1001
catalyst, 1157
hydration and lactone formation, 887
with osmium catalysts, 993
cine substitution, 751
and aromatic nucleophilic substitution, 738
and *Stille coupling*, 682
CIP rules see Cahn-Ingold-Prelog
CIP rules see chirality
CIP rules, and groups, 139
and the steering wheel model, 140
circuambulatory rearrangement, 220
circuit resonance energy, 53
circular dichroism, 143
and conformations, 174
vibrational, 143
circular polarization of luminescence, 162
circularly polarized light, 124, 145
circularly polarized light, and asymmetric synthesis, 154
circulene, 48
circulenes, 84
circumambulatory rearrangements, 1394
cisoid conformation, 1392
cis-trans isomerism see isomers
cis-trans isomers see isomers
cis-trans isomers, 167
citric acid, 171
Claisen condensation also see *Dieckmann condensation*
Claisen condensation, 1154, 1234
and base strength, 1235
and *Dieckmann condensation*, 1234
and enolate anions, 232, 543, 1234
and *Evans auxiliaries*, 1155
and high pressure, 446
and *Hünig's base*, 1234
and LDA or LICA, 1234
and self condensation, 1234
and the *Reformatsky reaction*, 1154
crossed, 1234
intramolecular, 1234
mechanisms, 1235
mixed, 1234
mixed, and kinetic control conditions, 1234
retro, 1234

reverse, 723
solvent free, 1234
Claisen reaction also see *Claisen condensation*
Claisen reaction, 1236
and *Robinson annulation*, 1155
enantioselectivity, 1155
metal mediated, 1154
structural variations, 1154
with amides, 1154
Claisen rearrangement, 635, 1407–1413
Claisen rearrangement-Conia reaction, 1409
Claisen rearrangements, abnormal, 1412
acceleration by water, 1408
allyl allene ethers, 1409
allyl enol ethers, 1408
Claisen rearrangements, and *Carroll rearrangement*, 1409
and dimethylacetamide dimethyl acetal, 1409
and isotope labeling, 1407
and microwaves, 1408
and the *Diels-Alder reaction*, 1408
and the *Kimel-Cope rearrangement*, 1409
catalytic, 1408
Claisen rearrangements, enantioselectivity, 1408, 1411
ester enolate anions, 1409
heterocyclic carbene catalyst, 1408
in ionic liquids, 1408
Ireland-Claisen, 1409, 1410
isotopic labeling, 1407
Lewis acid catalysts, 1409
mechanism, 1407–1409
on silica gel, 1408
ortho rearrangement, 1407
para-, 1407
polymer-bond, 1408
retro-, 1407
solid phase, 1408
solvent effects, 1409
structural variations, 1410
thio- see thio-Claisen
with chiral Lewis acids, 1411
Claisen-Schmidt reaction, 1144, 1145
clathrate, H_2S and piancolone, 114
clathrates, 113
and hydroquinone as host, 114
cleavage, and formation of radicals, 808
anionic, 718
by alkoxides, 718, 722
Eschenmoser-Tanabe, 1309
gas phase cleavage, 223
hydration of vinylidene nitriles, 886
Norrish Type I and *Norrish Type II*, 303
of acetals, with Lewis acids, 456
of alkoxides, 654
of ammonium salts, 470
of aromatic ethers, 1537
of carboxylic esters, 477
of cyanohydrins, 718
of cyclic ethers, 504
of cyclopropane, and vinylcyclopropane rearrangement, 1399
of diketones with base, 723
of dioxetanes, 1040
of epoxides see epoxides
of esters, 470
of ethers, 474, 504, 505
of ethers, with HBr orHCl, 455
of ethers, with sulfuric acid, 454
cleavage, of ketones, 723
of ketones, haloform reaction, 723
of lactones, 477
of methyl esters, with NaCN-HMPA, 564
of methyl ethers, 486
of oxonium salts, 505
of peroxides, 246
of radicals, 246, 806
of selenides, 477
of thioethers, 853
oxidative see oxidative
photochemical, and radicals, 246
photolytic, 295
photolytic also see photolytic
reductive, of cyclopropanes, 920
thermal, and radicals, 245
Clemmensen reduction, 1540
mechanism, 1543
clocks, radical clocks, 814
Clostridium sporogenes, reduction of nitro compounds, 920
C-nitroso compounds, 596
Co catalysts, alkyl halides with *Grignard reagents*, 518
and the *Pauson-Khand reaction*, 975–977
carbonylation reactions, 568
catalyst for coupling reactions, 526
cyclization of enynes, 935
cyclotrimerization of alkynes, 1059
epoxidation, 1005
formation of alkynes form alkyl halides, 1297
CO_2 see carbon dioxide
cobalt salen, 458
cocatalysts, *Suzuki-Miyaura coupling*, 773
coefficient, extinction, 291
collidine, LiI with carboxylic esters, 508
Collman's reagent, 564
and electrolysis, 564
carbonylation, 564
preparation of aldehydes or ketones, 564
colloidal metals, and the *Arndt-Eistert synthesis*, 1353
colloids, and sonochemistry, 308
combinatorial chemistry, 1219
combustion, heat of, 29
common rings, strain, 201
common-ion effects, and rate of reaction, 381
Communications, publication type, 1570
complexes, metal, optical resolution, 134
Compendium of Chemical Terminology, 1591
Compendium of Organic Synthetic Methods, 1591
complete neglect of differential overlap, 34
complexation, in hydride reductions, 1511
complexation, organolithium reagents, and conjugate addition, 953
complexes, activated, 265
alkyne-mercuric salts, 888
alkyne-metal carbonyl, and the *Pauson-Khand reaction*, 976
and alkenes, 107
and carbon tetrahalides, 107
and cyclodextrins, 116
and the *Kolbe-Schmidt reaction*, 629
ate, borane with ethers, 921
borane-dimethyl sulfide, 1547
bromine-alkene, 983
cage, 116
calixarene-proton, 110
channel-type, 117
charge transfer, 104
charge transfer, UV, and solvents, 441
chiral Lewis acid-dienophile, 1026
chlorine radical-solvent, 821
chromyl chloride-acylal, 1480
Co-salen, 987
Cr carbene, and imine-ketene cycloaddition, 1244
Cu, and the *Hay reaction*, 842
cyclobutadiene-metal, and cyclotrimerization, 1062
cyclodextrins and iodoaniline, 117

complexes, diastereomeric, 155
Dibal-amine, 1221
EDA, 653
EDA, and photochemical [2+2]-cycloaddition, 1050
electron donor-acceptor, 104
electron donor-acceptor, and electrophilic substitution, 653
electron donor-acceptor, charge transfer spectra, 104
encounter, 575
η-complexes, 41, 42
η-complexes, and hydrogenation, 908
complexes, *Fischer carbenes*, in [3+2]-cycloadditions, 1017
complexes, formation of, and [2+2]-cycloadditions, 1047
and *Fries-rearrangement*, 636
metal, and mechanism of homogenous catalytic hydrogenation, 908
metals and alkenes, 897
with metals, in catalytic hydrogenation, 907, 908
complexes, guest-host, 108
hydrogen bond, 329
ion-dipole, and S_N2, 377
complexes, iron, of cyclobutadienes, 69
and *Nazarov cyclization*, 975
iron-norbornadienone, 106
complexes, Lewis acid, and cleavage of ethers, 504
Lewis acid-acyl halides, 625
Lewis acid-base, 330
complexes, metal catalyzed, decarbonylation of aldehydes, 858
complexes, metal, acyl addition of dialkyzinc, 1120
and benzene, 106
and cyclooctatetraene, 106
and cyclotrimerization, 1062
and ferrocene, 105
and hapto complexes, 105
and π-donors, 105
in carbonylation reactions, 567
of cyclobutadienes, 69
with carbenes, 1053
complexes, metal-carbene, and metathesis, 1422, 1423
complexes, metal-salen, and epoxidation, 1005
complexes, Mn, and dihydroxylation, 993
monohapto, 106
complexes, π- and η-, 41
complexes, π-allyl, acylation of dienes, 685
and rearrangement of alkenes, 663
mechanism, 663
complexes, π-allylnickel, coupling, 514
complexes, π-complex, and arenium ions, 573
complexes, *Pauson-Khand*, 977
Pd, chiral, 1409
peroxo, Pd, 773
π-complexes, 41
and arenium ions, 573
and encounter complexes, 575
and S_NAr reactions, 735
halogenation of alkenes, 863
stability, 575
complexes, Pt, and resolution of alkenes, 174
radicals in aromatic solvents, 820
rate, 330
rate also see rate, complexes
ring-in-ring, 118
complexes, σ allylic copper, 527
complexes, Ti, and acyl addition, 1118
Ti-methylene, and *Tebbe's reagent*, 1173
transition metal, 786
transition metal, and [2+2]-cycloaddition, 1041
complexes, with biphenyl, 112
with crown ethers, 108
with cryptates, 108
with fluoranthene, 112
with *Grignard reagents*, 229, 230, 1112
with hydrazine, 114
with picric acid, 107
with pyrene, 112
with trinitrobenzenes, 107
with urea, 113
zinc, 1134
complex-induced proximity effect, and directed ortho metalation, 784
Comprehensive Chemical Kinetics, 1587
Comprehensive Heterocyclic Chemistry, 1587
Comprehensive Medicinal Chemistry, 1587
Comprehensive Organic Chemistry, 1587
Comprehensive Organic Functional Group Transformations, 1588
Comprehensive Organic Synthesis, 1588
Comprehensive Organic Transformations, 1591
Comprehensive Organometallic Chemistry, 1587
computational study, activation energy enolate anions, 1146
mechanism of aldol reaction, 1146
concentration, and aromatic diazonium salts, 736
and specific rotation, 124
and structure of *Grignard reagents*, 231
of radicals, 235
concerted mechanisms, 1372
concerted reactions, 1030
concerted reactions, and S_N2', 411
condensation, aldol see aldol
condensation, acyloin ester, 1560
benzoin, 1187
bis(aldol), 1145
Claisen see *Claisen* or *Claisen condensation*
Dieckmann see *Dieckmann*
Pechmann, 617
self condensation, aldol reaction, 1144
self, and *Claisen condensation*, 1234
Tollen's, 1562
conducted tour mechanism, 656, 662
conducting polymers, 364
conductivity, and arenium ions, 663
configuration, absolute see absolute configuration
and carbocations, 396
and *Grignard reagents*, 231
definition, 174
electron see electron configuration
of migrating group in sigmatropic rearrangements, 1396, 1397
racemization of migrating group during rearrangement, 1325
retention of migrating group during rearrangement, 1324
retention, and carbanions, 227
configurational stability, organolithium reagents, 228
conformational analysis, 173–190
conformational energy, substituted ethanes, 177
conformational isomer, and conformers, 174
conformational mobility, annulenes, 79, 80
conformational radical clock, 937
conformational transmission, 351

conformations, % axial in substituted cyclohexanes, 185
conformations, and *aa/ee/ae* nomenclature, 183
conformations, and $A^{1,3}$-strain, 182, 184
and acidity, 340
and amides, 179
and atropisomers, 180
and axial preference for polar groups, 186
and bisecting bonds, 178
and conjugation, 195
and dihedral angle, 178
and dipole moment, 177
and eclipsing bonds, 178
and homoanomeric interactions, 186
and keto-enol tautomerism, 665
and *Meldrum's acid*, 340, 341
and molecular mechanics, 174
and *Newman projections*, 175
and NMR, of macrocycles, 189
and optical activity, 175
and *Pitzer strain*, 199
and pK, 340
and polar groups, 186
and polarizability, 177
and pseudorotation, 189
and radicals, 816
and reactivity, 351
and silyl substituents, 184
and solvent effects, 178
conformations, and solvent, 178
and spectroscopic analysis, 174
and stability of aziridines, 127, 128
and stability, and optical activity, 129
and steric hindrance, 179
and steric hindrance, 179
and strain, 351
and substituted cyclohexanes, 182
and sulfoxides, 189
and syn elimination, 1259
and syn or anti elimination, 1258
and temperature, 79
and tetrahedral mechanisms, 1072
and the 3^n rule, 175
and the anomeric effect, 186, 187
and the E2 reaction, 1255
and transannular strain, 199
and X-ray crystallography, 178
conformations, anti or anticlinal or antiperiplanar, 177
anti-periplanar, and E2 reagents, 1255
bisecting, 179
boat, 180
butane, 177, 178
conformations, chair, 180
and bulky substituents, 184
and carbocations, 216
and gauche, 183
axial and equatorial, 181
cyclohexanes, and E2 reactions, 1256
half-life, 181
observation of, 181
onformations, chair-to-chair energy barrier, 184
chair-to-chair interconversion, 181
conformations, cisoid, 1392
and the *Diels-Alder reaction*, 1024
conformations, definition, 174
eclipsing, 179
energy, and cyclohexane, 181
estimation of numbers, 175
conformations, gauche, 176, 177
and butane, 178
and elimination, 1260
and solvent effects, 178
conformations, in the solid-state, 205
isolation of conformers, 178
MO calculations, 340
conformations, of acyclic compounds, 175
of amides, torsional barrier, 180
of annulenes, 72
of biaryls, 180
of caprolactams, 189
of carbamates, torsional barrier, 180
of cyclobutane, 188
of cyclodecane, 189
of cycloheptane, 189
of cyclohexanone, 185
of cyclohexene, 185
of cyclopentane, 188
of cyclopentane, and envelope conformations, 188, 189
of cyclopentane, and half-chair conformations, 188, 189
of cyclopentanone, 189
of cyclopropane, 188
of cyclopropylalkenes, 195
of dienes, and the *Diels Alder reaction*, 1024
of dioxanes, 186
of dithianes, 186
of enamides, torsional barrier, 180
of glucosides and the anomeric effect, 186
conformations, of heteroatom substituted rings, 186
of hydroxamic acids, torsional barrier, 180
of lactones, 189
of macrocyclic ketones, 189
of medium-size rings, 199
of oxacyclooctane, 189
of oxetane, 188
of six-membered rings, 180
of tetrahydrofurans, 189
of thioamides, torsional barrier, 180
conformations, orthogonal, 180
pseudo-axial and pseudo-equatorial, 190
puckered, 189
s-E/s-Z diazoketones, 1354
stability of, 178
staggered, 177
synclinal, 176, 177
synperiplanar, 177
syn-periplanar, and E2 reactions, 1255
tub, 134
tub, cyclooctatetraene, 134
conformations, twist also see twist conformations
conformations, twist, 180, 181
and norbornane, 182
and twistane, 182
conformers, 174
isolation of, 178
Conia reaction-Claisen rearrangement, 1409
conjugate acid, definition, 312
conjugate addition see addition
conjugate addition, 943–949
conjugate addition, 1, 2- versus 1,4-, organocuprates, 952
conjugate addition, 1, 6-, 954
conjugate addition, aldehydes with cyanide, 969
conjugate addition, and anhydrides, 969
and borates, 953
and conjugated alkynes, 954
and dialkylzinc, 970
and enamines, 552
and HMPA, 970
and ionic liquids, 945
and metal catalysts, 967
and metal catalyzed addition of amines, 966
and metal catalyzed addition of silyl enol ethers, 948
and microwave irradiation, 967, 969
and organocatalysts, 967
and PEG, 967, 968
and phosphonate esters, 969
and photolysis, 960
and radicals, 956
and SET mechanism, 956
and the *Sakurai reaction*, 956
and thioesters, 969
and trialkylalanes, 954
and vinylboranes, 958

conjugate addition, cyclic mechanism, 955
definition, 866
enantioselectivity, 947, 967
formation of enolate anions, 951
in chiral ionic liquids, 954
in ionic liquids, 968
intramolecular, 946, 947
limitations of organocuprates, 950
metal catalyzed, 945
metal mediated, 954
Michael addition, 943
conjugate addition, of alanes, 954
of alcohols, 967
of aldehydes, and microwaves, 969
of alkynyl alanes, 954
of allylic silanes, 956
conjugate addition, of amines, 965
to conjugated thiolactams, 966
enantioselectivity, 966, 969
metal catalyzed, 966
conjugate addition, of anilines, 966
of azides, 967
of boranes, 957
of borates, 958
of boronates, 958
of boronic acids, 955, 958
of carbamates, 967
of carbamates, metal catalyzed, 966
of cyanides, 981
of dialkylzinc compounds, 953
of enolate anions, 947
of *Grignard reagents*, 952, 1107
of HCN, 981
of heteroatom nucleophiles, 965
of higher order cuprates, 969, 1122
of hydroperoxide anion, 1003
of hydroxylamines, 967
of imides, 966
of imines, 966
of lactams, 966
conjugate addition, of organobismuth compounds, 955
of organocopper reagents, 713
of organocuprates, 949
of organocuprates, enolate ion formation, 951
of organolithium reagents, 952, 953
of organolithium reagents, metal catalyzed, 969
of organometallics, 949–956
of organometallics, and radicals, 956
of organometallics, mechanism, 955
of organotitanium compounds, 1120
of organozinc compounds, 953
of organozinc compounds, 953
of peroxide anions, 967
of phosphines, 967
of phosphites, 967
of radicals, 959
of selenols/organolithium reagents, 968
of silanes, 968
of silyl ketene acetals, 956
of thiocarbamates, 968
of thiolate anions, 968
of thiols, 967, 968
of thiophenols, organolithium reagents, 968
conjugate addition, photochemical, 966
to alkynes, 954
vinylogous, 944
with boron compounds, 955
conjugate bases see bases
conjugate, bases, base in the E1 reaction, 1261
conjugate bases, definition, 312
conjugate elimination, 1282
conjugate reduction, and silanes, 917
reagents for, 917
conjugate systems, and delocalization, 38
conjugated carbonyls, and hydride reduction, reagents, 1504
with sulfur ylids, 1176
conjugated carboxylic acids see carboxylic acids
conjugated compounds, acylation, 968
addition of hydroperoxide anions, 1436
and *Grignard reagents*, 1109
and organolithium reagents, 1109
and photochemical [2+2]-cycloaddition, 1048
and the *Baylis-Hillman reaction*, 1127
and the *Stork enamine reaction*, 550
by dehydrogenation, 1440
by the *Knoevenagel reaction*, 1157
halogenation, 983
radical addition, 870
with acyl halides, 968
with aldehydes, 1127, 1181
with sulfur ylids, 1178
conjugated dienes, 685
conjugated diketones, by α-oxidation of alkenes, 1477
conjugated ketones see ketones
and the *Nazarov cyclization*, 946
conjugated systems, alternant and nonalternant hydrocarbons, 63, 64
conjugated-circuit model, and aromaticity, 53
conjugation, and absorption, 293
and bathochromic shift, 293
and carbanions, 223
and carbocations, 211, 212
and conformations, 195
and cyclopropane, 195
and delocalization, 37
and denralenes, 42
and elimination, 1270
and enol content, 90
and homoconjugation, 43
and keto-enol tautomerism, 90
and radical stability, 240
and rearrangement of double bonds, 662
and S_N1 reactions, 382
and wavelength of light, 293
cross, 42
conjugation, cross also see cross conjugation
conjugation, cyclobutanes and carbocations, 214
cyclopropanes and carbocations, 214
energy, 39
heteroatoms with carbocations, 214
p orbitals with double or triple bonds, 39
simple, carbocations, 212
stabilization, 39
conrotatory process, a *Möbius system*, 1384
conrotatory, and 4n versus 4n+2, 1388
and electrocyclic rearrangements, 1381, 1382
cyclobutene ring opening, 1385, 1386
conservation of orbital symmetry, 1346
constant, equilibrium see equilibrium
constant, rate see rate
constants, *Planck's*, 3
contact ion pair, 384
contra *Friedel-Crafts alkylation*, 610
cooperative hydrogen bonding, 99
coordinate covalent bonds, 15
coordinate, reaction, 265
Cope elimination, 1279, 1292, 1373, 1400
Ei mechanism, 1293
in DMSO, 1293
mechanism, 1293

rate of reaction, 1292
solvent effects, 1293
Cope reaction, 1280, 1292
Cope rearrangement, 1400–1407
$(CH)_n$ compounds, 1406
1,5-allenic dienes, 1402
1,5-diynes, 1402
amino see *amino-Cope*
Cope rearrangement, and *Bergmann cyclization*, 1404
and bicyclo[5.1.0]octadiene, 1404
and bullvalene, 1405
and diradical intermediates, 1403
and high pressure, 446
and valence tautomerism, 1404
Cope rearrangement, anionic oxy-, 1401
Cope rearrangement, aza- see *aza-Cope*
Cope rearrangement, azo- see *azo-Claisen*
Cope rearrangement, boat transition state, 1403
chair transition state, 1403
degenerate, 1404
diene stability, 1401
diradical mechanism, 1404
divinyl oxiranes, 1402
divinyl phosphiranes, 1402
divinyl thiiranes, 1402
fluxional structures, 1405
mechanism, 1403
metal catalyzed, 1402
nonconcerted, 1404
Cope rearrangement, oxonia see *oxonia-Cope*
Cope rearrangement, reversibility, 1400
semibullvalene, 1406
shift equilibrium, 1401
silyloxy, 1401
six-center mechanism, 1404
stereochemistry, 1403
thermodynamic stability of dienes, 1400
transition metal catalyst, 1402
transition state, 1403
uncatalyzed, 1403
Cope, oxy- see *oxy-Cope*
copper (III) complex, an organocuprates, 950
copper compounds, and *Stryker's reagent*, 1150
with organolithium reagents, 520
copper cyanide, and the *Rosenmund-von Braun reaction*, 758
with aryl diazonium salts, 847
copper halides, and the *Hurtley reaction*, 779
coupling active methylene compounds with aryl halides, 779
copper salts, and alkyne coupling, 840
and the *Glaser reaction*, 841
halosulfonation of aryldiazonium salts, 848
nitration of aryldiazonium salts, 848
copper, alkyl-magnesium bromide *Normant reagent*, 940
and coupling of aryl halides, 768
and coupling of aryldiazonium salts, 796
and the *Gatterman reaction*, 846
and the *Ullmann reaction*, 768
copper-free *Sonogashira coupling*, 776
corannulene, 84
Corey-Seebach procedure, for hydrolysis of dithioketals, 1088
Corey-Winter reaction, 1301
corner-protonated cyclopropane, 880
Cornforth model, *and asymmetric synthesis, 151*
and diastereoselectivity, 151
Corporate Index, 1599
Co-salen complex, halolactonization, 987
coulombic interactions, and molecular mechanics, 190, 191
coumarins, and *Friedel-Crafts alkylation*, 617
and *Pechmann condensation*, 617
counterattack reagent, 510
counterions, and ambident nucleophiles, 449
and nucleophiles, 449
and the *Ireland-Claisen rearrangement*, 1410
of carbocations, 209
of diazonium salts, 792
solvation, 428
coupling constants, 17
and hydrogen bonding, 100
coupling reactions, 839
boranes, 558
cross-coupling, 510
coupling, and SET mechanisms, 531
and the *Stille reaction*, 524
and the *Wurtz reaction*, 513
and π-allylnickel complexes, 514
aryl halides and boronic acids see *Suzuki-Miyaura*
aryl halides, and the *Ullmann reaction*, 768
aryldiazonium salts with active methylene compounds, 674
cross, radical coupling of alkanes, 839
definition, 510
coupling, metal catalyzed, enantioselective, 525
with silanes, 511
coupling, metal mediated, alkyl halides, 518
conjugated ketones, 514
vinyl halides, 514
with allylic esters, 527
coupling, of alcohols, 532
of alkanes, 690
of alkenes, 935
of alkyl halides, 513
of alkylalkynylborates, 851
of arylboranes, 851
of arylboronic acids, Pd catalyst, 620
of carbenes, 255
of diazonium compounds, 674
of diazonium salts, 598
of *Grignard reagents*, 849
coupling, of organolithium reagents, 516
with sulfones, 531
coupling, of organometallics, (Group I and II) with alkyl halides, 515, 516
coupling, of organometallics, solvent cage, 519
with alcohols, 532
with alkyl halides, 523–526
coupling, of photosensitized alkanes, 839
of radicals, 246, 808
of silanes, 840
of silanes, with alkyl halides, 510
of vinyl triflates and phenols, 460
coupling, organometallic, metal catalyzed, 525
coupling, oxidative see oxidative coupling
Pd catalyzed, with organometallics, 524, 525
pinacol see pinacol
radical, and the *Kolbe reaction*, 853
radical, of amides, 839
reductive, of alkynes, 933
Sonogashira, 776
Stephens-Castro, 775
Stille, 682
Suzuki-Miyaura, 701, 770
symmetrical, of allylic or benzylic alcohols, 532
unsymmetrical, metal mediated, 514

coupling, oxidative see oxidative coupling (*Continued*)
with alkylboronic acids, 524
with allylic esters, 527
with polymer-supported phosphine ligands, 530
covalent bonds, and soft acids and bases, 332
covalent compounds, and electronic structure, 15
Cr carbene complex, and imine-ketene cycloaddition, 1244
Cr catalyst, cyclopropanation, 1055
Cr complex, and cyclopropanation, 1053
Cr compounds see organochromium
Cr compounds, and oxidation of aromatic hydrocarbons to quinones, 1480
Cram's rule, and asymmetric synthesis, 150
and diastereoselectivity, 150
and reactions at carbonyls, 1068
and reduction of ketones, 1515
CRC Handbook of Data on Organic Compounds, 1582
cresol, dipole moment, 19
Criegee mechanism, and ion pairs, 1460, 1461
of ozonolysis, stereochemistry, 1462
ozonolysis, 1460–1462
critical temperature, and carbon dioxide, 363
cross conjugation, 42
and bond distance, 43
and trienes, 43
cross coupling reactions, 510
Buchwald-Hartwig, 752
cross coupling see coupling
alkynes, 934
carbonylative, 525
Hiyama, 545
organometallics, 850
Pd free, 771
Sonogashira, 842
with alkynes, 561
cross dimerization, of alkanes, 840
cross metathesis, 1420
alkynes, 1422
crossed aldol reaction, 1145
crossed Cannizzaro reaction, 1164, 1563
crossed Claisen condensation see *Claisen*
crossed pinacol coupling, 1556, 1557
crossed *Tischenko reaction*, 1564
crossover experiments, 377
and *Fries rearrangement*, 636
and rearrangement, 1322
and S_N2, 377
crowding, intramolecular, 206
crown ethers see ethers
crown ethers, 444
crown ethers, acyl halides with amines, 1299
amination reactions, 751
and acylation of amines, 1215
and aryldiazonium salts, 789
and coupling with cyanide ion, 563
and decyanation, 726
and elimination reactions, 1260
and ion pairing in elimination reactions, 1260
and kinetic resolution, 156, 157
and metal ions, 108
and preparation of alcohols from amines, 475
chiral, 109, 157
in the *Gabriel synthesis*, 494
with $KMnO_4$, 1463
with $LiAlH_4$, 1511
with metals, 726
with permanganate, oxidative cleavage of alkenes, 1463
cryptands, 109, 110, 444
addition of organolithium reagents, to aldehydes and ketones, 1113
and phase transfer catalysis, 443
and resolution, 157
and solvation, 429
cryptates, 109, 169
and complex formation, 108
and out-in isomers, 168
cryptophanes, 111
crystallization, fractional, and resolution, 154–157
seeding method, 158
crystallographic scale, acidity, 319
crystals, and mechanical resolution, 157
CS_2 see carbon disulfide
Cu catalysts, allylic silanes with aldehydes, 1126
and decarboxylation of alkyne-acids, 721
and hydroxylation of aryldiazonium salts, 790
and *Meinwald rearrangement*, 1344
and the *Gatterman reaction*, 847
arylation of amides, 755
chiral, oxidation of diols, 1447
coupling of alkynes, 840
nitro compounds with imines, 1137
thiolates with aryl halides, 749, 750
with diazoesters, 1054
Cu complexes, and the *Hay reaction*, 842
Cu compounds, chiral aldol reactions, 1149
with dialkylzinc reagents, 525
Cu, immobilized, and *Ullmann coupling*, 769
Cu reagents, vinyl, dimerization, 850
Cu, and diazo compounds, 692
Cu, and *Grignard reagents*, 517
cubane, and strain, 198
rearrangement, 1423
cubene, 207
cubyl carbocation, 383
cubyl compounds, and S_N1 reactions, 382
cubylcarbinyl radicals, 1334, 1335
cucubituril gyroscane, 121
cucurbiturils, 121
cumene, and radical reactions, 520
cumulenes, and optical activity, 133
cyclic, 203
from alkynyl epoxides, 1305
from propargylic halides, 1305
via 1,4-elimination, 1305
cuneane, 1423
cuprates see organocuprates
cuprous bromide, with Grignard reagent, 535
cuprous cyanide, with diazoalkanes, 487
with organometallics, 709
Cu-quinoline decarboxylation, mechanism, 644
Current Abstracts of Chemistry and Index Chemicus, 1586
Current Chemical Reactions, 1586
Current Contents Connect, 1575
Current Contents, 1575, 1586
Curtius reaction, 497
Curtius rearrangement, 1324, 1354, 1361
and Lewis acid catalysis, 1361
mechanism, 1362
cyanamides, addition of ammonia, 1104
and the *Ritter reaction*, 1240
decarboxylation, 483
formation of amines, 483, 509
hydrolysis, 1081
cyanates, from alkyl halides and isocyanate, 447
halo, 988
phenyl, with organolithium reagents, 759
cyanation, and ion radicals, 689
enantioselective, 981
metal catalyzed, 689
metal sulfonate esters, 759
of alkanes, 689
of aromatic compounds, 633
of aryl halides, 759
of aryl halides, metal free, 759
of carbonyl compounds, 689

of nitro compounds, 689
radical, 563
cyanide, trimethylsilyl see trimethylsilyl cyanide
cyanide, trimethylsilyl, 564
and formation of cyanohydrins, 1181
formation of cyanohydrins, catalysts for, 1181
with alkenes and silver salts, 981
cyanide ion, ambident nucleophile, 563
amides from esters, 1220
and isonitriles, 563
and the Strecker synthesis, 1182
as a nucleophile, 1182
as an ambident nucleophile, 448
conjugate addition, 981
copper, and acyl halides, 1237
diethylphosphoryl, 563
in *Michael reactions*, 946
metal see metal cyanides
metal, and *Rosenmund-von Braun reaction*, 758
metal, with alkyl halides, 563
metal, with aryl halides, 758
potassium, and the benzoin condensation, 1187
with aldehydes or ketones, 1182
with aldehydes or ketones, biocatalysts, 1181
with aldehydes or ketones, metal catalysts, 1181
with aldehydes, 1187
with aldehydes, and conjugate addition, 969
with alkyl halides, 448, 562
with aryl nitro compounds, 797
with boranes, 1376
with vinyl triflates, 563
zinc see zinc
cyanides also see nitriles
cyanides, acyl formation of, mechanism, 1237
from acyl halides and copper cyanide, 1237
with allylic halides, 1232
cyanides, by dehydration of ureas, 1313
hydrolysis, 276
tosyl, with enolate anions, 689
trimethylsilyl, and the Ritter reaction, 1239
vinyl, from vinyl halides, 563
vinyl, from vinyl triflates, 563
cyano group, reduction to methyl, with terpenes, 1531
cyano imines, by *Ehrlich-Sachs reaction*, 1164
cyanoacetic ester synthesis, 541
cyanoamines, and cyclotrimerization, 1061
formation, enantioselectivity, 1183
from addition of HCN to C=N compounds, 1183
from aldehydes or ketones, 486
from amines, 689
from hydroxy-ketones, 486
with anhydrides, 1376
with trifluoroacetic anhydride, 1376, 1377
cyanoborohydride, sodium, and reduction of alkyl halides, 1533
and reduction of conjugated alkenes, 916
cyanocuprates, 950
cyanoethylation, 866
cyanogen bromide, 510
and isotopic labeling, 277
with amines, 509
with carboxylate salts, 1241
with carboxylate salts, mechanism, 1242
cyanogen chloride, with alcohols, 1086
cyanohydrins, 969
and the benzoin condensation, 1181
and the *Kiliani-Fischer method*, 1182
and Umpolung, 549
cleavage, 718
formation in ionic liquids, 1181
formation of amines, 561
formation, enantioselectivity, 1181, 1182
from aldehydes or ketones, 1180
from bisulfite addition products, 1182
from HCN with carbonyls, 1180
from lyases, 1181
from metal cyanohydrins, 1181
from trimethylsilyl cyanide, 1181
hydrolysis, 1080
with alkyl halides, 563
cyanoimines, from nitriles, 1164
cyanoketones, 1180
displacement of cyano, 532
with benzotriazoles, 1232
cyanomethanes, pK_a, 336
cyanomethylamines, 689
cyanuric acid, with amides and alcohols, 1208
cyanuric fluoride, with carboxylic acids, 1224
cyclams, 339
cyclazines, and antiaromaticity, 79
cyclic amines, from halo-amines, 482
cyclic compounds, and cis/trans isomers, 165, 166
and I strain, 350
cyclic cumulenes, 203
cyclic dienes, in the *Diels-Alder*, 1021
cyclic epoxides, 1040
cyclic intermediate mechanism, 1457
cyclic intermediates, 863
cyclic mechanism, 869, 1113
addition to alkenes, 869
and decarboxylation, 720
conjugate addition, 955
deoxygenation of diols, 1301
reduction of hydrazones, 1542
cyclic molecules, and entropy, 265
cyclization, addition of alkenes to alkenes, 931
aldehydes or ketones with amines, 1091
amidation of alkenes, 900
aminyl-radical, 484
cyclization, and active methylene compounds, 541
and amination of alkenes, 897
and *Dieckmann condensation*, 1234, 1235
and extrusion reactions, 1318
and *Grignard reactions*, 1109
and metal catalyzed coupling of *Grignard reagents*, 849
and neighboring group effects, 394
and radicals, 991
and the *Bradsher reaction*, 617
and the *Pauson-Khand reaction*, 976
and the *Stork enamine reaction*, 552
and the *Thorpe reaction*, 1179
and the *Thorpe-Ziegler reaction*, 1179
and the *Wittig reaction*, 1172
and the *Wurtz reaction*, 513, 514
cyclization, arylation of amines, 754
cyclization, *Bergman*, 1386
cyclization, by acyloin condensation, 1560
by halogenation of homoallylic alcohols, 986
by hydroamination of alkenes, 897
by hydroformylation, 980
by intramolecular aldol reactions, 1149
by nitrene insertion, 680
cyclization, electron demand, 1030
cyclization, *Friedel-Crafts acylation*, 623
Friedel-Crafts alkylation, 613
Friedel-Crafts, 616
cyclization, intramolecular, 928
cyclization, *Johnson polyene*, 932

cyclization, metal catalyzed coupling of allenes to alkenes, 934
cyclization, *Nazarov*, 946
cyclization, of aldehydes, 971
of alkene- aldehydes, 1123
of alkene amides, 1013
of alkene-acids, 892, 1013
of alkene-alcohols, 890
of alkene-silanes, 930
of alkyne-acids, 1013
of alkyne-alcohols, 890
of alkynes to alkenes, 931
of alkynes, 935
of allene-alcohols, 890
of allenes and allylic halides, 935
of amines with aryl halides, 754
of aryl halides with alkenes or alkynes, 939
of aryl ketones, 616
of carbonates with ketones, 1236
of dialdehydes, 1557
of dicarboxylic acids, 1235
of dienes, 931
of diols, 1557
of diynes, 934
of diynes, metal catalyzed, 934
of enynes, 934
of enynes, metal catalyzed, 935
of ester enolate anions, 1235
of hydroxy acids, 1204
of iminium ions, 618
of organolithium reagents, with alkenes, 937
of organolithium reagents, with imines, 1133
of radicals, 390, 868
of triflamide alkenes, 900
cyclization, photochemical, 303
Prins, and *oxonia Cope rearrangements*, 1401
Pschorr ring closure, 795
radical, 876
cyclization, radical see radical cyclization
radical, to aldehydes, 1188
cyclization, *Rauhut-Currier*, 1128
cyclization, *Ruzicka*, 1238
cycloaddition reactions, and microwaves, 311
of enamines, 1042
[1+2]-cycloaddition, and carbenes, 1051
[2+2]-cycloaddition, 1040–1051
[2+2]-cycloaddition, and cyclopropanes, 1044
and *Dewar benzene*, 1050
and *Diels-Alder reactions*, 1042
and diradicals, 1044, 1047
and frontier orbital method, 1032
and photosensitizers, 1049
and transition states, 1033
and valence isomers, 1050
cycloreversion, 1047
[2+2]-cycloaddition, diion mechanism, 1046, 1047
diradical mechanism, 1046
diradicals, 1050
electronic effects, 1046
enantioselectivity, 1043
endo/exo selectivity, 1045
forbidden reactions, 1050
forbidden, 1388
formation of lactams, 1041
formation of β-lactams, 1041, 1042
HOMO-LUMO overlap, 1044
imines and ketenes, 1244
intramolecular, 1041
[2+2]-cycloaddition, ketenes, with aldehydes or ketones, 1243
with alkenes, 1041
with alkynes, 1042
[2+2]-cycloaddition, masochistic steric effects, 1045
mechanism, 1044, 1045
metal catalyzed, 1041
of alkynes, 1047
of allenes, 1043
of ylids with carbonyls compounds, 1171
orbital overlap, 1044
Paterno-Büchi reaction, 1049
[2+2]-cycloaddition, photochemical, 1041, 1043, 1047, 1048, 1243
and conjugated compounds, 1048
and EDA complexes, 1050
and exciplex formation, 1050
and orbital symmetry, 1050
and wavelength of light, 1048
and *Wigner spin conservation rule*, 1049
and *Woodward-Hoffmann rules*, 1050
catalysts for[2+2]-cycloaddition, 1043
diradical mechanism, 1049
formation of oxetanes, 1049
intramolecular, 1048
[2+2]-cycloaddition, photosensitizers, 1047
polar solvent acceleration, 1045
rate, 1045
solventless, 1043
solvents, 1043
stereochemistry, 1045
steric effects, 1045
substrates for, 1041
thermal, 1043
transition metal catalysts, 1402
triplet state, 1049
[2+2]-cycloaddition, with alkenes, 1041
with alkenes, and ketenes, MO, 1045, 1046
with alkenes, with aldehydes or ketones, 1243
with alkynes, 1041
with allenes, 1041, 1045
with allenes, with alkenes, 1041
with allenes, with alkynes, 1042
with benzynes, 1041
with bicyclic compounds[2+2]-cycloaddition, 1044
with biphenylenes, 1041
with cyclopropanes, 1044
with enamines, 1042
with imines, 1041
with ketenes, 1041
with strained compounds, 1044
[2+2]-ring closures, 1424
[2+2]-ring opening, 1423
[2+2+1]-cycloaddition, 1066
[2+2+2]-cycloaddition, 1066
[2+2+2]-cycloaddition see cyclotrimerization
[2+6]-cycloadditions, 1034
[2+8]-cycloadditions, 1034
[3+2]-cycloaddition, 1014–1020
alkyl azides, 1017
alkynes, 1018
all carbon, 1019
allylic carbocations, 1020
[3+2]-cycloaddition, and alkynes, 1019
and allylic carbanions, 1020
and diradicals, 1019
and Fischer carbene complexes, 1017
and FMO, 1016
and LDA, 1020
and orbital coefficients, 1016
and phosphines, 1019
and the *Diels-Alder reaction*, 1016
[3+2]-cycloaddition, antibody catalyzed, 1017
diionic intermediates, 1017
enantioselectivity, 1017, 1018
in situ generated dipoles, 1018
in supercritical CO_2, 1016
intramolecular, 1017
mechanism, 1016
metal catalysts, 1018
metal catalyzed, 1017
rate, 1016
regioselectivity, 1016
stereoselectivity, 1017
[3+2]-cycloaddition, with azides, 1018
with dienes, 1018
with dipolar compounds, 1015
with fulminic acid, 1017
with hydrazones, 1014
with nitrile oxides, 1016
with nitrones, 1018

with permanganate, 1014
with trimethylenemethane, 1019
[3+2+2]-cycloaddition, 1064
[3+4]-cycloaddition, 1064
[3+4]-cycloaddition, with dienes, 1018
[4+1]-cycloaddition, 1064
[4+2]-cycloaddition see Diels-Alder
[4+2]-cycloaddition, 1020–1039
and frontier orbital method, 1032, 1033
Hückel-Möbius allowed, 1033
photochemical, 1036
transition states, 1033
[4+2+1]-cycloaddition, 1066
[4+2+2]-cycloaddition, 1066
[4+3]-cycloaddition, 1064
with chiral carbocations, 1064
[4+4]-cycloaddition, 1034
[4+4]-cycloaddition, 1063, 1065
[4+4+4]-cycloaddition, 1063
[4+4+4]-cycloaddition, 1065
[4+6]-cycloaddition, 1034
[5+2]-cycloaddition, 1064–1066
[5+2+1]-cycloaddition, 1066
[6+2]-annulation, and Brook rearrangement, 1431
[6+2]-cycloaddition, 1064, 1065
[8+2]-cycloaddition, 1065
cycloadditions, 981
1,3-anionic, 1020
and *Hückel's rule*, 1032, 1033
and *Möbius strip*, 1034
Diels-Alder, 1020–1039
ketenes with ketenes, 1242
metal catalyzed, 1063, 1066
Möbius-Hückel method, 1032, 1033
of 1,3-dipoles, 1014–1020
of alkenes to alkenes, 1040–1051
other, 1063
photochemical, 1039
suprafacial concerted, 1064
thermal, 1043
heat of combustion, table, 200
cycloalkanes, and strain, 199, 200
cycloalkenes, and strain, 202
by the *Wittig reaction*, 1172
cycloalkynes, and Pt complexes, 202
and strain, 202
cycloamyloses see cyclodextrins
cyclobutadiene derivatives, and the captodative effect, 69
cyclobutadiene, 1047
and aromaticity, 65, 67
and carcerands, 68
and low-temperature matrix, 68
and NMR, 68
antiaromaticity, 37
in the *Diels-Alder reaction*, 67
iron complex, 69
metal complex, 69
MO calculations, 68
PES, 68
stable derivatives, 68
synthesis of, 67
cyclobutadiene-metal complex, and cyclotrimerization, 1062
cyclobutadienes, and antiaromaticity, 67
and steric hindrance, 68
and strain, 69
and X-ray, 69
cyclobutane, [2+2]-ring opening, 1423
and bromine, 195
and pyrolysis, 195
and strain, 195
conformations, 188
conjugation with carbocations, 214
pyrolysis, 195
cyclobutanes, and strain, 194
divinyl, rearrangement, 1402
from dienes, 1424
thermal cycloreversion, 1047
vinyl, rearrangement, 1399
cyclobutanones, by [2+2]-cycloaddition of ketenes, 1041
extrusion of carbon monoxide, 1317
photolysis, 1317
cyclobutene ring opening, Hückel system, 1383
cyclobutene, conrotatory ring opening, and HOMO symmetry, 1383
conrotatory versus disrotatory, 1385, 1386
from cyclopropylcarbenes, 256
cyclobutene, ring opening, torquoselectivity, 1381
cyclobutene-butadiene, and orbital symmetry, 1388
cyclobutene-diene interconversion, orbital requirements, 1384, 1385
cyclobutenes, by [2+2]-cycloaddition, 1041
by [2+2]-cycloaddition, of alkenes and alkynes, 1047
from alkenes, 1041
from cyclic sulfones, 1319
from cyclohexadienes, 1386
from diallenes, 1402
from methylenecyclopropanes, 1346
HOMO, and photochemistry, 1383
orbitals, and thermal ring opening, 1383
thermal ring opening to dienes, 1380
cyclobutyl compounds, and solvolysis, 405
cyclobutyl groups, and nonclassical carbocations, 405
as neighboring groups, 398
cyclobutyl, and rate enhancement, 406
from cyclopropylmethyl, 406
cyclobutylcarbinyl radical see radicals
cyclobutylcarbocations, 214
cyclodecane, conformations, 189
cyclodecapentaene, and aromaticity, 65
cyclodehydration, 469, 616
cyclodextrin, 488, 116
and cage complexes, 116
and channel-type complexes, 117
and complex formation, 116
and formation of amino-alcohols, 489
and oxidation of alcohols, 1451
and resolution, 157
and water solubility, 116
capped, 117
catalysis of *Diels-Alder reactions*, 1022
chlorination of aromatic compounds, 581
complex with iodoaniline, 117
shape and dimensions, 117
toxicity, 117
cyclodiastereomerism, 120
cycloenantiomerism, 120
cycloheptadiene, 203
cycloheptadienes, by rearrangement of divinylcyclopropanes, 1402
from divinylcyclopropanes, 1402
cycloheptane, conformations, 189
cycloheptatriene, 1056
and aromaticity, 59
from carbene addition to benzene, 1056
cycloheptatrienes-norcaradiene, valence tautomerism, 1406
cycloheptatrienyl (substituted) cations, 60
cycloheptatrienyl anions, aromaticity and antiaromaticity, 71
cycloheptatrienyl cation see tropylium ion
cycloheptatrienyl derivatives, and NMR, 71
cyclohexacenes, 78
cyclohexadiene to triene interconversion, 1402

cyclohexadienes, by the *Diels-Alder reaction*, 1021
  from benzene, 914
  from *Grignard* addition to aromatic compounds, 955
  rearrangement, 1349
  ring closure to cyclobutenes, 1386
cyclohexadiene-triene interconversion, orbital requirements, 1384, 1385
cyclohexadienones, and tautomerism, 93
  rearrangement, 1349
cyclohexane derivatives, stereoisomers, 184
  and equilibrium, 180
  conformations, 181
  methylene, and chirality, 133
  pseudorotation, 180
  substituted, conformations, 183
cyclohexanes, $A^{1,3}$-strain, 182, 184
  and stereochemistry, 148
  substituted, with $LiAlH_4$, 878
  conformations, 185
  hydrogenation of phenols, 913
cyclohexatriene, HOMO, 1384
cyclohexene, conformations, 185
  formation of radicals, selectivity, 879
cyclohexenes, by rearrangement of vinylcyclobutanes, 1399
  trans, 1386
cyclononyne, and strain, 202
cyclooctadiene, 203
  preparation of 9-BBN, 922
  with iodine, 200
cyclooctadienes, from divinylcyclobutanes, 1402
cyclooctatetraene dications, 62
cyclooctatetraene, and aromaticity, 65, 71
  and chirality, 134
  and metal complexes, 106
  conformation and bond angles, 71
  cyclotrimerization of alkynes, 1060
  dehydrohalogenation, 71
cyclooctatrienes, by cyclization of octatetraenes, 1387
cyclooctene, and chirality, 134
  and cis/trans isomers, 164
  photoisomerization, 305
  trans double bond, 202
  trans, and chirality, 134
  trans, resolution of, 155
  trans, strain energy, 204
cyclooctyne, and strain, 202
  heat of hydrogenation, 202
  IR, 202
cyclopentadiene, and annellation, 59
  and metallocenes, 61, 62
  pK_a, 58
  with ketene, orbital overlap in [2+2]-cycloaddition, 1045, 1046
  and circumambulatory rearrangement, 1394, 1395
  and hyperconjugation, 88
  [1,5]-sigmatropic rearrangements, 1394
cyclopentadienide ion, 58, 59
  and aromaticity, 5, 58
  canonical forms, 58
  diatropic, 59
  resonance energy, 58
cyclopentadienone, 60
cyclopentadienyl anion, 70
cyclopentadienyl cation, and aromaticity, 69
  nonaromatic and aromatic, 70
  preparation and diradical character, 70
cyclopentane, conformations, 188
  energy barrier to planarity, 189
cyclopentanes, by [3+2]-cycloadditions, 1019
cyclopentanone, conformation, 189
cyclopentenes, by rearrangement of vinylcyclopropanes, 1398
cyclopentenone, photodimerization, 306
cyclopentenones, by *Nazarov cyclization*, 946
  via the *Pauson-Khand reaction*, 976
cyclopentyne, and strain, 202
cyclophanes see paracyclophanes
cyclophanes, 47
  and a chiral axis, 140
  and anisotropy, 51
  and aromaticity, 47
  and chirality, 134
  and pseudorotation, 48
  and ring current, 51, 52
  belt, 47
cyclopropabenzene, 48
cyclopropanation, alternative methods, 1058
  and C-H insertion, 692
  and chiral Rh catalysts, 1054
  and diiodomethane, 1057
  and *Grignard reagents*, 1058
  and organocatalysts, 1054
  by metal catalyzed diazoalkane reactions, 1051
  Cr catalyst, 1055
  Cr complex, 1053
  enantioselectivity, 1179
  intramolecular, enantioselectivity, 1055
  isomer formation, 1056
  metal catalysts, 1057
  metal catalyzed, chiral additives, 1054
  organocatalysts, 1179
  rate, 1055
  stereoselectivity, 1056
cyclopropane dihalides, carbene formation, 1347
cyclopropane intermediates, 1326
  and the *Claisen rearrangement*, 1411
cyclopropane, and bent bonds, 194
  and bond angles, 194
  and bromine, 194
  and conjugation, 195
  and electron density, 194
  and MO calculations, 194
  and stabilization of carbocations, 395
  and UV, 195
  conjugation with carbocations, 214
  corner-protonated, 880
  from alkenes, 937
  from organolithium reagents, 937
  isomerization and carbenes, 256
  orbital overlap, 195
  orbitals, 195
  protonated, 1326, 1327
  pyrolysis, 194
  radicals, 244
  ring opening, conrotatory versus disrotatory, 1389
  ring opening, mechanism, 1346
  strain, 193
  to propene, and entropy, 268
  with amines, 492
cyclopropanediazonium ions, 598
cyclopropanes, 70
cyclopropanes, addition reactions, 879
  and Markovnikov's rule, 880
  mechanism, 879–881
  stereochemistry, 880
cyclopropanes, addition, carbocation mechanism, 880
  of halogens, and UV, 881
  of metal carbenes to alkenes, 1053
  radical mechanism, 881
cyclopropanes, and [2+2]-cycloaddition, 1044
  and diiodomethane, 1057, 1058
  and diradicals, 1347
  and *Markovnikov's rule*, 881
  and sigmatropic shifts, 1395
  and the S_E2 mechanism, 880
cyclopropanes, by [1+2]-cycloaddition, 1051
  by [3+2]-cycloaddition, 1017
  by carbene transfer, 1051
  by extrusion of nitrogen from pyrazoles, 1316, 1317

by extrusion of nitrogen from pyrazolines, 1316, 1317
by the *Simmons-Smith procedure*, 1057
by thermolysis of pyrazolines, 1017
cyclopropanes, carbene addition to alkenes, 1051
cleavage with metals in ammonia, 920
dihalo, with organolithium reagents, 1347
divinyl, rearrangement, 1402
edge protonated, 881
from carbenes, 1053
from carbenoids with alkenes, 1057
from carbenoids, 1057
from conjugated carbonyl compounds, 1176
from diols, 532
from ketenes, 1053
from organozinc compounds, 1057
from pyrazolines, 1017
from sulfur ylids and conjugated compounds, 1178
from sulfur ylids, 1176
from triazolines, 1017
cyclopropanes, hydrogenation, formation of gem-dimethyl groups, 920
photolysis, and carbenes, 253
protonated, 880
protonated, and rearrangements, 1326
protonation, ab initio studies, 881
pyrolysis, 1347
reductive cleavage, 920
solvolysis, 1390
solvolysis, rate, 1390
stabilization of carbanions, 224
via conjugate addition, 953
via sulfur ylids, 1176
cyclopropanes, vinyl also see vinyl
cyclopropanes, vinyl also see vinylcyclopropanes
vinyl, from dienes, 1425
cyclopropanes, with HBr, 879
with lead tetraacetate, 879
with $LiAlH_4$, 911
cyclopropanones, by photolysis of cyclobutanones, 1317
cycloproparenes, 48, 49
cyclopropene, and strain, 201
cyclopropenes, 70
and hydrogen exchange, 70
by carbene addition to alkynes, 1055
by extrusion of nitrogen from pyrazolines, 1316, 1317
by extrusion reactions, 1317
catalytic hydrogenation, 920
from diketones, 1559
rearrangement to allenes, 1055
with chlorosulfonyl isocyanate, 1245
cyclopropenium diazonium salts, 434
cyclopropenone, 67
cyclopropenones, 1055
cyclopropenyl anion, and aromaticity, 69
cyclopropenyl cations, 70
and aromaticity, 66, 67
and tropones, 67
cyclopropyl alkynes, and radicals, 240
cyclopropyl anion, conrotatory ring opening, 1389
cyclopropyl carbocations, and ring opening, 1389
cyclopropyl cations, disrotatory ring opening, 1389
cyclopropyl groups, and carbocations, 214
cyclopropyl groups, and solvolysis, 423
cyclopropyl halides, 700
cyclopropyl, and anchimeric assistance, 398
cyclopropyl, as a neighboring group, 398
cyclopropylalkenes, conformations, 195
cyclopropylboronic acid, with vinyl halides, 683
cyclopropylcarbinyl alcohols see alcohols
cyclopropylcarbinyl carbocations, 395
cyclopropylcarbinyl radicals also see radicals
cyclopropylcarbinyl cations see carbocations
cyclopropylcarbinyl radicals, 247, 248
as a radical clock, 248
cyclopropylcarbinyl also see cyclopropylmethyl
cyclopropylidenoids, formation of allenes, 1305
cyclopropyllithium, stability, 696
cyclopropylmethyl carbocations, 213
cyclopropylmethyl cation, and NMR, 406
cyclopropylmethyl groups, and carbocations, 404, 405
and nonclassical carbocations, 404, 405
cyclopropylmethyl see cyclopropylcarbinyl
and rate enhancement, 406
and rearrangement, 406
and solvolysis, 404, 405
and σ-bond participation, 404, 405
formation of cyclobutyl, 406
cycloreversion, thermal, of cyclobutanes, 1047
cyclotrimerization, alkyne, metal catalyzed, 1060
cyclotrimerization, and cyclobutadiene-metal complex, 1062
and *Diels-Alder reactions*, 1062
and diynes, 1063
and *Dötz benzannulation*, 1063
and *Fischer carbene complexes*, 1062
and *Grignard reagents*, 1061
and metal complexes, 1062
and metal extrusion, 1062
and sonication, 1061
cyclotrimerization, intramolecular, 1060
isoquinoline synthesis, 1061
metal catalysts, 1060
metal catalyzed, mechanism, 1062
cyclotrimerization, of alkynes, 1059, 1060
of alkynes, metal catalysts for, 1060
of alkynes, metal catalyzed, 1060
of diynes, 1060
of triynes, 1060, 1061, 1062
cyclotrimerization, reactive functional groups, 1062
regioselectivity, 1062
solid-supported, 1060
structural variations, 1062
triketones, 1061
with metal carbenes, formation of heterocycles, 1063
cyclpentanes, methylene, 1019
cycobutanedione, by ketene dimerization, 1242
cysteine-cystine interconversion, 1497

d orbitals, 15
d orbitals see orbitals
D_2O, and the *Cannizzaro reaction*, 1564
DABCO, 168
and diynes, 843
and *Michael addition*, 946
and *Morita-Baylis-Hillman alkylation*, 1129
and solventless acylation of amines, 1213
and the *Baylis-Hillman reaction*, 1127, 1128
tosylimines and conjugated esters, 1137
daisy chains, 118

Dakin reaction, 1370, 1466
and the *Baeyer Villiger reaction*, 1467
in ionic liquids, 1467
Dakin-West reaction, 722
dammaradienol, 931
Danishefsky's diene, 1037
Darzen's condensation, 1142, 1161
and Knoevenagel reaction, 1161
enantioselectivity, 1162
functional group compatibility, 1162
mechanism, 1161
structural variation, 1162
Darzens glycidic ester synthesis see *Darzens condensation*
DAST (diethylaminosulfur trifluoride), 1106
fluorination of alcohols, 501
fluorination of sulfoxides, 674
with acyl halides, 1225
with aldehydes or ketones, 1106
databases, *CAS*, 1594
DBDMH, and halogenation, 827
DBN (1,5-diazabicyclo[3.4.0]non-5-ene), 1297
and elimination of alkyl halides, alkenes, dehydrohalogenation, 1297
DBr, addition to alkenes, 864
DBU (1,8-diazabicyclo[5.4.0] undec-7-ene), 968, 969, 1297
and amide formation, 631
and carbonylation of aryl halides, 781
and elimination of alkyl halides, alkenes, dehydrohalogenation, 1297
and Hofmann rearrangement, 1360
and hydrocarboxylation, 973
and malonic ester synthesis, 540
and NBS, with carbamates, 1361
and thioethers, 476
catalysts, 966
epoxidation, 1003
imines and nitriles, 1136
urea-hydrogen peroxide, 1003
with epoxides and diamines, 1287
with NBS, 1360
with phosphonate esters, 1172
DCC (dicyclohexylcarbodiimide)
and DMSO, 632, 1448
and esterification, 1205
amides to isocyanides, 1314
amines with CS_2, 1105
and anhydride formation, 1210
and dehydration, 1284
and DHU, 1205
and Moffatt oxidation, 1448
and peptide synthesis, 1217
and the Merrifield synthesis, 1218
carboxylic acids with amines, 1217
carboxylic acids with H_2O_2, 473
dehydrating agent, 1210
esterification of carboxylic acids, mechanism, 1205
lactone formation, 1205
with carboxylic acids and alcohols, 1205
with carboxylic acids and amines, 1217
DCl, with pentadiene, 870
DDQ: (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), 1439
and alkyl azide formation of, 497
and aromatization, 1439
and cleavage of ethers, 504
and nitriles, 564
and ultrasound, oxidation of alcohols, 1452
dehydrogenation, 1441
deactivating groups, and multiple substituents, 583
aromatic substitution, 578, 742
in aromatic compounds, 576
in S_NAr reactions, 742
nitro, 594
in photochemistry, 301
DEAD also see azodicarboxylates
DEAD (diethyl azodicarboxylate), and alkylation of amides, 461, 494
and carboxylate salt alkylation, 469
and decarboxylation, 1309
and keto esters, amination, 1476
and the *Mitsunobu reaction*, 464
with aromatic compounds, 600
dealkylation, of amides, reagents, 1554
of amines, reagents, 1553, 1554
reduction of ethers, reagents, 1536
sulfonamides, 1554
with ethanolamine, 487
deamination, of amines, 1543
of aromatic amines, 1550
Dean's Handbook of Organic Chemistry, 1581
Debyes, and dipole moment, 18
decahydroquinazolines, tautomerism, 94
decalin, cis/trans isomers, 167
decalones, 667
decane, as a solvent, 1319
decarbonylation, acyl halides, 721
and peroxides, 857
and photolysis, 857
and radicals, 857
formation of isocyanates, 1223
metal catalyzed, of acyl halides to alkenes, 1300
of acyl halides, 857
of aldehydes, 303, 1333
of aldehydes, metal catalyzed, 856
of aldehydes, metal catalyzed, mechanism, 857
of aldehydes, with *Wilkinson's catalyst*, 856, 857
of aromatic acyl halides, 647
of aryl aldehydes, 643
S_E1 mechanism, 643
decarboxylase, and the benzoin condensation, 1188
decarboxylation, allylic acetates with keto-acids, 856
decarboxylation, and anhydrides, 722
and borinates, 721
and *Bredt's rule*, 720
and carbanion formation, 233
and carboxylate ions, 719
and electrolysis, 1318
and labeling, 645
and quinoline, 645
and silver acetate, 645
and the arenium ion mechanism, 644
and the cyclic mechanism, 720
and the *Dakin-West reaction*, 722
and the *Hunsdiecker reaction*, 854
and the malonic ester synthesis, 540
and the S_E1 mechanism, 644
and the six-center mechanism, 720
decarboxylation, mechanism, 719, 720
metal mediated, 644
decarboxylation, of amino acids, 721
of aromatic acids, 719
of aryl carboxylic acids, 644
of carboxylate salts, with cyanogen bromide, 1241
of carboxylic acids, 718, 1238, 1288
of carboxylic acids, photolytic, 845
of conjugated acids, 719
of conjugated carboxylic acids, 720
of cyanamides, 483
of glycidic acid, mechanism, 719
of glycidic acids, 719
of keto acids, 720, 721
of keto esters, 721
of lactones, 1318
of malonic acids, 718, 1210

of radicals, 838, 845
of silver carboxylates, 854
of β-lactones, 1318
decarboxylation, oxidation, metal mediated, 1467
decarboxylation, oxidative see oxidative
decarboxylation, oxidative, of carboxylic acids to alkenes, 1467
of carboxylic acids, mechanism, 1468
decarboxylation, photochemical, 721
rate constants, 720
rate, 720
S_E1 mechanism, 645
special reagents, 721
structural limitations, 719
structure, and carboxylic acid reactivity, 719
reaction of alkenes and ArCOOH, 767
decomposition temperatures, peroxides, 804
decomposition, of acyl azides, 1323
of AIBN, 804
of chloroformates, 409
of peroxides, 804
of radicals, 247
decyanation, and crown ethers, 726
of nitriles, 726
with sodium borohydride, 726
dediazoniation, of aryldiazonium salts, reagents, 1549
of diazonium salts, 1549
suppression by calixarenes, 1550
degenerate carbocations, 1324
degenerate *Cope rearrangement*, 1404
degenerate rearrangements, 1324
dehalogenation, of acyl halide to ketenes, metal induced, 1306
of aryl halides, 647
of aryl halides, and *Grignard reagents*, 648
of aryl halides, electrochemical, 648
of aryl halides, photochemical, 648
of aryl halides, reagents for, 647
of dihalides, mechanism, 1305
with *Grignard regents* and a Ni catalyst, 1305
dehydrating agents, Amberlyst-15, 1205
and amides from carboxylic acids, 1217
and an aminopyridine, 1205
and DCC, 1205, 1210, 1217
and esterification of acids, 1202
carbonyldiimidazole, 1205, 1206
chlorosilanes, 1205
for amides to isonitriles, 1314
for carboxylic acids, 1284
for dehydration of alcohols, 1282
molecular sieves, 1202
phosphorous pentoxide, 1210
silica gel, 1202
dehydration, 1,4-, 617
dehydration, acid catalyzed, of alcohols, 1282–1285
alkenes from alcohols, 664
of alcohols, and Hofmann's rule, 1283
of carboxylic acids, 1284
of oximes, of nitriles and microwaves, 1311
reagents, amides to nitriles, 1313
reagents, for ureas, 1314
and DCC, 1284
and HMPA, 1284
and the aldol condensation, 1283
and the *Henry reaction*, 1283
and the *von Braun reaction*, 1313
and zeolites, 1283
dehydration, of alcohols, 463
acid catalyzed, E1, mechanism, 1284
and microscopic reversibility, 1284
and *Zaitsev's rule*, 1283
dehydrating agents, 1283
with metal oxides, 1283
dehydration, of aldols, 1283
of alkyne-alcohols, 1284
of amides, 1284, 1313
of amides, with PCl_5, 1313
of halohydrins, 1284
of hydroxy lactams, 1283
of oximes, 1310
of serine derivatives, 1283
of ureas, 1314
dehydrative acylation of carboxylic acids, 622
dehydroannulene, 75, 76
dehydrobenzenes see benzynes
dehydrobenzoannulenes, 76
dehydrogenation, base-induced, 1442
catalytic, and oxidation of alcohols, 1450
metal catalyst, 1440
of aldehydes or ketones, 1441
of amines to nitriles, 1453, 1454
of amines, 1440
of amines, and imine formation, 1454
of lactones, 1441
remote, 1441
with DDQ, 1441
dehydrohalogenation, alkyl halides with metal oxides, 1298
and nonionic bases, 1297
and radical mechanism, 1298
E1 and E2 mechanisms, 1298
in HMPA, 1297
of alkyl halides, and radicals, 1298
of alkyl halides, mechanism, 1298
of prochiral carboxylic acids, 1298
pyrolysis of alkyl halides, 1298
Delépine reaction, 483
delocalization, and bond distance, 37
and bond length, 53
and butadiene, 38
and carbocation structure, 211
and conjugated systems, 38
and hyperconjugation, 42, 86, 87
and nonclassical carbocations, 395
and vinyl chloride, 40
migrating aryl radicals, 1335
delocalized bonds, 37
Demyanov rearrangement, 1345
dendralenes, 42
dendrimers, as a catalyst, 1245
dendritic catalysts, and the *Pauson-Khand reaction*, 977
and transfer hydrogenation, 912
density functional theory, 72
and *Simmons-Smith procedure*, 1057
deoxycholic acid, as host, 115
deoxygenation, of alcohols, mechanism, 1535
of alcohols, reagents, 1535
of aldehydes or ketones, 1540
of aryl ethers, 646
of diols, and mechanism, 1301
deoxyribonucleic acids see DNA
deprotonation, by metals, 698
of alkynes, 648
of arenium ions, and steric hindrance, 572
to form carbanions, 233
with *Grignard reagents*, 696
with organolithium reagents, 695, 696
with organometallics, 695, 696
deracemization, and resolution, 159
and *Sphingomonas pauchimobilis*, 159
biochemical, 159

Dess-Martin periodinane, 457
and oxidation of alcohols, 1449
azides formation, 497
halogenation of conjugated ketones, 672
stability and sensitivity, 1449
destabilizing groups, and carbocations, 421
desulfonation of arylsulfonic acids, 646
desulfurization, by catalytic hydrogenation, 851, 852
of dithioacetals and dithioketals, 1088
of dithioacetals, 1551
of dithioketals, 1089
of sulfones, 1551
of sulfoxides, 1551
of thioethers, 1551
of thiols, 1551
of thiophene, 1551
of thiophenes, 852
to methylene units, 1551
with Raney nickel, 852, 1552
with Raney nickel, mechanism, 852, 1552
with samarium in acid, 852
detection of intermediates, 276
deuterium ion, and isotope effects, 571
deuterium quadrupole echo spectroscopy, 113
deuterium, and bond distance, 24
and hydrogen exchange, 592
and proton, 312
and secondary isotope effects, 424
and tautomerism, 666
deuterium, exchange with alkanes, 906
deuterium, isotope effects, 285–287
and dissociation energy, 285
and E1cB reactions, 1263, 1264
and E2 reactions, 1258
deuterium, labeling, and E2 reactions, 1257
and *Hofmann degradation*, 1291
and the *Shapiro reaction*, 1294
in cationic rearrangements, 1327
deuterium, reaction with alkenes, 908, 909
deuterium-hydrogen exchange, 660
Dewar benzene structures, 55
Dewar benzene, 1051, 1059, 1406
and [2+2]-cycloaddition, 1050
and steric crowding, 55
by photolysis of benzenes, 1387
Dewar benzenes, and benzene derivatives, 1387
and cyclotrimerization of alkynes, 1060
and electrocyclic rearrangements, 1387
and photochemical [2+2]-cycloaddition, 1050
pyrolysis, 1387
stability, 1387
Dewar structures, 31
and naphthalene, 55
and resonance, 46
dextro isomer, 123
$(DHQ)_2PHAL$, and aminohydroxylation, 1007
and asymmetric dihydroxylation, 996
hydroamination, 1008
$(DHQD)_2PHAL$, and asymmetric dihydroxylation, 996
DHU (dicyclohexylurea), and esterification, 1205
from DCC, 1205
from DCC and esterification, 1205
from DMSO-DCC oxidation, 1448
diacetamides, 1009
diacetates, gem-, 1469
with allylic silanes, 1126
diacetoxylation, of alkenes, 997
DIAD, 469
diadamantyl compounds, barrier to rotation, 176
diagonal hybridization, 7
dialdehydes, and the *Cannizzaro reaction*, 1563
by oxidative cleavage of epoxides, 1457
photochemical coupling, 1557
radicals coupling, 1557
dialklylzinc, with alkyl halides, 525
dialkoxylation, of alkenes, 995
dialkyl amide bases see amides, dialkyl
dialkyl amides, as bases, 1287
and the aldol reaction, 1146
as bases, chiral, 1298
dialkylboranes see boranes
dialkylmagnesium compounds, and Grignard reagents, 229, 230
dialkylmagnesium, 1108
dialkylzinc compounds, 1,6-addition, 954
acyl addition and metal complexes, 1120
addition to aldehydes or ketones, 1115
and conjugate addition, 970
and Pd catalyst, with allylic alcohols, 1117
and the Reformatsky reaction, 1130
conjugate addition, 953
rearrangement of halohydrins, 1343
with carbonyls, enantioselectivity, 1117
with Cu compounds, 525
with dihalomethanes, 1058
with imines, 1134
with propargylic acetates, 1121
diallenes, conversion to dimethylenecyclobutenes, 1402
from diynes, 1402
diamagnetic ring current, 51, 53
and aromaticity, 66
diamantane, 1341
diamides, by radical coupling of amides, 839
dimeric, from conjugated amides, 839
diamination, alkynes, 1009
of alkenes, 1008
diamine protonic acids, catalyst for the aldol reaction, 1148
diamines, by coupling of iminium salts, 1558
by metal catalyzed coupling of imines, 1558
chiral, 1103, 1137
from addition of amines to alkenes, 1008
from azido-tosylamines, 491
from aziridines, 491
from bis(azides), 1009
oxidative cleavage to diketones, 1456
with LDA and DBU, elimination of epoxides, 1287
diamino aromatic compounds, oxidative cleavage to dinitriles, 1465
diaminocyanocuprates, 536
dianion zincates, 929
dianions, active methylene compounds, 541
alkylation, 448, 541
from ketones and CS_2, 1164
from ketones, 1236, 1237
of carboxylic acid salts, 552
of carbolic acids, acylation, 1237
of carboxylic acids, with esters, 1237
of diketones, acylation, 1237
diaryl carbenes, 251
diarylamines, 599, 754
diastereomer, definition, 146
diastereomeric complexes, 155
diastereomers, “r” and “s”, 147
diastereomers, alkyl halides, and stereochemistry of elimination, 1273
diastereomers, and 2^n rule, 147

and absolute configuration, 148
and Cahn-Ingold-Prelog rules, 148
and catenanes, 119
and chiral recognition, 156
and cis-trans isomers, 162
and diastereoselectivity, 150
and diastereotopic atoms/groups, 170
and diastereotopic, 171
and differential absorption, 156
and fractional distillation, 156
and fractional recrystallization, 156
and GC, 156
and NMR, 172
and nomenclature, 148
and preparative LC, 156
and resolution, 154
and the E2 reaction, 1255
and X-ray crystallography, 148
diastereomers, epi and peri prefixes, 148
epimers, 147
erythro/threo nomenclature, 148
HPLC separation, 162
meso compounds, 166
meso form, 147
physical properties, 146
pseudoasymmetric carbon, 147
syn/anti nomenclature, 149
tartaric acid, 147
torsional, 132
diastereoselectivity, and conjugate addition of organocuprates, 951
and synthesis, 150
in dihydroxylation, 997
in *Friedel-Crafts alkylation*, 610
in *Mannich reactions*, 1102
in reduction with Selectride, 1505
in the aldol reaction, 1145, 1146
in the *Diels-Alder reaction*, 365
in the *Grignard reaction*, 1108
in the *oxonia-Cope rearrangement*, 1401
in the *Paterno-Büchi reaction*, 1243
in the reduction of ketones, 1515
of radical cyclization, 963
with sulfur ylids, 1176
with *Grignard reagents*, 1108
diastereotopic atoms, 171
diastereotopic atoms/groups, 170
diastereotopic compounds, and NMR, 172
diastereotopic faces, 172
diastereotopic, and *Cahn-Ingold-Prelog rules*, 172
diastereotopic, definition, 171
diatomic molecules, and bond energy, 27
energy curve, 291
diatropic, 51
annulenes, 73
cyclooctatetraene dications, 62
cyclopentadienide ion, 59
1,8-diazabicyclo[5.4.0]undec-7-en see DBU
diazabicyclcooctane see DABCO
diazabicyclcoundecane, 168
diazaborane derivatives, chiral, 1155
diazirines, and carbenes, 254
diazo alkanes, base induced elimination of nitroso compounds, 1315
diazo compounds, alkylation, 462
alkylation, of carboxylic acids, 471
and phosphonate esters, 1054
by the *Bamford Stevens reaction*, 1294
from active methylene compounds, 677
from anilines, 789
from nitroso amides, 1316
from nitroso carbamates, 1316
from nitroso ureas, 1316
photooxidation, 1462
protonation of, 434
reduction, 1521
versus a diazonium salt, 789
with alkenes, 1139
with amides, 495
with amines, 487
with boranes, 559
with imines, 1139
with ketones, 1188
with metals, 1053
with sulfene, 1178
with sulfur, 1178
with thioketones, 1178
diazo esters, with ketones, 1356
diazo hydroxide, 597
diazo ketones, and the *Wolff rearrangement*, 1244
with imines, and microwave irradiation, 1245
diazo transfer reactions, formation of carbene complexes, 1054
diazoacetate, ethyl, 688
with ketones, 1356
diazoacetates, metal catalyzed addition to alkenes, 1010
with imines, 1010
diazoalkanes, cleavage to ethers, 463
decomposition to carbenes, 254
from nitroso compounds, 1315
in [3+2]-cycloaddition, 1015
reaction with carbenes, 256
Rh catalyzed decomposition, 255
with aldehydes or ketones, and mechanism, 1177
with aldehydes, 1059
with CuCN, 487
with enols, 463
with mineral acids, 508
with oximes, 463
with Rh compounds, 1051
diazoboron derivatives, chiral, 1155
diazocarbonyl compounds, insertion, 692
diazoesters, insertion, 692
metal catalyzed addition to imines, 1139
with aldehydes, 688
with amines, 1058
with Cu catalysts, 1054
diazoketones, 471
and the *Arndt-Eistert synthesis*, 1352–1354
and the *Wolff rearrangement*, 1353
by diazo transfer, 678
by diazo-transfer reactions, 678
by the *Arndt-Eistert synthesis*, 1238
conformations, s-E/s-Z, 1354
decomposition, 1244
from acyl halides and diazoalkanes, 1238
from acyl halides, 1352
hydrolysis, 454
photolysis, and ring contraction, 1353
rearrangement to carboxylic acids, 1352
with mineral acids, 508
diazomethane, alkylation of amines, 487
alkylation of carboxylic acids, 471
and formation of methylene, 1056
and homologation of aldehydes to methyl ketones, 1355
and methylene, 691
and the *Arndt-Eistert synthesis*, 1238
conversion of aldehydes to ketones, 694
flash photolysis, 251
formation of carbenes, 253
photochemical decomposition, 1056
photodecomposition, 250
photolysis, 691
reagents for preparation, 1316
trimethylsilyl, Li derivative, 687
with acyl halides, 1238
with alcohols, 462

diazomethane, alkylation of amines (*Continued*)
with aldehydes or ketones, 1177, 1355
with metals, 1053
with sulfonyl halides, 1178
diazonium compounds, as leaving groups, 434
coupling, 674
from amines and nitrous acid, 434
protonation of diazo compounds, 434
diazonium fluoroborates, 792
diazonium group, and a leaving group, 788
diazonium ions, and electrophilicity, 790
aromatic, 597
as a leaving group, 846
diazonium salts also see benzenediazonium
diazonium salts, 728
diazonium salts, and aromatic substitution, 736
and azo compounds, 597
and carbocations, 434, 690
and IUPAC mechanisms, 435
and *Meerwein arylation*, 794
and metal catalysis, 788
and radicals, 788
and S_N1 reactions, 434
and *Sonogashira coupling*, 777
and superacids, 434
and the *Heck reaction*, 764, 788
and triiodide, 792
diazonium salts, aromatic, isolation of, 434
diazonium salts, aryl,
and crown ethers, 789
and *Heck-like reactions*, 793
and resonance, 788
and the *Gatterman reaction*, 847
and the *Gomberg-Bachmann reaction*, 795
and the *Sandmeyer reaction*, 846
and the *Schiemann reaction*, 792
fluorination and iodination, 847
fluorination, 792
fluorination, radical mechanism, 792
hydroxylation, 790
in the *Heck reaction*, 763
iodination, 791
methylation, 793
preparation, 791
reduction, reagents, 1549
the *Gatterman method*, 796
with active methylene compounds, 674
with alkenes, 794
with hydrosulfide anion, 791
with metal halides, 846
with organometallics, 793
with silyl enol ethers, 848
with sulfide anion, 791
with sulfur dioxide, 848
with thiocyanate, 791
with thiol anions, 791
with trifluoroborates, 794
diazonium salts, canonical forms, 788
diazonium salts, coupling, 598
coupling, mechanism, 675
coupling, with trialkylfluoroborates, 560
cyclopropenium, 434
fluorination of aromatic compounds, 608
diazonium salts, from anilines, 788
from aromatic compounds, 598
from diazoketones, 454
from nitrous acid, 598, 788
from sulfanilic acid, 789
from ureas, 790
diazonium salts, in the *Heck reaction*, 788
in the *Sandmeyer reaction*, 788
mechanism of diazoniation, 788
diazonium salts, metal catalyzed, carbonylation, 848
coupling with alkenes, 793
methylation, 793
nitration, 847
diazonium salts, metal mediated, coupling, 796
diazonium salts, nitration with nitric acid, 848
nucleophilic aromatic substitution, and S_N1, 735
diazonium salts, reduction to amines, 1530
to aromatic compounds, 1550
with sodium sulfite, mechanism, 1530
reagents for, 1550
stability of, 434
stability, 788
versus a diazo compound, 789
with amides, 1198
diazonium salts, with aromatic compounds, 794
with boronic acids, 772, 793
with nitrite ion, 848
with oximes, 848
with sodium nitrite, 847
with sulfur, 1178
with transition metal catalysts, 788
diazotates, alkyl, with alkyl halides, 498
diazotization, and nitrosonium ion, 790
mechanism, 790
of amides, 1200
of amines, 1327, 1345
of amino acids, 508
of anilines, 788
of ureas, 790
with metal halides, 509
diazo-transfer reactions, 678, 1054
formation of diazoketones, 678
versus azidination, 678
Dibal (diisobutylaluminum hydride), chemoselectivity, 1505
and reduction of allenes, 912
and reduction of ethers, 1537
and reduction of nitriles, 1523
and reduction of sulfones, 1553
metal mediated reduction of alkenes, 911
reduction of alkynes, 912
reduction of amides to aldehydes, 1519
reduction of esters to aldehydes, 1518
reduction of oximes, 1528
reduction of tosylates, 1537
with amides, 1519
Dibal-amine complex, 1221
dibenzo[*g,p*]chrysene, from bifluorenylidene, 1391
dibenzoannulene, 76
dibenzosemibullvalenes, thermal isomerization, 305
diborane, 920
diboration, of alkenes, 997
diboron carbenes, 252
dibromides, gem-, from aldehydes and bromine-triphenyl phosphite, 1105
dibromoborane, with alkynes, 925
dibromo-dimethylhydantoin (DBDMH) see DBDMH
dibromoethane, and dipole moment, 19
conformations, 177
dibromoisocyanuric acid, halogenation of aromatic compounds, 605
dibutylphosphine, complex with organocuprates, 522
dicarboxylic acids, 630
and hydrogen bonding, 98
bis(decarboxylation) to alkenes, 1468
bis(decarboxylation), mechanism, 1469
by cleavage of cyclic ketones, 1458
cleavage to ketones, 1469
cyclization, 1235
decarboxylation versus anhydride formation, 1210
dehydration, 1210
electrochemical carboxylation of alkenes, 973

from cyclic ketones, reagents for, 1458
halogenation, 823
oxidative cleavage of cyclic alkenes, 1464
pyrolysis, 1238
with alcohols, 1202
with $Pb(OAc)_4$, 1469
dicarboxylic esters, and the *Stobbe condensation*, 1154
oxidative cleavage of 1, 3-diketones, 1458
dications, 241
dichlorine monoxide, 827
and allylic radical chlorination, 827
dichlorocarbene, 249, 627, 268
dichlorocarbenes, 252
dichloromethylene, 249
dichloromethylene, carbene, 252
2,3-dichloro-5,6-dicyano-1, 4-benzoquinone see DDQ
dichroic behavior, 132
dichromate, oxidation of alcohols, 1442
oxidation of hydroquinone, 1452
pyridinium see PDC
dicobalt octacarbonyl silanes and epoxides, 537
and carbonylation of aryl halides, 781
and cyclotrimerization of alkynes, 1060
and hydroformylation, 979, 980
and the *Pauson-Khand reaction*, 976
formation of ketones, 708
with organometallics, 708
Dictionary of Organic Compounds, 1593
*Dictionary of Organometallic Compound*s, 1581
dicyclohexano-18-crown-6, 444
dicyclohexyl urea, and Moffatt oxidation, 1448
dicyclohexylcarbodiimide see DCC
dicyclohexylurea see DHU
Dieckmann condensation also see *Claisen condensation*
Dieckmann condensation, 1234, 1235
and ring size, 1235
and the acyloin condensation, 1560
catalyst for, 1235
mechanism, 1235
regioselectivity, 1235
Dieckmann-like condensation, 1235
dielectric constant, and solvent acidity, 325
dielectric heating, and microwaves, 310
dielectric screening effects, algorithm, 437
dielectric screening effects, in solvents, 437
Diels-Alder reactions, 1020–1039
Diels-Alder reactions, acceleration by hydrogen bonding, 1022
Diels-Alder reactions, and [1,2]-cycloaddition, 1027
and [2+2]-cycloaddition, 1042
and [3+2]-cycloaddition see [3+2]-cycloaddition
and alumina, 1023
and benzyne intermediates, 276
and biradicals, 1030
and chiral auxiliaries, 1026
and chiral catalysts, 1026
and chiral Lewis acids, 1026
and chromatographic absorbents, 1022
and cisoid conformation, 1024
and cycloaddition, 1064
and cyclotrimerization, 1062
and diene conformation, 1021, 1024
and diions, 1029
and encapsulation, 1022
and frontier orbital method, 1032, 1033
and high pressure, 446, 1023
and hydrophobic acceleration, 363
and hydrophobic effects, 1023
and isotope effects, 1029
and Lewis acids, 1022
and micellar effects, 1023
and microwave irradiation, 310, 1022
and orbital overlap, 1032, 1035
and orbital symmetry, 1030
and principle of conservation of orbital symmetry, 1030
and radical cations, 1022
and rearrangements, 1023
and secondary orbital interactions, 1025
and six-membered transition state, 869
and sonochemistry, 309
and substituent electronic effects, 1021
and sulfolene, 1028
and suprafacial overlap of orbitals, 1035
and the *Claisen rearrangement*, 1408
and the *Möbius-Hückel method*, 1031–1033
and the *retro-Diels Alder reaction*, 1310
and the *Woodward-Hoffmann rules*, 1030
and transoid dienes, 1021
and ultrasound, 1022
and zeolites, 1023
Diels-Alder reactions, antarafacial overlap of orbitals, 1035
Diels-Alder reactions, aza- see *aza-Diels-Alder*
Diels-Alder reactions, cationic, 1022
compatible functional groups, 1021
concerted, 1030
diastereoselectivity, 365
diradical stepwise versus concerted mechanism, 1028–1030
enantioselectivity, 1023, 1025, 1026
endo addition, 1025, 1036
exo addition, 1025
Diels-Alder reactions, heteroatom, 1037–1039
catalysts for, 1038
chiral catalysts, 1038
enantioselectivity, 1038
in water, 1038
polymer supported, 1038
ultrasound, 1038
Diels-Alder reactions, homo-, 1027
Diels-Alder reactions, in an ultracentrifuge, 1023
in ionic liquids, 365, 1023
in supercritical carbon dioxide, 1023
in supercritical water, 1023
in water, 363, 1023
Diels-Alder reactions, intramolecular, 1028
inverse electron demand, 1030
isotope effects, 1029
Lewis acid catalysts used, 1022
mechanism, 1028–1030
metal catalyzed, 1022
photochemical, 1022
polar, 1029
radical cation, 1029
rate of reaction, 1026, 1028, 1029
regioselectivity, 1023–1026
Diels-Alder reactions, retro-, 1023
Diels-Alder reactions, reversibility, 1028
selectivity, and solvent effects, 1025
solid-state, 1023
solventless, 1023
stereochemistry, 1024
stereochemistry, and s-cis dienes, 1024
stereospecificity, 1025–1029
substituent effects and mechanism, 1030
synthetic applications, 1027

Diels-Alder reactions, reversibility (*Continued*)
tethered, 1028
transition state, 1024
twisted, 1035
Diels-Alder reactions, with aldehydes, 1037
with arynes, 738
with azadienes, 1038
with benzynes, 1021
with cyclic dienes, 1021, 1024
with cyclobutadiene, 67
with furans, 1039
with heterocycles, 1038
with lithium perchlorate in ether, 1023
with nitroso compounds, 1039
with organocatalysts, 1025, 1026
with singlet oxygen, 1040
diene-carboxylic acids, cyclization to lactones, 892
diene-cyclobutene interconversion, orbital requirements, 1384, 1385
with aromatic rings, 1387
dienes also see Diels-Alder
dienes, acylation, 685
and π-allyl complexes, 685
dienes, addition, 869
and S_N2' mechanism, 870
of alkanes, 928
of bromine, cyclic intermediates, 870
of carbenes, 1053
1,5-dienes, allenic, and *Cope rearrangement*, 1402
dienes, and [3+4]-cycloadditions, 1018
and 1,4-addition, 884
and cis/trans nomenclature, 163
and cycloaddition, of oxygen, 1039
and cycloaddition, of singlet oxygen, 1039
and cycloaddition, with alkenes, 1020–1039
and cycloaddition, with alkynes, 1021
and E/Z nomenclature, 163
and homoconjugation, 43
and photochemistry, 293
and radicals, 868
1,5-dienes, and rearrangements, 1400
dienes, and ring closing, orbital overlap, 1383, 1384
and sigmatropic migration of hydrogen, 1392
and suprafacial migration, 1392
and symmetry of orbitals, 1381–1386
and the *Heck reaction*, 765
and the *Prins reaction*, 1185
and the *Simmons-Smith procedure*, 1058
and UV light, 293
antarafacial migration, 1392
bicyclic, and strain, 203
bond rotation, 1021
dienes, by alkyne coupling, 935
by alkyne dimerization, 933
by based induced elimination of halo sulfones, 1302
by cheletropic reactions, 1303
by coupling of organocuprates, 849
by dehydration of alkyne-alcohols, 1284
by dimerization of vinylalanes, 849
by elimination of cyclic epoxides, 1287
by hydrogenation of diynes, 906
by metal mediated coupling, 514
by pyrolysis of propargylic ethers, 1286
by *Stille coupling*, 683
by thermal extrusion of carbon dioxide from lactones, 1310
by thermolysis of sulfolene, 1028
by vinyl coupling reactions, 768
catalytic hydrogenation, 905
dienes, conjugated, 685
and carbocations, 212
from alkynes, 940
hydration, 886
regioselectivity, 876
with electrophiles, 876
with *Grignard reagents*, 937
dienes, coupling, alkynes to allylic silyl ethers, 933
coupling, of alkynes, 933
dienes, cyclic, from monocyclic alkenes, 1421
in the *Diels-Alder reaction*, 1024
lactone formation, 1013
photochemical ring opening to trienes, 1380
thermal extrusion of carbon monoxide, 1309
dienes, cyclization, 931
dienes, cyclohexyl see cyclohexyldienes
dienes, dimerization in the *Kolbe reaction*, 854
dimerization of vinylboranes, 851
electronic effects, in the *Diels-Alder reaction*, 1021
electrophilic addition, 870
epoxidation, 1003
extrusion of CO, 1310
dienes, from aldehydes, 1170
from alkene-halo sulfones, 1302
from alkenyl boranes, 1377
from alkynes, 938
from allylic halides, 514
from allylic stannanes and Pd catalyst, 527
from allylic sulfones, 1296
from bicyclobutanes, 1424
from boronic acids, 684
from conjugated esters, 1174
from cyclic amines, 1290
from cyclobutenes, 1380
1,5-dienes, from 1,5-dienes, 1400
dienes, from dienes and alkenes, 933
from metal catalyzed coupling, 514
from organocuprates, 521
from organometallics, with allylic halides, 523–526
from organometallics, with vinyl halides, 523–526
from propargylic ethers, 1285
from thiophene-1,1-dioxides, 1303
from vinyl halides, 514
from vinyl organometallics, 682
from vinylboranes, NaOH, and iodine, 1377
from vinylsulfonate esters, 682
dienes, hybridization, 38
hydroboration, 925, 1376, 905
in *Diels-Alder reactions* with aldehydes, 1037, 1038
in the [3+2]-cycloaddition, 1018
1,5-dienes, in *the Cope rearrangement*, 1400
dienes, intramolecular metathesis, 1421
intramolecular metathesis, 1421
metal catalyzed cyclization with arylboronic acids, 940
metal catalyzed, carbonylation, 973, 976
metal catalyzed, *Cope rearrangement*, 1402
metal catalyzed, coupling of *Grignard reagents*, 849
molecular orbitals, 1031
organolithium reagents, and carbon dioxide, 978
photochemical, ring closure to cyclobutenes, 1380
photochemical, ring closure, 1424
photochemistry, 1425
radical addition, 876
reaction with cations, 869
reactivity in the *Diels-Alder reaction*, 1021
ring opened, from cyclic alkenes, by metathesis, 1421

s-cis, and *Diels-Alder* stereochemistry, 1024
thermal opening of cyclobutenes, 1380
thermodynamic stability, and *Cope rearrangement*, 1400
transoid, and the *Diels-Alder reaction*, 1021
via organometallic coupling, 524
via *Stille coupling*, 682
via the *Shapiro reaction*, 1294
dienes, with aldehydes, 1123
with amines, 896
with chlorosulfonyl isocyanate, 1245
with diketones, 939
with silanes, and a Pd catalyst, 929
with silanes, and a Zr catalyst, 929
with silanes, and an organocatalyst, 929
with ureas, 1009
with ynolates, 1232
dienone-phenol rearrangement, 1349
dienones, 663
photolysis, 1426
dienophiles, alkynes, 1021
allenes, 1021
and endo addition, 1036
complex with chiral Lewis acids, 1026
definition, 1020
in the ene reaction, 942
diesters, from dihalides, 469
with alkynes, 939
diethyl azodicarboxylate see DEAD
diethyl succinate see succinates
diethyl tartrate, and epoxidation, 1004, 1005
diethylaminosulfur trifluoride see DAST
diethylene glycol, 466
and *Huang-Minlon modification*, 1540
and *Wolff-Kishner reduction*, 1540
diethylmagnesium, 230
diethylmercury, 233
diethylphosphoryl cyanide, 563
diethylzinc, and Simmons-Smith procedure, 1058
differential absorption, and diastereomers, 156
and resolution, 156
differential hydration, and amines, 343
and basicity, 343
differential solubility, 154
diffusion control, proton-transfer reactions, 323
diffusion rate, and reactivity, 362
diffusion-controlled reactions, 267
difluorides, gem-, 1106
from oximes, 1106
dihalides, and aldol, 452
and *Cannizzaro reaction*, 452
and ester enolates, 541
base induced elimination, 1297
conversion to aldehydes, 452
conversion to ketones, 452
dehalogenation, 1304
dehalogenation, and microwave irradiation, 1305
dehalogenation, mechanism, 1305
dehalogenation, with metals, 1305
dialkylation and boranes, 558
formation of diesters, 469
formation of dithioacetals, 478
formation of *Grignard reagents*, 713
dihalides, from alkenes, 828
from alkyl halides, 824
from alkynes, 884
from halogenation of alkenes, 982
dihalides, gem-, from aldehydes and metal halides, 1105
from aldehydes or ketones, 1105
from amines, 1483
hydrolysis of, 452
dihalides, with active methylene compounds, 541
with alkoxides, 460
with enolate anions, 541
with HMPA, 1304
with ketones, 545
with magnesium, 1109
with metals, 1109
with organocuprates, 521
dihalo esters, with boranes, 558
dihalo nitriles, with boranes, 558
dihaloalkenes see alkenes
dihalogenation, of ketones, 670
dihalomethanes, with dialkylzinc reagents, 1058
dihalosulfones, metal catalyzed reaction with ketones, 1175
dihalosulfones, with imides, 1174
dihedral angle, and anti-elimination, 1257, 1258
and conformation, 178
and E2 reactions, 1257, 1258
dihedral angles see angle
dihydrofuran, with *Grignard reagents*, 1285
dihydroindole, 753
dihydroisoquinolines, and *Friedel-Crafts cyclization*, 618
dihydrophenathrenes, oxidative cleavage, 1466
dihydropiperazine, 1009
dihydropryans, via the *Prins reaction*, 1186
acid catalyzed alcoholysis, 891
dihydropyrans see pyrans
dihydroquinidines, and asymmetric dihydroxylation, 995, 996
dihydroquinines, and asymmetric dihydroxylation, 995, 996
dihydrothiepin-1–1-dioxides, thermal elimination to trienes, 1303
dihydrothiophene-1–1-dioxides, thermal elimination to dienes, 1303
dihydroxylation, an alkene structure, 997
and chiral ligands, 996
and *Cinchona alkaloids*, 996
and hypervalent iodine, 995
and ionic liquids, 996
and microwave irradiation, 997
and Os complex, 993
and phase transfer reagents, 994
and phthalazines, 996
and potassium ferricyanide, 996
and *Pseudomonas putida*, 998
and steric hindrance, 997
anti, 994
anti, neighboring group mechanisms, 994
dihydroxylation, asymmetric, 995, 996
and $(DHQ)_2PHAL$, 996
and $(DHQD)_2PHAL$, 996
and AD-mix-α, 996
and AD-mix-β, 996
and phthalazines, 996
dihydroxylation, diastereoselective, 997
flavin catalyst, 997
in ionic liquids, 365
dihydroxylation, of alkenes, 992–997
of alkenes, and kinetic resolution, 159
of alkenes, and lipases, 997
of alkenes, catalysts for, 993
of alkenes, enantioselectivity, 995
of alkenes, in ionic liquids, 993
of alkenes, regioselectivity, 995
of alkenes, syn addition, 992
of alkyne, 1471
of aromatic compounds, 998
of aromatic compounds, enzymatic, 998
of phenol, 1535
of phenols, reagents, 1536

dihydroxylation, *Prevost reaction*, 994
reaction, and microwaves, 311
Sharpless asymmetric, 996
syn, 992–994
ultrasound, 994
Woodward modification of the Prevost reaction, 994
diimide, from hydrazine, 910
from hydroxylamine, 910
reduction of alkenes, 910
reduction of alkenes, mechanism, 910
reduction of nitro compounds, 1530
stability, 910
with alkenes, 909
diiodides, carbonylation, 568
diiodomethane, and Simmons-Smith procedure, 1057, 1058
cyclopropanation, 1057
with methyllithium, 1110
diioinic intermediates, [3+2]-cycloaddition, 1017
diion mechanism, and [2+2]-cycloaddition, 1046, 1047
diionic compounds, betaines, 1168
diionic mechanism, 1245
diionic mechanism, ketones with imines, 1245
diions, and the *Cannizzaro reactions*, 1563
and the *Diels-Alder reaction*, 1029
diisobutylaluminum hydride see Dibal
diisopinocampheylborane, 158, 924
diisopropyl azodicarboxylate (DIAD), 469
diisopropylamide, lithium see LDA
diisopropylcarbodiimide, and halogenation of alcohols, 503
diisopropylethylamine, 688
diisopropylethylamine see *Hünig's base*
1,4-diketones, 969
diketones, acid catalysis, 1083
acid catalyzed formation of furans, 1083
acid catalyzed formation of pyrans, 1083
by coupling of acyl halides, 1232
α-oxidation of ketones, reagents, for, 1476, 1477
diketones, by oxidation of alkynes, 1489
by oxidation of alkynes, reagents, 1489
by oxidation of cyclic alkenes, 1489
by oxidative cleavage of diamines, 1456
by oxidative coupling of enolate anions, 1496
by oxidative coupling of silyl enol ethers, 1496
by rearrangement of epoxy ketones, 1344
by α-oxidation of ketones, 1476
diketones, cleavage by base, 723
coupling acyl halides, 1232
coupling of acyl nitriles, 1557
enols and oxidative cleavage, 1458
diketones, from acyl halide conjugate addition, 968
from acyl halides and acylation, 1232
from alkynes, reagents, 1490
from bis(imidazole) oxalic acid derivatives, 1230
from dithianes, 1236
from furan, 458
1,4-diketones, from furans, 458
diketones, from ketones and esters, 1236
intramolecular aldol reaction, 1150
O_2, and oxidative cleavage, 1458
oxidative cleavage of cyclic alkenes, 1464
pK_a, 336
rearrangement to hydroxy acids, 1350
via *Wurtz coupling*, 515
with amines, 1091
1,3-diketones, with diazomethane, 1355
diketones, with dienes, 939
with hydrazines, 1093
with low valent titanium, 1559
dilithiated carboxylic acids, 699
dilongifolylborane, 924
dimagnesium compounds, with acid derivatives, 1228
dimagnesium compounds, 714
dimer mechanism, and S_NAr reactions, 735
dimeric borane, 921
dimerization, alkenes, 935
alkyne, metal catalyzed, 933
ketenes, 1041, 1046
of acetals, 535
of alkenes, 931
of alkynes, 933
of aryldiazonium salt, 796
of carbenes, 255
of ketals, 535
of ketenes, 1242
of nitrenes, 259
of radicals, 238, 844
of ylids, 1173
reductive, 1085
vinyl Al reagents, 850
dimetallic compounds, 941
dimethoxyethane see DME
dimethyl dioxirane, 1001
dimethyl sulfide see sulfide
dimethyl sulfoxide see DMSO
dimethyl(methylthio)sulfonium salts, and amines, 1012
eimethylacetamide dimethyl acetal, and Claisen rearrangement, 1409
dimethylaluminum amide, and conversion of esters to nitriles, 1096
dimethylbenzylamine, and absolute configuration, 144
dimethylformamide dimethyl acetal, and elimination of hydroxy acids, 1308
dimethylhydrazones see hydrazones
dimethyloxosulfonium methylid, 1175
and resonance, 1175
with *Michael alkenes*, 1178
dimethylsulfonium leaving group, 1275
dimethylsulfonium methylid, 1175
and resonance, 1175
dimethylsulfoxonium methylid see ylids
dimethyltitanocene, 1174
dimethyltitanocene also see *Petasis reagent*
dimolybdenum tetraacetate, and circular dichroism, 143
and enantiomers, 143
dinitrates, from epoxides, 474
from oxetanes, 474
dinitriles, and the *Thorpe reaction*, 1179
and the *Thorpe-Ziegler reaction*, 1179
by oxidative cleavage of ortho-diamino aromatic compounds, 1465
formation of imidines, 1104
from conjugated dinitriles, 886
from cyanoamines and HCN, 1184
from phenylenediamine, 1465
reduction with SmI_2, 1546
dinitrofluorobenzene, with amines, 752
diolboranes, 701
diols, acid catalyzed rearrangement to ketones, 1342
and formation of cyclic sulfates, 451
aromatic, oxidation to quinones, 1452, 1453

by photochemical dimerization of ketones, 1557
by pinacol coupling, 1342, 1555–1558
by the *Gomberg-Bachmann pinacol synthesis*, 1555
by the *Prins reaction*, 1184
by the *Tollens' reaction*, 1164
carbocations, and rearrangements, 1328
chiral, 1082
cleavage by lead tetraacetate, cyclic transition state, 1457
cleavage with lead tetraacetate, mechanism, 1457
conversion to epoxides, 461
cyclic, by coupling of dialdehydes, 1557
cyclic, by pinacol coupling, 1557
cyclodehydration, 469
deoxygenation, mechanism, 1301
deoxygenation, to give alkenes, 1301
dihydroxylation of alkenes, 992–997
formation, and *Grignard reactions*, 1113
diols, from aldehydes, 1555
from alkenes, 992–997
from alkynes, 997
from epoxides, 458, 994
from epoxides, and peroxyacids, 1428
from ketones, 1555
from lactones, 1232
in situ generation, and oxidative cleavage, 1456
mechanism of formation, and S_N2, 994
diols, oxidation, 994
to lactones, 1484
with NBS and chiral Cu catalyst, 1447
diols, oxidative cleavage, 1456, 1457
and electrochemistry, 1458
enantioselectivity, 1456
mechanism, 1457
reagents for, 1456
with lead tetraacetate, 1456
with periodic acid, 1456
diols, rearrangement, 1342
reductive coupling of aldehydes or ketones, reagents, 1555
diols, with acids, 1342
with DEAD, 461
with periodic acid, mechanism, 1457
with sulfuric acid, 1343
with thiophosgene, 1301
with thiophosgene, and DMAP, 1302
dioxane, and oxonium ions, 389
and solvolysis, 389
dioxanes, and conformations, 186
via the *Prins reaction*, 1185
dioxaspiro compounds, 1243
dioxetanes, cleavage, 1040
cycloaddition of singlet oxygen to alkenes, 1040
dioxiranes, and epoxidation of alkenes, 1001
and insertion reactions, 1001
and Oxone, 1001
and ozonolysis, of ethylene, 1463
and peroxyimidic acid, 1002
and strain, 194
and α-hydroxylation, 1474
CH oxidation, 1472
chiral, 1002
dioxiranes, dimethyl, and epoxidation of alkenes, 1001
oxidation of isocyanates to nitro compounds, 1491
oxidation of thiols, 1493
oxidative cleavage of diamines, 1457
dioxiranes, esters from silyl ketene ethers, 1475
α-hydroxylation, enantioselectivity, 1474
oxidation of CH to alcohols, 1474, 1475
oxidation of isocyanates, 1491
dioxolanes, 1082
dipamp, and catalytic hydrogenation, 904
diphenyl diselenide, 681
diphenyl nitroxide, 844
diphenyliodonium tetrafluoroborate, 599
diphenylmethyl carbanions, 223
diphenylphosphide, lithium, 486
diphenylpicrylhydrazyl radical, 240
diphosphines see bis(phosphines)
diphosphorus tetraiodide, 1212
dipleiadiene, paratropic, 80
[1,3]-dipolar addition also see addition
[1,3]-dipolar addition, 1014–1020
and ozonolysis of alkenes, 1460, 14462
1,3-dipoles, canonical forms, 1188, 1016
structural types, 1014, 1015
dipolar addition see addition
dipolar compounds, 1015
dipole induced bonding, 109
dipole moment, 18
and C-H, 19
and conformation, 177
and Debyes, 18
and symmetry, 19
azulene, 63
MO calculations, 35
of substituted aromatics, 18, 19
dipoles, and ionization reactions, 860
generated in situ, 1018
parallel, and anomeric effect, 187
dipyrrinones, and hydrogen bonding, 102
diradical intermediates, 1347
diradical mechanism, and [2+2]-cycloaddition, 1046
and carbenes, 1055
and the *Cope rearrangement*, 1404, 1664
photochemical [2+2]-cycloaddition, 1049
diradicals see biradicals
diradicals, 244
diradicals, and [2+2]-cycloaddition, 1044, 1047, 1019
and carbenes, 1055
and *Criegee mechanism* of ozonolysis, 1460
and cyclopropane ring opening, 1347
and cyclopropane ring opening, 1347
and di-π-methane rearrangements, 1425
and extrusion of nitrogen, 1317
and ozonolysis, 1460
and pyrazoles, 1317
and rearrangements, 1335
and resonance, 44
and singlet oxygen, 834
and tritium labeling, rearrangements, 1335
diradicals, biphenylene pyrolysis, 1391
in the *Paterno-Büchi reaction*, 1243
intermediates, and *Cope rearrangement*, 1403
lifetime, 1050
oxygen, 832
directed aldol reaction, 1149
directed ortho metalation, 517, 784
directed ortho metalation also see aryllithium compounds
directing effects, in hydroboration, 924
directionality, approach of nucleophiles to carbonyls, 1072
dirhodium catalyst, and insertion, 693
dirhodium catalyzed insertion, 691
diselenides, 478
catalytic hydrogenation, 851
reduction to selenols, 1555
diselenides, with alkenes, 1007

disiamylborane, 921
  with alkenes, 922
disilanes, 854
  with aryl halides, 783
displacement mechanism, and oxidation-reduction, 1436
disproportionation, and aryl radicals, 809
  and benzidine rearrangement, 1415
  and dehydration of carboxylic acids, 1210
  and radicals, 247, 694, 806, 816
  and the benzidine rearrangement, 1415
  aryl carboxylate ions, 645
  $NaBH_4$ reduction of aldehydes or ketones, 1511
  of aldehydes, 1564
  of radicals, 844
  with $NaBH_4$, 1511
disrotatory motion, and cyclohexadiene-triene interconversion, 1384, 1385
  stereochemistry, *Diels-Alder reaction*, 1024
disrotatory, and 4n versus 4n+2, 1388
  and electrocyclic rearrangements, 1381, 1382
  cyclobutene ring opening, 1385, 1386
energy, dissociation, 27
  and bond energy, 27
  and deuterium isotope effects, 285
  carbocations, table, 216
  of radicals, 242
  radicals, table, 242
dissociation, of radicals, and *photo-Fries rearrangement*, 637
dissociative state, and photolytic cleavage, 296
dissolving metal reductions, 913
dissolving metals, cleavage of ethers, 504
distance, bond see bond distance
distillation, fractional, and diastereomers, 156
  and resolution, 156
distorted aromatics, 47
disulfide ions, with alkyl halides, 479
disulfide, aryl, with alkenes, and metal salts, 1006
disulfides, 479
  and *Smiles rearrangement*, 801
  and sulfurization, 1089
  by oxidation of thiols, 1493, 1497
  by oxidation of thiols, mechanism, 1497
  by oxidation of thiols, reagents, 1497
  by reduction of sulfonyl halides, 1552
  from alkyl halides, 479
  from aryl halides, 750
  from *Bunte salts*, 479
  from thiols, 1496
  halo, with base, 988
  reduction to thiols, reagents, 1555
  with alkenes, 1007
  with enolate anions, 680, 681
disulfides, with organometallics, 703
dithianes, 1087
  and acylation, 1236
  and alkylation, 552–556
  and anion relay chemistry, 553
  and butyllithium, 553
  and conformations, 186
  and epoxides, 553
  and fluorination, 1106
  and ring closing reactions, 553
  and the *Brook rearrangement*, 553, 1431, 1432
  and Umpolung, 553
  from aldehydes, 553
  from carbon disulfide and dihalides, 478
  hydrolysis, 553
  oxidative hydrolysis with NBS or NCS, 1236
  with epoxides, 1432
  with organolithium reagents, 1432
  with *Raney nickel*, 554
dithioacetals, and alkylation reactions, 552–556
  and the *Corey-Seebach procedure*, 1088
  as protecting groups, 1087, 1088
  catalytic hydrogenation, 851
  from aldehydes, 1087
  from alkynes, 895
  from dihalides, 478
  hydrolysis, 1087, 1088
  ketene see ketene
  reaction with base, 1087, 1088
  reagents for formation of, 1088
  reagents for hydrolysis, 1088
  reduction, 1551
  with Lewis acids for preparation of, 1087, 1088
  with Raney nickel, 554
dithiocarbamic acid salts, from carbon disulfide and amines, 1104
dithiocarbonates, and radicals, 960
  ene reaction, 942
dithiocarboxylic acids, 1132
dithiocarboxylic acids, from ketones and carbon disulfide, 1164
dithiocarboxylic esters, and potassium thioacetate, 470
  with organocuprates, 1132, 1133
dithioketals, and the *Corey-Seebach procedure*, 1088
  as protecting groups, 1087, 1088
  by alkylation, 552–556
  desulfurization with *Raney nickel*, 1089
  from alkynes and thiols, 894
  hydrolysis, 1087, 1088
  hydrolysis, by the *Corey-Seebach procedure*, 1088
  Lewis acids for preparation of, 1087, 1088
  reaction with base, 1087, 1088
  reagents for formation of, 1088
  reagents for hydrolysis, 1088
  with Raney nickel, 554
dithiols, from carbonyls, 1087
ditosylate leaving groups, 433
ditosylates, formation of azetidines, 483
divalent atoms, abstraction, 812
divinyl ether, and cross conjugation, 42
divinylcyclobutanes, rearrangement, 1402
divinylcyclopropanes, rearrangement, 1402
divinylidinium chloride, 767
divisions of Beilstein, 1579, 1580
diynes, amination, metal catalyzed, 898
  and cyclotrimerization, 1063
  and DABCO, 843
  and formation of dimethylenecyclobutenes, 1402
  and hyperconjugation, 39
  and metathesis, 1421
1,5-diynes, and the *Cope rearrangement*, 1402
diynes, and the *Eglinton reaction*, 840
  and the *Glaser reaction*, 841
  and the *Hay reaction*, 841
  by *Cadiot-Chodkeiwicz reaction*, 841
  by *Sonogashira coupling*, 842
  by *Suzuki-Miyaura coupling*, 770
  by the *Glaser reaction*, 841
  by the *Hay reaction*, 841
  catalytic hydrogenation, 906
  conjugated, 38
  cyclization, 934
  cyclization, metal catalyzed, 934
  cyclotrimerization, 1060

from alkyl-alkynylborates, 851
from alkynes, 842
from alkynylboronates, 843
metal catalyzed amination, 898
metal catalyzed coupling of alkynes, 840
problems in formation, 777
thermal conversion to diallenes, 1402
with sulfinyl imines, 1136
di-π-methane rearrangements, 1425
DMAP [4-(N,N-dimethylamino) pyridine]
and $POCl_3$, 507
methiodide salt, 648
and mixed anhydrides, 1204
with thiophosgene and diols, 1302
DME (1,2-dimethoxyethane)
and organolithium reagents, 231
solvent, 1159, 1162
and enolate anions, 686
DMEAD (di-2-methoxyethyl azodicarboxylate), 469
DMF (dimethylformamide)
as a solvent, 1464
and phosphorus oxychloride, 626
and the *Gabriel synthesis*, 494
as a solvent, 757, 1550
with acyl halides, 1213
with alcohols, 1208
with dihaloalkenes, 686
with NaI, 1301
DMSO (dimethyl sulfoxide)
and carbanions stereochemistry, 655
and DCC, 632
and DCC, oxidation of alcohols, 1448
and dihalosulfone extrusion reactions, 1303
and *Gomberg–Bachmann reaction*, 795
and HBr, 604
and KOH, in ionic liquids, 1178
and *Moffatt oxidation*, 1448
and nitrites, 795
and oxidation of alkyl halides to aldehydes, 1481
and pK_a, 319
and sulfur trioxide, for oxidation of alcohols, 1448
and *Swern oxidation*, 1447
and trifluoroacetic anhydride, for oxidation of alcohols, 1448
as a solvent, 749, 757, 1293, 1303
oxidation of alkyl halides, mechanism, 1481
reagents utilized for oxidation of alcohols, 1448
reagents, and oxidation of alcohols, 1447
with acetic anhydride, 1566
with aromatic compounds, 632
with base, 786
with silyl halides and alkenes, 988
DNA, and molecular knots, 121
DNP (dynamic nuclear polarization), and NMR, 238
and biradicals, 238
dodecahedral carbocations, 217
dodecahedrane, and dehydrogenation, 1442
Doebner modification, and microwaves, 1158
of the *Knoevenagel reaction*, 1158
domino metathesis, 1420
domino *Mukaiyama aldol reaction*, 1152
donor-acceptor atoms in the benzoin condensation, 1187
donor-acceptor complexes, electron, 104
donors, in the benzoin condensation, 1188
DOSP ligand, in Rh catalysts, 1054
Dötz benzannulation, 1063
double aldol reaction, 1144
double alkylation, 539
double asymmetric synthesis, 153, 1148
double *Baylis-Hillman reaction*, 1137
double bond strain, 206
double bonds, and bond energy, 30
and delocalization, 37
conjugated with p orbitals, 39
cumulative, 132
from carbocations, 220
in conjugation with carbocations, 212
double carbonylation, 536, 568
double hyperconjugation, 212
double metathesis, 1420
double *Michael addition*, 944
double *Michael reaction*, 944
double *Suzuki coupling*, 772
double-asymmetric synthesis, 924
doubly interlocking catenanes, 119
downfield shift, 51
dppf, 560, 753
dry ice, see carbon dioxide
dry media reactions, 366
drying agents, and acetal formation, 1081
and acetal or ketal formation, 1081
and imine/enamine formation, 1091, 1092
dry-reaction microwave chemistry, 310
dual substituent parameter equation, 358
Duff reaction, 628
mechanism, 628
dynamic NMR, 189
dynamic nuclear polarization see DNP
dyotropic rearrangement and σ-bond migration, 1430, 1431
dyotropic rearrangements, 1430
Brook rearrangement, 1431
lactones, 1431

E/Z nomenclature, definition, 163
E1 see elimination, E1
E1cB see elimination, E1cB
E2 see elimination, E2
E2C see elimination, E2C
E^i see elimination, E^i
eclipsing conformation, 179
EDA complex, 653
edge protonated cyclopropanes, 881
EDTA, and CH oxidation of lactams, 1478
ee see enantiomeric excess
% ee see enantiomeric excess
eEROS, 1588
Eglinton reaction, 840
mechanism, 842
scope, 841
Ehrlich-Sachs reaction, 1164
Elbs reaction, 634
electric field, and microwaves, 310
electrical effects, and reactivity, 347
electrochemistry, allylic acetates with ketones, 1122
amination, 838
and *Michael addition*, 948
and *Michael reactions*, 948
and pinacol coupling, 1557
and radical cyclization, 963
and the haloform reaction, 724
and the *Pschorr ring closure*, 795
and the *Ullmann reaction*, 769
and zinc, 718
aryl halides with aldehydes, 1123
aryl halides with sulfur nucleophiles, 750
carbonylation of alkyl halides, 5650565
conversion of esters to amides, 1220
coupling of silanes, 840
dehydration of oximes to nitriles, 1311
dicarboxylation of alkenes, 973
formation of carbenes, 253

electrochemistry, allylic acetates with ketones (*Continued*)
oxidation of thiols to disulfides, 1497
oxidative cleavage of diols, 1458
reduction of nitro compounds to hydroxylamines, 1526
reduction of vinyl halides, 1534
$S_{RN}1$ reactions, 740
electrocyclic reactions, and formation of aromatic compounds, 1390
and *Möbius-Hückel method*, 1383–1385
ene-diynes, 1386
electrocyclic reagents, pyrocalciferols, 1386
electrocyclic rearrangements, 1380–1391
4n versus 4n+2, 1388
allowed versus forbidden, 1388
and carbenes, 1056
and *Dewar benzenes*, 1387
and orbital symmetry, 1388
and overlap of HOMO orbitals, 1381, 1382
conrotatory versus disrotatory, 1381, 1382, 1387
definition, 1382
forbidden, and metal catalysts, 1388
frontier orbital method, 1382
metal catalyzed, 1388
of alternant aromatic compounds, 1391
stereochemistry, 1381, 1382
electrocyclic ring closure, diallenes, 1402
electrocyclic ring opening, and UV light, 1380
benzocyclobutenes, 1380
conrotatory versus disrotatory, 1382
cyclic dienes, 1380
cyclobutenes, 1380
substituent effects, 1381
torquoselectivity, 1381
electrofugal activity, CO_2, 644
electrofugal acyl groups, 643
electrofuge, definition, 262
electrolysis, and carbonylation of amines, 731
and *Collman's reagent*, 564
and coupling with silanes, 511
and decarboxylation, 1318
and *Friedel-Crafts alkylation*, 610
and halogenation of carboxylic acids, 673
and phenol formation, 635
and *Stephens-Castro coupling*, 775
and the *Hofmann rearrangement*, 1360
formation of haloalkynes, 705
homocoupling of aryl halides, 760
of carboxylate salts, 853
sulfoxide reduction, 540
electromagnetic spectrum, 290
electromagnetic waves, and microwaves, 310
electromotive series, and transmetallation, 710
metals, 710
electron affinity, and organolithium reagents, 232
electron cloud distortion, and electronegativity, 15, 16
electron configuration, of boron, 8
of carbon, 8
electron delocalization, and enol stabilization, 665
of amides, 90
electron demand cyclization, 1030
electron density map, acetylene, 11
electron density potential map, aniline, 45
electron density, and cyclopropane, 194
and electronegativity, 17
and neighboring groups, 397
and nodes, 4
and resonance, 45
electron diffraction, allyl radical, 238
and bond distance, 22
and conformations, 174
electron donating groups, 20
and the tetrahedral mechanism, 423
and σ-values, 352–354
substituent effects, 422
electron donor-acceptor complexes, 104
electron paramagnetic resonance see EPR
electron potential map, benzenonium ion, 573
pyrrole, 57, 58
electron repulsion, and nucleophilic strength, 431
electron spin resonance see ESR
electron spin, 4
18 electron systems, and metallocenes, 61
electron transfer mechanism, 786
electron transfer, and *Grignard reactions*, 1113
and metal exchange, 718
and photosensitization, 301
and radicals, 804
electron withdrawing groups, 20
and bond energy, 30
and the tetrahedral mechanism, 423
and vinylic substitution, 414
and σ values, 352–354
substituent effects, 422
electron, delocalization, 88
electronegativity scale, *Pauling*, 17
electronegativity scale, *Sanderson*, 17
electronegativity, 15, 16
and acidity or basicity, 337
and bond energy, 16, 28
and chemical shift, 17
and E/Z inversion barrier for radicals, 239
and electron cloud distortion, 15, 16
and electron density, 17
and I effects, 20
and ionic bonds, 18
and ionization potential, 16
and NMR, 17
and resonance, 45
and valence shell electrons, 17
formula, 16
group electronegativities, 17
of C and H, 19
of groups, 17
scales, 17
table, 17
electronic configuration, boron, 8
electronic effects, and [2+2]-cycloaddition, 1046
and the *Diels-Alder reaction*, 1021
and the E2 reaction, 1265
electronic excitation, 292
electronic heterolytic mechanism, 1017
electronic spectrum, 290
electronic structure, 14
and electrons, 14
and the Periodic table, 14
of boron trifluoride, 15
of covalent compounds, 15
of ethylene, 14
of imines, 15
of mercury, 7
of nitrogen, 13
of oxygen, 15
of P and S compounds, 15
of PCl_5 and SF_6, 15
of sulfuric acid, 15
of the methane radical, 15
electronic transfer, oxidation-reduction, 1435
electronic transitions, 290
and photochemistry, 290
electrons, and electronic structures, 14
and esr, 235
and radicals, 234
and resonance, 43

as waves, 3
bonding, 31
lone pair, and carbanions stability, 225
lone pairs, 26
nonbonded, and carbenes, 250
promotion, 8
solvated, 740
steric requirements, 26
unpaired, and ESR, 236
unpaired, and radicals, 235
unshared, and arenium ions, 577
valence shell, and electronegativity, 17
valence, 14
electrophiles, and Lewis acids, 569
definition, 262
proton, 863
sulfur trioxide, 601, 602
sulfur, 600
with allenes, 876
with carbanions, 233
with conjugated dienes, 876
electrophilic addition see addition
electrophilic addition, 263
electrophilic aromatic substitution see substitution
electrophilic carbenes, 1055
electrophilic fluorination, 826
electrophilic halogenation, 821
electrophilic mechanisms, 786, 885, 991
halogenation of alkenes, 982
electrophilic nitration, 677
electrophilic radicals, 808, 874
electrophilic reactions, 262
electrophilic rearrangements, 264, 1321, 1337
electrophilic substitution see substitution
electrophilicity indexes, 380, 1029
electrophilicity, and carbocations, 380
and diazonium ions, 790
and S_N1 reactions, 379
and the *Diels-Alder reaction*, 1021
of aldehydes, 1152
electrospray ionization mass spectrometry see mass spectrometry
electrostatic potential map, of benzene, 32
of butadiene, 37
electrostatic potentials, and addition reactions, 875
electrostatic scale, resonance effects, 35
element effect, and leaving groups, 414
elimination-addition mechanism, 530, 1249, 1534
elimination-addition mechanism also see mechanism
elimination-addition reactions, and *Mannich bases*, 416, 433
and sulfones, 416
α-eliminations, 1253
β-eliminations, 263, 253
1,3-eliminations, 1307
Grob fragmentation, 1307
halo amines, 1307
1,4-eliminations, 1282, 1303
formation of cumulenes, 1305
of allylic sulfoxides, 1296
1,6-eliminations, 1303
eliminations, (E1cB)ip mechanism, 1267
eliminations, acidity of β-hydrogens, 1271
eliminations, activation-strain model, 1275
eliminations, and 1,2-dihalides, 714
and acid-base reactions, 1271
and alkene stability, 1270
and aromatic rings, 1270
and *Bredt's rule*, 1269, 1270
and buffers, 1263
and carbenes, 257
and carbenoids, 254
and cis/trans isomers, 1273
and conjugation, 1270
and decarbonylation of aldehydes, 857
and dehydration of alcohols, 463
and entropy of activation, 268
and extrusion reactions, 1253
and formation of C=O and C≡N, 1267
and formation of nitrenes, 258
and formation of the thermodynamic alkene, 1271
and *Grignard reactions*, 1111
and *Grignard reagents*, 714, 1306
and *Hammet values*, 1268
and *Hofmann's rule*, 1270, 1272
and hyperconjugation, 1270
and isotope effects, 1267, 1268
and leaving group ability, 1259, 1266
and microscopic reversibility, 1265
and nucleofuge ability, 1266
and organocuprates, 521
and phosphonate esters, 1289
and pyridinium ions, 1266
and pyridyl leaving groups, 1266
and radicals, 1280
and rate, 1265
and solvent effects on the base, 1274
and steric effects, 1271
and the *Brønsted equation*, 1269
and the *Heck reaction*, 767
and the *Mannich reaction*, 1101
and the *silyl-Wittig reaction*, 1162
and *Wagner-Meerwein rearrangement*, 1339
eliminations, anti- and ion pairing, 1260
anti elimination, 1255
anti, phosphines with epoxides, 1286
base induced of ethers, and mechanism, 1285
base induced, of sulfones, 1296
carbocations and transition state, 1274
conjugate, 1282
eliminations, *Cope*, 1400
eliminations, *Cope* see *Cope*
eliminations, cyanide and alkyl halides, 563
cyclic transition state, 1278
determination of mechanism, 1267
eliminations, E1, and alkene stability, 1270
and carbocations, 1261
and dehydrohalogenation, 1298
and E2 mechanism, and dehydrohalogenation, 1298
and ion pair mechanism, 1262
and ion pairs, 1262
and substitution, 1261
and Zaitsev's rule, 1262, 1270
eliminations, E1, mechanism, 1261, 1262
and *Grob fragmentation*, 1308
and nucleofugal ability, 1265
and S_N1 reaction, 1262
and solvent effects, 1262
conjugate base effects, 1261
IUPAC designation and IUPAC mechanism, 1261
mechanism, kinetics, 1261
mechanism, rate determining step, 1261
eliminations, E1, reactions, base strength, 1267
stereochemistry of elimination, 1273
versus E2 versus E1cB, 1274
versus E2, 1262
versus E2, and leaving groups, 1276
versus E2, solvent effects, 1277
versus E2, ρ values, 1276
eliminations, E1anion, mechanism, 1266
reactions, mechanism, 1266
eliminations, E1cB, and benzyne formation, 1265
and carbanion ion pairs, 1267
and carbanion mechanism, 1262
and proton exchange, 1263

eliminations, E1cB, and benzyne formation (*Continued*)
character, and leaving group ability, 1268
deuterium isotope effects, 1263, 1264
mechanism, 1262–1267
mechanism, alkenes from halo ethers, 1306
mechanism, and acidic protons, 1265
mechanism, and poor leaving groups, 1265
mechanism, orientation of the alkene, 1272
versus E2, 1263
eliminations, E2, and antiperiplanar conformations, 1255
and base strength, 1272
and bond angles, 1257
and conformations, 1255
and dehydrohalogenation, 1298
and deuterium isotope effects, 1258
and deuterium labeling, 1257
and diastereomers, 1255
and dihedral angle, 1257, 1258
and E1 mechanisms and dehydrohalogenation, 1298
and electron withdrawing groups, 1265
and enantiopure alkyl halides, 1255
and gauche orientations, 1259
and *Hofmann degradation*, 1290
and *Hofmann's rule*, 1270
and isotope effects, 1254
and leaving groups, 1254
and meso alkyl halides, 1255
and strain, 351
and syn-anti dichotomy, 1258, 1259
and syn-periplanar conformations, 1255
and *Zaitsev's rule*, 1256, 1270
eliminations, E2, anti elimination, 1255
axial versus equatorial leaving groups, 1256, 1257
controlling factors, 1260
cyclohexyl halides, 1256
formation of alkynes, 1257
from vinyl halides, 1257
eliminations, E2, mechanism, 861, 1254–1260
ab inito study, 1254
and *Grob fragmentation*, 1308
and *Hofmann degradation*, 1290
IUPAC designation and IUPAC mechanism, 1254
eliminations, E2, rate law, and E1cB, 1263
rate of reaction, 1256
eliminations, E2, reaction, alkene distribution, 1272
and bond rotation, 1256
and carbanionic character, 1266
and E1 character, 1267
and strain, 1258
and vinylogy, 1258
base strength, 1267
Hofmann versus *Zaitsev* orientation, 1272
rate determining step, 1255
eliminations, E2, regioselectivity, 1270
stereochemistry, 1259
stereospecificity, 1255
substituent effects in alkyl halides, 1274
suitable bases, 1274
transition state, 1269
versus S_N2, 1261
with alkyl halides, 1255–1260
Zaitsev's rule versus *Hofmann's rule*, 1270
eliminations, E2C, and Zaitsev's rule, 1273
mechanism, 1269
eliminations, effect of alkyl halides structure, 1275
effect of base strength, 1274
effect of leaving groups, 1276
eliminations, E^i, and cis β-hydrogen, 1281
and *Cope elimination*, 1293
and *Hofmann degradation*, 1290, 1291
and pyrolysis of sulfoxides, 1296
and radical mechanism, 1280
and substrate structure, 1280
and the *Chugaev reaction*, 1289
and the *Woodward-Hofmann rules*, 1280
eliminations, E^i, benzotriazole leaving groups, 1292
halide reactivity, 1280
isotope effects, 1279
kinetics, 1279
eliminations, E^i, mechanism, 1163, 1278
ammonium salts with organolithium reagents, 1292
and *Cope elimination*, 1279, 1293
and *Cope reactions*, 1280
and organolithium reagents with ammonium salts, 1292
and pyrolysis of carboxylic acids, 1288
and stereochemistry of alkyl halides, 1279
and syn elimination, 1279
and the *Chugaev reaction*, 1289
rate of reaction, 1280
eliminations, E^i, reactions, and activation entropy, 1279
and radical initiators, 1279
and the radical mechanism, 1280
of esters, 1280
eliminations, E^i, stereochemistry, 1279
syn elimination, 1279
transition states, 1280
eliminations, fragmentations, 1307
from haloethers with magnesium, 714
gas phase, 1272
Hofmann products, 1281
Hofmann, 799, 1272
in the *Stork enamine synthesis*, 550
influence of temperature, 1278
intramolecular, 1278
IUPAC mechanisms, 1278
IUPAC nomenclature, 369
kinetics, 1264
mechanistic ambiguity, 1267
mechanistic spectrum, 1267
metal induced, of dihalides to alkenes, 1304
Norrish type II cleavage, 1254
eliminations, of dihalides to alkenes, reagents for, 1304
of epoxides, with LIDAKOR, 1287
of halide, from gem-dihalides, 1105
of selenoxides, 554, 1296
of sulfinate esters, 1296
of sulfoxides see sulfoxides
eliminations, *Peterson alkenylation*, 1161, 1162
eliminations, photochemical, 1254
eliminations, pyrolytic, 1254
and *Bredt's rule*, 1281
and cis β-hydrogen, 1281
and *Hofmann's rule*, 1281
and steric interactions, 1282
and *Zaitsev's rule*, 1281
mechanism, 1278–1281
regioselectivity, 1281
transition state, 1278
eliminations, radical, and bis (xanthates), 1301
and sulfoxides, 1296
mechanism, 1281
eliminations, rate, effect of alkyl halides structure, 1275
regiochemistry, 1269
stereochemistry, and diastereomeric halides, 1273
stereochemistry, of the alkene product, 1273

substrate reactivity, 1274
suitable bases, 1276
suitable leaving groups, 1276
eliminations, syn, 1257
and conformations, 1259
and E^i reactions, 1279
and ion-pairing, 1260
and leaving groups, 1260
and the E^i mechanism, 1279
and the syn-anti dichotomy, 1258, 1259
from thiiranes, 1288
solvent effects, 1260
transition states, 1269
eliminations, transition states, 1269
types, 1253
eliminations, versus substitution, 1261, 1274, 1275
and base strength, 1276
and leaving groups, 1276
charge dispersal, 1277
solvent effects, 1277
eliminations, *Zaitsev products*, 1281
Emde reduction, 1548
emission of light, and sonochemistry, 307
emission, and NMR, 237
enamides, from allylic amides, 882
torsional barrier, 180
with silanes, 929
enamine salts, 551
and alkylation, 550
enamine-imine tautomerism, 1180
enamines, acylation, 551
addition of siloxanes, 930
alkylation, 550
alkylation, metal mediated, 552
allylic, and *Claisen rearrangements*, 1410
enamines, and allylic amine carbanions, 556
and aminals, 1091, 1092
and *Michael addition*, 552
and *Michael reactions*, 947
and N-alkylation, 550
and radical cyclization, 964
and tautomerism with imines, 898
and tautomerism, 94
and the *Stork enamine reaction*, 548, 550
and the *Thorpe reaction*, 1180
and the *Thorpe-Ziegler reaction*, 1180
enamines, aromatization, 1439
by metal catalyzed amination of alkynes, 898
by reduction of nitro compounds, 897
chiral, 669
condensation, with aldehydes or ketones, 1145
cycloaddition reactions, 1042
enamines, formation, and azeotropic distillation, 1091, 1092
and microwave irradiation, 1091, 1092
in ionic liquids, 1091
metal catalyzed, 1092
enamines, from aldehydes or ketones, 1170
from aldehydes, 1092
from amines, 489, 1440
from amines, by dehydrogenation, 1440
from amines, with ketones, 1090
from vinyl triflates, 708
enamines, halogenation, 551
hydrogenation, 905
hydrogenation, to amines, 898
hydrolysis, 458, 551
hydrolysis, mechanism, 1079
in [2+2]-cycloadditions, with ketenes, 1042
in ionic liquids, 548
N-alkylation, 551
enamines, reduction, 911
reduction, to amines, 1521
reduction, with alane, 1547
reduction, with boranes, 1547
reductive cleavage, 1547
enamines, with 9-BBN, 923
with acyl halides, 550
with alkyl halides, 551
with benzotriazoles, 551
with epoxides, 551
with *Michael type alkenes*, 1042
with organolithium reagents, 556
with proline, 552
with siloxanes, 930
enantioenrichment, 159
enantiomer formation, and the Grignard reaction, 1108
enantiomeric excess (% ee), definition, 160
and amides, 160, 161
and NMR, 160
enantiomeric purity, and circular polarization of luminescence, 162
and GC, 161
and HPLC, 161
and isotopic dilution, 162
and kinetic resolution, 162
and NMR, 162
enantiomerization, free energy, 697
enantiomers also see chiral compounds
enantiomers also see chirality
enantiomers, and absolute configuration, 137, 138
and atropisomers, 131
and bosons, 123
and catalysts, 123
and circularly polarized light, 124
and enantiotopic atoms/groups, 170
and *Fischer projections*, 136
and helical molecules, 133
and isomers, 123
and kinetic resolution, 156
and mirror plane, 125
and $Mo_2(OAc)_4$, 143
and nucleons, 123
and plane of symmetry, 125
and plane polarized light, 138
and polarizability, 126
and priority of electrons, 123
and prochiral, 171
and pyramidal inversion, 127–129
and quadrivalent stereogenic atoms, 126
and racemates, 124
and rate of reaction, 146
and specific rotation, 124
and superimposability, 126, 136
and symmetry, 123
and temperatures, 125
and tervalent stereogenic atoms, 127
and *Tröger's base*, 129
enantiomers, called enantiomorphs, 123
definition of, 122
IUPAC names, 148
levo and dextro, 123
enantiomers, of adamantanes, 129
of allenes, 132
of biphenyls, 130
of catenanes, 120
of glyceraldehyde, 137
of molecular knots, 120
of monocyclic compounds, 166
of spiranes, 133
of tartaric acid, 124
enantiomers, steering wheel model, 140
enantiomorphs see enantiomers
enantioselective see enantioselectivity
enantioselective, alkylation, 544
enantioselective, insertion reactions, 463
enantioselective, protonation, 458
enantioselective, reactions, 153
enantioselectivity, and enolate anion formation, 672
and formation of allenes, 663
and formation of aziridines, 497
and formation of cyanoamines, 1183
and formation of homoallylic alcohols, 537

enantioselectivity, and enolate anion formation (*Continued*)
and formation of β-lactams, 1244
and halolactonization, 987
and hydroformylation, 980
and *Meerwein-Ponndorf-Verley reduction*, 1508
and *Michael addition*, 947
protonation of enolate anions, 668
and radical addition, 960, 1189
and the *Lossen rearrangement*, 1363
enantioselectivity, dihydroxylation, 997
enantioselectivity, for acyl addition, of boranes, 1124
of organotin compounds, 1118, 1119
with dialkylzinc, 1120, 1121
with Ti catalysts, 1120
enantioselectivity, for addition of alcohols to ketenes, 892
of metal carbene complexes to alkenes, 1054
of organometallics to carbonyls, 1115
enantioselectivity, for alcohols, from amines, 475
for alcoholysis, of anhydrides, 1202
for aldehydes, with boranes, 1125
for alkenes, with alcohols, 889
for alkyne anions, with aldehydes or ketones, 1115
for alkyne-boranes, 1379
for alkynes, and hydroboration, 1379
for allylic alcohols, by base induced elimination of epoxides, 1287
for allylic CH oxidation, 1471
for allylic silanes with hydrazones, 1137
for amines with epoxides, 489
for aminohydroxylation, 1007
for anhydrides with organometallics, 1229
for azidination, 678
for aziridination, of alkenes, 1011
for aziridine formation, 1011
for baker's yeast reduction of alkenes, 912
for baker's yeast reduction of alkynes, 912
for boranes, with epoxides, 506
for boronic acids, with aldehydes, 1124
for boronic acids, with imines, 1136
for carbamates, with aldehydes or ketones, 1160
for carbene additions to alkenes, 1054
for carbene insertion, 692
for catalytic hydrogenation, 903, 905, 919
for CH oxidation, 1472
for cyanation, 981
for cyanohydrin formation, 1181, 1182
for cyclopropanation, 1054, 1179
for dihydroxylation of alkenes, 995, 996
for epoxidation, of alkenes, 1000, 1001, 1003, 1004
for epoxide formation, 461
for epoxides with organometallics, 535
for formamidine alkylation, 555
for *Friedel-Crafts alkylation*, 611, 612
for haloboranes with azides, 707
for halogenation of ketones or aldehydes, 669
for hydroamination, of alkenes, 1007
for hydroboration, of alkenes, 924
for hydrogenation, of conjugated compounds, 918, 919
for hydrogenation, of indoles, 913
for hydrolysis, of epoxides, 458
for hydrolysis, of esters, 1192
for hydroxylation of hydrocarbons, 1470
for imine alkylation, 548
for imines with nitro compounds, 1137
enantioselectivity, for intramolecular aldol reaction, 1149
enantioselectivity, for intramolecular cyclopropanation, 1055
enantioselectivity, for K monoperpoxysulfate with O_2, 1451
for ketene cycloaddition to carbonyls, 1242
for *Michael addition*, 947
for nitrene formation, 1010
for organochromium acyl addition, 1121
for organolithium compounds with sparteine, 516
enantioselectivity, for organolithium reagents with alkenes, 937
with carbon dioxide, 1132
acyl addition, 1110
enantioselectivity, for organometallic addition to imines, 1134
organometallics, 697
for organometallics, with imines, 1135
for oxidative cleavage of diols, 1456
for reductive alkylation, 1099
for sulfinic ester preparation, 473
for the aldol reaction, 1147–1149
for the *Claisen rearrangement*, 1408, 1411
for transfer hydrogenation, 912
for α-hydroxylation of ketones, 1473
for α-hydroxylation with dioxiranes, 1474
for α-hydroxylation with oxaziridines, 1474
enantioselectivity, forhalogenation of epoxides, 506
enantioselectivity, in [2,3]-rearrangements, 1414
in [2+2]-cycloadditions, 1043
in [3,3]-sigmatropic rearrangements, 1403, 1410
antioselectivity, in [3+2]-cycloadditions, 1017, 1018
in biaryl formation, 762
in conjugate additions, 947
enantioselectivity, in conjugate additions, 947, 967
of amines, 966, 969
of *Grignard reagents*, 952
of organocuprates, 951, 952
of organozinc reagents, 953
enantioselectivity, in ene reactions, 942, 943
in epoxide hydrolysis, 458
in *Grignard reactions*, 1108
in heteroatom *Diels-Alder reactions*, 1038
in hydroboration, 924, 926
in *Jacobsen-Katsuki epoxidation*, 1005
in *Julia-Colonna epoxidation*, 1004
in *Mannich reactions*, 1102, 1103
in metal catalyzed coupling, 525
in metal catalyzed cyclopropanation, 1054
in metal catalyzed halogenation of ketones, 671
in nitrene insertion, 680
in pinacol coupling, 1556
in radical coupling of conjugated amides, 839
in radical cyclization, 963
in reactions with oxygen, 834

enantioselectivity, in reduction, of azirines, 1011
of chiral phosphine oxides, 1549
of epoxides, 1502
of imines, 1521
of ketones, 1511–1515
of nitro compounds, 1524
of oximes, 1527
of phosphine oxides, 1549
with boranes, 1509
Enantioselectivity, in enolate alkylation, 544
and chiral bases, 546
enantioselectivity, in reductive amination, 1099
enantioselectivity, in *Sharpless aminohydroxylation*, 1007
in *Sharpless asymmetric epoxidation*, 1004
in *Stille coupling*, 684
in the *[2,3]-Wittig rearrangement*, 1414
in the *Arndt-Eistert synthesis*, 1353
in the *aza-Baylis-Hillman reaction*, 1137
in the *aza-Cope rearrangement*, 1401
in the *aza-Michael reaction*, 966
in the *Baeyer-Villiger reaction*, 1369
in the *Baylis-Hillman reaction*, 1128, 1137
in the benzoin condensation, 1188
in the *Carroll rearrangement*, 1409
in the *Claisen reaction*, 1155
in the *Darzens condensation*, 1162
in the *Diels-Alder reaction*, 1023, 1025, 1026
in the *Eschenmoser-Claisen rearrangement*, 1409
in the *Heck reaction*, 766, 767
in the *Henry reaction*, 1156
in the *Ireland-Claisen rearrangement*, 1410
in the *Mukaiyama aldol*, 1153
in the *Nazarov cyclization*, 946
in the nitro aldol reaction, 1156, 1157
in the oxidation of thioethers to sulfoxides, 1494
in the *Pauson-Khand reaction*, 977
in the *Pictet-Spengler reaction*, 618
in the *Prins reaction*, 1186
in the *Pummerer rearrangement*, 1565
in the *Robinson annulation*, 1150
in the *Simmons-Smith procedure*, 1058
in the *Stevens rearrangement*, 1372
in the *Stork enamine synthesis*, 550, 552
in the *Strecker synthesis*, 1182
in the *Ullmann reaction*, 769
in the *Weitz-Scheffer epoxidation*, 1003
in vinylogous aldol reactions, 1148
in *Wagner-Meerwein rearrangements*, 1340
enantioselectivity, organometallics with aldehydes or ketones, 1117
enantioselectivity, with alkene metathesis, 1420
with amino acid surrogates, 548
with biaryls, and *Suzuki-Miyaura coupling*, 773
with BINAP, 958
with BINOL, 1115
with chiral alcohols, and ketenes, 892
with chiral boranes, 924
with chiral hydrazones alkylation, 549
with chiral oxazolines, 557
with dialkylzinc reagents and carbonyls, 1117
enantioselectivity, with enolate anions, and alkylation, 544
and aryl halides, 779
enantioselectivity, with insertion reactions, 693
with oxyamination, 1007
with radicals, 809
with reduction, 1513
with reduction, of alkenes, 912
with ring opening, aziridines, 467
with salen complexes, 564
with silanes, 1514
with silyl enol ethers and hydrazones, 1137
with sulfones and palladium catalysts, 480
enantiospheric, 173
enantiotopic atoms, 170
isotopic labeling, 171
enantiotopic faces, 172
enantiotopic, 170
and *Cahn-Ingold-Prelog rules*, 172
definition, 170
encapsulated osmium tetroxide, and dihydroxylation of alkenes, 993
encapsulation, and *Diels-Alder* reactions, 1022
encounter complex, 575
electrophilic aromatic substitution, 589
Encyclopedia of Reagents for Organic Synthesis, 1587
ene-diynes, and *Bergman cyclization*, 1386
electrocyclic rearrangement, 1386
endo addition, and orbital symmetry, 1036
in the *Diels-Alder reaction*, 1025
endohedral metals, and fullerenes, 85
ENDOR, and radicals, 236
ene reactions, 941–943
ene reactions, and [1,5]-sigmatropic rearrangement of hydrogen, 1392
and Lewis acids, 942, 943
and microwave irradiation, 310
and SeO_2 oxidation, 1470
and steric acceleration, 942
and the *Prins reaction*, 1186
aza-, 943
carbonyl, 943
dienophiles, 942
enantioselective, 942, 943
enantioselectivity, 943
imino, 943
in ionic liquids, 943
intramolecular, 942
mechanism, 942
metal catalyzed, 942
retro-, 942
stepwise mechanism, 943
stereoselective, 942
temperature requirements, 942
typical functional groups, 942
with oxygen, 834
ene synthesis see ene reaction
energetics, of ylid formation, 1168
energy barrier, causes of, 175
measurement of, 175
to planarity, cyclopentane, 189
to pyramidal inversion, 127, 128
to rotation in biphenyls, 176
to rotation in diadamantyl compounds, 176
to rotation in ethane, 175
to rotation, MO calculations, 176
energy cascade, and photolytic cleavage, 297
energy curve, for diatomic molecule, 291
for substituted ethanes, 177
energy diagram, for ethane, 176
energy levels, of alternant hydrocarbons, 64
of radical anions, 740
of the benzyl cation/radical/carbanion, 64

energy, activation, and rotational barriers, 130
of chair-to-chair interconversion, 181
and hyperconjugation, 85, 86
bond dissociation, and small rings, 194
bond resonance, 59
bond see bond energy
energy, dissociation see dissociation
energy, free see free energy
energy, of axial and equatorial substituents, 183
of butadiene, 37, 38
of chair conformation, 181
of conjugation, 39
of cyclohexane conformations, 181
of light, and photochemistry, 290
of singlet carbenes, 250
of transition energies, 441
of triplet carbenes, 250
energy, potential see potential energy
energy, resonance see resonance energy
energy, strain, 193
and molecular mechanics, 191
and trans cyclooctene, 204
calculations, 193
energy, π, 40
enol acetates, and the *Mukaiyama aldol reaction*, 1153
formation of enolate anions, 547
from enolate anions, 688
metal mediated halogenation, 672
with methyllithium, 547
with organocuprates, 527
enol borates, and the aldol reaction, 1146
enol borinates see borinates
enol carbonates see carbonates
enol content, and conjugation, 90
and *Meerwein-Ponndorf-Verley reduction*, 1507
and solvent effects, 92
and steric hindrance, 91
of amides, 91
of carbonyl compounds, table, 90
of esters, 90
of *Fuson-type enols*, 91
enol esters see esters
enol ethers also see ethers
enol ethers, addition of hydrazoic acid, 901
alkylation, 544
allyl, and the *Claisen rearrangement*, 1408
enol ethers, and addition of hydrazoic acid, 901
and base induced elimination of acetals, 1286
and enolate anions, 1146
and hydride shifts, 687
and metal catalyzed alcoholysis, 891
and the *Fischer indole synthesis*, 1412
and the *Mannich reaction* with imines, 1102
and the *Mannich reaction*, 1102
and the Mukaiyama aldol reaction, 1151–1153
and transetherification, 465
and *Wittig rearrangement*, 1374
enol ethers, by the *Wittig reaction*, 1167
cleavage by Grignard reagents, 535
elimination of ketals, 1286
epoxidation, 1000
formation of enolate anion, 544
formation of thioalkyl ketones, 681
formation of thioaryl ketones, 681
enol ethers, from acetals or ketals, 1083
from acyloins, 687
from alcohols, 465
from aldehydes or ketones, 1160
from aldehydes, 687
from alkynes and alcohols, 891
from enolate anions, 686
from enols, 463
from esters, 1173
from ketals, 1285
from ketones, 686
from phenols, 460
from vinyllithium and silylperoxides, 700
enol ethers, hydrolysis, 454, 887, 1167
hydrolysis, mechanism, 457
α-hydroxylation, 1474
in the ene reaction, 942
kinetic, 687
metal catalyzed conjugate addition, 948
nucleophilicity, 1152
oxidation to carboxylic acids, 1489
oxidative coupling to diketones, 1496
pyrolysis, 1286
pyrolysis, to alkenes and aldehydes, 1286
enol ethers, silyl, 458
and enolate anions, 1146
and *Hiyama coupling*, 545
silyl, nucleophilicity, 1146
silyl, with acetals, 534
enol ethers, sulfenylation, 681
thermodynamic, 687
enol ethers, with alcohols, 891
with alcohols, and halogens, 986
with aldehydes, 1152
with aldehydes, and chiral boranes, 1148
with alkynes, 931, 939
with aryldiazonium salts, 848
with hydrazones, and enantioselectivity, 1137
with imines, 1102, 1153
with methyllithium, 547
with protons, 864
with sulfur dioxide, 1251
with thiols, 894
enol phosphates, 1286
enol triflates, 1286
enolate acetates, with methyllithium, 547
enolate alkylation, and chiral additives, 546
and chiral ligands, 544
and chiral oxazolidinones, 546
and *Evan's auxiliaries*, 546
solvent effects, 539
enolate anions, activation energy, 1146
acylation, 688
aggregate formation, 342
aggregation state, 232
aggregation, ab initio study, 233
enolate anions, alkylation, 232, 447, 542, 547, 548
and phase transfer, 543
metal catalyzed, 544
solvents for, 544
enolate anions, and *Baldwin's rules*, 271
and enol borinates, 547, 1146
and enols, 92
and HSAB, 334
and *O*-acylation, 1233
and *O*-alkylation, 539
and pK_a of starting materials, 539
and racemization, 667
and regioselectivity, 546
and resonance, 224
and silyl enol ethers, 1146
and temperature effects, 1144
and X-ray crystallography, 232
enolate anions, as bases, 342
as nucleophiles, 447
base induced formation, 1146
bases required for formation, 543
by reaction with metals, 698
by *Wittig rearrangement* of vinyl ethers, 1374
canonical forms, 92
computation study of the activation energy, 1146

conversion to vinyl halides, 704
E/Z stereochemistry, 1146
enantioselective formation, 672
enantioselective protonation, 668
equilibrium reactions, 1143
enolate anions, formation, and UV light, 778
of dianions, 447
of E/Z isomers, 687
substituent effects, 667
from compounds with α-protons, 539
from organocuprate conjugate addition, 951
enolate anions, in aprotic solvents, 687, 1143
in arylation reactions, 778–780
in arylation reactions, and radicals, 780
in arylation reactions, and SET mechanism, 780
in conjugate addition reactions, 947
in coupling reactions, with allylic carbonates, 529
in coupling reactions, with allylic esters, 528
in coupling reactions, with aryl halides, 762
in cyclization reactions, with dihalides, 545
in dimethoxyethane, 686
in *Michael reactions*, 866, 867, 945
in protic solvents, 1143
in the *Claisen condensation*, 1234
in the aldol condensation, 232, 543
in the *Claisen condensation*, 232, 543
in the *Claisen reaction*, 1154
in the *Claisen Schmidt reaction*, 1144, 1145
in the Perkin reaction, 1161
in the *Robinson annulation*, 1150
enolate anions, Mg, 1148
of esters, and the *Claisen rearrangement*, 1409
reactions, 1142
via LDA, 1143
via organolithium reagents, 1113
with conjugated ketones, 547
with dihalides, 541
with metal catalysts, 1145
with metals, 1145
enolate anions, ester also see *Claisen condensation*
enolate anions, ester also see *Dieckmann condensation*
enolate anions, ester, 1155, 1243
and alkoxide bases, 1236
kinetic control, 1234
enolate anions, formation, from aldehydes or ketones, 1143
of conjugate addition of organocuprates, 949
of enol acetates, 688
of silyl enol ethers, 686
enolate anions, from amides, 1155
from carboxylic acid derivatives, 1153–1155
from carboxylic esters, 1154
from conjugate addition, 951
from conjugated ketones, 780
from dialkylamides, 687
from enol acetates, 547
from enols, 666
from esters, 1153, 1154
from ketones, 666
from ketones, 680
from organogallium reagents, 696
from silyl enol ethers, 544
from unsymmetrical ketones, 546
enolate anions, halogenation, 705
hydrolysis, 698
α-hydroxylation with sulfonyl oxaziridines, 1474
ketones, 1233
kinetic, 687
lithium, 1146
metal catalyzed coupling with aryl halides, 780
metallic, 1145
Michael addition, 947
Michael reactions, 947, 948
monomeric, 233
nitrile, with alkenes, 939
of amides, 1154
of carboxylic acid derivatives, 1153–1155
of lactams, with aryl halides, 780
of nitro compounds, reduction to hydroxylamines, 1526
oxidative coupling to diketones, 1496
photochemical arylation, 780
preformed, 945
protonation, 698, 867
thermodynamic, 687
torsional barrier, 180
enolate anions, with acyl hypofluorites, 670
with aldehydes, 232
with aldehydes or ketones, 1141–1153
with aldehydes or ketones also see aldol
with alkyl halides, 342, 447, 538
with allylic esters, 530
with aryl halides, enantioselectivity, 779
with chlorotrimethylsilane, 686
with disulfides, 680, 681
with halosilanes, 686
with heterocycles, 846
with ketones, 232
with LiBr, 233
with nitro compounds, 531
with selenyl halides, 681
with tosylcyanide, 689
enolate condensations, and amide bases, 544
and *Grignard reactions*, 1111
solvents, 543
thermodynamic conditions, 543
enolates see enolate anion
enolates, boron, chiral, 1148
enolboranes, 151
enolene rearrangement, 1412
enolizable diketones, and *Baeyer-Villiger rearrangement*, 1370
enolization, and *Grignard reactions*, 1111
and *Grignard reactions*, mechanism, 1113
and the aldol condensation, 1146
enols, acyloxylation, 836
alkylation, and Lewis acids, 544
amphiprotic properties, 665
enols, and oxidative cleavage of diketones, 1458
and *Bredt's rule*, 720
and enolate anion formation, 92
and formation of furans from diketones, 1083
and hydrogen bonding, 90, 99
and isotope effects, 666
and mechanisms, 286
and nitrosation, 676
and *Stille coupling*, 683, 684
and tautomerism, 89
and the aldol reaction, 1146
and the *Claisen rearrangement*, 1412
by hydration of alkynes, 887
by hydration of allenes, 888
by isomerization of allylic alcohols, 663
enols, chiral, 1147
electron delocalization, 665
fluorinated compounds, 91
Fuson-type, 91
halogenation, 671
hydrogen bonding, 665
in the solid state, 91
intramolecular stabilization, 665
isolation of, 91, 663
mechanism of the acid catalyzed aldol reaction, 1149
metal catalyzed preparation, 663

enols, chiral (*Continued*)
of amides, and dehydration to nitriles, 1313
preformed, with metals, 1146
stabilization, 665
stable, 90, 91, 205
steric stabilization, 666
tautomerism, 664, 665, 719
unstable, 90
with base, 666
with diazoalkanes, 463
with metal acetates, 836
with oxocarbenium ions, 1149
entgegen, and alkene nomenclature, 163
enthalpy, 284
and free energy, 264
and kinetics, 265
and nitrenes, 258
and reactions, 265
and temperature, 265
formal steric, 206
of activation, 267
entropy, acyclic and cyclic molecules, 265
and acidity, 345
and free energy, 264
and intramolecular aldol reactions, 1149
and kinetics, 284
and reactions, 265
and ring size, 268
and temperature, 265
cyclopropane to propane, 268
entropy, of activation see activation
envelope conformation, and cyclopentane, 188, 189
environmentally friendly chemistry, 361
enynes, and the *Pauson-Khand reaction*, 976, 1185
by *Stille coupling*, 684
carbonylation, and the *Pauson-Khand reaction*, 976
conjugate addition, 870
cyclic, from diynes, 933
cyclization, 934
cyclization, with metal catalysts, 935
cycloisomerization, 1395
halogenation, 984
metal catalyzed coupling of alkynes to alkynes, 933
metathesis, 1422
rearrangement, 664
Rh catalyzed cyclization, 934
with thiols, 895
enzymatic see enyzmes
Enzyme YNAR-1, NADP-H, reduction of nitro compounds, 920
enzymes, 141, 170, 581
enzymes, amino cyclase I, 1220
and molecular recognition, 112
and TEMPO oxidation of alcohols, 1448
Bacillus, megaterium, CH oxidation, 1472
decarboxylase, and benzoin condensation, 1188
epoxide hydrolase, 458
enzymes, for amidation of esters, 1220
for asymmetric *Michael reactions*, 947
for *Baeyer-Villiger rearrangement*, 1369
for carboxylation, 630
for carboxylic ester hydrolysis, 1191
for CH hydroxylation, 1472
for dihydroxylation of aromatic compounds, 998
for epoxidation, 1000
for ester hydrolysis, 1192
for hydrolysis, of nitriles, 1080
for α-hydroxylation, 1472
for hydroxylation, of amines, 1476
for α-hydroxylation, of ketones, 1473
for lactamization, 1217
for oxidation, of alcohols, 1725
for oxidation, of thioethers to sulfoxides, 1494
for reduction, in supercritical CO_2, 1510
for reduction, of aldehydes or ketones, 1510
for reduction, of aldehydes or ketones, 1512
for reduction, of conjugated ketones, 919
for the aldol reaction, 1144
for transesterification, 1207
enzymes, *Gossypium hirsutum*, CH oxidation, 1472
lipases, for dihydroxylation, 997
Pisum sativum, CH oxidation, 1472
eosin, as photosensitizer, 1039
ephedrine, and resolution, 173
epimerization, of chiral ketones, 667
epimers, definition, 147
episulfides see thiiranes
episulfides, conversion to alkenes, reagents for, 1288
from diazonium salts, 1178
reduction, 1502
with base, 1286
with $LiAlH_4$, 1288
episulfones, and the *Ramberg-Bäcklund reaction*, 1302
from diazo compounds, 1178
from sulfonyl halides and diazomethane, 1178
synthesis of, 1302
episulfoxides, conversion to alkenes, 1288
epoxidation, alternative methods, 1000
epoxidation, and chiral dioxiranes, 1002
and chiral iminium salts, 1000, 1002
and *Cinchona alkaloids*, 1001
and *Cinchona* phase transfer catalysts, 1003
and DBU, 1003
and diethyl tartrate, 1004, 1005
and hydroperoxides, 1004
and hydrotalcites, 1003
and hypochlorites, 1005
and isomerization (cis/trans) of alkenes, 1003
and kinetic resolution, 1005
and metalloporphyrins, 1000
and molecular sieves, 1004
and organocatalysts, 1000
and oxygen, 1001
and photooxygenation, 1006
and polyleucine, 1003
and the *Baeyer-Villiger reaction*, 1004
and Ti catalysts, 1004
and tolerable functional groups, 999
epoxidation, asymmetric, 1002
and alkene structure, 1005
and allylic alcohols, 1005
and manganese salen complexes, 1004
Sharpless, 1004
epoxidation, catalysts for, 1003
enzymatic, 1000
Jacobsen-Katsuki, 1005
Julia-Colonna, enantioselectivity, 1004
epoxidation, of alkenes, 998–1006
additives, 1002
and kinetic resolution, 159
epoxidation, of alkenes, enantioselectivity, 1000, 1001
enantioselectivity, catalysts, 1003
in ionic liquids, 1000
kinetics, 999
metal catalysts, 1001
reagents for, 998, 999
stereochemistry, 878
with Chloramine-M, 1002
with dioxiranes, 1001
with oxaziridinium salts, 1002
with Oxone and ketones, 1001
with peroxides and co-reagents, 999, 1000
with sodium hypochlorite, 1004
epoxidation, of cyclic alkenes, stereochemistry, 877

of dienes, 1003
Michael type alkenes, mechanism, 1003
of norbornene, 878
of vinyl ethers, 1000
Sharpless, mechanism, 1004
Shi-, 1002
Waits-Scheffer, 1003
Weitz-Scheffer, 1000
enantioselectivity, 1003
epoxidation, with alkyl hydroperoxides, and co-reagents, 1001
with catalytic antibodies, 1000
with chlorites, 1000
with Oxone, 1001
with peroxides, 1001
with peroxomonosulfate, 1001
with peroxyimidic acid, 1002
with salen catalysts, 1005
with tartrate, 1004, 1005
with urea-peroxide, 1003
epoxide hydrolase, enzyme, 458
epoxides, acids catalyzed rearrangement, 1343
alkynyl, with BF_3, 1305
allene, 1004
allylic, from allylic alcohols, 1357
an ambident substrate, 450
epoxides, and anion relay chemistry, 553
and elimination with phosphines, 1286
and formation of isocyanides, 492
and formation of lactones, 536
and *Friedel-Crafts alkylation*, 536, 611
and leaving groups, 432
and neighboring group mechanisms, 392
and oxidative amidation, 838
and strain, 194
and the *Brook rearrangement*, 553
and the pinacol rearrangement, 1344
epoxides, by modified *Peterson alkenylation*, 1163
cyclic, elimination, to dienes, 1287
diastereoselectivity, from sulfur ylids, 1176
diaxial ring opening, 879
elimination, with diamines, LDA, and DBU, 1287
elimination, with organolithium reagents, and alkoxides, 1287
enantioselective hydrolysis, 458
enantioselectivity of halogenation, 506
enantioselectivity, with sulfur ylids, 1176
formation of aziridines, 490
formation of dinitrates, 474
formation of thiiranes, 478
epoxides, from aldehydes, 1110
from alkenes, 994
from diazoalkanes with aldehydes or ketones, 1177
from dihalides and carbonyl compounds, 1110
from diols, 461, 469
from halohydrins, 393, 461
from halo-sulfones and ketones, 1177
from ketones or aldehydes, 1175
from selenium ylids, 1176
from sulfur ylids and carbonyls, 1175
epoxides, halogenation, 1502
halogenation, and organocatalysts, 506
hydrolysis, 458, 994
hydrolysis, enantioselective, 458
in the *Stork enamine reaction*, 550
in the *Williamson reaction*, 461
in the *Wittig reaction*, 490
intramolecular alcoholysis, 466
lithio, rearrangement, 489
epoxides, metal catalyzed, azide ring opening, 489
halogenation, 507
reaction with allylic boranes, 537
ring opening, 489
epoxides, reaction, with alcohols, 465
with nucleophiles, 466
with sulfur ylids, 1176
epoxides, reagents, for elimination, 1287
for halogenation, 506
epoxides, rearrangement, 1343
with acids, 1343
epoxides, reduction to alcohols, reagents, 1502
enantioselectivity, 1502
epoxides, regioselectivity, of halogenation, 506
ring-opening, 937
silyl, 511
sterically hindered, hydride reduction, 1502
via sulfur ylids, 1175
epoxides, vinyl, and S_N2' reactions, 537
rearrangement, 1344
with *Grignard reagents*, 537, 937
epoxides, with acyl halides, 507
with alkynes, 536
with allylic silanes, 511
with amide bases, 489
with amines, microwave irradiation, 488
with ammonia, 488
with ammonium thiocyanates, and ceric ammonium nitrate, 1178
with aromatic amines, 488
with azide ion, 489, 490
with azide ion, and the *Mitsunobu reaction*, 489
with borates, 560
with boronic acids, 560
with CO, 471
with cyanide, 564
with dithianes, 553, 1432
with enamines, 551
with *Grignard reagents*, 537
with hydrosilanes, 537
with $LiAlH_4$, 1435
with LTMP, 489
with metal halides, 506
with mineral acids, 506
with organocuprates, 536
with organocuprates, and Lewis acids, 536
with organolithium reagents, 537
with organometallics, 535, 536
with oxazine carbanions, 556, 557
with peroxyacids, 1428
with phosphine sulfide, 478
with phosphines, 1169
with selenosilanes, 466
with silylazides, 489
with sodium azide, 496
with sodium nitrate, 490
with sulfur ylids, 1287
with tosylamines, 490
with vinyl sulfides, 554
epoxy alcohols, 1006
and *Payne rearrangement*, 466
rearrangement, 466
epoxy carboxylic acids, 507
epoxy esters, from diazoesters and aldehydes, 1058
from halo esters, and aldehydes or ketones, 1161
epoxy hydrazones, base induced fragmentation, 1309
via *Eschenmoser-Tanabe ring cleavage*, 1544
epoxy ketones, 1004
by *Julia-Colonna epoxidation*, 1004
rearrangement to diketones, 1344
reduction with silanes, 1509
EPR, and carbenes, 251
and electrophilic aromatic substitution, 586
and radicals, 235

equations, *Brønsted catalysis*, 328
duel substituent parameter, 358
Grunwald-Winstein, and solvent effects, 439
Grunwald-Winstein, and solvolysis, 420
Hammett see Hammett
Schrödinger, 3, 4
Swain-Lupton, 360
Swain-Scott, 429
Taft, 360
wave, 6
equatorial, in chair conformations, 181
equilibrium constants, 132, 267
and atropisomers, 132
and free energy, 355
and solvent acidity, 327
and the *Brønsted equation*, 329
and the *Hammett equation*, 352
equilibrium, acid-base, 312
and arenium ions, 577
and carbocations, 407
and enolate anion formation, 1143
and excess reagents, 1202
and formation of hydrates, 1076
and HSAB, 333
and isomerization of alkenes, 1299
and leaving groups, in the tetrahedral mechanism, 1074
and pseudorotation, 180
and rate-determining step, 280
and S_N1 reactions, 383
and solvent acidity, 326
and tautomerism, 89
and *Wagner-Meerwein rearrangements*, 1341
equilibrium, cyclopropylcarbinyl versus cyclobutyl cations, 1345
equilibrium, for alkyne isomerization, 664
for cyclohexane conformations, 180
in borane isomerization, 1358
in ester hydrolysis, 1190
in the aldol condensation, 1143
in the *Claisen condensation*, 1235
in the Cope rearrangement, 1401
in the pyrolysis of alkyl boranes, 1299
in the reaction of carboxylic acids with alcohols, 1202
in the reaction of carboxylic acids, water, and alcohols, 1190
in the *Sommelet-Hauser rearrangement*, 799
keto-enol, 665
of enolate anions, and solvent effects, 1143
organolithium-alkyl halides, 222
Schlenk, 229, 230
Ergänzungswerks, and Beilstein, 1579
ergost-7-en-3-one, 351
EROS, 1588
erythro nomenclature, 148
erythro/threo, and electrophilic addition, 860
ESCA (X-ray photoelectron spectroscopy), and carbocations, 467
Eschenmoser-Claisen rearrangements, enantioselectivity, 1409
Eschenmoser's salt, and the *Mannich reaction*, 1102
Eschenmoser-Tanabe ring cleavage, 1309
Escherichia coli, and reduction of imines, 1521
Eschweiler-Clarke procedure, 1098
ESR (electron spin resonance specdtroscopy)
ESR, and *Birch reduction*, 914
and bridged radicals, 811
and captodative effect, 240
and carbenes, 251
and *Grignard reactions*, 1112
and kinetics, 282
and magnetic anisotropy, 236
and magnetic fields, 235
and radical rearrangements, 1335
and radicals, 235, 236, 240, 390, 729
and splitting, 235
and unpaired electrons, 236
ESR, for azoxy compounds, 729
for bridged bromine radicals, 869
for the methyl radical, 243
for the reaction of organolithium compounds with alkyl halides, 520
studies, and the *Étard reaction*, 1480
esterases, and resolution, 157
Marchantia polymorpha, hydrolysis of vinyl acetates, 1192
pig liver, and hydrolysis of esters, 1191
esterification, allylic methylene groups, 1471
esterification, and ammonium salts, 1203
and azopyridines, 1203
and lactone formation, 1203, 1204
and phosphines, 1203
and polymer bound urea, 1203
and steric hindrance, 1204
and sulfuric acid, 1204
and the *Mitsunobu reaction*, 469, 1203
and the *Mukaiyama's reagent*, 1204
and zeolites, 1203
in ionic liquids, 1203
IUPAC mechanism, 1204–1206
of carboxylic acids, 1202–1206
of carboxylic acids, and DCC, 1205
of carboxylic acids, and microwaves, 1203
of carboxylic acids, photochemistry, 1203
of carboxylic acids, with DCC, mechanism, 1205
of carboxylic aids, catalysts, 1203
solid state, 1203
esters also see acetates
esters, see carboxylic esters
esters, boronate, oxidation, 1376
esters, boronic, carbonylation, 708
for reduction, 1509
esters, carbonate see carbonates,
esters, *Hantzsch* see *Hantzsch*
esters, inorganic, decomposition to alkenes, 1289
from alcohols, 473
esters, manganate, 993
esters, nitrate, from alkyl halides, 474
from alcohols, 473
esters, of inorganic acids, hydrolysis, 453
esters, ortho see ortho esters
esters, osmate, 993
osmium, 993
oxime, with acids, 1366
esters, phosphate, 474
from ylids, 1169
esters, phosphinate, 484, 474, 1169
and elimination, 1289
aryl, reduction, 1536
conjugate addition of amines, 967
diazo compounds, 1054
from alcohols, 473
with aldehydes, 1123
with DBU, 1172
with HPMA, 1172
with *Lawesson's reagent*, 1289
esters, phosphonic, with *Grignard reagents*, 531
with thiols, 1211
esters, seleno, 1201
by carbonylation, 781
esters, spiroborate, 1509
reducing agents, 1522

esters, sulfamate, and amination, 679
esters, sulfinate, and deoxygenation of diols, 1301
elimination reactions, 1296
from alcohols, 480
from sulfinyl chlorides, 480
esters, sulfinic, alkylation, 554
enantioselective preparation, 473
esters, sulfonate see sulfonate esters
and oxytosylation, 1475
esters, thio, hydration of alkyne thioethers, 888
esters, thiohydroxamic, 854, 855
esters, thiono see thionoesters
esters, trifluoromethanesulfonate, 1083
esters, vinyl phosphonate, Markovnikov addition, 899
esters, xanthate also see *Chugaev* and the *Chugaev reaction*, 1289
from alcohols, 1289
Étard reaction, 1479
and acylals, 1479
and chromyl chloride, 1479
and ESR studies, 1480
and magnetic susceptibility, 1479
mechanism, 1479
ethane, energy barrier to rotation, 175
energy diagram, 176
heat of atomization, 28
supercritical, hydrogenation of aromatic compounds, 913
ethanes, substituted, conformational energy, 177
ethanolamine, and dealkylation, 487
as a solvents, 488
ethanolysis also see solvolysis
ethanolysis, of alkyl tosylates, rate of reaction, 420
ethanonium ion, IR, 661
ethene also see ethylene
ethers, acidity, 336
alkynyl, hydration of, 888
allyl allene, and *Claisen rearrangement*, 1409
allyl vinyl, and [3.3]-sigmatropic rearrangement, 1398
allylic aryl, rearrangement, 1407
ethers, allylic, and Wittig *rearrangement*, 555
carbanions, and alkylation, 555
cleavage with *Grignard reagents*, 534
conversion to aldehydes, 1374
pyrolysis, 1315
with organolithium reagents, 555, 1374
ethers, and ionic liquids, 459
and microwave irradiation, 459
and the *Mitsunobu reaction*, 460, 464
and the *Wittig rearrangement*, 1374
aromatic, reductive cleavage, 1537
aryl allyl, *Claisen rearrangement* of 2-allyl phenols, 1407
ethers, aryl, and microwave irradiation, 747
and phase transfer, 747
deoxygenation, 646
from alkoxides, 747
from aryl halides, 747
with *Grignard reagents*, 518
ethers, azacrown, 109
base-induced elimination, 1285
base-induced elimination, mechanism, 1285
benzylic, hydrogenation, 504
ethers, by insertion of carbenes, 692
by reduction of peroxides, 1540
by reduction of thiono esters, 1543
by the *Williamson reactions*, 459
by *Ullmann ether synthesis*, 748
ethers, α-CH oxidation to carboxylic esters, 1478
ethers, CH oxidation, 1478
ethers, cleavage, 471, 474, 486, 504, 505
in ionic liquids, 504
with alkylsilanes, 504
with HBr or HCl, 455
with HI or HBr, 504
with Lewis acids, 505
with organometallics, 534
with silyl halides, 505
with sulfuric acid, 454
ethers, crown, 108–113
and ambident nucleophiles, 449
and chirality, 135
and complex formation, 108
and hydrogen bonding, 110
and molecular recognition, 112
and phase transfer catalysis, 444
and spherands, 110
and synthesis, 108
as cavitands, 110
as hosts, 109
bicyclic, 109
binding K^+ or Li^+, 108
cryptands, 111
cryptaphanes, 111
hemispherands, 111
in guest-host interactions, 110
ion binding, 108
ion-dipole interactions, 112
lariat ethers, 111
macrocyclic, 109
NMR and guest-host interactions, 112
podands and starands, 111
ethers, cyclic, by insertion reactions, 692
α-CH oxidation to lactones, 1478
cleavage, 504
from alcohol, with lead tetraacetate, mechanism, 831
from alcohols, 830
from epoxides, 466
from thionolactones and organolithium reagents, 1133
reagents from oxidation of alcohols, 831
reduction of lactones, 1543
transetherification, 464
with organolithium reagents, 1285
ethers, demethylation, 477
ethers, enol see enol ethers
ethers, formation, and phase transfer catalysts, 460
of amines, 485
ethers, from acetals, 534
from alcohols and trifluoroborates, 462
from alcohols, 462, 463
from aldehydes or ketones, 1085
from alkenes and alcohols, 889
from alkenes and phenols, 889
from alkoxides, 459, 462
from alkyl halides, 459
from alkyl sulfates, 462
from diazo compounds, 462
from diazoalkanes, 463
from diazomethane, 462
from esters, 1543
from *Grignard reagents*, 534, 700
from inorganic esters, 462
from onium salts, 467
from organotrifluoroborates, 700
from oxonium salts, 505
from phenols, 462, 464, 533
ethers, α-halo, 1106
ethers, halo, and elimination with magnesium, 1306
and the *Boord reaction*, 1306
by radical halogenation, 823
from alcohols and halogens, 986
metal induced elimination to alkenes, 1306

ethers, halomethyl, with boranes, 1376
homoallylic, by coupling of silanes, 840
hydrolysis of, 462
hydroxy, 466
lariat, 111
MEM, 460
metal catalyzed, cleavage, 505
MOM, 460
nitrate, from alcohols, 473
oxidative cleavage, of carboxylic acids, 1484
oxime, reduction, 1522, 1527
photochemistry, 292
protection of alcohols, 460
radical dimerization, 840
reduction of esters, reagents, 1543
reduction to hydrocarbons, reagents, 1536
reductive alkylation, of aldehydes, 1084
reductive dealkylation, reagents, 1536
selenoalkyl, 891
ethers, silyl enol see enol ethers
ethers, silyl, 461
conversion to alkyl iodides, 503
reaction with fluoride ion, 461
ethers, as solvents also see solvents, ether
ethers, as solvents, and *Grignard reagents*, 229, 230, 1107
ethers, tetrahydropyranyl, oxidation, and zeolites, 1452
thiacrown, 109
transetherification, 464
trimethylsilyl, oxidation with O_2, 1452
ethers, vinyl see enol ethers
ethers, with alkyl halides, 472
with alkynes, microwave irradiation, 928
with anhydrides, 471
with *Grignard reagents*, 534
with mineral acids, 504, 505
with organolithium reagents, 1285, 1374
with organolithium reagents, *Wittig rearrangement*, 1373, 1374
with organosodium reagents, 1285
with oxonium salts, 472
with sulfonic acids, 474
with sulfuric acid, 454
ethyl diazoacetate, 688
ethyl nitrate, and nitration of aromatic compounds, 594
ethylene glycol, as a solvent, 1294, 1376
ethylene oxide, strain, 193
ethylene, and electronic structure, 14
and hybrid orbitals, 9
and π orbitals, 9
and π-bonds, 41
canonical forms, 44
complex with silver, 105
ozonolysis, formation of dioxirane, 1463
structure, 14
ethylenediaminetetraacetic acid, and *Udenfriend's reagent*, 830
ethylmagnesium bromide, and X-ray, 230
ethylmercuric chloride, 233
ethyne, addition of HCN, 981
and orbitals, 10
and triple bonds, 10
electron density map, 11
excited state, 295
triplet, 252
σ electrons, 10
europium compounds, chiral shift reagents, 161
Evans auxiliaries, and the *Claisen condensation*, 1155
exchange mechanism, 660
exchange reactions, 474
amine salts with amides, 1222
carboxylic acids, and acyl halides, 1224
exchange, carboxylic acids, with amides, 1210, 1218
with esters, 1210
exchange, halogen-metal, and organocuprates, 523
hydrogen, 592
isotope, 1072
Li-H, organolithium compounds, 516
lithium-halogen, 953
metal halogen, and aryllithium compounds, 516
metal halogen, and organolithium compounds, 516
organolithium compounds, 516
R_2Mg and R_2Hg compounds, 222
exciplex formation, in photochemistry, 301
exciplex, and photochemical [2+2]-cycloaddition, 1050
excitation, electronic, 292
excited states, acetylene, 295
and photochemistry, 294
fluorescence, 297
formaldehyde, 295
intersystem crossing, 298
Jablonski diagrams, 297
photosensitization, 299
physical processes, 296
pK of naphthol, 295
promotion, 297
properties, 294
exhaustive alkylation, and amines, 482
exo addition, and bicyclic alkenes, 878
and the *Diels-Alder reaction*, 1025
extinction coefficient, 291
extrusion reactions, and elimination, 1253
and tetrahedranes, 1318
definition, 1316
of thiirene dioxides, 1303
the *Ramberg Bäcklund reaction*, 1303, 1304
extrusion, of nitrogen, 1316
extrusion, of CO, 1309, 1317
and *Diels-Alder reaction*, 1310
extrusion, of CO_2, 1309, 1310, 1319
from lactones, 1318
of nitrogen, and diradical, 1317
of nitrogen, mechanism, 1317
of sulfur dioxide, from sulfones, 1318

F and R values, table, 359
F strain, and acidity, 338
F values, and σ values, 359
face strain, and acidity, 338
faces, diastereotopic, 172
faces, enantiotopic, 172
facial selectivity see selectivity
peroxyacid epoxidation of alkenes, 999
Far UV, 293
and photochemistry, 290
Favorskii reaction, 1114
in connection with the *Nef reaction*, 1158
Favorskii rearrangement, 1350
isotopic labeling, 1351, 1352
mechanism, 1351, 1352
quasi-, rearrangement, 1352
Fe catalysts, alkoxides with aryl halides, 748
and *Sonogashira coupling*, 777
cross coupling, 850
with bromoalkynes, 562
Fe, amide formation, 495
and metallocenes, 61
complexes, and *Grignard reagents*, 933
in ammonium chloride, 1554
nanoparticles, 518
Felkin-Anh model, and addition of radicals, 871
and asymmetric synthesis, 151
and diastereoselectivity, 151
Fenton's reagent, 830
and heterocycles, 846
ferricyanide, K, and dihydroxylation, 996

ferrocene, 61, 106
bonding, 61
formylation, 626
structure, 105
ferrous sulfate, and peroxides, 830
field effect constants, 356
field effects, 19, 20, 45
+I and –I, 20, 21, 347
+M and –M, 348
and acid strength, 334
and aromatic compounds, 21
and base strength, 334
and benzyne reactions, 744
and bond polarization, 19, 20
and carbanions, 225
and carboxylic acids, 20
and hybridization, 21
and organometallics, 697
and pK_a, 334
and reactivity, 347
and substituent effects, 421
and the *Hammett equation*, 352
ylids, 225
and σ values, 357–359
and σ^* values, 357, 358
arenium ions, 577
benzoic acids, 335
electrophilic aromatic substitution, 580
halogenation of aldehydes or ketones, 672
of groups, 21
Fieser's Reagents for Organic Synthesis, 1590
Finkelstein reaction, 498
and phase transfer, 499
metal catalyzed, 498
first order rate, and neighboring groups, 391
first order reactions, 380
and racemization, 383
first-order rate constant, 283
first-order rate law, 282
first-order reactions, 279
Fischer carbene complexes, 1062
and *Dötz benzannulation*, 1063
in [3+2]-cycloaddition reactions, 1017
Fischer carbenes, 1054
Fischer indole synthesis, 1412
and [3,3]-rearrangements, 1413
and isotope labeling, 1413
and microwaves, 1412
and NMR, 1413
in ionic liquids, 1412
mechanism, 1413
solid phase, 1412
with vinyl ethers, 1412
Fischer projection, definition of, 136
Fischer, Emil, 136
Fischer-Hepp rearrangement, 639
and urea, 639
flash photolysis, 306
and the *photo-Fries rearrangement*, 637
of bromoform, 252
of diazomethane, 251
flash vacuum pyrolysis see FVP
flavin, catalysts for dihydroxylation, 997
flow reactor technology, 751
fluoranthene, and complex formation, 112
fluorene carbanions, 656
and organolithium reagents, 695
pK_a, 59
fluorescence, and promotion, 299
characteristics, 298
fluoride ion, and silanes, 956
and the *Tamao-Fleming oxidation*, 468
metal, fluorinating agents, 499
reaction with silyl ethers, 461
with aryl nitro compounds, 797
with aziridines, 538
fluorides, acyl, 1190, 1224
by oxidation of alcohols, 1484
from acyl chlorides, 1225
from anhydrides, 1225
from HF and anhydrides or acyl halides, 1224
from KF and acyl halides, 1225
hydrolysis, 1190
with amine, 751
fluorides, alkyl, base induced elimination, and *Hofmann's rule*, 1297
from carboxylic acids, 855
fluorides, and *Grignard reagents*, 714
and the *Finkelstein reaction*, 498
and the *Schiemann reaction*, 792
fluorides, aryl, and the *Schiemann reaction*, 792
from aryl diazonium salts, 847
from HF, 792
with keto esters, 779
fluorides, fluorinating agents, 499
from arylthallium compounds, 786
from tetrafluoroborate salts, 704
gem, and DAST, 1106
sulfonyl, 603
vinyl, from iodonium salts, 704
fluorinated compounds, enol content, 91
fluorinated solvents, and the Heck reaction, 764
fluorination, 822
and dithianes, 1106
and pyridinium polyhydrogen fluoride, 1106
boronic acids, 705
electrophilic, 826
of carboxylic acids, 673
of aldehydes or ketones, 669
of amides, 673, 730
of amines, 730
of aromatic compounds, 608
of aryldiazonium salts, 792
of carboxylic esters, 673
reagents, 468, 499, 669
with polyhydrogen fluoride-pyridine, 1225
with SF_4, 1106
fluorine, addition to alkenes, 982
and aromatic compounds, 608
and halogenation of aromatic compounds, 608
and keto-enol tautomerism, 91
electronic versus radical pathways, 822
handling fluorine, 822
stabilization of carbanions, 696
fluorobenzenes, 791
from nitro compounds, 797
fluoroborates, acyl and acetic anhydride, 1012
diazonium, 792
fluorosulfonic acid-SbF5, superacid, 320
fluorosulfuric acid, and cation stability, 210
fluoroxytrifuoromethane, and fluorine radicals, 822
fluroanthrene, from benzobiphenylene, 1391
fluxional isomerization, 166
fluxional structures, and Cope rearrangement, 1405
FMO (frontier molecular orbital), 1016
and [3+2]-cycloaddition, 1016
and regioselectivity of [3+2]-cycloadditions, 1016
forbidden reactions, [2+2]-cycloaddition, 1050
in photochemistry, 292, 296, 298
formal charge, and bonding, 15
formal steric enthalpy, 206
formaldehyde, acid catalyzed addition to alkenes, 1184
and amines, 631
and chloromethylation, 619
and the *Eschweiler-Clarke procedure*, 1098
and the *Mannich reaction*, 1100
and the *Prins reaction*, 1184
and the *Tollens' reaction*, 1164
and trioxane, 1240
excited state, 295
with aromatic compounds, 619
with glycoluril, 121
with ketones, 1164

formamides, and phosphorus oxychloride, 685
and the *Leuckart reaction*, 1098
and the *Vilsmeier-Haack reaction*, 625
and the *Wallach reaction*, 1098
by hydrogenation of isocyanates, 1522
by hydrolysis of isocyanides, 1246
carbonylation of amines, 730
from chloroamines, 492
from imines, 1366
with acetals, 685
with aromatic compounds, 625
with *Grignard reagents*, 709, 1229
with organolithium reagents, 709, 1229
with thionyl chloride, 1314
formamidines, alkylation, 555
bases, 322
formamidines, from amines, 555
formate ion, with peroxydisulfate, 1538
formates, ammonium, and enantioselective reduction, 1514
reduction of aldehydes or ketones, 1510
with amines, 730
with Pd/C, and reduction of conjugated aldehydes, 919
formates, chloro see chloroformates
formation, of vinyliodonium salts, 703
formic acid, and the *Koch-Haaf reaction*, 972
and the *Wallach reaction*, 1098
formation of formates, 1510
from chloroform, 453
with *Grignard reagents*, 708
with hydroxylamine and aldehydes, 1095
with iodine and amines, 1213
with Pd, with conjugated carboxylic acids, 916
with reductive alkylation, 1098
formic anhydride, 625, 1202
stability, 1215
formula Periodic table, for benzenoid polyaromatics, 54
formyl chloride, 625
formylation, alternative methods, 628
and carbenes, 627, 628
and formamides, 685
and *Friedel-Crafts acylation*, 623
and organolithium reagents, 628
and paraformaldehyde, 628
and the *Duff reaction*, 628
and the *Gatterman reaction*, 627
and the *Gatterman-Koch reaction*, 627
and the *Reimer-Tiemann reaction*, 627
of alkenes, 685
of aromatic compounds, 625
of heterocycles, 626
of ketones, 686
of phenols, 628
para selectivity, 628
formylcarbene, lifetime, 254
formylpiperidine, formylation of phenols, 628
four-center mechanisms, addition to alkenes, 869
and hydroboration, 922
fractional crystallization, and resolution, 154–157
fractional distillation, and diastereomers, 156
and resolution, 156
and diastereomers, 156
and resolution, 156
fragmentation, and abnormal *Beckmann rearrangement*, 1312
carbenes, 257
definition, 1307
dialkylamino halides, 1307
mechanism, 1307
of carbenes to radicals, 257
of epoxy hydrazones, base induced, 1309
of oxonium ions, 1308
Franck-Condon principle, 296
free carbenes, 1053
free energy, amide hydrolysis, 349
and acidity, 345
and *Brønsted equation*, 328
and carboxylic acids, 345
and catalysis, 277
and enthalpy or entropy, 264
and equilibrium constant, 355
and *Grunwald-Winstein relationship*, 355
and intermediates, 269
and kinetic control, 272
and reaction intermediates, 268
and S_N2 reactions, 379
and S_NAr reactions, 744
and solvent acidity, 327
and solvent effects, 439
and thermodynamic control, 272
enantiomierization, 697
equation, 264
intrinsic, 273
kinetic versus thermodynamic, 272
linear, 355
of activation, 265
profile, gas phase SN2, 378
spontaneous reactions, 264
"free" hydride, 1511
free radicals see radicals
freeing point depression, and ester hydrolysis, 1195
free-radical addition, 263
free-radical mechanism, 262
free-radical rearrangement, 263
free-radical substitution see substitution
freezing point depression, and *Grignard reagents*, 230
and organometallics, 229
Fremy's salt, oxidation of aromatic compounds, 1453
and oxidation of phenols, 1453
oxidation of alcohols, 1452
frequency factor, and rate law, 284
friedelanol, 1340
Friedel-Crafts acylation, 602, 621, 643
alternative formylation methods, 628
Friedel-Crafts acylation, and acyl carbocations, 624
and acylium ions, 621
and alkylbenzenes, 613
and formylation, 623
and IR, 625
and isotopic labeling, 625
and meta directing groups, 622
and metal catalysts, 622
and microwave irrdiation, 622
and the *Fries rearrangement*, 622, 636
and the *Gatterman amide synthesis*, 629
and the *Gatterman reaction*, 626
and the *Haworth reaction*, 623
and the *Vilsmeier-Haack reaction*, 625
and zeolites, 622
Friedel-Crafts acylation, carbonylation, 625
catalysts, 622
formation of aldehydes, 625
formation of aryl ketones, 632
formation of carboxylic acids, 629
in ionic liquids, 621–623
intramolecular, 623
mechanism, 624
no rearrangement, 621, 622
solvent free, 622
transition metal catalysts, 622
Friedel-Crafts acylation, with anhydrides, 622
with anhydrides, 623, 624
with biaryls, 625
with carboxylic acids, 621
with cyclic anhydrides, 624
with formamides, 625
with heterocyclic compounds, 623

with indoles, 623
with ketenes, 622
with keto-acids, 623
with microwave irradiation, 624
with mixed anhydrides, 623
with phosgene, 629
with sulfonic anhydrides, 622
Friedel-Crafts alkylation, 609, 1323
activating groups in product, 612
alkyl migration, 640
alkylating reagents, 611
Friedel-Crafts alkylation, and alkynes, 610
and cyclodehydration, 616
and iodine, 610
and labeling, 615
and reversal, 642
and the S_N2 mechanism, 614
Friedel-Crafts alkylation, coordination of Lewis acids, 612
cyclization, 613
diastereoselective, 610
in ionic liquids, 609, 610
in the *Pechmann condensation*, 617
intramolecular, 609
mechanism, 613
metal catalyzed, 610
paradoxical selectivity, 612
polyalkylation, 612
reactivity order of Lewis acids, 611, 612
Friedel-Crafts alkylation, rearrangement, 615
of carbocations, 613
Friedel-Crafts alkylation, reversal, 641
intramolecular, 642
mechanism, 642
temperature dependence, 642
Friedel-Crafts alkylation, reverse, and isotope labeling, 642, 643
mechanism, 642
Friedel-Crafts alkylation, tight ion pairs, 614
Friedel-Crafts alkylation, with epoxides, 536
with alcohols, 610
with alkenes, 609, 610
with alkyl halides, 609
with anilines, 612
with aryltrifluoroborates, 616
with chiral catalysts, 611, 612
with coumarins, 617
with deactivated compounds, 612
with epoxides, 611
with functional group substrates, 614
with fused ring aromatics, 611
with heterocyclic compounds, 611
with Lewis acid catalysts, 611
with Lewis acids, 611
with naphthalene, 611
with protonic acids, 610
Friedel-Crafts arylation, and the *Hoesch reaction*, 632
Friedel-Crafts catalysts, addition of alkyl halides to alkenes, 991
and halo, 992
dehalogenation of aryl halides, 647
Friedel-Crafts cations, cyclization, 623
formylation, 625
Friedel-Crafts coupling, and atropisomerism, 616
with aldehydes and ketones, 615
Friedel-Crafts cyclization, and aldehydes, 617
and amides, 617
and ketones, 617
and *Pictet-Spengler reaction*, 618
Bischler-Napieralski reaction, 617
high dilution methods, 624
Friedel-Crafts reactions, 786, 940
, and heterocycles, 846
amide formation, 631
Bradsher reaction, 617
chloromethylation, 619
Duff reaction, 628
haloalkylation, 619
with alkenes, 685
friedelin, and the *Wagner-Meerwein rearrangement*, 1340
Friedländer quinoline synthesis, 1091
Fries rearrangements, 635, 636
and *Friedel-Crafts acylation*, 622
and ionic melts, 636
and LDA, 637
and microwave irradiation, 636, 637
and UV light, 637
anionic Snieckus-, 637
anionic, 637
ate complex formation, 636
crossover experiments, 636
intramolecular, 637
mechanism, 636
metal catalyzed, 636
ortho/para ratio, 636
para migration, 636
thia-, 637
Fries, photo see *photo-Fries*
Fritsch-Buttenberg-Wiechell rearrangement, 1298
frontier molecular orbitals see FMO
frontier orbital method, 1031–1037
and [2+2]-cycloaddition, 1032
and [4+2]-cycloaddition, 1032
and the *Diels-Alder reaction*, 1032, 1033
electrocyclic rearrangements, 1382
photochemical reactions, 1032
thermal reactions, 1032
Fukuyama coupling, 1231
fulgide, and helical chirality, 134
fullerenes, and aromaticity, 84
and MO calculations, 84
and rotaxanes, 118, 120
bowl-to-bowl inversion, 84
homofullerenes, 85
synthesis, 84
fulminene, 78
fulminic acid, [3+2]-cycloaddition, 1017
fulvalenes, 63
and aromaticity indices, 63
fumaric acid, 165
fuming sulfuric acid, with aromatic compounds, 600
functional group compatibility, Darzens condensation, 1162
functional groups, and active methylene compounds, 539
and catalytic hydrogenation, 903
and CIP rules, 139
and *Grignard reagents*, 714
and hydroboration, 923
and nucleophilic strength, 431
compatible with organocuprates, 950
compatible with *Suzuki-Miyaura coupling*, 772
ease of reduction, 1499–1501
for the *Knoevenagel reaction*, 1157
oxidation state, 1434
reactivity with sodium borohydride, 1505
type, synthesis of, 1605–1629
furan, and aromaticity, 57, 58
catalytic hydrogenation, 913
electrophilic aromatic substitution, 584
resonance energy, 58
furanose compounds, and tautomerism, 94
furans, *Birch reduction*, 914
by metal catalyzed reaction with alkynyl ketones, 1083
formation of 1,4-diketones, 458
from alkynes, 891
from diketones, 1083
halogenation, 703

furans, *Birch reduction* (*Continued*)
hydrolysis, 458
in the *Diels-Alder reaction*, 1039
in the *Friedel-Crafts acylation reaction*, 623
in the *Friedel-Crafts alkylation reaction*, 611
fused ring aromatic compounds, 48
and bond distance, 55
and resonance energy, 56
fused rings, electrophilic aromatic substitution, 584
fused-ring aromatics, Friedel-Crafts alkylation, 611
Fuson-type enols, 91
FVP (flash vacuum pyrolysis)
and alternant aromatics, 1391
and vinylcyclopropane rearrangement, 1399
cyclopropylcarbinyl alcohols, 1399
of halocyclopropanes, 1347
of phosphorus ylids, 1293
polycyclic aromatics, 1391

Ga compounds, rearrangement of vinyl epoxides, 1344
Ga, allylic reagents, 526
Gabriel synthesis, 482, 494
and hydrazine, 494
hydrolysis reagents, 494
Ing-Manske procedure, 494
galvinoxyl, radical inhibitor, 959
gas chromatography see GC
gas phase acidity, 344
gas phase basicity, 343
gas phase elimination, 1272
gas phase ozonolysis, 1463
gas phase protonation, alkylbenzenes, 575
gas phase pyrolysis of carboxylic acids, 1288
gas phase S_N2, 376
free energy profile, 378
gas vacuoles, and sonochemistry, 307
Gatterman amide synthesis, 629
Gatterman method, 796
Gatterman reaction, 626, 633, 846
and heterocyclic compounds, 626
and superacids, 627
with aryl halides, mechanism, 847
Gatterman-Koch reaction, 627
reverse, 643
gauche conformations, 176
and elimination, 1260
gauche conformations also see conformations
gauche orientations, and E2 reactions, 1259
GC (gas chromatography)
and diastereomers, 156
and resolution, 156
and determining absolute configuration, 142
and enantiomeric purity, 161
geared molecules, 205
gegenion, of carbocations, 209
gel-entrapped base, for the *Henry reaction*, 1156
gem-diacetates, 1469
gem-difluorides see fluorides, gem-
gem-dihalides see dihalides
gem-dihalides also see halides
gem-dimethyl effect, halolactonization, 987
gem-dimethyls, by hydrogenation of cyclopropanes, 920
general acid catalysis, 328, 456
geometric structure, carbocations, and migratory aptitudes, 1331
geometry, alkenes, and photochemistry, 305
and molecular conformation, 191
of carbenes, 252
of electrophilic allylic rearrangement, 658
of hydrogen bonds, 98
of propellanes, 198
of radicals, 243, 244
gerade orbital, 5
Gibbs energy, and microwave irradiation, 311
Gif system, CH oxidation, 1472
reactivity of alkyl substituents, 1472
Gilman reagents see organocuprates
Girard's reagent P, and hydrazones, 1093, 1094
Girard's reagent T, and hydrazones, 1093
Girgnard-$LiNEt_2$ reagents, 1226
Glaser reaction, 841
and the Hay reaction, 841
in ionic liquids, 841
in supercritical carbon dioxide, 841
mechanism, 842
glucosides, and the anomeric effect, 186
glyceraldehyde, and absolute configuration, 137, 138
oxidation to glyceric acid, and chirality, 137
glyceric acid, and chirality, 137
chiral, from glyceraldehyde, 137
glycidic acids, decarboxylation, 719
glycidic esters, 1161
glycidic esters also see epoxy esters
glycols, see diols
glycoluril, with formaldehyde, 121
glyoxals, and the benzoin condensation, 1187
Goldberg reaction, 753
Gomberg reaction see *Gomberg-Bachmann*
Gomberg-Bachmann pinacol synthesis, 1555
Gomberg-Bachmann reaction, 795
and aryl carbocations, 796
and the *Pschorr ring closure*, 795
intramolecular, 795
Google searching, 1574
Gossypium hirsutum, CH oxidation, 1472
α-hydroxylation, 1472
graphite ribbons see phenacenes
graphite, 84
green chemistry, 361
Grignard coupling reactions, 518
Grignard reactions, 1107–1114
1,2- versus 1,4-addition, 1107
Grignard reactions, and carbonylation, 1111
and elimination, 1111
and enolate condensation, 1111
and enolization, 1111
and halogen-Mg exchange, 1108
and metal catalyst, 1108
and *Michael addition*, 1109
and organocatalysts, 1108
and radicals, 241, 1113
and reduction, 1111
and SET mechanism, 1112, 1113
and steric hindrance, 1111
and the *Barbier reaction*, 1108
and the *Reformatsky reaction*, 1130
and *Wittig type reactions*, 1109
and *Wurtz type coupling*, 1111
Grignard reactions, diastereoselectivity, 1108
enantioselectivity, 1108
formation of enantiomers, 1108
formation of triazenes, 707
hydrolysis, 1107
in ionic liquids, 1107
intramolecular, 1109
ketyl intermediates, 1112, 1113
mechanism, 1111–1113
protonation, 1533
transition state, 1112
Grignard reagents also see organomagnesium
Grignard reagents, 515, 526

1,2- versus 1,4-addition, 1109
addition to aldehydes or ketones, mechanism, 1111, 1112
addition to alkenes, 926
addition to aromatic compounds, 955
amination, 706, 754
amine complexes, 714
Grignard reagents, and alkylation of aromatic compounds, 785
and alkylation or aryl nitro compounds, 785
and boiling point elevation, 230
and CIDNP, 715
and complexation, 1112
and conformational stability, 231
and Cu, 517
and cyclopropanation, 1058
and cyclotrimerization, 1061
and dehalogenation of aryl halides, 648
and dialkylmagnesium, 1108
and elimination, 1306
and ESR, 1112, 1113
and ether solvents, 229, 230
and Fe complexes, 933
and freezing point depression, 230
and functional groups, 714
and halo esters, 1131
and HMPA, 231, 1229
and metal additives, 1112
and metal salts, radical cyclization, 962
and NMR, 230, 231
and SET mechanism, 715, 716
and solvents, 231
and temperature, 714
and the *Bouveault reaction*, 1229
and the *Bruylants reaction*, 531
and the S*chlenk equilibrium*, 229–231
and the *Wurtz reaction*, 849
and *Wurtz coupling*, 713
Grignard reagents, aryl, 231
and coupling, 520
formation of, 1301
homocoupling, 620
hydrolysis, 648
Grignard reagents, arylation of amines, 754
as bases, 322
basicity, 1109
bonding, 229
chiral, 716
cleavage of allylic ethers, 534
cleavage of vinyl ethers, 535
complex formation, 229, 230
conjugate addition, 952, 1107
coupling of alkyl halides, 513, 520
coupling with aryl halides, 519
coupling with vinyl halides, 519
cyclic mechanism, 955
deprotonation, 696
diastereoselectivity, 1108
dioxane and magnesium halide, 229
electron transfer, 1113
elimination, 714
fluorides, 714
formation of phenols, 746
from alkyl halides, 713
from dihalides, 713
heat of formation, 230
hydrogen-metal exchange, 716
hydrolysis, 698, 699
hydrolysis, and reduction of alkyl halides, 1534
in benzene or toluene, 714
in THF, 231
in triethylamine, 231
initiators, 713
interfering groups, 714
intramolecular, 1109
mechanism of formation, 715
Grignard reagents, metal catalyzed, addition to alkenes, 936
addition to alkynes, 936
coupling, 520, 849
cyclization, 849
Grignard reagents, metal mediated, coupling, 517
metals for coupling, 761
migration of Mg with TiCl4, 711
nitrogen-containing, 714
norbornyl, 653
optical activity, 652
powdered, 714
premixing with metal salts, 1117
protonation, 698
reduction, mechanism, 1113
solvation, 230
stability, 714
structural limitations for conjugate addition, 952
structure and concentration, 231
structure, 229
vinyl, formation of vinyl boronic esters, 702
Grignard reagents, with acetals, 534
with acyl halides, 1226
with acyl halides, 1227
with acyl halides, metal catalysts, 1227
with acyl peroxides, 700
with acylperoxides, 700
with aldehydes, 1107–1114
with alkyl borates, 701
with alkyl halides, 517
with alkynes, 648, 696, 933
with allyl halides, 550
with allylic acetates, 527
with allylic alcohols, 533
with allylic halides, 515
with amides, 1228, 1229
with amino-ethers, 534
with anhydrides, 1228, 1229
with aryl halides, 518
with azides, 754
with aziridines, 538
with azo compounds, 707
with boron trifluoride, 712
with bromoform, 717
with carbamoyl halides, 1231
with carbon dioxide, 1132
with carbon disulfide, 1132
with chiral alcohols, 1110
with chiral templates, 952
with chloroformates, 1226, 1227
with chloroiminium salts, 1138
with CO, 708
Grignard reagents, with conjugated compounds, 1109
with conjugated dienes, 937
with CuBr, 535
with dihydrofuran, 1285
with dry ice, 1132
with epoxides, 535, 537
with esters, 1228, 1229
with ethers, 534
with formamides, 709, 1229
with formic acid, 708
with *Grignard reagents*, benzyne mechanism, 761
with halogens, 704
with halonitriles, 1140
with hydrazones, 1138
with imines, 1133
with imines, transition metal catalyst, 1133
with iminium ions, 532
with iminium salts, 1137, 1138
with iron pentacarbonyl, 708, 709, 0782
with isocyanates, 1139, 1140
with isocyanides, 1247
with isothiocyanates, 1141
with ketones, 1107–1114
with lactams, 534
with metal halides, 711, 849
with metal halides, mechanism, 711
with Ni catalyst, dehalogenation, 1305
with nitriles, 1139
with nitriles, mechanism, 1140
with nitro compounds, 1137
with nitrones, 1138
with ortho esters, 534
with oximes, 1138
with oxygen, 714

Grignard reagents, with conjugated compounds (*Continued*)
with oxygen, free radicals, 700
with phosphonic esters, 531
with propargyl esters, 527
with propargyl halides, 517
with selenium, 703
with sulfonate esters, 513, 1248
with sulfones, 762
with sulfonyl halides, 1252
with sulfur, 703
with sulfuryl chloride, 703
with tellurium, 703
with vinyl epoxides, 537, 937
with vinyl halides, 520
with water, 714
with *Weinreb amides*, 1230
with Yb compounds, 535
X-ray diffraction, 230
Grignard-Barbier reaction, 1109
Grob fragmentation, 1307
and *Cinchona* alkaloids, 1307
mechanism, 1308
ground state, and excited state, 289
and photochemistry, 289
groups in substitution reactions, table, 425
Grovenstein-Zimmerman rearrangement, 1342
Grubb's catalysts, and oxidation of alcohols, 1445
and ring opening metathesis polymerization, 1421
I and II, for metathesis, 1418, 1419
Grunwald-Winstein equation, and solvent effects, 439
and solvolysis, 420
Grunwald-Winstein, relationship, 355
guanidine, addition of ammonia to cyanamide, 1104
and alkyl halides, 494
guanidine-nitric acid, 593
guanidines, and formation of aziridines, 490
and supercritical ammonia, 364
from amines, 1104
guest-host complexes see complexes
guest-host interactions, and a carciplex, 115
and carcerands, 115
and cyclodextrins, 116
and molecular shape, 113
and urea, 113
and water as host, 114
guests, in guest-host interactions, 114
guests, ions in guest-host complexes, 108
gyroscane, 121
H abstraction, by radicals, stereoselectivity, 816
H atoms, abstraction of by radicals, 815
rate of abstraction by radicals, and structure, 815
H transfer, perepoxides, 834
half-chair conformation, and cyclopentane, 188, 189
half-life, 428
and kinetics, 282
definition, 282
enol tautomerization, 664
of equatorial chair conformation, 181
halide alkyl, Lewis acid catalyzed addition to alkenes, 990
halide exchange, and aryl halides, 757
and arylboronic acids, 757
halide ions, and phase transfer, 499
and the *Finkelstein reaction*, 498
with ditosylamines, 509
halide leaving groups, and benzyne formation, 738
halide reactivity, in E^i reactions, 1280
halides, acyl, and acyl carbocations, 624
and amino acids, 679
and enamines, 550
and *Friedel-Crafts acylation*, 624
and *Friedel-Crafts acylation*, with alkenes, 685
and nitration of anilines, 594
and *O*-acylation, 1233
and *Suzuki-Miyaura coupling*, 774
and the *Arndt-Eistert synthesis*, 1238
and the *Rosenmund reduction*, 1517
and the *Schotten-Baumann procedure*, 1200
and the tetrahedral mechanism, 420
and the *Wurtz reaction*, 1232
halides, acyl, base induced elimination to ketenes, 1298
conversion to isocyanates or isothiocyanates, 498
coupling to diketones, 1232
coupling, 1232
decarbonylation, 647, 721
exchange with carboxylic acids, 1224
formation of acyl azides, 497
halides, acyl, from aldehydes, 829
from carbocyclic acids, reagents, 1224
from carboxylic acids, 1223
from halogens, 829
from ketenes and HX, 884
from oxalyl halides and carboxylic acids, 1224
from trihalides and sulfur trioxide, 453
hydrogenolysis, 1517
hydrolysis, 1189
hydrolysis, and S_N2 mechanism, 1189
hydrolysis, mechanism, 1189
hydrolysis, reactivity order of halides, 1189
intramolecular *Friedel-Crafts acylation*, 623
Lewis acid catalyzed addition to alkenes, 992
metal catalyzed decarbonylation to alkenes, 1300
metal induced dehalogenation to ketenes, 1306
peroxides induced decarbonylation, 857
reduction reagents, 1517
reduction to alcohol, 1544
reduction to aldehydes, reagents, 1517
reduction with silanes, 1539
halides, acyl, with ketones, 1084
with active methylene compounds, 1232
with active methylene compounds, 1233
with acylation, 1232
with alcohols and Zn, 1201
with alcohols, 1200
with alcohols, S_N1 mechanism, 1200
with alcohols, S_N2 mechanism, 1200
with alcohols, tetrahedral mechanism, 1200
with alkenes, 684
with allylic silanes, 1180
with amides, 1222
with amines, 751, 1299
with amines, and *Schotten-Baumann* procedure, 1213
with amines, ketene formation, 1042
with ammonia or amines, 1213
with antimony alkynes, 1227
with aromatic compounds, 621
with aromatic compounds, 642
with arylboronic acids, 774
with azide ion, 496
with boronic acids, 1225, 1226
with boronic acids, Pd catalysts, 1226
with carboxylates, 1209
with copper cyanides, 1237
halides, acyl, with diazomethane, 1238, 1352

with DMF, 1213
with epoxides, 507
with ethers, 1201
with *Grignard reagents*, 1226, 1227
with *Grignard reagents*, metal catalysts, 1227
with *Grignard*-$LiNEt_2$ reagents, 1226
with hydrogen peroxide, 472
with hydrogen sulfide, 1211
with hydroxylamine-O-sulfonic acid, 1363
with metal catalyst, 1300
with organocadmium reagents, 1227, 1229
with organocuprates, 1225
with organolead compounds, 1227
with organometallic reagents, 1225–1227
with sulfonic acids, 1211
with thiols, 1201, 1211
with urea, 1223
with water, 1189
halides, alkyl dihalides see dihalides
halides, alkyl, acetylide ion, 561
acidity of β-hydrogen, and elimination, 1271
addition to alkenes, Friedel-Crafts catalysts, 991
alcohols and a Rh catalyst, 460
alcohols and an In catalyst, 460
alcohols and an Ir catalyst, 460
alkylation and ultrasound, 445
amines and hexamethylenetetramine, 483
amino, with water, 1356
halides, alkyl, and anti elimination, 1255
and B strain, 350
and bond angle, 25
and carbanions, 234
and carbocation formation, 211
and carbocations, 381
and *Collman's reagent*, 564
and E2 reactions, 1255–1260
and *Grignard reagents*, 231
and halide ions, 498
and *Hofmann elimination*, 1272
and hydroxides, 451
and I strain, 350
and isonitriles, 563
and lactams, 445
and microwave irradiation, 501
and oxazine carbanions, 556
and phase transfer catalysis, 501
and silver compounds, 439
and silver nitrate, 439
and strain in carbocation formation, 350
and the *Mentshutkin reaction*, 481
and the *Arbuzov reaction*, 1170
and the *Hunsdiecker reaction*, 854
and the *Kornblum reaction*, 1481
and the S_N1 mechanism, 349
and the *von Braun reaction*, 509
and water, 451
halides, alkyl, base induced elimination, 1296
and *Hofmann's rule* or *Zaitsev's rule*, 1297
suitable bases, 1297
halides, alkyl, carbonylation with alcohols to give esters, 565
carbonylation with alcohols, 566
carbonylation with sodium tetracarbonylferrate, 566
catalytic hydrogenation, 1532
chemoselective reduction, 1533
halides, alkyl, coupling and Li_2CuCl_4, 521
coupling with *Grignard reagents*, 513
with alkyboranes, Ni catalyst, 526
with arylboronic acids, 772
with *Grignard reagents*, 520
with lithioalkynes, 516
with metals, 513
with organocuprates, 520
with π-allylnickel complexes, 514
halides, alkyl, cyclohexyl, and E2 reactions, 1256
dehalogenation, reagents, 1531–1534
dehydrohalogenation, 1297
diastereomers and stereochemistry of elimination, 1273
E2 reaction, alkene distribution, 1272
effect of structure on elimination, 1275
effect of structure on rate of elimination, 1275
electrochemical carbonylation, 565
enantiopure, and E2 reactions, 1255
exchange with organolithium reagents, 222, 1109
Finkelstein reaction, 498
formation of amines, 485
halides, alkyl, formation of, carbenes, 253
dihalides, 824
isocyanates, 497
isothiocyanates, 497
onium salts, 331
sulfonate esters, 474
halides, alkyl, from alcohols, 485, 500
from alkanes, 821–826
from alkenes with peroxides, 1336
from alkyl halides, 498, 716
from alkyl sulfates, 500
from alkylsulfonic acids, 856
from amines, 509
from ammonium salts, 509
from carboxylic acids, 855, 1212
from carboxylic acids, reagents for, 855
from carboxylic esters, 508
from cyanogen bromide, 509
from *Grignard reagents*, 704
from halogens, 821–826
from mineral acids, 500
from organometallic reagents, 704
from organometallics, 704
from oxonium salts, 505
from silanes, 704
from silyl ethers, 503
from sliver carboxylates, 854
from sulfonate esters, 500
from thioethers, 554
from thionyl chloride, 500
from trichloroisocyanuric acid and alkenes, 884
halides, alkyl, *Gabriel synthesis*, 482, 494
halogen abstraction by radicals, 817
halogen replacement, 716
hydride reduction and Walden inversion, 1534
hydride reduction of, 1534
hydrolysis mechanism, S_N1, 349
hydrolysis of, 451
ionization to carbocations, 218
Katritzky pyrylium-pyridinium method, 509
Lewis acid catalyzed addition of alkyl halides to alkenes, 990
Lewis acid catalyzed addition to alkynes, 991
Lewis acids and organocopper compounds, 523
mechanism of hydrolysis, 451
meso, and E2 reactions, 1255
halides, alkyl, metal catalyzed carbonylation, 566
halides, alkyl, metal mediated, 513
carbonylation, 564, 565
coupling with alkynes, 561
coupling with allylic halides, 517
coupling, unsymmetrical, 514

halides, alkyl, microwave irradiation, reduction, 1533
oxidation to aldehydes, 1481
oxidation to aldehydes, the *Sommelet reaction*, 1482
oxidation with DMSO, mechanism, 1481
oxidative coupling with base, 1495
pyrolysis, 1298
radical conjugate addition, 959
rate of E2 reactions, 1256
rate of hydrolysis, table, 350
rates of solvolysis, 419
reaction with aromatic compounds, 609
reaction with organocuprates, 521
reactivity in carbonylation reactions, 566
reactivity in elimination reactions, 1274
reactivity with ethanol, 349
halides, alkyl, reduction with trialkyltin hydrides, 1532
by hydrolysis of *Grignard reagents*, 1534
to hydrocarbons, reagents, 1531–1534
with $LiAlH_4$, and SET mechanism, 1534
with metals, 1532
with Raney nickel, 1532
halides, alkyl, S_N1 in sulfur dioxide, 382
halides, alkyl, solvolysis, 659
halides, alkyl, solvolysis and carbocations, 287
and I strain, 350
and mechanism, 287
halides, alkyl, stereochemistry, and the E^i mechanism, 1279
steric hindrance and reactivity, 349
substituent effects n E2 reactions, 1274
halides, alkyl, trihalides see trihalides
halides, alkyl, with active methylene compounds, 538
with AgCN, 449
with alcohols, 460
with alkoxides, 459
with alkyl diazotates, 498
with alkynes, 991
with amide bases, 493
with amines or ammonia, 481
with aqueous silver oxide, 451
with arylboronic acids, 889
with azide ion, 496
with base in HMPA, 1297
with bases, 1297
with carboxylate salts, 468
with cyanide ion, 448, 562
with cyanohydrins, 563
with dialylzinc, 525
with dianions, 448
with disulfide ions, 479
with enamines, 551
with enolate anions, 342
with enolate anions, 538, 447
with ethers, 472
with *Grignard reagents*, 517
with Group I and II organometallics, 515, 516
with guanidine, 494
with hydrazones, 1138
with hydroperoxide ions, 472
with iron tetracarbonylferrate, 567
halides, alkyl, with lactams, 493
lithio propargyl compounds, 517
with lithium, 715, 1109
with magnesium, 713
with metal cyanides, 563
with metal oxides, 1298
with metals, 713, 715
with nitrite ions, 448
with nitro compounds, 448
with organocopperzinc reactants, 523
with organocuprates, 520, 951
with organolithium compounds, and CIDNP, 520
with organolithium compounds, and ESR, 520
with organolithium compounds, 516
with organolithum reaagents, radical intermediates, 237
with organometallic compounds, and radicals, 520
with organometallic compounds, mechanism, 519
with organometallics, 523–526, 715
with organopotassium, 515
with organosodium, 515
with organozinc compounds, 524
with oximes, 475, 1189
halides, alkyl, with Pd complex, carbonylation, 567
with phenoxide ions, 448
with phosphines, 484, 1165
with phosphites, 1170
with radicals, 811
with selenide ions, 478
with silver compounds, 472
with sodium nitrite, 495, 496
with sodium sulfide, 477
with sulfonamides, 495
with sulfonic acid salts, 480
with super hydride, 1531
with telluride ions, 478
with tetracarbonyl ferrate, 564
with thiocyanate ion, 480
with thiols, 476
with thiosulfate ion, 479
with thiourea, 476
with trimethylsilyl cyanide, 563
Wurtz coupling, 513
halides, allylic, and Pd complexes, 41
and the *Delépine reaction*, 483
coupling, 514
formation with no rearrangement, 500
from allylic esters, 508
metal mediated coupling with alkyl halides, 517
symmetrical coupling with Mg, 515
with acyl cyanides, 1232
with acyl zinc compounds, 565
with alkynes, 940
with anilines and hyponitrites, 793
with carbanions, 515
with epoxides and In compounds, 536
with *Grignard reagents*, 550
with In metal and ketones, 1116
with lactones, 1232
with nitriles, 1140
with organometallics, 523–526
with Sm and ketones, 1116
with transition metals and ketones, 1116
with Zn, acyl addition, 1121
halides, ammonium, with strong bases, 1292
halides, and allylic rearrangement, 827
halides, and S_N1 reactions, 381
halides, aromatic, dehalogenation, 647
halides, aryl also see fluorides, chlorides, bromides, iodides
halides, aryl, acyl aniline derivatives, 640
acylation, 689
aminomethylation, 632
halides, aryl, and coupling reactions, 518
and *Friedel-Crafts alkylation*, 609
and halide exchange, 757
and hyperconjugation, 44
and resonance, 44
and *Sonogashira coupling*, 776
and *Stephens-Castro coupling*, 775
and *Suzuki-Miyaura coupling*, 770
and the *Buchwald-Hartwig reaction*, 752

and the *Gatterman reaction*, 846
and the *Goldberg reaction*, 753
and the halogen dance, 647
and the *Heck reaction*, 763–768
and the *Hurtley reaction*, 779
and the *Orton rearrangement*, 640
and the *Sandmeyer reaction*, 846
and the $S_{RN}1$ mechanism, 739, 740
and the *Stork enamine reaction*, 550
and the *Ullmann reaction*, 768
halides, aryl, carbonylation with alcohols, 781
carbonylation with dicobalt octacarbonyl, 781
conversion to phenols, 746
halides, aryl, coupling with active methylene compounds, 778–780
coupling with alkenes, 763–768
coupling with aromatic compounds, 844
coupling with enolate anions, 778–780
coupling with *Grignard reagents*, 519
coupling with heterocycles, 760
halides, aryl, cyanation, 758
halides, aryl, dehalogenation, 647
and *Grignard reagents*, 648
electrochemical, 648
photochemical, 648
with Friedel-Crafts catalysts, 647
halides, aryl, electrolysis, 760
formation of aryl selenides, 478
formation of ketones, 782
halides, aryl, from amines, replacement of alkyl groups, 751
from anilines, 847
from aryl halides, 756
from arylboronic acids, 757
from aryldiazonium salts, 846
from arylsulfonyl halides, 647
from organometallic reagents, 704
from sulfonyl halides, 647
halides, aryl, *Grignard* formation, 513
halide exchange, and microwaves, 757
heteroaryl, coupling with alkenes, 763
homocoupling, 760
homocoupling, in ionic liquids, 760
hydroxylation, 746
intramolecular *Heck reaction*, 763
halides, aryl, metal catalyzed, alkylation, 545
carbonylation, 781
coupling with enolate anions, 780
coupling with silylalkynes, 777
reaction with alkoxides, 748
reaction with phosphines, 755
halides, aryl, metal free cyanation, 759
metal mediated coupling, 768
noncatalyzed coupling, 760
Pd catalyzed coupling with boranes, 702
Pd catalyzed coupling, 526
Pd catalyzed *Stille coupling*, 683
photochemical coupling with aromatic compounds, 844
photochemistry, 778
reagents for homocoupling, 760
rearrangement, 647
substitution by amines, base catalysis, 734
vinyl coupling reactions, 772
halides, aryl, with sulfinic acid salts, 603
with active methylene compounds, benzyne mechanism, 779
with aldehydes, 1123
with alkenes also see Heck reaction
with alkenylboranes, 559
with alkoxides, 747
with alkoxysilanes, 783
with alkyltrifluoroborates, 768
with alkynes, 775, 776, 939
halides, aryl, with alkynes also see Sonogashira
halides, aryl, with allylamines, 753
with allylic esters, 528
with amide bases, 493, 751
with amides, 755
halides, aryl, with amines, 734, 751–755
and a Pd catalyst, 752
metal catalyzed, 599
halides, aryl, with aryl halides, benzyne mechanism, 760
with arylborates, 774
with arylboronic acids, 770–775
with carboxylate salts, 748, 749
with copper thiocyanate, 750
with cyanides, 758
with enolate anions, 762, 890
with enolate anions, enantioselectivity, 779
with heterocycles, 755
with hydrazones, 555
with hydrosulfide anion, 749
with hydroxide, 746
with iodonium salts, Pd catalyst, 753
with lactam enolate anions, 780
with lactams, 755
with Lewis acids, 647
halides, aryl, with metal halides, 756
with metals, 648
with nitrite salts, 838
with organoboranes, 774
with organogermanes, 767
with organolithium reagents, 516, 757, 759
with organometallics, 523–526, 648, 759
with organotin compounds, 767
with oxazolidinones, 755
with phenols, in ionic liquids, 748
with phenoxides in ionic liquids, 748
with phenoxides, and microwaves, 748
with phosphines, 755
with selenide anions, 750
with silylamines, 752
with sulfonate anions, 750
with sulfonic acid salts, 750
with sulfoxides, 890
with sulfur nucleophiles, electrochemistry, 750
with thiolate ions, 749
with thiophenes, 755
with triaryl phosphate, 748
with trifluoroborates, 775, 890
with vinylboronic acids, 890
with vinyltrifluoroborates, 768
halides, benzylic or allylic, oxidation, 1481
halides, benzylic, and the *Delépine reaction*, 483
from alcohols with microwaves, 445
oxidation by the *Krönke reaction*, 1482
oxidation with hexamethylenetetramine, 1482
oxidative coupling to alkynes, 1495
oxidative coupling to tolanes, 1495
solvolysis, 423
halides, carbamoyl, with boronic acids, 1226
with *Grignard reagents*, 1231
with organocuprates, 1214
with organolithium reagents, 1231
halides, and carbamate formation, 470
arylation of alkenes, metal catalyzed, 763–768

halides, carbon tetrahalides and complex formation, 107
halides, carbonylation, and arylboronic acids, 782
with alkynes, 782
halides, cyclopropyl, 700, 1346
and allylic carbocations, 423
halides, cyclopropylcarbinyl, and organocuprates, 412
and S_N2' reactions, 413
halides, dialkylamino, fragmentation, 1307
diarylmethyl, 381
dihalides see dihalides
1,2-, and elimination, 714
halides, from alkenes, 979
from ethers, 504, 505
from iodonium salts, 704
from thiols, 503
from trialkylsilyl halides and alkenes, 884
gem-, with organolithium reagents, 1110
heteroaryl, Pd catalyzed Stille coupling, 683
inorganic acid, with carboxylic acids, 1224
inorganic, with anhydrides, 1225
inorganic, with carboxylic esters, 1225
lithium-betaines, 1168
magnesium, *Grignard reagents*, 229
halides, metal induced elimination to alkenes, 1304
halides, metal also see metal halides
halides, metal, and transmetallation, 710
with alcohols, 502
with aryl halides, 756
with aryldiazonium salts, 846
with epoxides, 506
with *Grignard reagents*, 711, 849
with *Grignard reagents*, mechanism, 711
with organolithium reagents, 711
with organometallics, 711
halides, organozinc, with thioesters, 1231
oxidation via the Kröhnke reaction, 1482
phosphorus, and the *Hell-Volhard-Zelenskii reaction*, 673
primary, S_N1 reactions, 439
halides, propargyl, and the *Glaser reaction*, 841
reduction to allenes, 1533
with *Grignard reagents*, 517
halides, reactivity order in benzyne mechanism, 738
in acyl halide hydrolysis, 1189
halides, reactivity, as a function of the halide, 481
in benzyne formation, 738
in metal mediated coupling, 592
halides, selenyl, with enolate anions, 681
halides, silyl, cleavage of ethers, 505
with alkenes and DMSO, 988
with allylsilanes, 510
with carboxylic esters, 508
with lactones, 508
halides, sulfinyl, with alcohols, 480
halides, sulfonyl and the *Reed reaction*, 837
addition to alkenes, 987
addition to alkynes, 988
and aromatic sulfonation, 602
and chlorosulfuric acid, 602
and formation of aryl sulfones, 602
base induced elimination to sulfenes, 1299
formation of aryl halides, 647
formation of sulfenes, 1249
from aromatic compounds, 602
from aryldiazonium salts, 848
from hydrocarbons, 837
from sulfonic acids, 1251
halogenation of sulfonic acids, 1251
hydrolysis, 1250
reactivity, 1248
reduction to disulfides, 1552
reduction to thiols, 1552
with alcohols, 473, 1250
with alkenes, 988
with alkyl halides, 480
with alkynes, 988
with amines, 1178, 1299
with ammonia or amines, 1251
with arylboronic acids, 1252
with diazomethane, 1178
with *Grignard reagents*, 1252
with halo esters, Lewis acids catalysis, 524
with organometallics, 1252
halides, tertiary alkyl, elimination in the *Stork enamine reaction*, 550
halides, trialkylsilyl, and indirect hydration, 886
with alkenes or alkynes, 884
with organocuprates, 949
halides, vinyl, 672
and addition-elimination, 413
and E2 reactions, 1257
and elimination-addition reactions, 416
and metathesis, 1421
and radical cyclization, 961–965
and S_N2 reactions, 416
and $S_{RN}1$ reactions, 417
and *Stille coupling*, 682
and substitution, 413
and the element effect, 414
and the tetrahedral mechanism, 413
and thiol anions, 413
by addition of alkyl halides to alkynes, 991
carbonylation, 568
coupling and Li_2CuCl_4, 521
coupling with alkyl groups, 684
coupling with Grignard reagents, 519
halides, vinyl, from aldehydes or ketones with PCl_5, 1105
from alkynes, 705, 884
from alkynes, with R_3SiX, 884
from carboxylic acids, 1212
from conjugated carboxylic acids, 856
from enolate anions, 704
from gem-dihalides, 1105
from vinyl halides, 498
from vinylboranes, 705
from vinyliodonium salts, 704
in the *Suzuki-Miyaura reaction*, 771
halides, vinyl, metal catalyzed, alkylation, 545
coupling with alkynes, 934
coupling, 514
halides, vinyl, oxymercuration, 452
reduction to alkenes, 1534
reduction with metal in alcohol, 1534
stereochemistry, 705
with alkenylboranes, 559
with alkylboronic acids, 683
with *Grignard reagents*, 520
with organometallics, 523–526
halides, with acyl halides, 1227
with amines, in ionic liquids, 751
with carbon dioxide, 1132
with conjugated carbonyls, 1129
with organometallics, 1226
Haller-Bauer reaction, 725, 1222
halo acetoxylation, of alkenes, 1012
halo alcohols see alcohols
halo amides, and the *Hofmann rearrangement*, 1361
halo ammonium salts, cyclization, 1426
halo azide see azides
halo esters, and *Grignard reagents*, 1131
metal mediated reaction with imines, 1244
halo ethers see ethers

halo ketones, and the *Favorskii rearrangement*, 1350
by oxidation of alkenes, 1489
with tributyltin hydride, 1347
halo sulfides see sulfides
halo sulfones see sulfones
halo-acetals, from vinyl ethers, 986
halo-acids, from carboxylic acids, 673
in the *Hell-Volhard-Zelenskii reaction*, 673
lactone formation, 269
haloacylation, of alkenes, 992
and the *Vilsmeier reaction*, 992
haloalcohols see alcohols, halo
haloalkenes see halides, vinyl
haloalkylation, 619
Friedel-Crafts reaction, 619
haloalkynes, by electrolysis, 705
from alkynes, 704
from organometallics, 704
metal catalyzed arylation, 561
metal mediated arylation, 561
with boranes, 1379
haloamides, and amidomethylation, 631
cyclization, 495
with aromatic compounds, 631
haloamines also see amines
haloamines, addition to alkenes, 988
amination of aromatic compounds, 599
and amination of alkenes, 897
and halogenation of aromatic compounds, 604
and *Stieglitz rearrangement*, 1367, 1368
by addition of haloamines to alkenes, 988
formation of aziridines, 482
formation of cyclic amines, 482
from amines, 729
reaction with acids, 1426
rearrangement, 1367, 1368
with acid, 1427
with silver nitrate, 1367, 1368
haloammonium salts, heating, 1427
rearrangement, 1427
haloarenes, 740
haloboranes see boranes
halocarbamates, addition to alkenes, 901
halocarbenes, 252, 1052, 1056
and insertion, 691
halo-carboxylic acids, 508
halochromates, phosphonium, 1443
picolinium, 1443
tetraalkylammonium, 1443
halocyclopropanes, flash vacuum pyrolysis, 1347
haloesters, addition to alkenes, 991
and the *Reformatsky reaction*, 1129
metal mediated addition to aldehydes, 1129
metal mediated addition to ketones, 1129
haloethers, 1007
from alkenes, 984
with magnesium, 714
haloform reaction, 723
electrochemical, 724
rate-determining step, 724
haloformic acids, from phosgene and alcohols, 1086
halogen dance, 647
halogen free *Heck reactions*, 763
halogen radicals see radicals
and bridged radicals, 811
halogen replacement, alkyl halides, 716
halogen substituents, deactivating groups, 579
electrophilic aromatic substitution, 579
ortho/para directors, 579
halogen, abstraction by radical, 817
of anilines, and Lewis acids, 604
order of reactivity in the *Ramberg-Bäcklund reaction*, 1302
with alkenes, mechanism, 982
halogenating agents, benzylic alcohols, 503
with alcohols, 502
with carboxylic acids, 1223
halogenation, amino, 988, 989
and acyl anilines, 640
and benzeneseleninyl chloride, 826
and DBDMH, 827
and enols, 671
α-halogenation, and halogenation of aldehydes, 829
and hydantoins, 827
and hypochlorites, 827
and peroxides, 826
and radical cations, 824
and UV light, 826
halogenation, aromatic compounds, and Lewis acids, 606
and ultrasound, 604
in ionic liquids, 604
metal catalyzed, 604
NBS in ionic liquids, 604
temperature dependence, 607
and temperature, 604
iodine reagents, 607
mixed halogens, 604
various halogenating reagents, 605
halogenation, at allylic hydrogen, with NCS, 827
base-induced, of alkanes, 823
electrophilic, 821
metal mediated, 826
halogenation, mixed, 983
with alkenes, 983
with alkynes, 984
halogenation, of active methylene compounds, 670
of alcohols, in ionic liquids, 502
of aldehydes, 829
of aldehydes, enantioselectivity, 669
halogenation, of alkanes, 821–826
and UV, 821
electrophilic conditions, 824
fluorine radicals, 822
rate-determining step, 824
regioselectivity, 823
halogenation, of alkenes, 883, 982
and bridged ions, 982
and isotopic labeling, 863
and radical initiators, 982
and UV, 982
and π-complexes, 863
in ionic liquids, 983
mechanism, 982
radical, mechanism, 824
the *Prins reaction*, 991
tolerable functional groups, 983
halogenation, of alkynes, 706, 982, 984
of allenes, 984
of allylic alcohols, 503
of aminopyridines, 606
of anilines, 606
of aromatic compounds, 585, 698
of aziridines, 507
of boranes, and radicals, 705
of carboxylic acids, 672
of carboxylic acids, and NBS, 673
of conjugated compounds, 984
of conjugated ketones, 672
of conjugated ketones, and *Dess-Martin periodinane*, 672
of cyclopropylcarbinyl alcohols, 503
of dicarboxylic acids, 823
of enamines, 551
of enol borinates, 672
of enolate anions, 705
of enynes, 984
of epoxides, 506, 1502
of furans, 703
halogenation, of ketones, and microwaves, 669
enantioselectivity, metal catalyzed, 671
mechanism, 671

halogenation, of ketones, and microwaves (*Continued*)
metal mediated, 669
rate, 671
reagents for, 668, 672
regioselectivity, 670, 672
halogenation, of lactams, 731
of organometallics, mechanism, 706
of pyrroles, 703
of silanes, 826
of silylalkynes, 706
of steroids, 824
of sulfoxides, 674
of sulfoxides, reagents for, 674
of thiiranes, 507
of thiophenes, 607, 703
of vinylboronic acids, 705
photolytic, 810
halogenation, radical, aldehydes with NBS, 829
allylic hydrogen, 826
allylic, mechanism, 827
and AIBN, 826
and alkenes, 826
and NBS, 823
and polyhalogenation, 823
and sulfuryl chloride, 823
and the *Hofmann-Löffler reaction*, 824
benzylic hydrogen, 826
bond dissociation energy, 825
metal catalyzed, 827
of methane, rate determining state, 824
halogenation, reactivity of HX, 825
side chain, photochemistry, 605
Wohl-Ziegler reaction, 821
halogen-free *Heck reactions*, 763
halogen-lithium exchange, 953, 1230
halogen-magnesium exchange, 1108
halogen-metal exchange, and organocuprates, 523
halogens, addition, to alkenes, 982
to alkenes, in ionic liquids, 989
to alkynes, 982
to cyclopropanes, and UV, 881
halogens, and bridge ions, 982
and haloform reaction, 724
and halonium ions, 860
and the *Reed reaction*, 837
halogens, cleavage of ketones, 724
inference of, radical cyclization, 963
mixed, reactivity with alkenes, 983
of ketones, enantioselectivity, 669
photochemical cleavage, 246
reaction with alkanes, 821–826
reaction with amides, 1361
reactivity in aromatic halogenation, 603
halogens, with alcohols, 986
with alcohols, and alkenes, 984
with aldehydes, 829
with alkenes, 828
with alkenes, and sulfur dioxide, 837
with alkenes, carbocations, 863
with aromatic compounds, 603
with *Grignard reagents*, 704
with organometallics, 704
with organozirconium compounds, 704
with phosphites, 1105
with silver carboxylates, 854
with trialkylboranes, 704
halohydrins also see alcohols, halo
halohydrins, and Chloramine-T, 985
and the *Williamson reaction*, 461
by halogenation of epoxides, 1502
dehydration, 1284
epoxide formation, 393, 461
from alkenes, 984
from alkenes, mechanism, 985
from epoxides, 506, 507
from *Grignard reagents* and epoxides, 537
reagents, with alkenes, 985
haloimines, 1244
haloketones, addition of acyl halides to alkenes, 992
and formation of conjugated ketones, 685
from diazo ketones, 508
from ketones, 668
from vinyl halides and NaOCl, 986
rearrangement to carboxylic esters, 1350
with boranes, 558
with boranes, mechanism, 559
with organocuprates, 548
with trialkylboranes, 548
halolactamization, reagents for, 986, 987
halolactams, from alkene-amides, 987
from sulfonyl-amino-alkenes, 987
halolactones, addition to alkenes, 991
by radical halogenation, 823
halolactonization, 986, 987, 1013
and *Markovnikov's rule*, 987
Co-salen complex, 987
enantioselectivity, 987
gem-dimethyl effect, 987
organocatalysts, 987
reagents for, 986, 987
halonitro compounds, from alkenes and nitryl chloride, 989
halonitroso compounds, from alkenes, 989
halonium ions, 214, 860
and halohydrin formation, 985
and open carbocations, 864
and structure, 864
and substituent effects, 864
from addition to alkynes, 873
from alkenes, 860
neighboring group effects, 394
reaction with nucleophiles, 875
stable, 394
halonium radicals, 811
halosilanes see silanes
halosulfones see sulfones, halo
halosulfonyl esters, 987
halothiocyanates, 988
halothioethers, from alkenes and silyl halides, 988
halotosylamine, 989
Hammet vales, and elimination, 1268
Hammett acidity function, and solvents, 325
Hammett equation, 357, 361
and aromatic carboxylic acids, 352
and aromatic substitution, 588
and equilibrium constants, 352
and linear free energy relationship, 355
and radicals, 817
and rate constants, 352
and reactivity, 352
field effects, 352
reactions that do not fit, 352
resonance effects, 352
Hammett relationships, and S_NAr reactions, 743
Hammett σ values, electrophilic aromatic substitution, 588
Hammett $\sigma\rho$ relationship, and substituent effects, 422
Hammett-Brown $\sigma+\rho$ relationship, 589
Hammond postulate, and arenium ions, 576
and carbocations, 418, 875
and *Markovnikov's rule*, 875
and transition states, 418
definition, 272
Handbook of Chemistry and Physics, 1581
Handbook of Naturally Occurring Compounds, 1581
Handbook of Organometallic Compounds, 1582
handedness, and enantiomers, 123
Hantzsch dihydropyridines, 1439
and reductive alkylation, 1098

Hantzsch esters*, and reduction of amides, 1545*
and reductive amination, 1099
and transfer hydrogenation, 917
reduction of amides, 1545
reduction of imine esters, 1521
hapto complexes, of cyclobutadiene, 69
hapto prefix, and metal complexes, 105
hard acids, and ionic bonds, 332
definition, 331
hard and soft acids, table, 332
hard bases, and ionic bonds, 332
definition, 331
hardness model, and aromaticity, 54
hardness, 331
absolute, 332
absolute, table, 333
activation, 587
and aromaticity, 59
and ionization potential, 332
and Lewis acids, 331
and S_N1, 379
hard-soft acid-bases see HSAB
Hartree-Fock calculations, and annulenes, 72
Hartree-Fock method, 34, 72
Hauptwerk (das Hauptwerk), of Beilstein, 1579, 1580
Haworth reaction, 623
Hay reaction, 841
and the *Glaser reaction*, 841
mechanism, 842
HBr, and DMSO, 604
and hydrogen bonding, 101
and peroxides, with alkenes, 883
and radicals, addition to alkenes, 960
cleavage of ethers, 455, 504
with alcohols, 500, 504
with alkenes, 876, 883
with cyclopropanes, 879
HCl, addition to alkenes, 864
and hydrogen bonding, 101
as an acid, 313
cleavage of ethers, 455
with alcohols, 500
with alkenes, 322, 883
with butadiene, 870
HCN and the Sandmeyer reaction, 847
addition to alkenes, 980
addition to C=N compounds, 1183
addition to HCN, 981
addition to iminonitriles, 1184
addition to nitriles, 1184
and cyanohydrins, 969, 1180
and isocyanides, 981
and proton transfer, 324
and the *Ritter reaction*, 1239
conjugate addition, 981
with aldehydes or ketones, 1180
heat of atomization, 27, 28
and isomers, 28
benzene, 35
butadiene, 38
ethane, 28
heat of combustion, 27, 29
and alkene stability, 1270
and cycloalkanes, table, 200
annulenes, 81
cis/trans isomers, 165
heat of formation, *Grignard reagents*, 230
heat of hydrogenation, 37
cyclooctynes, 202
for benzene, 36
Heck reaction, 683, 692, 763–768
and alkene migration, 765
and alkene substitution, 764
and *Meerwein arylation*, 794
and microwave irradiation, 311, 764
and Pd migration, 765
and proton abstraction, 767
and the Pd catalyst, 763–768
Heck reaction, atmosphere variation, 767
base free, 763
catalysts for, 763
dependence on alkene concentration, 767
enantioselective, 766, 767
halogen free, 763
high pressure, 764
Heck reaction, in aqueous media, 764
in ionic liquids, 365, 764
in perfluorinated solvents, 764
in supercritical CO_2, 764, 766
Heck reaction, intramolecular, 763, 766
intramolecular, with a silicon tether, 763
Heck reaction, mechanism, 766, 767
neighboring group effects, 765
on solid support, 764
phosphine free, 763
polymer supported, 763
rate-limiting step, 767
rearrangement, 766
recoverable catalysts, 764
regiochemistry, 764
regioselectivity, 765
regioselectivity and steric effects, 765
silane tethers, 763
silica supported, 763
stereospecific nature, 766
substituent effects, 767
tolerable functional groups, 765
Heck reaction, with a polymer-supported catalyst, 763
with alkynes, 765
with allenes, 765
with aryliodonium salts, 765
with diazonium salts, 788
with diazonium substrates, 764
with dienes, 765
with homogeneous catalysts, 764
with iodonium salts, 765
with metal catalysts other than palladium, 766, 767
with phosphine-free catalysts, 763
with substituted alkenes, 763
with vinyl organometallics, 767
with vinyltrifluoroborates, 768
Heck-like reactions, 768, 772
Heck-like reactiosn, alkenes with aryldiazonium salts, 793
Heilbron's Dictionary of Organic Compounds, 1581
helical chirality see chirality
helicenes, 134
and a chiral axis, 140
and chirality, 133
helix, and chirality, 133
Hell-Volhardt-Zelenskii reaction, 136, 673
hemiacetals, 1082
and acetal hydrolysis, 455
and formation of acetals, 1082
conversion to ketones, 1371
hydrolysis, 1371
stability, 1083
hemiaminals, and enamine formation, 1091
and formation of imines, 1090
and imine formation, 1091
detection by NMR, 1090
hemicarcerands, and carbenes, 252
and cyclobutadiene, 68
hemimercaptals, 1087
hemispherands, 111
hemispheric, 173
Henkel reaction, 645, 1156
Henry reaction, and dehydration, 1283
aza-, 1157
biocatalysts, 1156
chiral metals, 1156
enantioselectivity, 1156
in ionic liquids, 1156
organocatalysts, 1157
solventless, 1156
suitable bases, 1156
heptahelicene, and chirality, 134
and mechanical resolution, 158
heptalene derivatives, stability of, 62
heptalene, 62
and chirality, 133
Herndon model, 53
Hess-Schaad model, 53
hetarynes, 739

hetarynium ions, 584
hetereoannulenes, 73
hetereobimetallic complexes, 610
heteroaromatic compounds, 54
aminoalkylation, 753
and aromaticity, 54
aromaticity index, 58
heteroatom *Diels-Alder reactions*, 1037–1039
heteroatom *Diels-Alder reactions* also see *Diels-Alder, heteroatom*
heteroatom functional groups, and the *Diels-Alder reaction*, 1037
heteroatom nucleophiles, conjugate addition, 965
heteroatom stabilized carbocations, 219
heteroatom vinylcyclopropane rearrangement, 1399
heteroatoms, 2nd row, and the anomeric effect, 188
and acidity of α-protons, 552
and allylic carbanions, 556
and benzylic carbanions, 556
and catenanes, 119
and crown ethers, 109
and hydrogen bonding, 96
and organometallics, 696
and the *Pauson-Khand reaction*, 977
conjugated to carbanions, 224
conjugation with carbocations, 214
in six-membered rings, 186
heterocycles, acylation of, 845
heterocycles, alkylation of, 482
with organometallics, 787
and *Ziegler alkylation*, 785
heterocycles, amination, 787
heterocycles, and *Birch reduction*, 914
and directed ortho metalation, 785
and *Friedel-Crafts reactions*, 846
and radical cyclization, 965
and *Sonogashira coupling*, 776
and *Suzuki-Miyaura coupling*, 771, 772
and the *Chichibabin reaction*, 787
and the *Gomberg-Bachmann reaction*, 795
and the *Heck reaction*, 763
and vicarious substitution, 787
heterocycles, aromaticity, 58
arylation, 632, 755
by alcoholysis of alkynes, 891
by aromatization, 1439
by cyclotrimerization with metal carbenes, 1063
carbalkoxylation, 846
carbonylation and formation of ketones, 782
carbonylation with alcohols, 781
catalytic hydrogenation, 913
coupling with aryl halides, 760
electrophilic aromatic substitution, 584
electrophilic aromatic substitution, 584, 626
from alkynes and alcohols, 891
in *Diels-Alder reactions*, 1039
lithiation, 696, 594
protonated, 845
radical alkylation, 845
radical reaction with carboxylic acids, 845
reduction, 916
reduction, with metals in aqueous alcohols, 915
via hydroboration, 1376
via *Ullmann coupling*, 769
with amide bases, 787
with enolate anions, 846
with *Fenton's reagent*, 846
with hydrazide anions, 788
heterocyclic carbenes, 967
Heterocyclic Compounds, 1587
heterocyclic compounds, and *Friedel-Crafts acylation*, 623
and *Friedel-Crafts alkylation*, 611
and tautomerism, 94
and the *Gatterman reaction*, 626
and the *Reimer-Tiemann reaction*, 627
halogenation of, 606
hydrogenation, 913
heterofullerenes, 84
heterogeneous catalysts, and hydrogenation, 902
heterogeneous *Pauson-Khand reaction*, 976
heterolysis, radical, 810
heterolytic bond cleavage, 262
heteropolytungstic acid, 838
hexahelicene, and strain, 206
hexahydroazepin-2-one see caprolactam
hexaisopropylbenzene, 205
hexamethyldisilazane, with silyl halides, 686
hexamethyldisilazide, lithium, and the aldol reaction, 1144
with Te salts, 1177
hexamethyldisilazide, with ammonium carboxylates, 1216
with halo esters, 1161
hexamethylenetetramine, amine alkylation, 483
and oxidation of benzylic halides, 1482
and the *Delépine reaction*, 483
and the *Duff reaction*, 628
hexamethylphosphoramide see HMPA
hexamethylprismane, and photochemical [2+2]-cycloaddition, 1050
hexaphyrins, 82
HF, and hydrogen bonding, 97
and the *Merrifield synthesis*, 1219
fluorinating agent, 499
in pyridine, formation of aryl fluorides, 792
with acyl halides, 1224
with anhydrides, 1224
with triazenes, 792
HF-pyridine, and acetals or ketals, 457
HI, and hydrogen bonding, 101
cleavage of ethers, 504
with alcohols, 504
with alkenes, 883
high performance liquid chromatography see HPLC
high pressure mass spectrometry see mass spectrometry
high pressure see pressure
high pressure, amines with lactams, 1222
and activation volume, 362
and *Diels Alder reactions*, 1023
and oxime formation, 1094
and rate of diffusion, 362
and reactivity, 362
and the *Knoevenagel reaction*, 1158
and transition states, 362
high-dilution, and Friedel-Crafts cyclization, 624
higher order mixed organocuprate, 522
Highest occupied molecular orbital see HOMO
hindrance, steric see steric hindrance
Hinsberg test, and sulfonamides, 1251
hiscotropic rearrangement, 1345
Hiyama coupling, 545
HMO (Hückel Molecular Orbital theory)
and cyclopropenyl anion, 70
theory, and benzene, 36
HMPA (hexmethylphosphoramide)
and conjugate addition, 970
and conjugate additions, 953
and dehydration, 1284
and dehydrohalogenation, 1297
and dialkylamide bases, 341
and *Grignard reagents*, 231, 1229

and hydrogen bonds, 99
and *Normant reagents*, 940
and reaction of allenes with ketones, 1124
and sodium cyanide, 564
as a solvent, 749, 1172, 1229, 1432
with dihalides, 1304
with phosphonate esters, 1172
HOBr, with alkenes, 984
HOCl, with alkenes, 984
with peroxides, 985
Hoesch reaction, 632
and imino esters, 633
and thiocyanates, 633
and thioesters, 633
mechanism, 633
Hoesch synthesis, and the *Gatterman reaction*, 633
HOF, and explosions, 985
Hoffmann-Löffler-Freytag reaction, 1426
Hofmann degradation, 1290
and deuterium labeling, 1291
and E2 mechanisms, 1290
and *Hofmann's rule*, 1290
and the E^i mechanism, 1290, 1291
and ylids, 1290
and *Zaitsev's rule*, 1290
E^i versus E2 mechanism, 1291
mechanism, 1290
of bis(ammonium) salts, 1291
solvent effects, 1290
Hofmann elimination, 799, 1271, 1272
and the *Sommelet-Hauser rearrangement*, 798
and the *Stevens rearrangement*, 1373
in water, 1291
Hofmann exhaustive methylation, 1290
Hofmann orientation, and elimination, 1271
Hofmann products, elimination, 1281
Hofmann rearrangement, 1324, 1360
and DBU, 1360
and mechanism, 275, 1361
of imides, 1360
reagents, 1361
Hofmann's rule, and elimination, 1272
and *Hofmann degradation*, 1290
and rings, 1291
and sulfoxide elimination, 1296
Hofmann-Löffler reaction, 1426, 1428
and radical halogenation, 824
mechanism, 1427
Hofmann-Martius reaction, 640
Hofmann's rule, and acidity of β-hydrogens in elimination, 1271
and dehydration of alcohols, 1283
and elimination, 1270
and *Hofmann degradation*, 1290
and pyrolytic elimination, 1281
HOI, with alkenes, 984
HOMO, allylic carbocations, 1389
and elimination, 1275
and endo addition, 1036
and frontier orbital method, 1031
and overlap of orbitals in electrocyclic reactions, 1381, 1382
and symmetry of allylic cation, 1389
and the *Diels-Alder reaction*, 1020
of cyclohexatriene, 1384
of ethylene, 9
of tetraenes, 43
HOMO-LUMO overlap, [2+2]-cycloaddition, 1044
homoaldol reaction, and the Knoevenagel reaction, 1160
homoaldols, 1160
homoallylic acetates, 1126
homoallylic alcohols, 1123
homoallylic alkenes, 396
homoallylic carbocations, 395
homoanomeric interactions, 186
homoaromatic compounds, 83, 84
homoaromatic, spherical, 84
homoazulenes, and aromaticity, 74
homoazulenes, X-ray, 74, 75
homo-Brook rearrangement, 1431
homoconjugation, 43
and carbocations, 212
homocoupling, alkene trifluoroborates, 843
alkyne trifluoroborates, 843
alkynylboronates, 843
aryl *Grignard reagents*, 620
aryl halides, 760
boronic acids, 770
of aryl halides, reagents for, 760
homocubene, 207
homocubyl radicals, 1334, 1335
homodesmotic reactions, 36, 37
homo-Diels-Alder reaction, 1027
homodienyl [1,5]shifts, and vinylcyclopropane rearrangement, 1399
homodienyl [1,5]shifts, 1395
homodienyl [1,5]-sigmatropic hydrogen shift, 1412
homodimerization, of alkanes, 840
homoenolate ion, 226
homofullerenes, 85
homogeneous catalysts, 903
homogeneous reactions, and kinetics, 278
homogenous catalysts, and hydrogenation, 902
types, 904
homogenous catalytic hydrogenation, mechanism, 908
homologation, addition to aldehydes or ketones, 1355
by carbene insertion, 691
carbenoid, 691
of carboxylic esters, 1232
homolytic mechanism, 262
homo-metathesis, 1420
homopropargylic alcohols, 1123
[1,5]-homosigmatropic rearrangement, 1412
homospheric, 173
Hooke's law, and molecular mechanics, 190
Horner-Emmons see *Wittig-Horner*
Horner-Wadsworth-Emmons see *Wittig Horner*
horseradish peroxides, oxidation of thioethers, 1494
hosts, crown ethers in guest-host complexes, 108
hot spot, sonochemistry, 307
Houben-Hoesch reaction see *Hoesch reaction*
Houben-Weyl's Methoden der Organischen Chemie, 1587
HPLC, and annulenes, 82
and enantiomeric catenanes, 120
and enantiomeric purity, 161
diastereomer separation, 162
HSAB, 331
HSAB principle, 332
HSAB, and carbonyl carbon, 430
and enolate anions, 334
and equilibrium, 333
and nucleophiles, 428
and polarizability, 448
and substitution reactions, 448
electrophilic aromatic substitution, 587
table of acids and bases, 332
Huang-Minlon modification, and microwave irradiation, 1540
of *Wolff-Kishner reduction*, 1540
Hückel molecular orbital calculations, 34, 35
Hückel system, 1033
allowed reactions, 1033
and [1,5]-sigmatropic rearrangements, 1394
and cyclobutene ring opening, 1383
Hückel-Möbius method, 1031

Hückel's rule, 67
and annulenes, 72
and aromaticity, 65, 70
and cycloadditions, 1032, 1033
Hund's rule, and aromaticity, 66
and photochemistry, 292
and carbenes, 250
Hünig's base, and the aldol reaction, 1147
and the Claisen *condensation*, 1234
with amines, 1440
Hunsdiecker reaction, 854
and microwave irradiation, 855, 856
and radicals, 811
and the *Simonini reaction*, 855
catalytic, 855
mechanism, 855
Hurtley reaction, 779
HX, with alkynes, 865
hybrid orbitals, 9
sp, 7
sp^2, 8, 9
sp^3, 8, 9
hybridization, 7
and acidity, 341
and aromaticity, 48
and bond angle, 25
and bond distance, 23, 24
and bond energy, 30
and bond rotation, 175
and carbanion stability, 225
and conformations, 175
and inductive and field effects, 21
and PES spectra, 14
and resonance energy, 38
and S_N2 reactions, 374
diagonal, 7
of allenes, 132
of boron, 8
of butadiene, 38
of carbanions, 227
of carbon, 8
of carbon, and lithium, 696
of cyclophanes, 47
of dienes, 38
of ethyne, 10
of mercuric chloride, 8
of prismane, 198
of pyrenephane, 47
of radicals, 243
sp, 10
trigonal, 8
hydantoin, dibromo-dimethyl (DBDMH) see DBDMH
hydantoins, 758
and halogenation, 827
hydrates, and equilibrium, 1076
and relief of I strain, 1076
from aldehydes or ketones, 1075
stability, 1076
stable, 1076
Hydration, acid catalyzed, to alkenes, 873
anti-Markovnikov, 886
differential see differential hydration
indirect, 886
intramolecular, 887
mercuric catalyzed hydration of alkynes, mechanism, 888
of aldehydes and ketones, 1075
of aldehydes and ketones, catalysis, 1076
of alkenes, 885
of alkenes, *anti-Markovnikov addition*, 886
of alkenes, metal catalyzed, 886
of alkynes, 887
of alkynes, and metal catalyts, 887
of alkynes, metal catalyzed, 887
of alkynes, metal free, 888
of alkynes, rate-determining step, 889
of allenes, 888
of conjugated dienes, 886
of vinylidene nitriles, and cleavage, 886
hydrazide anions, and substitution of heterocycles, 788
hydrazides, 598
acyl, 1209
acyl, with alcohols, 1209
from alkenes, 897
from azodicarboxylates, 897
from hydrazines with esters, 1220
hydrolysis, 1197
with nitrous acid, 1362
hydrazine carboxylate, methyl ester, 99
hydrazine, and reduction of aldehydes or ketones, 1540
and *Wolff-Kishner reduction*, 1540
in a complex, 114
phenyl see phenylhydrazine
reaction with aldehydes or ketones, 1093
tosyl see tosylhydrazine
with carboxylic esters, 1220
with hydroxylamine, 1213
with phthalimides, 494
hydrazines, acyl see hydrazides
hydrazines, addition to alkenes, 897
aryl, loss of nitrogen, 1455
aryl, oxidation to azo compounds, 1454
arylation, 755
by *Hofmann rearrangement* with ureas, 1360
by reductive alkylation of azo compounds, 1099
chiral, 152
diaryl, reagents for oxidation, 1455
from aldehydes with hydrazones, 1138
from nitroso compounds, 1527
oxidation to azo compounds, reagents, 1455
reaction with oximes, 1093
with aldehydes or ketones, 1093
with nitrous acid, 727, 1361
hydrazo compounds also see hydrazines, aryl or diaryl
hydrazo compounds, by reduction of nitro compounds, 1562
reduction to amines, 1554
hydrazobenzenes, acid catalyzed rearrangement, 1415
by reduction of nitro compounds, 1525
hydrazoic acid, addition to enol ethers, 901
addition to *Michael-type alkenes*, 901
addition to silyl enol ethers, 901
and aromatic compounds, 598
and nitrile formation, 1095
and the *Schmidt reaction*, 1095, 1363
with alcohols, 485
with alcohols, and alkenes, 1364
with alkenes, and alcohols, 1364
with ketones, 1363
hydrazones, addition of HCN, 1183
addition of organometallics, 1137, 1138
alkylation, 548
and the *Fischer indole synthesis*, 1412
and the *Japp-Klingemann reaction*, 675
as derivatives, 1093
aziridino, LDA induced elimination to cis alkenes, 1294
by halogenation of hydrazines, 1106
chiral, 152
dimethyl, alkylation, 548
dimethyl, with butyllithium, 548
hydrazones, from active methylene compounds, 674
from aldehydes or ketones, 1412
from aryldiazonium salts, 674
from carboxylic acids, 675
from hydrazines and aldehydes or ketones, 1092
from oximes, 1093
hydrazones, hydrolysis, 1077
in [3+2]-cycloaddition reactions, 1014
oxidation, and microwave irradiation, 1455
oxidation, to nitriles, 1455

oxidation, with Oxone, 1455
reagents for hydrolysis, 1078
reduction, mechanism, 1542
reduction, to amines, 1520, 1528
reduction, to hydrocarbons, 1542
hydrazones, tosyl, and the *Bamford-Stevens reaction*, 1294
and the *Knoevenagel reaction*, 1160
and the *Shapiro reaction*, 1293
base induced elimination, 1293
suitable bases for elimination, 1294
with organolithium reagents, 1293
hydrazones, unsubstituted, 1094
hydrazones, with acid, 152
with aldehydes, 1138
with alkyl halides, 1138
with allylic silanes, 1137
with aryl halides, 555
with *Grignard reagents*, 1138
with ketenes, 1244
with Lewis acids, 1412
with silyl enol ethers, 1137
with silyl enol ethers, enantioselectivity, 1137
hydrazonium salts, and anilines, 598
elimination to nitriles, 1311
hydrazyl radicals, 240
hydride ions, and reduction, 1435
hydride migration, 687
hydride rearrangements, 1331
hydride reductions, and "free" hydride, 1511
and solvents, 1510
complex formation, 1511
role of cation, 1511
hydride shifts, 1428
1,3- and greater, 1332
1,3-, apparent, 1332
and silyl enol ethers formation, 687
transannular, 1428
Wagner-Meerwein rearrangements, 1338
hydride transfer, and oxidation-reduction, 1435
and the *Cannizzaro reaction*, 1564
hydride, "free", 1511
hydride, aluminum see aluminum hydride
hydride, lithium aluminum see lithium aluminum hydride
hydride, sodium borohydride see sodium borohydride
hydride, trialkyltin, and reduction of alkyl halides, 1532
and AIBN, reduction of thiocarbonates, 1538
and phenylboronic acid, reduction of aldehydes, 1509
reduction of aldehydes, 1509
with radicals, 806
hydrides, alkoxy, and reduction of nitriles, 1523
hydrides, metal also see metal hydrides
hydrides, metal, reduction of boranes, 1377
hydrides, reduction, of aldehydes or ketones, 1503–1515
of carbonyls, mechanism, 1510
of ketones, and Cram's rule, 1515
hydrides, tin, reduction of aldehydes or ketones, 1509
hydrides, tri-tert-butoxy, lithium reduction of acyl halides to aldehydes, 1517
hydrides, tri-tert-butoxyaluminum, with boranes, 1377
hydroamination, and (DHQ) PHAL, 1008
intramolecular, metal catalyze, 897
of alkenes, enantioselectivity, 1007
of alkenes, metal catalyzed, 1007
of alkynes, 898
of amines, intramolecular, 897
of *Michael type substrates*, 897
with a Au catalyst, mechanism, 897
with metal catalysts, 896
with organic lanthanide catalysts, 1008
hydroarylation, of alkynes, 937
hydroboration, 874, 920–926
hydroboration, and amination of alkenes, 899
and *anti-Markovnikov orientation*, 705
and enantioselective synthesis, 924
and ether solvents, 921
and functional groups, 923
and hydration of alkenes, 886
and oxidation of boranes, 923
and reduction of alkenes, 910
and reduction of alkynes to alkenes, 911
and steric effects, 874
and synthetic transformations, 923
and *Wilkinson's catalyst*, 926
hydroboration, conjugated versus nonconjugated, 926
cyclic, with dienes, 925
directing effects, 924
enantioselective, 924, 926
enantioselective, with metal complexes, 926
formation of anti-Markovnikov alcohols, 1375
mechanism, 922
of alkenes, 909
of alkynes, 925
of dienes or trienes, 1376
of dienes, 925
of norbornene, 878
regioselectivity, 922
retention of configuration, 559
hydrobromic acid see HBr
hydrocarbons, acidity of, 222
allylic CH, hydroxylation, reagents, 1471
allylic CH, oxidation, reagents, 1471
alternant and nonalternant, 63
hydrocarbons, and chirality, 135
and coupling, of boranes, 850
and coupling, of organocuprates, 849
and deamination of amines, indirect methods, 1547
and guest-host interactions, 113
and photochemical reactions with nitriles, 838
and radical coupling of carboxylate salts, 853
and radicals, 1469
and the *Kolbe reaction*, 853
hydrocarbons, benzylic CH, hydroxylation, 1471
hydroxylation, reagents, 1471
oxidation, 1471
oxidation, reagents, 1471
hydrocarbons, bond energy, 28
hydrbowl-shaped, 85
hydrocarbons, by deamination of amines, 1543
by deamination, reagents, 1547
by decarboxylation, 718
by dehalogenation of alkyl halides, reagents, 1531
by desilylation of silanes, 1531
by dihydroxylation of alcohols, reagents, 1534
by hydrogenation of thiophenes, 852
by metal catalyzed decarbonylation of aldehydes, 856
hydrocarbons, by reduction, of alcohols, reagents, 1534
of aldehydes, 1540
of alkyl halides, reagents, 1531
of amines, reagents, 1547
of carboxylic acids, 1546
of diazonium salts, 1549
of ethers, reagents, 1536
of ketones, 1540
of nitriles, 1546

hydrocarbons, by reduction, of alcohols, reagents (*Continued*)
of silanes, 1531
of sulfones, reagents, 1551
of sulfoxides, reagents, 1551
of thiocarbonates, 1537
of thioethers, reagents, 1551
of thiols, reagents, 1551
hydrocarbons, by reductive cleavage of esters, 1538
CH amination, 1475
CH oxidation, to amines, 1475
hydrocarbons, from alkyl halides, 1533
from amines, 1547
from arylhydrazines, 1455
from azo compounds, 1455
from carboxylic acids, 1546
from esters, 1546
from *Grignard reagents*, 1533
from nitriles, 1546
from nitro compounds, 1548
from silanes, 1546
from sulfides, 1551
from sulfoxides or sulfones, 1551
from thiols, 1551
hydrocarbons, halosulfonation, 837
hydroxylation, 1469–1473
hydroxylation, enantioselectivity, 1470
metal catalyzed, coupling of *Grignard reagents*, 849
metal mediated, carbonylation, 709
hydrocarbons, oxidation, 1469–1473
and hypervalent iodine, 1470
to alcohols, 1469
to hydroperoxides, 832
to peroxides, 835
to sulfonic acids, 1476
with Cr(VI), 1470
with permanganate, 1470
hydrocarbons, reagents, for oxidation to alcohols, 1470
remote CH oxidation, 1478
hydrocarbons, with acylperoxides, 835
with halogen and sulfur dioxide, 837
with hydroperoxides, 835
with oxygen, 832
with ozone, 1469
with sulfur dichloride, 837
hydrocarboxylation, acid catalyzed, 973
and CO, 972
and *Markovnikov's rule*, 973, 974
and nickel carbonyl, 973, 974
and the *Koch reaction*, 972
metal catalyzed, mechanism, 974
of alkenes, 972, 973
of alkynes, 973
hydrochloric acid see HCl
hydrochloric acid see HCl
hydrocyanic acid see HCN
hydrocyanic acid see HCN
hydroformylation, and dicobalt octacarbonyl, 979
and polymerization, 979
and the aldol reaction, 979
and the *Tishchenko reaction*, 979
and π-allyl complexes, 979
cyclization, 980
enantioselectivity, 980
metal catalyzed, oxo process, 979
of alkenes, 979
of alkynes, 979
of alkynes, metal catalyzed, 979
stereoselectivity, 980
tolerable functional groups, 980
hydrogen abstraction also see abstraction
hydrogen abstraction, and carbenes, 693
by radicals, 810
π-allyl complex, 663
hydrogen atom abstraction, 302, 306
hydrogen atom shifts, transannular, 1336
hydrogen atom transfer, and oxidation-reduction, 1435
hydrogen atoms, and oxidation or reduction, 1433
and the *Schrödinger equation*, 4
and wave functions, 4
transannular shifts, 1336
hydrogen bond distance, 99
hydrogen bond radii, 99
hydrogen bonds complexes, 329
hydrogen bonding, 96–103
and acidity, 98, 338
and acyl fluorides, 1190
and alcohol-alkynes, 103
and alkynes, 101
and amides, 103
and boiling point, 101
and bond energy, 29
and chemical properties, 101
and couping constants, 100
and dipyrrinones, 102
and enol content, 90
and IR, 102
and melting point, 101
and molecular recognition, 112
and pK, 338
and proton transfer, 323
and radicals, 240
and solubility, 101
and the ideal gas, 101
carboxylic acids, 97
C-H, 101
cooperative, 99
in amides, 98
in dicarboxylic acids, 98
in enols, 99
intermolecular, 98
internal, 323
NMR and IR, 100
S-H, 101
spectroscopic detection, 110
weak, 102
with heteroatoms, 98
with hydrogen halides, 101
with semirubin, 102
hydrogen bonding, acceleration of *Diels-Alder*, 1022
hydrogen bonds, and acceptor basicity, 98
and aqueous acetone, 98
and enol stabilization, 665
and guest-host interactions, 112
and neutron diffraction, 99
and ring size, 99
and symmetry, 99
and X-ray crystallography, 99
asymmetric, 99
basicity, 320
bifurcated, 99
geometry, 98
intramolecular, 97
three-center, 99
hydrogen cyanide see HCN
hydrogen exchange, and cyclopropenyl derivatives, 70
and hydrogenation, 909
coupling of alkenes, 690
electrophilic aromatic substitution, 592
in base, 661
in catalytic hydrogenation, 906
in superacids, 661
mechanism, 660
reactivity and structure, 660
with carbanions, 655
with carbocations, 690
hydrogen fluoride see HF
hydrogen peroxide also see peroxides
hydrogen peroxide, and alkenes, 999
and oxidation of thiols, 1493
and hydroxide, with boranes, 1375
and metal catalyst, *Baeyer-Villiger rearrangement*, 1369
and oxidation of thiols, 1497
oxidation of amines to amine oxides, 1492
oxidation of carboxylic acids, 1487

with carboxylic acids and DCC, 473
with cyclic ketones, 1319
[1,3]-hydrogen shifts, 1394
[1,5]-hydrogen shifts, 1394
with vinyl aziridines, 1395
[1,7]-hydrogen shifts, antarafacial migrations, 1395
photochemical, 1395
hydrogen shifts, and carbene rearrangements, 1337
hydrogen sulfide, addition to alkenes, 894
clathrate formation, 114
with acyl halides, 1211
with carbonyls, 1087
with ketones, 1087, 1088
hydrogen transfer, [1,4]-, in radical cyclization, 1395
and radical cyclization, 961
and radicals, 806
intramolecular, 810
radicals and tributyltin hydride, 806
radicals, and alkylsilanes, 807
hydrogen, as a leaving group, 810–813
as a neighboring group, 408
migrating group in rearrangements, 1328
participation solvolysis, 408
pressure, and hydrogenation, 904
sigmatropic migration in alkenes or dienes, 1392
with amines and aldehydes or ketones, 1096–1099
hydrogenation, and C=C migration, 909
and chiral catalysts, 153
and cleavage of alkanes, 726
and D_2, 908, 909
asymmetric catalysts, 1512
catalyst poisons, 903
hydrogenation, catalytic, alkene selectivity, 903
alkenes versus alkynes, 905
and acyl halides, 1517
and aromatization, 1438
and bond rotation, 909
and enantioselectivity, 903
and hydrogen exchange, 906
and isomerization of alkenes, 906
and metal complex formation, 907, 908
and metal complexes, 1450
and nanoparticles, 903
and poisoning, 903
and reduction of imines, 1520
and *Rosenmund reduction*, 1517
and steric effects, 904
and sulfur compounds, 851, 852
and *Wilkinson's catalyst*, 903
hydrogenation, catalytic, asymmetric catalysts, 918, 919
catalyst types, 902
hydrogenation, chiral catalysts, Chiraphos, 904
with enamines, 1521
with imines, 1521
hydrogenation, chiral ligands, 904
chiral poisoning, 904
conjugated compounds, enantioselectivity, 918, 919
cyclopropanes, 920
enantioselectivity, 903, 905, 919
functional group compatibility, 903
heterogeneous, mechanisms, 906
high pressure, 904
homogenous, mechanism of metal-complex formation, 908
homogenous, mechanism, 908
in ionic liquids, 913
catalysts, kink-type atoms, 907
catalysts, step-type atoms, 907
catalysts, terrace-type atoms, 907
ligands for enantioselectivity, 904
heat of, for benzene, 36
hydrogen exchange, 909
in situ, and sodium borohydride, 904
hydrogenation, catalytic, of alcohols, 1534
of aldehydes or ketones, 1506
of alkenes, 41
of alkenes, 902–909
of alkenes, stereochemistry, 906
of alkyl halides, 1532
of alkynes, 912
of alkynes, *Rosenmund catalyst*, 905
of allenes, 905
of aromatic compounds, 912, 913
of benzylic ethers, 504
of dienes, 905
of disulfides, 851
of enamines, 898
of heptalene, 62
of heterocycles, 913
of heterocyclic compounds, 913
of isocyanates, 1522
of nitriles, 1522
of nitro compounds, 1530
of oximes, 1520
of phenols, 1536
of thioethers, 851
of thiols, 851
of thiophene, 1551
of thiophenes, 852
hydrogenation, catalytic, poisoned catalyst, 905
poisons, 903
polymer-bound catalysts, 903
reaction conditions, 904
reduction of amides, 1545
reduction of hydroperoxides, 1539
reductive, 1097
selectivity with homogeneous catalysts, 903
surface and particle sites on the catalyst, 907
syn addition, 909
syn stereochemistry, 906
transfer, 910, 912, 1510, 1513
transfer, and *Hantzch esters*, 917
transfer, and organocatalysts, 917
types of homogeneous catalysts, 904
with allenes, 912
with homogeneous catalysts, 903
with soluble catalysts, 902
hydrogen-deuterium exchange, 660
hydrogen-lithium exchange, with aromatic compounds, 784
hydrogen-metal exchange, 717
and CIDNP, 717
and radicals, 717
mechanism, 717
hydrogenolysis, and hydrogenation of aromatic compounds, 913
cleavage of ethers, 504
hydroxy-amines, 1097
of acyl halides, 1517
of amines, 1547
of cyclopropanes, 920
hydrogen-transfer agent, and radicals, 960
hydrogen-tritium exchange, 660
hydrolysis, and acyl addition of organolithium reagents, 1109
aryl *Grignard reagents*, 648
and aryl organolithium reagents, 648
and aryl organometallics, 648
and enzymes, 1080
and nitrilases, 1080
and the *Gabriel synthesis*, 494
and the *Grignard reaction*, 1107
and the *Merrifield synthesis*, 1218
and the *Stork enamine synthesis*, 551

hydrolysis, of acetals, 454
acid catalysis, 455
and *Brønsted coefficient*, 456
and carbocations, 457
and hemiacetals, 455
and isotope labeling, 455
and the A2 mechanism, 456
and the S_N1 mechanism, 455
rate determining step, 456
hydrolysis, of acyl fluorides, 1190
of alkoxides, 1511
hydrolysis, of alkyl halides, 451
and the S_N1 mechanism, 349
rate, table, 350
hydrolysis, of aluminum compounds, 699
hydrolysis, of amides, 1197–1200
acid catalyzed, 1199
and twisted bonds, 1197
base catalyzed, 1199
isotopic labeling, 1199
IUPAC mechanism, 1198, 1200
kinetics, 1198
mechanism, 1198–1200
MO studies, 1198
nucleophilic catalysis, 1198
rate constants, 1199
water promoted, 1197
hydrolysis, of anhydrides, 1190
of anhydrides, nucleophilic catalysis, 1190
of aryl oximes, 800
of benzamide, 1073
of *Bunte salts*, 476
hydrolysis, of C=N compounds, 1077
ionic liquids, 1077
metal mediated, 1077
reagents for, 1077, 1078
hydrolysis, of carbamates, 1198
carbamates, mechanism, 1196, 1197
carboxylic acid esters, and mechanism, 356
hydrolysis, of carboxylic esters, 1190–1197
and isotopic labeling, 1195, 1196
and microwave irradiation, 1192
and phase transfer, 1192
and retention of configuration, 1195
and steric hindrance, 1191
and ultrasound, 1192
mechanism, 1192–1197
tetrahedral mechanism, 1192–1197
hydrolysis, of chloroform, 453
of compounds, and microwaves, 1078
of compounds, mechanism, 1078
of cyanide, 276
of cyanohydrins, 1080
of diazoketones, 454
of dihalides, 452
of dithianes, 553
hydrolysis, of dithioacetals, 1087, 1088
hydrolysis, of dithioketals, 1087, 1088
and dithioacetals, reagents for, 1088
Corey-Seebach procedure, 1088
hydrolysis, of enamines, 458
of enamines, mechanism, 1079
hydrolysis, of enol esters, 1197
of enol ethers, 454, 887
of enolate anions, 698
of epoxides, 458
of epoxides, enantioselectivity, 458
hydrolysis, of esters, activation energy, 1192
and carbocations, 1196
and malonic esters synthesis, 540
and molecular dynamics, 1192
catalysts, 1191
IUPAC mechanism, 1192–1197
rate constants, 356
rates, 350
S_N1 and S_N2 mechanisms, 1195
transition states, 1196
with enzyme, 1192
hydrolysis, of ethers, 462
of furans, 458
of gem-diacetates, 1469
of *Grignard reagents*, 699
of *Grignard reagents*, and reduction of alkyl halides, 1534
of hemiacetals, 1371
of hydrazides, 1197
of hydrazones, 1077
of hydrazones, reagents for, 1078
of hydroxamic acid, 1080
of imides, 1197
of imines, 1077
hydrolysis, of iminium ions, 1078
and the *Stork enamine reaction*, 1078
mechanism, 1078
hydrolysis, of iminium salts, 551, 633, 1140, 1312
of inorganic esters, 453
of isocyanates, 1085
of isocyanides, acid catalyzed, mechanism, 1246
of isothiocyanates, 1085
of ketene dithioacetals, 458
of ketones, 1354
of lactams, 1197
of lactones, 1191
of β-lactones, 1221
of metalloids, 699
hydrolysis, of nitriles, 563, 1080, 1081
and microwave irradiation, 1080, 1081
metal catalysts, 1081
reagents for, 1080
hydrolysis, of nitro compounds, 1079
and the *Nef reaction*, 1079
reagents for, 1079
hydrolysis, of nitroso compounds, 1428
of organocadmium reagents, 698
of organolithium reagents, 698
of organometallic compounds, 648
of organometallic reagents, 698
of organozinc compounds, 698
of ortho esters, 456
of oxazolidines, 557
of oximes, 1077, 1427
of phthalamic acid, 1073
of phthalimides, 494
of *Schiff bases*, 1077
of semicarbazones, 1077
of sulfonic acid derivatives, 1249, 1250
of sulfonic acid esters, 454
of thioacetals, 457
of thiocyanates, 1081
of thioesters, 1072
of thioketals, 457
of trihalides, 452
of trioxolanes, 1461
of vinyl esters, 1192
of vinyl ethers, labeling, 457
of vinyl ethers, mechanism, 457
hydrometalation, of alkenes, 926
of alkynes, 927
hydroperoxide anion, Michael addition, 1003
hydroperoxide ions, with alkyl halides, 472
hydroperoxide radicals, bond dissociation energy, 242
hydroperoxides, 804
acid catalyzed rearrangement to ketones, 1370
acyl, from anhydrides, 472
alkyl, co-reagents, and epoxidation, 1001
and alkenes, 999
and epoxidation, 1004
and ozonolysis of alkenes, 1461
and singlet oxygen, 833
by autoxidation, 832
chiral, 1001
from alkyl halides, 472
from carboxylic acids, 472
from *Grignard reagents*, 699
from organometallics, 699
oxidation of sulfoxides, mechanism, 1495

oxidation of thioethers, mechanism, 1495
protonated, 1371
reduction to alcohols, 1539
tert-butyl, and dihydroxylation of alkenes, 993
with alkynes, 892
hydrophobic acceleration, in water, 363
hydrophobic effects, and Diels Alder reactions, 1023
hydroquinones, by reduction of quinones, 1505
host for clathrates, 114
oxidation to quinone, 1452
hydrosilanes, with epoxides, 537
hydrosilation, and metals, 918
of alkenes, 928
of alkynes, 929
hydrostannation, and sonochemistry, 309
of conjugated esters, 919
hydrosulfide anion, with aryl halides, 749
hydrotalcite, and epoxidation, 1003
hydroxamic acid, hydrolysis, 1080
hydroxamic acids, from hydrazine and hydroxylamine, 1213
from hydroxylamines and esters, 1220
O-acyl, and *Lossen rearrangement*, 1363
O-acyl, base catalyzed rearrangement, 1362
torsional barrier, 180
hydroxide ion, and alkyl halides, 451
and the *Reimer-Tiemann reaction*, 627
reaction with amides, 348
reaction with silanes, 223
with aryl halides, 746
hydroxide radical, 810
hydroxy acids, and macrocyclic lactones, 1204
and zwitterionic intermediates, 1308
by rearrangement of diketones, 1350
elimination to alkenes, 1308
esterification to form lactones, 1203
formation of lactones, 1204
from keto aldehydes, 1563
ring closure to lactones, 1563
spontaneous lactone formation, 1191
hydroxy aldehydes, by aldol reaction, 1141–1153
by the *Mukaiyama aldol*, 1151–1153
with hydrazines, 1093
hydroxy-alkyl halides see halohydrins
hydroxy amides, from addition of amides to aldehydes, 1099
from lactones, 1221
hydroxy amines see amino alcohols
hydroxy esters, 1154
by α-hydroxylation, 1473
hydroxy ethers, 466
from epoxides, 465
oxidation to acetals, 831
hydroxy halides see halohydrins
hydroxy ketones, 1160
by oxidation of alkenes, 1489
by the aldol reaction, 1141–1153
by the benzoin condensation, 1187
by the *Mukaiyama aldol reaction*, 1151–1153
by the α-ketol rearrangement, 1349
by α-hydroxylation of silyl enol ethers, 1474
by α-hydroxylation, 1473
formation of cyanoamines, 486
from aldehydes and potassium cyanide, 1187
from diketones, 1507
from imines and ketones, 1149
from metallated imines, 1248
from organolithium reagents with ketones, 1111
with hydrazines, 1093
hydroxy lactams, dehydration, 1283
hydroxy sulfides see hydroxy thioethers
hydroxy thiols, from carbonyls, 1087
hydroxyalkylation, 615
and the *Lederer-Manasse reaction*, 616
of aromatic compounds, 615
polymerization, 616
hydroxyamides, 563, 1155
bis-, chiral, 1005
hydroxyamines, from alkenes, 1007
from isocyanides, 493
hydroxybenzyl silanes, *Brook rearrangement*, 1431
hydroxylamine *O*-sulfonic acid, formic acid and the *Beckmann rearrangement*, 1366
with organoboranes, 707
hydroxylamines also see oximes
hydroxylamines, addition to alkenes, 897
and conjugate addition, 967
and the *Stieglitz rearrangement*, 1368
by *Meisenheimer rearrangement*, 1373
by oxidation of amines, reagents for, 1491
by oxidation, of amines with Caro's acid, 1490
by reduction of nitro compounds, 1525
by reduction of nitro compounds, reagents, 1526
by the *Cope elimination*, 1292
from oxides, 1526
from oximes, 1138
metal reduction to amines, 1527
oxidation, 1491
oxidation, to nitroso compounds, 1455
reaction with aldehydes and formic acid, 1095
reduction with CS_2, 1527
with aldehydes or ketones, 1094
with aldehydes, 1095
with carboxylic esters, 1220
with hindered ketones, 1094
with hydrazine, 1213
with metal-salen complex, 1311
with organometallics, 706
α-hydroxylation, of allylic compounds, 1472
of benzylic compounds, 1472
of carbonyl compounds, reagents, 1473
of carboxylic esters, 1473–1475
of enolate anions, with sulfonyloxaziridines, 1474
of ketones, 1473–1475
of silyl enol ethers, 1474
with dioxiranes, 1474
with dioxiranes, enantioselectivity, 1474
with enzymes, 1472
with oxaziridines, enantioselectivity, 1474
hydroxylation, CH, with enzymes, 1472
of alkenes, 885
of allylic groups, with SeO_2, 1471
of allylic methylene groups, reagents, 1471
of amines, enzymatic, 1476
of aromatic compounds, 634
of aromatic compounds, by *Boyland-Sims oxidation*, 634
of aromatic compounds, by the *Elbs reaction*, 634
of aromatic compounds, potassium persulfate, 634
of aryldiazonium salts, 790
of benzylic methylene groups, and reagents, 1471
of hydrocarbons, 1469–1473

hydroxylation, CH, with enzymes (*Continued*)
of hydrocarbons, and oxaziridines, 1471
of hydrocarbons, enantioselectivity, 1470
of silanes, 467
of THF, 1476
photolytic, 635
with aniline derivatives, 634
[hydroxyl(tosyloxy)iodo]benzene, 600
hydroxynitriles, alkylation, 549
from epoxides, 564
hydroxypropanoic acid, proton transfer, 323
hydroxypyridine, and tautomerism, 93
hydroxy-selenides, from epoxides, 478
hydroxy-silanes, for lithio-silanes and aldehydes or ketones, 1162
hydroxysuccinimide, and CH oxidation of lactams, 1478
and the *Ritter reaction*, 1240
hydroxysulfenylation, of alkenes, 1006
hydroxysulfinamides, by *Knoevenagel reaction*, 1159
hydrozirconation, of alkenes, 926
hyperconjugation, 42, 85
and alkene stability, 1270
and aromatic substitution, 580
and aromaticity, 86
and bond distance, 46, 87
and bond elongation, 88
canonical forms, 46
and carbanions stability, 225
and carbocations, 86, 211, 212, 217, 287, 420
and charge separation, 88
and cyclopentadienes, 88
and delocalization, 87
and diynes, 39
and elimination reactions, 1270
and isotopic effects, 287
and orbitals, 87
and p character, 86
and radicals, 86, 238
and resonance, 87, 211
and ring strain energy, 89
and s character, 88
and solvolysis, 287
and tautomers, 88
and temperature, 287
and the anomeric effect, 187
and the *Baker-Nathan effect*, 86
and the tetrahedral mechanism, 415
and UV light, 85
and X-ray analysis, 87
hyperconjugation, aryl halides, 44
electrophilic aromatic substitution, 580
isovalent, 86
negative, 187
sacrificial, 88
hyperconjugative stabilization, 87
hyperconjugative stretching, 87
hypervalent aryliodine derivatives, biaryls, 621
hypervalent iodine see iodine
hypervalent iodine, 469
and benzylic CH oxidation, 1471
and dihydroxylation, 995
and nitrile formation, 1096
with alkenes, 985
with sulfonamides, 1554
hypochlorite, sodium, and oxidative cleavage of cyclic ketones, 1458
with amines, 729
with organoboranes, 707
hypochlorites, alkyl, decomposition to radicals, 804
and epoxidation, 1005
and halogenation, 827
and radical halogenation of silanes, 826
with azides and aldehydes, 1223
hypofluorites, acetyl, 608
hypofluorites, acyl, with enolate anions, 670
hypohalides, and N-haloamines, 729
acyl, as an intermediate, 855
halogenation of aromatic compounds, 607
hypohalous acids, addition to alkynes, 986
with alkenes, 984
hypoiodite, *tert*-butyl, and iodination of alkenes, 823
hyponitrites, and addition to alkenes, 970
with amines, 793
hypophosphite, reducing agent, 1528
hypophosphorus acid, and reduction of aryldiazonium salts, 1549
and resonance, 49
and ylids, 49
hypostrophene, 1406
and *Cope rearrangements*, 1405
hypsochromic shift, 293

+I effect, 20, 21
+I effects, arenium ions, 577
–I effect, 20, 21, 336, 579, 580
arenium ions, 577
I strain see strain
IBr, with alkenes, 983
IBX (o-iodoxybenzoic acid)
IBX, with aldehydes, 1096
ICl, and boranes, 705
with alkenes, 983
ideal gas, and hydrogen bonding, 101
imidates, with ammonia or amines, 1220
imidazoles, reduction to aldehydes, 1519
with bromoalkynes, 562
with carboxylic acids, 1216
imidazolides, as intermediates, 1205, 1206
imidazolidinone catalysts, and transfer hydrogenation, 917
imidazolidones, 1025
imidazolinyl carbenes, chiral ligands, 1122
imidazolium carbene complex, and alkyl halide coupling, 518
imidazolium ligands, 772
imidazolium salts, catalysts, 1187
ionic liquids, 365
imides, acyl, intermediate in *McFadyen Stevens reduction*, 1519
alkylation, 494
and *Hofmann rearrangement*, 1360
by carboxylation of alkenes, 979
by oxidation of lactams, 1478
conjugate addition, 966
cyclic, 1215
cyclic, amines and cyclic anhydrides, 1215
formation, anhydrides with amines, 1215
from acyl halides and amides, 1223
from isothiocyanates, 630
hydrolysis, 1197
metal catalyzed, addition to alkenes, 901
metal catalyzed, addition to alkynes, 901
reaction with dihalosulfones, 1174
reduction, to amines, 1545
reduction, to hydroxy lactams, 1546
with alcohols, 494
imidines, from dinitriles, 1104
imido selenium compounds, with alkenes, 679
imidoyl radicals, 805
imine esters, reduction with Hantzsch esters, 1521
imine-enamine tautomerism, 1180
imine-enamine tautomerism also see tautomerism
imines(bis), from aldehydes and imines, 1558
imines, acylcyanation, 1184

imines, addition, of boronates, 1136
of boronic acids, 1136
of carbenes, 254
of diazoacetates, 1010
of HCN, 1183
of organometallics, enantioselectivity, 1134
of radicals, 1138
imines, alkylation, 548, 1099
imines, and carboxylic acids, 1244
and E/Z nomenclature, 163
and enamine salts, 550
and hemiaminals, 1090
and *Mannich bases*, 1100
and *Mannich reactions* with enol ethers, 1102
and metals used for catalytic hydrogenation, 1521
and pinacol coupling, 1558
and tautomerism, 94
and the *aza-Baylis-Hillman reaction*, 1137
and the *Barton reaction*, 1427
and the Ugi reaction, 1247
imines, as amino acid surrogates, 548
azomethine, in [3+2]-cycloaddition reactions, 1015
by dehydrogenation of amines, 1454
by oxidation of amines, 1482
by reduction of oximes, reagents, 1528
α-carbanion, with ketones, 1149
carbonylation, 709, 978
chiral additives, with organolithium reagents, 1134
chiral, 966, 1103
condensation with ketones, 1149
conjugate addition, 966
cyano, from nitriles, 1164
imines, cyclic, from allene amines, 898
from cycloalkyl azides, 1362
from halo-nitriles and organometallics, 1140
via radical cyclization, 1188
imines, cycloaddition with ketenes, 1244
with ketenes, mechanism, 1245
with thioketenes, 1244
imines, cyclopropyl, rearrangement, 1399
E/Z isomers, 204
electronic structure, 15
formation, in ionic liquids, 1091
imines, from aldehydes, 551
from alkyl azides, 1362
from amines, 551, 1454
from amines, and aldehydes or ketones, 1090
from amines, by dehydrogenation, 1440
from azides, 1362
from aziridines, 1304
from carboxylic acids, 1518
from *Grignard reagents* with nitriles, 1139
from ketones, 551
from nitriles, 1140
from nitroso compounds, 676
imines, halo, 1244
from amides, 1429
imines, hydrolysis, 1077
to aldehydes or ketones, 1482
imines, in situ formation, 1099
imines, in [2+2]-cycloaddition reactions, 1041
in situ generation, 1100
imines, in the *Diels-Alder reaction*, 1037
in the ene reaction, 943
lithiated, 548
α-lithio, with ketones, 1149
magnesio, 549
imines, metal catalyzed, addition of allyl silanes, 1180
addition of diazoesters, 1139
imines, metal mediated, reaction with halo esters, 1244
imines, metallated, 1247
synthetic applications, 1248
imines, nitrile, in [3+2]-cycloaddition reactions, 1015
O-tosyl, base catalyzed rearrangement to amino ketones, 1359
phosphinyl, reduction, 1521
radical addition, 1188, 1189
imines, reduction, by silanes, 1520
to amines, and microwaves, 1520
to amines, enantioselectivity, 1521
with *Escherichia coli*, 1521
with silanes, 1521
imines, strained bicyclic, 204
sulfinyl, 1134
sulfinyl, with alkenes or diynes, 1136
sulfonyl, 1100
tautomerism with enamines, 898
imines, tosyl, cyclopropyl, rearrangement, 1399
with alkenes, metal catalysts, 1136
with alkynes, 1134
with conjugated esters, 1137
with ketones and proton sponge, 1244
with trifluoroborates, 1136
with ylids, 1177
imines, with aldehydes, 1558
with alkynes, 1133, 1134
with allylic alcohols, 1138
with allylic silanes, 1137
with amide bases, 548
with boronic acids, enantioselectivity, 1136
with chlorosulfonyl isocyanate, 1245
with conjugated compounds, enantioselectivity, 1137
with *Danishefsky's diene*, 1038
with dialkylzinc, 1134
with diazo compounds, 1139
with diazo ketones, and microwaves, 1245
with diazoketones, 1245
with *Grignard reagents*, 1133
with *Grignard reagents*, transition metal catalysts, 1133
with halo esters, 1162
with ketene acetals, 1152
with ketene silyl acetals, 1137, 1152
with ketenes, 1041, 1529
imines, with Lewis acids, 1312
with nitriles, 1136
with nitro compounds, 1137
with nitro compounds, enantioselectivity, 1137
with nitroalkanes, 1157
with organoaluminum compounds, 1136
with organolithium reagents, 1133
with organolithium reagents, intramolecular, 1133
with organometallic compounds, 1133–1138
with organometallics, enantioselectivity, 1135
with organozinc reagents, 1134
with phosphorus ylids, 1173
with silyl enol ethers, 1102, 1153
with Te ylids, 1177
with thioketenes, 1244
with transition metals, 1135
iminium ions, an intermediate in the *Mannich reaction*, 1101, 1102
and *Eschenmoser's salts*, 1102
and the *Bruylants reaction*, 532
cyclization, 618
hydrolysis, 1078
hydrolysis, and the *Stork enamine reaction*, 1078
hydrolysis, mechanism, 1078
protonolysis, 219
with *Grignard reagents*, 532

iminium salts, addition of cyanide, 1183
amines with aldehydes or ketones, 1091
and reductive amination, 1097
and the *Fischer indole synthesis*, 1413
and the *Gatterman-Koch reaction*, 627
and the *Hoesch reaction*, 633
and the *Pictet-Spengler reaction*, 618
chiral, 1002
coupling with SmI_2, 1558
formation of aldehydes, 627
formation of nitriles, 633
fragmentation of amines, 1307
iminium salts, from aldehydes, 618
from dialkylamino halides, 1307
from enamines, 551
from oxazines, 557
from oximes, 1312
from the *Stork enamine reaction*, 550
iminium salts, hydrolysis, 551
hydrolysis, 633, 1140
in the *Diels-Alder reaction*, 1037
reactivity, 1102
reduction to amines, 1520
with *Grignard reagents*, 1138
with Oxone, 1002
imino chlorides, 618
imino ene reactions, 943
imino esters, 1086, 1429
allylic, in *Claisen rearrangements*, 1410
and ketone formation, 633
and the *Chapman rearrangement*, 1429
and the *Hoesch reaction*, 633
and the *Pinner synthesis*, 1086
from amides and phosphorus pentachloride, 1429
from nitriles and alcohols, 1085
hydrolysis, 1085
rearrangement to amides, 1428
with aldehydes, 541
iminonitriles, from addition of HCN to nitriles, 1184
immobilized Cu, and *Ullmann coupling*, 769
In catalysts, alcohols and alkyl halides, 460
alkoxysilanes with aldehydes, 1084
alkyl halides with hydrazones, 1138
allylic silanes with gem-diacetates, 1126
aromatic sulfonation, 602
cyclopropanation, 1057
hydration of alkynes, 887
with alkynes, 938
In, acyl cyanides with allylic halides, 1232
amide formation, 495
and acetal cleavage, 456
and acyl addition of allylic halides, 1116
and dehalogenation of dihalides, 1305
and epoxides with alkyl bromide, 536
and reduction of hydroxylamines, 1527
and reduction of quinolines and indoles, 915
and selenide formation, 479
and the *Barbier reaction*, 1115
and the *retro-Claisen condensation*, 1234
with allenic alcohols, 533
with tosylaziridines, 1304
inclusion compounds, 113
and rotaxanes, 120
thiourea, 114
indacene, and antiaromaticity, 79
indanones, 692
indene, 864
and the *Heck reaction*, 765
pK_a, 59
Index Chemicus, 1586
Index of Scientific Reviews, 1585, 1600
indicators, and acidity scales, 325
and solvent acidity, 325
and spectrophotometric measurements, 325
indirect hydration, with ammonium salts and TMSCl, 886
indirect methods, deamination of amines, 1547
indoles, addition of carbenes, 1056
allyl, and *aza-Claisen rearrangement*, 1411
and arylation of keto amides, 779
and *Friedel-Crafts acylation*, 623
and the *Reimer-Tiemann reaction*, 627
by radical cyclization, 964
by the *Fischer indole synthesis*, 1412
catalytic hydrogenation, 913
from alkynes and hydrazines, 898
from hydrazones, 1412
via *Neber rearrangement*, 1359
with aldehydes, 1123
indolizines, metal catalyzed coupling with aryl halides, 760
indolones, and radical cyclization, 963
in the *Birch reduction*, 914
inductive destabilization of groups, 421
inductive effects, 19, 20
and bond polarization, 19, 20
and carboxylic acids, 20
and hybridization, 21
infrared see IR
Ing-Manske procedure, 494
inhibitors, and radicals, 807
radical, 807
in-in isomers, 168
initiation, and radicals, 803, 805
initiators, for *Grignard reagents*, 713
radical, 971
radical, azobis compounds, 960
inorganic esters, with alkoxides, 462
in-out isomerism, 102
in-out isomers, 168
insertion reactions, and dirhodium catalysts, 693
and nitrenes, 259
carbenes, 254
enantioselective, 463
labeling, 693
mechanism, 693
oxygen, 1355
insertion, and aldehydes, 692
and carbenoids, 694
and carbocations, 690
and carbonyl nitrenes, 680
and cyclopropanation, 692
and halocarbenes, 691
and organozinc compounds, 694
and radicals, 694
by carbenes, 691
by nitrenes, 679
insertion, carbene, and ring expansion, 692
and ultrasound, 692
enantioselectivity, 692
intramolecular, 692
isotopic labeling, 693
mechanism, 693
metal catalyzed, 692
insertion, C-H, with dimethyl dioxirane, 1001
diazocarbonyl compounds, 692
diazoesters, 692
direct, and carbenes, 694
intramolecular, 690–692
mechanism, 690
metal carbenes, 693
methylene, 691
insertion, nitrene, cyclization, 680
enantioselectivity, 680
insertion, nitrogen, 679
of carbenes, 255, 1051
of nitrenes, formation of carbamates, 680
silylene, 692

interconversion, diene-cyclobutene, 1384
interfacial mechanism, 443
inter-halogen compounds, with alkenes, 982
interlocked catenanes, 119
intermediates, allene, 664
and CIDNP, 276
and free energy, 268, 269
and IR, 276
and mechanism, 275
and NMR, 276
and Raman, 276
arenium ions, 570
bromonium ion, 860
carbocations, 1185
cyclic, 863
cyclic, addition of bromine to dienes, 870
cyclopropane, 1326, 1329
detection of, 276
halonium ions, 860
in Friedel-Crafts *alkylation*, 613
in the *Reformatsky reaction*, 1130
isolation of, 275
oxocarbenium ions, 1185
radical, 237, 276
radical, and CIDNP, 236, 237
radical, and *Grignard reactions*, 1113
reaction, 268
sulfene, 1299
tetrahedral, 348
trapping, 276
ylids, 1292
intermolecular hydrogen bonding, 98
internal conversion, 297
internal coupling, of alkynes, 935
internal nucleophilic substitution see substitution, S_Ni
internal return, and ion pairs, 384
and S_N1 reactions, 384
and stereochemistry, 386
internal strain see strain, I
International Union of Pure and Applied Chemistry see IUPAC
interrupted *Nazarov*, 947
intersystem crossing, 298
and angular momentum, 298
photochemistry, 1426
intimate ion pair, 384
and S_Ni reaction, 409
intimate ion pairs, 410
intramolecular [2+2]-cycloadditions, 1041
intramolecular [3+2]-cycloadditions, 1017
intramolecular addition, alcohols to alkenes, 890
intramolecular aldol reaction, 1149
acid catalyzed, 1149
intramolecular aldol also see aldol
intramolecular alkenes coupling, 934
intramolecular arylation, 844
intramolecular *Baylis-Hillman reaction*, 1128
intramolecular cyclization, 928
intramolecular cyclotrimerization, 1060
intramolecular *Diels-Alder reactions*, 1028
intramolecular elimination, 1278
intramolecular ene reaction, 942
intramolecular *Grignard addition* to alkenes or alkynes, 936
intramolecular *Heck reactions*, 763, 766
intramolecular hydration, 887
intramolecular hydroamination, alkyne, 898
intramolecular hydrogen transfer, 810
intramolecular insertion, 690–692
intramolecular *McMurry coupling*, 1559
intramolecular *Michael reactions*, 946, 947
intramolecular *Mukaiyama aldol*, 1353
intramolecular nucleophilic substitution, 801
intramolecular *oxy-Michael reactions*, 967
intramolecular *Paterno-Büchi reaction*, 1243
intramolecular pinacol coupling, 1557
intramolecular proton-transfer, 323
intramolecular radical additions, 876
intramolecular reactions, *Scholl reaction*, 620
intramolecular rearrangements, mechanism, 643
intramolecular rearrangements, photochemical, 304
intramolecular *Schmidt reaction*, 1364
intramolecular *Stille coupling*, 682
intramolecular *Thorpe reaction*, 1179
intramolecular *Wittig reaction*, 1172
intramolecular *Wittig-Horner reaction*, 1170
intramolecular, [3+2]-cycloadditions, 1017
intramolecular, acyl addition, 971
intramolecular, carbene insertion, 692
intramolecular, *Friedel-Crafts alkylation*, 609
intramolecular, *Gomberg-Bachmann reaction*, 795
intramolecular, *Grignard reactions*, 1109
intramolecular, hydroamination of alkenes, 897
intramolecular, photochemical [2+2]-cycloaddition, 1048
intramolecular, reaction of ketones with alkenes, 939
intramolecular, silicon-tethered *Heck reaction*, 763
intrinsic acidity, 344
intrinsic barrier, 273, 274
intrinsic barriers to S_N2, and strain energy, 392
intrinsic free energy, 273
inverse electron demand, *Diels-Alder reactions*, 1030
inverse isotope effects, 286
inversion barrier, buckybowls, 85
E/Z for vinyl radicals, 239
inversion of configuration, and addition reactions, 875
alkylation of enolate anions, 542
and azide ion, 389
and chlorination of alcohols, 409
and organocuprates, 521
and radicals, 809
and S_N2 reactions, 375, 376
and solvolysis, 389
at sulfur, 129, 1248
of phosphorus, 169
inversion, bowl-to-bowl, 84
inversion, pyramidal, 127, 128
and bridgehead atoms, 129
and carbanions, 227
and enantiomers, 129
and N,P,As,Sb, 129
energy barrier, 127, 128
iodide ion, oxidation of, 792
iodide, radioactive, in S_N2 reactions, 377
iodide, sodium, and Chloramine-T, 792
in DMF, 1301
iodides, aryl, coupling with Pd catalyst, 511
aryl, from aryl diazonium salts, 847
aryl, from aryldiazonium salts, 791
in the *Finkelstein reaction*, 498
vinyl, from vinyl bromides, 498
with boranes and base, 1377
iodination reagents, 607, 608, 669
iodination, 822
of aldehydes and ketones, 669
of aromatic compounds, 607
of aromatic compounds, 607
iodine azide, addition to alkenes, 990

iodine reagents, aromatic halogenation, 607
iodine, and alkenes, 982
and *Friedel-Crafts alkylation*, 610
and PhI(OAc)2, 823
and the *Hunsdiecker reaction*, 855
catalyst, 1208
cocatalysts, with hypervalent iodine, 1450
iodine, hypervalent, α-acetoxylation of ketones, 1475
alternative reagents of oxidation of alcohols, 1450
and hydrocarbon oxidation, 1470
and iodoxybenzoic acid, 1449
and lactone formation, 469
and oxidation of alcohols, 1449
and the *Dess-Martin periodinane*, 1449
CH oxidation, 1473
oxidation of alcohols, and microwave irradiation, 1450
oxidation of alcohols, in ionic liquids, 1450
polymer bound, with TEMPO, 1449
with an iodine catalyst, 1450
iodine, light and radical formation, 822
promotion of the *Prins reaction*, 1185
with alkyne-boranes, 1379
with biaryls, 1390
with cyclooctadiene, 200
with epoxides, 506
with formic acid and amines, 1213
with $NaBH_4$, 1515
iodoacetyl addition, to alkenes, 986
iodo-aldehydes, and radical cyclization, 964
iodoaniline, complex with cyclodextrins, 117
iodobenzenesulfonic acids, with Oxone, 1450
iodoboranes, intermediates, 1379
iodocyclopentane, reaction with silver perchlorate, 70
iodohydrins, with HgO or AgNO3, 1343
iodo-ketones, and radical cyclization, 964
iodolactamization, 987
iodolactonization, 964, 986, 1013
iodoles, amination, 599
iodomethylzinc phosphates, 1057
iodonium salts, addition of iodo azide to alkenes, 990
and *Sonogashira coupling*, 778
and the *Heck reaction*, 765
aryl, and S_N1 reactions, 736
aryl, and the *Heck reaction*, 765
aryl, with trifluoroborates, 890
with alkynes, 778
with aryl halides, Pd catalyst, 753
with thiophenols, 750
iodonium tetrafluoroborates, heating, 704
iodosobenzene, with sodium azide, 1009
iodoxybenzoic acid see IBX
and oxidation of alcohols, 1449
ion exchange resins, and sodium tetroxide, 993
ion pairing, and anti-elimination, 1260
allylic carbocations, 410
and diazonium salts, 737
and E1 reaction, 1262
and *Friedel-Crafts acylation*, 624
and internal return, 384
and isotope labeling, 385
and MO calculations, 386
and ozonolysis, 1460, 1461
and phase transfer catalysis, 444
and rearrangements, 1331
and solvent effects, 210
and stereochemistry, 386
and syn-elimination, 1260
and the *Criegee mechanism*, 1460, 1461
and the S_N1 mechanism, 383
and the S_N1 reaction, 383, 384, 1262
and the S_N1' reaction, 410
and the S_Ni' reaction, 412
carbanion, and E1cB reactions, 1267
contact, 384
destruction, and S_N2 reactions, 387
formation, and S_N2 reactions, 387
intimate, 384, 410
intimate, and S_Ni reactions, 409
mechanism, 387, 799, 1262
Sneen's ion pair mechanism, 659
solvent separated, 386, 655
tight, 384
with cyclopropanes, 881
ion radicals, and cyanation, 689
ions, bridged see bridged
ion-dipole interactions, 112
ionic bonds, and electronegativity, 18
and hard acids and bases, 332
ionic configuration, and bond energy, 30
ionic liquids also see solvents
ionic liquids, 364, 471, 1127
ionic liquids, acetal formation, 1082
acyl addition of allyltin compounds, 1118
addition of haloamines to alkenes, 989
addition of organometallics to imines, 1135
aldol reaction, 1143
alkene dihydroxylation, 993
amines with aryl halides, 751
ionic liquids, and acidity, 324
and acylation of amines, 1215
and addition of aldehydes to alkenes, 972
and addition of organometallics to carbonyls, 1115
and alkene metathesis, 1420
and aromatic sulfonation, 601, 603
and *aza-Diels-Alder reactions*, 1038
and azide formation, 496
and aziridination of alkenes, 1011
and bromination of alkenes, 983
and carboxylate salt alkylation, 469
and catalytic hydrogenation, 913
and CH oxidation, 1473
and cleavage of ethers, 504
and conjugate addition, 945, 954, 968
and coupling of alcohols, 532
and coupling of metal sulfonates and organometallics, 530
and cyclization of alkenes to alkanes, 928
and cyclization of hydroxy esters, 1220
and cyclopropylcarbinyl rearrangement, 1345
and *Diels Alder reactions*, 1023
and dihydroxylation, 365, 996
and dihydroxylation, of alkenes, 993
ionic liquids, and enamines, 548
and epoxidation of alkenes, 1000
and epoxide halogenation, 507
and esterification, 1203
and ether formation, 459
and formation of aryl sulfones, 602
and formation of biaryls, 760, 761
and formation of cyanohydrins, 1181
and formation of enamines, 1091
and formation of imines, 1091
and formation of oximes, 1094

and *Friedel-Crafts acylation*, 621–623
and *Friedel-Crafts alkylation*, 609, 610
and halogenation of alcohols, 502
and halogenation of alkenes, 983
and halogenation of aromatic compounds, 604
and halohydrin formation, 985
and homocoupling or aryl halides, 760
and hydrogenation of conjugated acids, 919
and hydrolysis of C=N compounds, 1077
and imidazolium salts, 365
and Lewis bases, 366
and *Mannich reactions*, 1103
and metal catalyzed arylation of amines, 752
and metal catalyzed coupling of allylic esters, 529
and *Michael reactions*, 945
and microwave irradiation, 366
and *Nazarov cyclization*, 946
and nitration of aromatic compounds, 593
and oxidation of alcohols with hypervalent iodine, 1450
and pyridinium salts, 365
and pyrrole alkylation, 482
and reactions of sulfur ylids, 1179
and reduction of aldehydes or ketones, 1512
and reductive alkylation of alcohols, 1084
and reductive alkylation, 1099
and *Robinson annulation*, 1150
and S_N2 reactions, 437
ionic liquids, and *Sonogashira coupling*, 776
and substitution, 451
and sulfur ylids, 1178
and *Suzuki-Miyaura coupling*, 771
and TEMPO oxidation of alcohols, 1448, 1449
and the *Baeyer-Villiger rearrangement*, 1369
and the *Baylis-Hillman reaction*, 1127
and the *Beckmann rearrangement*, 1366
and the *Bischler-Napieralski reaction*, 618
and the *Claisen rearrangement*, 1408
and the *Dakin reaction*, 1467
and the ene reaction, 943
and the *Fischer indole synthesis*, 1412
and the *Glaser reaction*, 841
and the *Grignard reaction*, 1107
and the *Heck reaction*, 764
and the *Henry reaction*, 1156
and the *Knoevenagel reaction*, 1157
and the *Michael reaction*, 945
and the *Mukaiyama aldol reaction*, 1152
and the *Pechmann condensation*, 617
and the *Rosenmund-von Braun reaction*, 758
and the *Williamson reaction*, 459
and thiirane formation, 478
and transesterification, 1208
chiral, 365, 954
and oxidation of alcohols, 365
reaction of halocarbamates with alkenes, 901
with aryl halides with amines, 751, 752
with aryl halides with phenols, 748
with aryl halides with phenoxides, 748
with DMSO and KOH, 1178
ionic melts, *Fries rearrangement*, 636
ionic polymer supported OsO_4, 997
ionic solvents see ionic liquids
ionic strength, and acidity, 346
and basicity, 346
and rate of reaction, 381
and S_N1, 381
ionic transition states, and polar solvents, 435
ionization potential, 12
alkenes and addition reactions, 873
and electronegativity, 16
and hardness, 332
and PES, 200
in keto-amines, 200
ionization ratio, 326
ionization, and carbocation formation, 218
and carboxylic acids, 345
and S_N1 reactions, 379
and superacids, 382
and the S_E1 mechanism, 654
of chlorotriphenylmethane, 213
of diazonium compounds to carbocations, 219
of protonated alcohols to carbocations, 219
rate, and azide ions, 388
rate, of sulfonate esters, 438
ionizing power of solvents, 439
ion-molecule pairs, and S_N1, 385
ion-pair mechanism, 656
ion-radical pairs, and S_NAr reactions, 735
ions, and rearrangements, and leakage, 1331
as guests in crown ethers, 111
binding by crown ethers, 108
bridged also see bridged ions
bridged, and halogenation of alkenes, 982
mesomeric, and tautomerism, 666
nitrenium, 259, 800
nitrenium, singlet and triplet, 260
pentacoordinated, 209
radical see radical ions
thiiranium, with alkenes, 1012
ipso attack, 581
and aryl radicals, 818
and carbenes, 628
and phenol formation, 634
and the *Boyland-Sims oxidation*, 634
in electrophilic aromatic substitution, 587
ipso carbon and rearrangement, 582
and substituent migration, 582
and the S_NAr mechanism, 732
ipso partial rate factors, 591
ipso position, definition, 581
ipso substitution, and the Wallach rearrangement, 1430
Ir catalyst, alcohols and alkyl halides, 460
and alkylation of amines, 485
and *Claisen rearrangement*, 1408
and cyanation of aryl halides, 759
and decarbonylation of aldehydes, 1300
and esterification of aldehydes with alcohols, 1485
and *Oppenauer oxidation*, 1447
for alcohol coupling, 532
in [2+2]-cycloadditions, 1043
IR (infrared), and acidity, 325
and arynes, 738, 739
and carbenes, 251
and carbocations, 209, 216
and conformations, 174
and *Friedel-Craft acylation*, 625
and hydrogen bonding, 100, 102
and intermediates, 276
and strained aromatic compounds, 204
cyclooctynes, 202
of methane, 11, 1583
of the ethanonium ion, 661
of the methyl radical, 243
ReactIR, 276
step-scan time-resolved, 235

Ireland-Claisen rearrangement, 1409, 1410
enantioselectivity, 1410
influence of counterion, 1410
iron, see Fe
iron carbenes, 1053
iron carbonyl, complex, 663
iron compounds, and acetal cleavage, 456
and acetal cleavage, 457
iron pentacarbonyl, with *Grignard reagents*, 708, 709, 782
with organolithium reagents, 782
iron tetracarbonylferrate, with alkyl halides, 567
isoamyl nitrite, 789
isoborneol, reaction with acid, 1338
isobutane, and dipole moment, 19
and superacids, 211
bond energy, 28
isocyanate, chlorosulfonyl, with alkenes, and microwave irradiation, 1245
with allenes, 1245
with cyclopropenes, 1245
with dienes, 1245
with imines, 1245
isocyanate ion, formation of isocyanates, 497
with alkyl halides, 447
with aromatic compounds, 630
isocyanates, addition of alcohols, 1085
addition of amines, 1103
and carbonylation of amines, 730
and catalytic hydrogenation of formamides, 1522
and dioxirane oxidation to nitro compounds, 1491
and formation of amides, 630
by carbonylation of azides, 730
by *Hofmann rearrangement*, 1360
by *Lossen rearrangement*, 1362
by rearrangement of acyl nitrenes, 1323
by the *Curtius rearrangement*, 1361
by the *Schmidt reaction*, 1363
by thermolysis of acyl azide, 1361
isocyanates, from acyl azides, 1323, 1361
from acyl halides, 498
from acyl nitrenes, 1323
from alkyl halides and isocyanate, 447
from alkyl halides, 497
from amides and hypohalites, 1360
from amides, 1223
from amines and phosgene, 1214
from azides, 730
from carboxylic acids and hydrazoic acids, 1363
from isocyanate ion, 497
from nitrile oxides, 1431
from *O*-acyl hydroxamic acids, 1362
isocyanates, hydrolysis, 1085, 1360–1363
oxidation with dioxiranes, 1491
reaction with carbamates, 1085
reduction to amines, 1530
isocyanates, with boronic acids, 1140
with *Grignard reagents*, 1139, 1140
with organolithium reagents, 1140, 1141
with oxetanes, 1085
with phosphine oxides, isotopic labeling, 1241
with phosphine oxides, mechanism, 1241
with phosphorus ylids, 1173
with water, 1362, 1363
isocyanides also see isonitriles
isocyanides, 449
isocyanides, acid catalyzed hydrolysis, mechanism, 1246
addition of water, 1246
addition reaction, 1246
and HCN, 981
and the free *Ugi reaction*, 1247
from alkenes, trimethylsilyl cyanide and silver salts, 981
from amides, 1314
from amides, microwave irradiation, 1314
from epoxides, 492
from formamides, 1314
from oxetanes, 492
hydrolysis, 1246
in situ generation, 1247
rearrangement to nitriles, 1373
reduction with Bu_3SnH, 1548
tosyl, and the *Knoevenagel reaction*, 1159
with alkynes, 1061
with *Grignard reagents*, 1247
with ketones and carboxylic acids, 1246
with organolithium reagents, 1247
with *Schwartz's reagent*, 981
isodesmic reactions, 36
isoinversion, 656
isolation, of enols, 663
of intermediates, *Neber rearrangement*, 275
isomer distributions, electrophilic aromatic substitution, 586, 587
isomerism see isomers
isomerism, cis to trans, organolithium reagents with ammonium salts, 1292
isomerism, in-out, 102
and carbocations, 102
and the *Hofmann-Martius reaction*, 640
and the *Jacobsen reaction*, 646
isomerization, cis to trans, and isotope effects, 288
cis to trans, mechanism, 276
cis to trans, of alkenes, and epoxidation, 1003
cis to trans, photochemical, 304
E to Z, of azo compounds, 598
isomerization, of aldol products, 1147
of alkenes, allylic to propenyl, 881
of alkenes, in catalytic hydrogenation, 906
of alkenes, in hydration of alkynes, 887
of alkenes, via boranes, 664
of alkyl boranes, 1299
of alkynes, acid catalyzed, 665
of allylic alcohols, 1357
of allylic amines, 882
of allylic arenes, 882
of aryl triazenes, 597
of biphenyls, 645
of boranes, 1358
of carbenes, 251
of conjugated acyl radicals, 805
isomerization, photochemical, 882
photochemical, cyclooctene, 305
thermal, of dibenzosemibullvalenes, 305
isomers, and configuration, 174
and cyclopropanation, 1056
and enantiomers, 123
and heat of atomization, 28
and rotaxanes, 118
and the 2^n rule, 163, 166
isomers, cis/trans, 132, 162
and conformations, 178
and cyclohexene, 1386
and cyclooctene, 164
and diastereomers, 162
and elimination reactions, 1273
and isomerization of triazenes, 882
and monocyclic compounds, 165, 166
and restricted rotation, 205
and silicon, 11
and stability, 202

and steric hindrance, 165
fused ring systems, 167
heat of combustion, 165
isomers, conformational, and conformer, 174
isomers, dextro, 123
isomers, E/Z, and carbon-hetereocycle double bonds, 163
and radical induced isomerization, 882
and radicals, 239
and strained bicyclic imines, 204
Cahn-Ingold-Prelog rules, 163
isomerization of alkenes, 881
of azo compounds, 305
of enolate anions, 687
of oximes, 1325
photochemical isomerization of alkenes, 882
photoisomerization, 882
selectivity in the *Wittig reaction*, 1171
isomers, exo/endo, and radical cyclization, 963
isomers, fluxional, 166
isomers, in-in, 168
and proton transfer, 323
isomers, in-out, 168
levo, 123
of amides, 164
isomers, out-in, 168
and bis(phosphoranes), 169
and cryptates, 168
and proton transfer, 323
quaternary ammonium salts, 168
racemization, 168
isomers, out-out, 168
isomers, positional, isomerization of alkenes, 881
r symbol, 167
isomers, syn/anti, and the aldol reaction, 1146, 1147
carbonyl oxides, 1463
from reaction at carbonyls, 1068
isomers, *t* symbol, 167
transitional, rotaxanes, 118
valence bond, 166
valence, and [2+2]-cycloaddition, 1050
isonitriles also see isocyanides
isonitriles, and cyanide ion, 563
conversion to isothiocyanates, 498
dehydration of amides, 1314
dehydration to isonitriles, reagents for, 1314
from amides, reagents, 1314
from amines, 492
from chloroform, 492
with alkynes, uranium complex, 1141
isopentane, bond energy, 28
isopropylation, benzene, rate and product distribution, 588
toluene, rate and product distribution, 588
isopropyllithium, and X-ray, 231
isoquinolines, by cyclotrimerization, 1061
by the *Bischler-Napieralski reaction*, 617
by the *Pictet-Spengler reaction*, 618
dihydro see dihydroisoquinolines
from alkynes, 898
from imines, 898
from nitrilium ions, 618
isoracemization, 655, 656
isoselenoureas, 1105
isothiocyanate ion, formation of isothiocyanate ions, 497
isothiocyanates, addition to alkenes, 988
cyclization, 630
formation of thioamides, 630
from acyl halides, 498
from addition of amines to carbon disulfide, 1104
from alkyl halides, 497
from amines and thiophosgene, 1214
from dithiocarbamic acid salts, 1104
from isonitriles, S, Rh catalyst, 498
from isothiocyanate ion, 497
hydrolysis, 1085
reduction to amines, 1530
reduction to thioformamides, 1522
with alcohols, 1085
with *Grignard reagents* or organolithium reagents, 1141
with imines, 1245
isothiouronium salt, from thiourea, 476
isotope effects, alkane halogenation, 824
isotope effects, and arenium ions, 571, 572
and *Baeyer-Villiger rearrangement*, 1370
and carbocations, 211
and cis-trans isomerization, 288
and E2 reactions, 1254
and E^i reactions, 1279
and elimination, 1267, 1268
and enol formation, 666
and *Grignard reactions*, 1113
and halogenation of aldehydes or ketones, 671
and hyperconjugation, 287
and mechanism, 285
and NMR, 286
and phenonium ions, 402
and radicals, 810
and rearrangements, 1326, 1329
and temperature, 288
and the *Chugaev reaction*, 1289
and the *Diels-Alder reaction*, 1029
and the S_E1 mechanism, 654
and the S_N2 reaction, 288
and the S_NAr reaction, 735
isotope effects, calculations, 286
deuterium ion, 571
isotope effects, deuterium, 285–287
and dissociation energy, 285
and E1cB reactions, 1263
and E2 reactions, 1258
isotope effects, heavy-atom, 286
in the *Diels-Alder reaction*, 1029
inverse, 286
partitioning effect, 571
secondary, 287, 1268
solvent, 288
tritium, 286
isotope exchange, 1072
rate, with carbanions, 655
isotopes C-14, 1113
isotopes, and acetal hydrolysis, 455
and alkynyl carbocations, 415
and chirality, 135
and ion pairs, 385
and S_N2 reactions, 377
and solvolysis, 385
secondary isotope effect in substitution reactions, 424
isotopic dilution, and enantiomeric purity, 162
isotopic effect, and bridged radicals, 811
isotopic labeling also see labeling
isotopic labeling, and aldehyde or ketone rearrangements, 1348
and amide hydrolysis, 1199
and aromatic S_N1 reactions, 736
and aromaticity, 60
and carbene insertion, 693
and chirality, 135
and *Claisen rearrangement*, 1407
and cyanogen bromide, 277
and *Fischer indols synthesis*, 1413
and Friedel-Crafts acylation, 625
and hydration of aldehydes and ketones, 1076
and hydrolysis of esters, 1195, 1196
and mechanism, 277
and NMR, 278

isotopic labeling, and aldehyde or ketone rearrangements (*Continued*)
and ozonolysis of alkenes, 1462
and phosphine oxides with isocyanates, 1241
and radical rearrangements, 1334
and rearrangement of N-nitroanilines, 638
and reduction of sulfoxides, 1553
and reverse *Friedel-Crafts alkylation*, 642, 643
and substitution at sulfur, 1248, 1249
and tetrahedral intermediates, 1072
and the benzidine rearrangement, 1416
and the benzyne mechanism, 737
and the *Favorskii rearrangement*, 1351, 1352
and the Fischer indole synthesis, 1413
and the *Pummerer rearrangement*, 1566
and the *Steven's rearrangement*, 1372
and the tetrahedral mechanism, 1071, 1072
and the *Wallach rearrangement*, 1430
and the *Wolff rearrangement*, 1354
and *Wagner Meerwein rearrangements*, 1341
in the *Kolbe-Schmidt reaction*, 630
with alkynes, 416
isotropic UV, 143
isovalent hyperconjugation, 86
IUPAC mechanisms, amide hydrolysis, 1198, 1200
amines with esters, 1221
and carbenes, 435
and diazonium salts, 435
aromatic S_N1 mechanism, 735
aromatic substitution, 576
chain reaction, 808
E1, 1261
E2, 861, 1254
elimination, 1278
ester hydrolysis, 1192–1197
esterification, 1204–1206
nucleophilic addition to alkenes, 865
Schmidt reaction, 1364
S_E2, 650, 653
S_E2' mechanism, 657
S_Ei mechanism, 651
S_Ei' mechanisms, 657
S_N1, 859
S_NAr mechanism, 733
substitution reactions, 432
termolecular additions, 861
tetrahedral mechanism, 1070
IUPAC names, bridged systems, 195
enantiomers, 148
Schleyer adamantization, 1341
IUPAC nomenclature, addition-elimination mechanism, 413
for transformations, 368
mechanisms, 370–371
of carbocations, 208
S_N1', 410
S_N2', 411
S_Ni, 408
IUPAC, and spectroscopy, 12
IUPAC, terminology for acids and bases, 312

Jablonski diagram, 297
Jacobsen reaction, 645
and isomerization, 646
and rearrangement, 645
and sulfonation, 646
intramolecular processes, 646
Jacobsen-Katsuki epoxidation, 1005
Japp-Klingemann reaction, 675, 676
Johnson polyene cyclization, 932
Jones reagent, and oxidation of alcohols, 1442
with OsO_4, 1464
Journal of Synthetic Methods, 1586
journals, discontinued, 1571
how to locate articles, 1600
irregular publications, 1584, 1585
languages, 1571
literature, 1570–1573
reviews, 1583, 1584
supplementary information, 1571
Julia-Colonna epoxidation, 1004

Kamlet reaction see *Henry reaction*
Kamlet reaction, 1156
Katritzky pyrylium-pyridinium method, 470, 1547
alkylation of nitro compounds, 542
and alkyl halides, 509
and thiocyanates, 480
KBr, and Oxone, halogenation of aromatic compounds, 605
Kekulé structures, 55
and polyacenes, 57
kekulene, and NMR, 78
ketals, and enol ethers, 1083
and transacetalization, 1083
as protecting groups, 1082
dimerization, 535
elimination, to vinyl ethers, 1286
formation, mechanism, 1082
from alcohols and ketones, 1081
from internal alkynes, 890
reduction, 1537
with organoaluminum reagents, 1285
ketene acetals, silyl, and conjugated ketones, 1152
conjugate addition, 956
from esters, 1152
ketene acetals, with imines, 1152
ketene dithioacetals, hydrolysis, 458
ketene silyl acetals see acetals
ketene silyl acetals, with imines, 1137
ketenes, addition of acids HX, 884
addition of alcohols and phenols, 892
addition of carboxylic acids, 893
addition reactions, 884
ketenes, and enamine acylation, 550
and formation of carbenes, 253
and *Friedel-Crafts acylation*, 622
and hydrolysis of carbamates, 1197
by base induced elimination of acyl halides, 1298
by dehydration of carboxylic acids, 1284
ketenes, cycloaddition to carbonyls, enantioselectivity, 1242
with imines, 1244
with imines, mechanism, 1245
ketenes, dimerization, 1041, 1046, 1242, 1242
ketenes, from acyl carbenes, 256
from acyl halides and amines, 1042
from acyl halides, 1299, 1306
from carbenes, 256
from the *Wolff rearrangement*, 1353
hydrolysis to carboxylic acids, 1354
hydrolysis, 1354
ketenes, in [2+2]-cycloaddition reactions, 1041, 1044, 1045
with alkenes, 1041
with alkenes, MO, 1045, 1046
with alkynes, 1042
with enamines, 1042
ketenes, in situ formation, 1299
ketenes, in situ generation, 1042

ketenes, in the *Diels-Alder reaction*, 1021
metal catalyzed cycloaddition with carbonyls, 1242
metal induced dehalogenation of acyl halides, 1306
orbital overlap in [2+2]-cycloaddition, 1044
photolysis of, 304
photolysis with diazomethane, 694
reaction with water, 1353
silyl, and *Claisen rearrangement*, 1409
thio, cycloaddition with imines, 1244
via *Wolff rearrangement*, 256
ketenes, with alcohols, 892, 1353
with aldehydes or ketones, 892
with amines, 1100
with ammonia or amines, 1353
with carbenes, 1053
with chiral alcohols, 892
with cyclopentadiene, orbital overlap in [2+2]-cycloaddition, 1045, 1046
with hydrazones, 1244
with imines, 1041, 1529
with ketenes, 1242
with ketones, 1242
with phosphorus ylids, 1173
with thiols, 895
ketenyl radicals, 805
ketimines see imines
by dehydration of amides, 1284
with aldehydes, 1122
keto acids, 1163
allyl esters, and *Kimel-Cope rearrangement*, 1409
allylic esters, *Carroll rearrangement*, 1409
and decarboxylation, 720
and *Friedel-Crafts acylation*, 623
by indirect carboxylation, 1164
decarboxylation, 720, 721
from ketones with metal carbonates, 1164
from metallated imines, 1248
metal catalyzed decarboxylative allylation, 856
oxidative cleavage of cyclic alkenes, 1464
keto aldehydes, and aliphatic Vilsmeier reaction, 685
Cannizzaro reaction to hydroxy acids, 1563
keto amides, and Friedel-Crafts acylation, 622
arylation, 779
from amide-acids and organolithium reagents, 1229
keto esters, 1012
keto esters, and acetoacetic acid synthesis, 540
α-acetoxylation of ketones, 1475
base catalyzed condensation of esters, 1234
by the *McMurry reaction* to give cyclic ketones, 1559
by the *Reformatsky reaction*, 1131
cleavage with base, 723
cyclic, *Dieckmann condensation*, 1234, 1235
decarboxylation, 721
from aldehydes, 688
from aldehydes, with carbonates, 1236
from carboxylic acid dianions and esters, 1237
from diazoesters, 688
from ketones and diazoesters, 1356
with boric anhydride, 721
with aryl fluorides, 779
with DEAD and a Cu complex, amination, 1476
with hydrazines, 1093
with phenols, 617
keto nitriles, from esters and nitriles, 1236
keto sulfonate esters, 1475
keto-enol tautomerism, 866
and torsion strain, 666
keto-enol tautomerism see tautomerism
α-ketol rearrangement, 1349
ketones, 1, 4-, from 1,3-ketones, 1355
ketones, acetal formation, 1081
α-acetoxylation, with hypervalent iodine, 1475
α-acyloxylation, 836
acid catalyzed rearrangement, 1348
acidity of γ-protons, 549
ketones, addition, of alcohols, 1081
of allylic boranes, 1124
of dialkylzinc reagents, 1115
of diazomethane, 1355
of *Grignard reagents*, mechanism, 1111, 1112
of organolithium reagents, mechanism, 1113
of organometallics, 1114–1125
of thiols, 1087
of water, 1075
ketones, alkoxy, with silyl ketene acetals, 1153
alkylation, 542
alkylation, *Stork enamine synthesis*, 550
ketones, alkynyl see alkyne-ketones
amino, and *Michael addition*, 1230
amphiprotic properties, 665
ketones, and azine formation, 1092
and bisulfite addition products, 1090
and cyclodehydration, 617
and enolate anion formation, 1113
and formation of aminals, 1091, 1092
and formation of cyanoamines, 486
and formation of dianions, 1236.1237
and formation of enolate anions, 680, 1143
and formation of esters, 1083
and formation of halo-ketones, 668
and formation of nitroso compounds, 675
and formation of oximes, 675
and formation of oxocarbenium ions, 1348
and formation of thioketones, with hydrogen sulfide, 1087
and *Peterson alkenylation*, 1162
and reagents for hydrolysis of C=N compounds, 1077, 1078
and tautomerism, 89
and the *Baeyer-Villiger rearrangement*, 1368
and the *Haller-Bauer reaction*, 725
and the *Haworth reaction*, 623
and the *Japp-Klingemann reaction*, 675
and the *McMurry reaction*, 1559
and the *Nozaki-Hiyama reaction*, 1121
and the *Reformatsky reaction*, 1129
and the *Strecker synthesis*, 1182
and the *Willgerodt reaction*, 1566
ketones, aryl, and imino esters, 633
and the *Hoesch reaction*, 632
from carboxylic acids, 621
from *Friedel-Crafts acylation*, 621
from nitriles, 632
from acyl halides, 621
from aromatic compounds, 621
ketones, base catalyzed addition to carbon disulfide, 1164
base cleavage, and strain, 725
base cleavage, steric effects, 725
bicyclic conjugated, and *Robinson annulation*, 1150

ketones, base catalyzed addition to carbon disulfide (*Continued*)
bicyclic, and thermal extrusion of carbon monoxide, 1309
bicyclic, by metal catalyzed carbonylation of alkynes, 975
bicyclic, from dienones, 1426
ketones, by acetoacetic acid synthesis, 540
by acid catalyzed rearrangement of epoxides, 1343
by addition of aldehydes to alkenes, 971
by carbonylation of aryl halides, 782
by cleavage of diketones, 723
by DMSO-type oxidation of alcohols, 1448
by *Friedel-Crafts cyclization*, 617
by *Fries rearrangement*, 635, 636
by *Fukuyama coupling*, 1231
by hydration of alkynes, 887
by hydration of allenes, 888
ketones, by hydrolysis, of alkoxides, 1511
of C=N compounds, 1077
of enol ethers, 887
of imines, 1482
of oximes, 848
ketones, by *Oppenauer oxidation*, 1447
ketones, by oxidation, of alcohols, 1442–1452
of alcohols, reagents for, 1446, 1447
of alkenes, 1487–1489
of alkenes, reagents for, 1489
of amines, 1482
of vinylboranes, 1380
ketones, by oxidative cleavage of, diols, 1456, 1457
of alkenes, 1463
ketones, by ozonolysis, of alkenes, 1459
by pyrolysis, of allylic ethers, 1315
by rearrangement, of hydroperoxide, 1370
by the *Nef reaction*, 1079
by the *Prins reaction*, 1013
by the *Stork enamine reaction*, 550
by the *Wacker process*, 1488
ketones, carboxylation, 1163
catalytic hydrogenation, 1506
α-CH oxidation, with selenium dioxide, mechanism, 1478
chemoselective reducing agents, 1505
ketones, chiral, 1147
and chiral amide base, 668
epimerization, 667
ketones, cleavage, and carbocations, 725
and the haloform reaction, 723
with amide bases, 725
with base, 723, 724
with base, solvent effects, 724
with halogen, 724
ketones, condensation see aldol
ketones, condensation, with esters, 1153, 1154, 1236
with imines, 1149
ketones, conjugated also see conjugated compounds
ketones, conjugated, α-acyloxylation, 836
and enolate anions, 547
and *Meyer-Schuster rearrangement*, 412
and *Nazarov cyclization*, 946
and organolithium reagents, 1109
by the aldol reaction, 1141–1153
by *Wurtz coupling*, 514
by α-oxidation of alkenes, 1477
carbonylation, 978
from acyl halides, 684
from alkenes, 684
from allenes, 412
from epoxy ketones, 1287
from haloketones, 685
from ketones, 1441
from selenoalkyl ketones, 681
from *Weinreb amides*, 1230
ketones, conjugated, halogenation, 672
and the *Dess-Martin periodinane*, 672
ketones, conjugated, proton acidity, 549
reagents for conjugate reduction, 917
reduction, with enzymes, 919
reduction, with reductases, 919
via *Weinreb amides*, 1230
with aldehydes, and radicals, 1188
with boranes, 957
with *Grignard reagents*, 1109
with LDA, 780
ketones, conversion to amides, 1566
ketones, cyclic, and I strain, 351
and reactivity, 351
and the *Schmidt reaction*, 1364
aromatization to phenols, 1438
by expansion of bicyclic ketones, 1356
by *McMurry reaction* with keto esters, 1559
by *Ruzicka cyclization*, 1238
conjugated, by carbonylation of alkynes, 975
conjugated, by hydrogenation of phenols, 913
conjugated, by the *Pauson-Khand reaction*, 976
from acid catalyzed rearrangement of amino alcohols, 1346
from aldehydes and conjugated esters, 1123
from keto esters, 1559
in the *Baeyer-Villiger rearrangement*, 1369
oxidative cleavage, reagents for, 1458
oxidative cleavage, to dicarboxylic acids, 1458
oxidative cleavage, with sodium hypochlorite, 1458
pyrolysis, of dicarboxylic acids, 1238
ring expansion, 1355
via *Weinreb amides*, 1230
with dihalides and *Collman's reagent*, 564
with hydrazoic acid, 1364
with hydrogen peroxide, 1319
ketones, cyclization, with dihalides, 545
cycloaddition, to alkenes, 1243
cyclopropyl, from conjugated ketones, 1178, 1179
decarboxylation, of carboxylic acids, 1238
dehydrogenation, 1441
diastereoselectivity, of reduction with Selectride, 1505
diazo, decomposition, 1244
dihalogenation, 670
diketones see diketones
dimerization, with UV, 1557
divinyl, 565
divinyl, from vinyl organometallics, 564
enantioselective acyl addition see acyl addition
enol content, 90
enolate anion blocking groups, 546
enzymatic reductions, 1510
epoxy, 1004
fluorination, 669, 670
formation of hemiaminals, 1090
formylation, 686
ketones, from acid chlorides, 565
ketones, from acyl halides, 624, 1226
and boronic acids, 1225, 1226
and organocadmium reagents, 1229
and organocuprates, 1225
and organometallics, 1225, 1226

ketones, from aldehydes, 553, 688, 689, 1355
from aldehydes, and diazomethane, 694
from alkenes, oxidizing reagents, 1489
from alkoxides, 654, 722
from alkyl halides, 565, 959
from allylic alcohols, 1357
from amides, 626
from anhydrides, and boronic acids, 1227
from aryl halides, 782
from arylboronic acids, 782
from boranes, 558
from boronic acids, 1226
from carboxylic acids, 722, 1131, 1238
from carboxylic acids, and organolithium reagents, 1131
from cyanoboranes, 1376, 1377
from cycloaddition, of singlet oxygen to alkenes, 1040
from diazoketones, and *Wolff rearrangement*, 1244
from dicarboxylic acids, 1469
from dicobalt octacarbonyl, 708
from dihalides, 452
from diols, 1342
from dithianes, 553
from enamines, 551
from enol borinates, 957
from epoxides, 1343
from esters, 635, 1228
from esters, and organolithium reagents, 1229
from formamides, and organolithium reagents, 1229
ketones, from *Grignard reagents*, 708
and acyl halides, 1227
and nitriles, 1139
and *Weinreb amides*, 1230
ketones, from halo amides, 1360
from halo amines, 1307
from halohydrins, 1343
from haloketones, 558
from homoallylic alcohols, 1315
from hydrazones, 152, 549
from hydroperoxides, 1370
from hydroxynitriles, 549
from iminium salts, 633, 1140
from metallated imines, 1248
from organocerium reagents, 1230
from organolithium reagents, 708
from organolithium reagents, and carboxylic acids, 1229
from organolithium reagents, and Weinreb amides, 1230
from organometallics, 564, 708
from organosulfur carbanions, and esters, 1236
from oxazolidines, 557
from oxocarbenium ions, 1149
from silyl enol ethers, 534, 686
from silyl-epoxides, 1163
from the *Collman's reagent*, 564
from thioesters and organozinc halides, 1231
from thioesters, 1231
from vinyl halides, 452
from vinylic compounds, 453
ketones, halo, and *Favorskii rearrangement*, 1351
from diazo ketones, 508
radical ring expansion, 1347
ring contraction, 1351
ketones, halogenation, and microwave irradiation, 669
enantioselectivity, 669
enantioselectivity, metal catalyzed, 671
mechanism, 671
rate, 671
reagents for, 668, 672
regioselectivity, 672
ketones, heteroaryl, by carbonylation, 782
hindered, with hydroxylamine, 1094
homoallylic, from keto acids, 856
homologation, 1355
hydration of, 1075
hydroxy, 1160
hydroxy, from epoxy alcohols, 1344
α-hydroxylation, 1473
α-hydroxylation, and mcpba, 1474
α-hydroxylation, enantioselectivity, 1473
α-hydroxylation, metal catalysts, 1473
α-hydroxylation, with enzymes, 1473
aldol condensation, with aldehydes, 1144
Claisen condensation, 1154
Claisen-Schmidt reaction, 1144, 1145
Henry reaction, 1156
Knoevenagel reaction, 1157
Mannich reaction, 1100
Mukaiyama aldol reaction, 1151–1153
Paterno-Büchi reaction, 1049, 1243
Wolff-Kishner reduction, 1540
in the aldol condensation, 1141–1153
ketones, indirect carboxylation, 1163
iodination, 669
less reactive than aldehydes, 1069
$LiAlH_4$ reduction, mechanism, 1508
macrocyclic, conformation, 189
mechanism of hydration, 1076
Meerwein-Ponndorf-Verley reduction, 1507
ketones, metal catalyzed, coupling to oximes, 1558
cycloaddition with ketenes, 1242
reaction with dihalosulfones, 1175
ketones, metal mediated, addition of haloesters, 1129
halogenation, 669
ketones, methyl, and the haloform reaction, 724
by homologation of aldehydes with diazomethane, 1355
α-methylation, and the *Simmons-Smith procedure*, 1058
nitrosation, mechanism, 676
α-oxidation to diketones, 1476
α-oxidation with SeO_2, 1476
α-oxidation, metal catalysts, 1477
α-oxidation, reagents for, 1476, 1477
ketones, nitro, with amines, 725
oxytosylation, 1475
photochemical [2+2]-cycloaddition, with alkenes, 1049
photochemical cleavage, 246
photochemical dimerization to diols, 1557
photochemical dimerization, mechanism, 1557
photochemistry, 293
photoreduction, 306
prochiral, reduction of, 1511
protecting groups, 1088
protection, 457
radical coupling, 840
ketones, reaction, with alcohols, compatible functional groups, 1082
with amines, 1090
with base, 1143
ketones, reduction, and *Cram's rule*, 1515
diastereoselectivity, 1515
enantioselectivity, 1511–1515
in ionic liquids, 1512
in supercritical alcohols, 1542
to alcohols, 1503–1515
to methylene, reagents for, 1541
versus aldehydes, 1505
with alanes, 1509

ketones, reduction, and *Cram's rule* (*Continued*)
with aluminum isopropoxide, 1507
with ammonium formates, 1510
with baker's yeast, 1510
with boranes, 1508
with enzymes, 1512
with hydrides, 1503
with metals, 1507
with sodium in ethanol, 1506
with sodium in ethanol, mechanism, 1506
with tin hydrides, 1509
ketones, reductive amination, 1096–1099
ketones, reductive cleavage, of nitriles, 1539
ketones, reductive coupling, to alkenes, reagents, 1558
to diols, reagents, 1555
ketones, reductive dimerization, 1085
regioselectivity, of halogenation, 670
selenoalkyl, formation of conjugated ketones, 681
singlet, 1557
steric hindrance, and reduction, 1505, 1506
sterically hindered, and $LiAlH_4$, 1504
sterically hindered, and *Wolff-Kishner reduction*, 1540
structural requirements, and the *Wittig reaction*, 1166
sulfenylation, 681
sulfonation, 680
tautomerism, 665
thermal extrusion of carbon monoxide, 1309
thioalkyl, from enolate anions, 680
thioalkyl, from silyl enol ethers, 681
thioaryl, from silyl enol ethers, 681
triplet, 1557
ketones, unsymmetrical, acidity of α-protons, 547
and enolate anions, 546
formation of silyl enol ethers, 687
regioselectivity, 546
ketones, via decarboxylation, 722
ketones, with acyl halides, 1084
with alcohols and HX, 1106
with aldehydes, 1164
with alkenes or alkynes, 1122
with alkenes, intramolecular, 939
with alkyne anions, 1114
with alkyne anions, enantioselectivity, 1115
with alkynes, 1122
with allenes, 1122, 1123
with allylic halides, and transition metals, 1116
with allyltin compounds, 1118
with aluminum cyanides, 1181
with amide bases, 680
with amines and hydrogen, 1096–1099
with amines, 551, 1090, 1096
with an acid catalyst, 1149
with aromatic compounds, 615
with base, 666
with 9-BBN, 923
with bis(*Grignard*) reagents, 1109
with borane reduction reagents, 1509
with carbanions, 234
with carbonates, 1236
with chiral hydrazines, 152
with cyanide ion, 1182
with diazo compounds, 1188
with diazo esters, 1175, 1356
with diazoalkanes, 1177
with diazomethane, 1177
with diazosilylalkanes, 1175
with dihalocarbenes, 1177
ketones, with enamines, 1145
with enol esters, 545
with enolate anions, 232, 1141–1153
with enolate anions see aldol
with esters, 1155, 1236
with formaldehyde, 1164
with *Grignard reagents*, 1107–1114
with H_2S and an acid catalyst, 1088
with halo esters, 1161
with halogens, 668
with halo-sulfones, 1177
with HCN, 1180
with hydrazines, 1092
with hydrazoic acid, 1363
with hydrogen sulfide, 1087
with hydroxylamine, 1094
with isocyanides and carboxylic acids, 1247
with isocyanides, 1246
with LDA, 686, 1143
with lithio-silanes, 1162
with methyltrioxorhenium, 1175
with Mo peroxide, α-hydroxylation of enolate anions, 1473
with MoOPH, α-hydroxylation of enolate anions, 1473
ketones, with nitro compounds, 1156
with nitrous acid, 675
with nitrous acids, 675
with organoaluminum or organotitanium compounds, 1119
with organochromium compounds, 1121
with organocuprates, 1122
with organolithium reagents, 1108, 1160
with organometallics, 153
with organometallics, enantioselectivity, 1117
with Oxone, epoxidation of alkenes, 1001
with phenylhydrazine, 1412
with phosphorus ylids, 1165
with silanes, metal catalyzed, 687
with sodium bisulfite, 1090
with sulfones, 1159
with sulfur ylids, 1175–1177
with the *Petasis reagent*, 1174
with the *Tebbe's reagent*, 1174
with the Tollens' reagent, 1164
with thiobenzilic acid, 1320
with tosylimines and proton sponge, 1244
with various metal salts, 1122
with ylids, 1165–1173
keto-nitriles, by the Thorpe reaction, 1179
from esters and nitriles, 1236
keto-sulfones, alkylation, 540, 548
keto-sulfoxides, alkylation, 540, 548
ketoximes see oximes
keto-ylids, and resonance, 1167
ketyl intermediate, *Grignard reactions*, 1112, 1113
ketyls, and reduction of carbonyls with sodium in ethanol, 1506
and the acyloin condensation, 1561
and the *Gomberg-Bachmann pinacol synthesis*, 1555
and the *Wittig rearrangement*, 1374
radical ions, 248
KHMDS, arylation of active methylene compounds, 778
Kiliani-Fischer method, 1182
Kimel-Cope rearrangement, 1409
Kindler modification, Willgerodt reaction, 1566
kinetic acidity see acidity
kinetic and thermodynamic control, arenium ions, 576
kinetic control, and sulfur ylids, 1176
ester enolate anions, 1234
kinetic isotope effects, 458, 639
kinetic reactions, free energy, 272
kinetic resolution also see resolution
kinetic resolution, 136, 156
and enantiomeric purity, 162
and epoxidation, 1005

ketones, 668
kinetically controlled reactions, 271, 272
kinetics, amide hydrolysis, 1198
and aliquots, 282
and bond rotation, 283
and calorimetric methods, 282
and enthalpy, 265
and entropy, 284
and ESR, 282
and frequency factor, 284
and half-life, 282
and homogenous reactions, 278
and ion pairs in the S_N1 reactions, 383
and *Marcus theory*, 279
and mechanisms, 283, 278
and molecularity, 279
and NMR, 283, 382
and pressure, 282
and quenching, 282
and rate constant, 279
and rate law, 278, 280
and rate-determining step, 279
and reactions, 265
and salt effect, 381
and secondary isotope effects, 287
and solvent isotope effects, 288
and spectroscopic methods, 282
and steady state, 280
benzidine rearrangement, 1416
E1 reaction, 1261
E^i reactions, 1279
epoxidation of alkenes, 999
fast reactions, 282
kinetics, first order, 380, 381
and the S_E1 mechanism, 654
rate law, 282
reactions, 279
kinetics, gas phase reactions, 282
Heck reaction, 767
inverse isotope effects, 286
lead tetraacetate cleavage of diols, 1457
methods for determining, 281
nitration of aromatic compounds, 596
nitrosation of aromatic kings, 597
nitrous acid with amines, 789
of elimination, 1264
of the *Mannich reaction*, 1101
overall rate, 281
periodic readings, 281
pseudo first-order, 281
radical chain reactions, 807
radical cyclization, 962
radical heterolysis, 810
rearrangement of cyclopropylcarbinyl radicals, 814
kinetics, second order reaction, 279, 280
HBr with alkenes, 883
kinetics, S_N1, 382
and leaving groups, 380
kinetics, S_N2, 375
kinetics, spectral readings, 281, 282
substitution at sulfur, 1249
thioester hydrolysis, 1072
very fast reactions, 282
kink-type atoms, catalytic hydrogenation, 907
Kishi's NMR method, and absolute configuration, 143, 144
Knoevenagel carbanions, with allylic esters, 528
Knoevenagel condensation, 1142, 1157
acid catalyst, 1157
and acyl anion equivalents, 1160
and ammonium salts, 1158
and carbamates, 1160
and *Darzens condensation*, 1161
and high pressure, 446, 1158
and the homoaldol reaction, 1160
and the *Nef reaction*, 1158
and the Wittig reaction, 1159, 1160
and tosylhydrazones, 1160
and tosylisocyanides, 1159
Doebner modification, 1158
hydroxysulfonamides, 1159
in ionic liquids, 1157
metal catalyzed, 1158
microwave irradiation, 1158
on silica gel, 1158
on zeolites, 1158
products, 1158
solventless, 1158
special variations, 1159, 1160
structural variations, 1157
suitable functional groups, 1157
ultrasound, 1158
knots, molecular, 120, 121, 135
Koch reaction, *972*
Koch-Haaf reaction, 566, 972
KOH, aqueous, and *Stille coupling*, 682
with amines, 474
Kolbe electrosynthesis, see *Kolbe reaction*
Kolbe reaction, 853, 1318
and electron transfer, 1435
mechanism, 853
Kolbe-Schmidt reaction, 629
in supercritical carbon dioxide, 629
isotopic labeling, 630
mechanism, 629
metal catalyzed, 630
Kornblum reaction, 1481
Kornblum's rule, and ambident nucleophiles, 449
Krebs cycle, and enantiotopic, 170
Krönke reaction, and microwave irradiation, 1482

La catalysts, aldehydes with amines, 1486
labeling, and acetal hydrolysis, 455
and decarboxylation, 645
and enantiotopic atoms, 171
and insertion reaction, 693
and ion pairs, 385
and phenonium ions, 402
and solvolysis, 385
in vinyl ether hydrolysis, 457
in alkynyl carbocations, 415
in *Friedel-Crafts allylation*, 615
in the *von Richter rearrangement*, 798
isotopic, and mechanism, 277
with cyclopentadienide ion, 58
with peroxyesters, 836
with water, 798
lactamization, 1216
enzymatic, 1217
α-lactams, from halo-amides, 495
β-lactams, arylation, 755
by [2+2]-cycloaddition, 1041, 1042
by cycloaddition of imines and ketenes, 1464
by radical cyclization, 963
carbonylation of aziridines, 1245
formation of, enantioselectivity, 1244
from alkenes and chlorosulfonyl isocyanate, 1245
from carboxylic acids and imines, 1244
from enamines, 1042
from imines and diazo ketones, 1245
from imines and halo esters, 1244
from ketenes and hydrazones, 1244
from β-amino esters, 1220
lactams, alkylation, 445, 493
α-alkylation, 543
alkylidene, from dihalosulfone and imides, 1174
alkylidene, from ynamides, 900
aminomethyl, 482
and allylboranes, 1231
and determining absolute configuration, 142
and *Friedel-Crafts acylation*, 622
and proton transfer, 324
and strain, 199
arylation, 755
bicyclic, 901
bicyclic, from carbamates, 900

lactams, alkylation (*Continued*)
lactams, by [2+2]-cycloaddition, 1041
by amidation of alkenes, 900
by *Beckmann rearrangement*, 1366
by carbene insertion, 692
by carboxylation of alkenes, 979
by *Diels-Alder reactions*, 1038
by halolactamization, 986, 987
by α-oxidation of amines, 1477
by α-oxidation of amines, reagents, 1477
by radical cyclization, 963, 964
by rearrangement of oxaziridines, 1344
by reduction of imides, 1545
by *Schmidt reaction* with cyclic ketones, 1364
lactams, carbonylation of alkenes, 978
CH oxidation, 1478
conjugate addition, 966
conjugated, from hydroxylactams, 1283
conversion to thiolactams, 1089
enolate anion, with aryl halides, 780
lactams, from alcohols, and amines or ammonia, 1220
from alkene-amides, 901, 1013
from alkenes, 1013
from amines, 1477
from amino acids, 1216
from amino esters, 1220
from azide-carboxylic acids, 1217
from cyclic ketones, 1364, 1366
from cyclic oximes, 1366
from halo amides, 1427
from ketenes with imines, 1529
from ketenes, 1354
from oxaziridines, 1367
lactams, hydrolysis, 1197
hydroxy, by reduction if imides, 1546
N-halogenation, 731
α-oxidation to imides, 1478
reaction with ylids, 1166
reduction to cyclic amines, 1545
reduction with 9-BBN, 1545
ring expansion, 1222
ring expansion, from cyclic amines, 731
sulfenylation, 681
via alkene metathesis, 1420
with alkyl halides, 493
with amines at high pressure, 1222
with *Grignard reagents*, 534
with organolithium reactions, 1230
with sodium hydride, 493
lactic acid, and absolute configuration, 137
lactim ethers, vinyl, Diels-Alder reactions, 1038
β-lactones, angle strain and reaction with amines, 1221
carbonylation of propargyl alcohols, 978
decarboxylation to alkenes, 1309
decarboxylation, 1318
from hydroxy acids, 1204
from ketenes and carbonyls, 1242
hydrolysis, 1221
pyrolysis to alkenes, 1309
lactones, and α-alkylation, 543
and *Baeyer-Villiger rearrangement* of cyclic ketones, 1369
and conformations, 189
and neighboring group mechanisms, 392
and seco acids, 1204
and the *Mukaiyama reagent*, 1204
by addition halo-esters to alkenes, 991
by carbonylation, 566
by carbonylation, of aryl halides, 781
by carboxylation, of alkenes, 978
by halolactonization, 986, 987
by metathesis reactions, 1421
by *Mukaiyama aldol reaction*, 1152
by radical cyclization, 964
by reduction of anhydrides, reagents, 1544
by *Stille coupling*, 524
carbonylation of diiodides, 568
α-CH oxidation of cyclic ethers, 1478
chiral, and Cinchonidine alkaloids, 888
chiral, from achiral lactones, 1369
chiral, via Bayer Villiger rearrangement, 1369
cleavage, 477
conjugated, reagents for reduction, 918
conversion to thiolactones, 1089
coupling with allylic esters, 528
cyclic, via the Story synthesis, 1319
decarboxylation, 1318
dehydrogenation, 1441
dyotropic rearrangements, 1431
lactones, extrusion of carbon dioxide, 1310, 1318
formation with DCC, 1205
formation, and ring size, 269
lactones, from aldehyde-carboxylic acids, 1155
from alkenes, 1013
from alkyne-carboxylic acids, 893
from allenic alcohols, 978
from cyclic peroxides, 1319
from dialdehydes and the *Cannizzaro reaction*, 1563
from dicarboxylic esters and the *Tischenko reaction*, 1564
from diene-carboxylic acids, 892
from diols, 1484
from epoxides, 536
from halo-acids, 269
from halo-amides, 1427
from hydroxy acids, 1203, 1204, 1563
from hydroxy carboxylate salts, 469
from hydroxy esters, in ionic liquids, 1220
from hydroxy-trimethylsilyl alkenes, 888
from iodo-alcohols, 566
hydration of alkene-carboxylic acids, 887
hydrolysis, 1191
iodo, with alkenes, 991
lactones, macrocyclic, from cyclic ketones, 723
from hydroxy acids, 1204
lactones, photolysis, 1318
lactones, pyrolysis, 1288
to alkene acids, 1288
lactones, reduction, 1543
spontaneous ring formation, 1191
sulfenylation, 681
thermal extrusion of carbon dioxide, 1310
thiono, 1133
transesterification, 1207
lactones, with allylic halides, 1232
with hypervalent iodine, 469
with lithium iodide, 508
with phosphorus ylids, 1173
with the *Petasis reagent*, 1174
with the *Tebbe's reagent*, 1174
with ylids, 1166
lactonization, 1203, 1204
and seco acids, 1204
and the *Yamaguchi protocol*, 1204
and ultrasound, 1013
from amides, 1013
from cyclic dienes, 1013
of alkenes, 1013
of alkenes, ultrasound, 1013
reagents for, 1204
Ladenburg formula, 1051
Lange's Handbook of Chemistry, 1581

lanthanide shift reagents, 142, 161
large angle strain see strain
large rings, strain, 201
lariat ethers, 111
laser flash photolysis, 209
Lawesson's reagent: [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]
Lawesson's reagent, 1089
  formation of amides, 1217
  with alcohols, 476
  with carboxylic acids, 1211
  with ketones, 1089
  with phosphonate esters, 1289
LC (liquids chromatography)
  preparative, diastereomers and resolution, 156
LCAO (linear combination of atomic orbitals), 5
LDA (lithium diisopropylamide)
LDA, 544
  aggregates of, 341
  and [3+2]-cycloaddition, 1020
  and allylic carbanions, 1020
  and anionic Fries rearrangement, 637
  and carboxylic acids, 552
  and *Claisen condensation*, 1234
  and elimination of ethers, 1285
  and enol borinates, 547
  and enolate anion formation, 1143
  and esters, 1234
  and formation of enolate anions, 698
  and the aldol reaction, 1144
  and the *Claisen-Schmidt reaction*, 1144, 1145
  and X-ray crystallography, 341
  with amides, 1155
  with carboxylate anions, 1237
  with conjugated ketones, 780
  with epoxides and diamines, 1287
  with esters, 1154
  with ketones, 686
lead carboxylates, chiral, 1456
lead tetraacetate, and acyloxylation, 835
  and bis(decarboxylation), 1468
  and oxidative cleavage of diols, 1456
  and oxidative decarboxylation, 1468
  cleavage of diols, cyclic transition state, 1457
  cleavage of diols, mechanism, 1457
  conversion of alcohols to cyclic ethers, 830
  hydroxysulfenylation, 1006
  radical mechanism, 1468
  reactions of, 836
  with cyclopropanes, 879
  with dicarboxylic acids, 1469
lead, pyrophoric, coupling of acyl halides, 1232
leakage, rearrangement of ions, 1331
leaving group ability, and E1cB character, 1268
  and elimination, 1266
  ability, table, 436
leaving group order, nucleophilic aromatic substitution, 744, 745
leaving groups, 373
leaving groups, amines, 433, 1258
  amino, in *Mannich bases*, 433
leaving groups, and basicity, 432
  and carbene formation, 435
  and conjugate bases, 1262
  and electrophilic aromatic substitution, 591
  and elimination, 1259
  and neighboring groups, 391
  and nucleophilic aromatic substitution, 734, 744, 745
  and nucleophilic substitution, 419
  and rate, 1074
  and reactions, 1269
  and rearrangement of nitrenes, 1323
  and S_E1 reactions, 659
  and S_N1 reactions, 380, 1074
  and S_N2' reactions, 410
  and S_N2 reactions, 1074
  and solvent ionizing power, 441
  and strain, 432
  and substitution reactions, 432
  and syn elimination, 1260
  and the E1cB mechanism, 1265
  and the element effect, 414
  and the tetrahedral mechanism, 1073, 1074
leaving groups, at saturated carbon, 432
  axial versus equatorial, in E2 reactions, 1256, 1257
  azide, 706
  aziridines, 432
  benzotriazoles, with E^i reactions, 1292
  CO, 1309, 1317
  CO_2, 644, 1210, 1238, 1242, 1310, 1318, 1319
  definition, 262
  diazonium groups, 788
  diazonium salts, 434
  dimethyl sulfide, 1481
  dimethylsulfonium, 1275
  ditosylates, 433
  E1 versus E2 reactions, 1276
  E1 versus E2 versus E1cB, 1277
  elimination versus substitution, 1276
  formation of amides from esters, 1219
  H atom, 810–813
  halides in halide exchange, aryl halides, 757
  halides, 738
leaving groups, in aromatic amination, 751
  in epoxides, 432
  in the E2 reaction, 1254
  in thiiranes, 432
  kinetics and S_N1 reactions, 380
  metal, 659
  N_2, 434, 788, 790, 797, 846, 1017, 1294, 1316, 1455, 1542
  nitronium ion, 591
  other, in aromatic substitution, 641
  p-nitrophenyl esters, 1219
  proton, 569
  pyridyl, 1266
  pyrylium salts, 433
  reactivity in elimination reactions, 1276
  SO_2, 1302, 1303, 1318
  solvation by, 655
  substitution versus elimination, 1277
  suitable for elimination, 1276
  sulfonate esters, 432, 433
  sulfonyl groups, 1249
  β-substituents, 391
Lederer-Manasse reaction, 616
Lemieux-von Rudloff reagent, oxidative cleavage of alkenes, 1463
length, bond see bond distance
length, cell, and specific rotation, 124
Leuckart reaction, and the *Wallach reaction*, 1098
leveling, carbon-14, 277
levo isomer, 123
Lewis acid catalysis, and the *Prins reaction*, 1185
  in the *Diels Alder reaction*, 1022
  of sulfonyl halides with halo esters, 524
Lewis acid-base complex, 330
Lewis acid-base, rate complex, 330
Lewis acids, addition of acyl halides to alkenes, 992
  addition of thiols to alkenes, 894
Lewis acids, and acetal cleavage, 456
  and acetals, 456
  and acyl carbocations, 625
  and addition of alkyl halides to alkenes, 990
  and alcohol dehydration, 464
  and arenium ions, 663

Lewis acids, and acetal cleavage (*Continued*)
and aryl halides, 647
and *Brønsted acidity*, 338
and condensation of enamines with aldehydes or ketones, 1145
and electrophiles, 569
and enol alkylation, 544
and epoxide alcoholysis, 465
and esterification of carboxylic acids, 1206
and formation of aryl ketones, 621
and formation of biaryls, 619
and formation of carbocations, 642
and formation of keto-esters, 688
and *Friedel-Crafts alkylation*, 611
and halogenation of aromatic compounds, 604
and hardness, 331
and imino esters, 633
Lewis acids, and nitration of aromatic compounds, 594
and oxonium ion formation, 472
and reaction of allylic silanes with aldehydes, 1180
and rearrangement of alkenes, 664
and reverse *Friedel-Crafts reactions*, 641
and softness, 331
and solvent effects, 343, 344
and steric effects, 338, 340
and the *Beckmann rearrangement*, 1312
and the *Gatterman-Koch reaction*, 627
and the *Johnson polyene cyclization*, 932
and the Periodic table, 330, 337
and the *Prins reaction*, 1186
and thioalkylation of aromatic compounds, 632
Lewis acids, as catalysts for *Curtius rearrangement*, 1361
as catalysts for transesterification, 1207
catalysis of hydroperoxide rearrangement, 1370
catalysis of ketene cycloaddition to carbonyls, 1242
catalysis, addition of carboxylic acids to alkenes, 892
catalysts *for Claisen rearrangement*, 1409
catalysts for formation of aryl sulfones, 602
chiral, 340
chiral, and the *Claisen rearrangement*, 1411
coordination with functional groups, 612
definition, 330
Lewis, acids, for addition of alcohols to carbonyls, 1081
for addition of allylic silanes to aldehydes, 1125
for carboxylic esters from ethers, 471
for cleavage of cyclic ethers, 504
for cleavage of ethers, 504, 505
for coupling alkenes with acyl halides, 684
for ethers with anhydrides, 471
for *Friedel-Crafts acylation*, 622
for halogenation of anilines, 604
for halogenation of aromatic compounds, 606, 607
for reaction of thiols with aldehydes or ketones, 1087, 1088
for rearrangement of epoxides to ketones, 1343
for reversal of *Friedel-Crafts alkylation*, 641
for the *Beckmann rearrangement*, 1365
Lewis acids, in the *Diels-Alder reaction*, 1022
in the ene reaction, 942, 943
in the *Nazarov cyclization*, 946
lithium perchlorate, 331
reaction types, 330
reactivity order in *Friedel-Crafts alkylation*, 611, 612
strength of, 331
used for the *Prins reaction*, 1186
used for the *Ritter reaction*, 1239
used in the *Diels-Alder reaction*, 1022
Lewis acids, with acyl halides, 621
with aldehydes and diazoesters, 688
with alkanes, 1341
with alkenes and aldehydes or ketones, 1122
with alkenes, in the *Friedel-Crafts alkylation*, 614
with alkynes and aldehydes or ketones, 1122
with allylic silanes and epoxides, 511
with amines, 492
with aryl esters, 636
with aryl halides, 647
with *Danishefsky's diene*, 1037
with epoxides and organocuprates, 536
with imines, 1312
with $LiAlH_4$, reduction of esters, 1543
with nitriles, 632
with organocopper compounds, and alkyl halides, 523
with potassium cyanide, 563
with sodium cyanide, 563
with tosylaziridines, 1304
Lewis bases, ab initio calculations, and base strength, 330
and nucleophiles, 373, 426
and steric effects, 338
definition, 330
in ionic liquids, 366
Lewis structures, 6, 14, 31
and resonance, 43
benzene, 36
Ley reagent see TPAP
LHMDS (lithium hexamethyldisilazide)
LHMDS, 543, 544
and aggregates, 342
and enolate anions, 1146
as a base, 342
Li powder, 716
$LiAH_4$ lithium aluminum hydride
LiBr, with enolate anions, 233
LICA, 544
and ester enolate anions, the *Claisen rearrangement*, 1409
and esters, 1234
and the *Claisen condensation*, 1234
LICKOR, 695
LiCN, with vinyl triflates, 564
LIDAKOR reagent, and elimination of epoxides, 1287
lifetime, of carbanions, 866
of radicals, 236, 814, 1335
oxocarbenium ions, 219
ligand free reactions, *Sonogashira coupling*, 776
Suzuki-Miyaura coupling, 771
ligands, amines, 41
and *Suzuki-Miyaura coupling*, 770
and η-complexes, 41
ligands, chiral, 1134, 1137, 1149, 1153
and dihydroxylation, 995–997
and *Suzuki-Miyaura coupling*, 773
carbenes, 1122
phosphines, 780
dppf, 560
imidazolium, 772
in enantioselective catalytic hydrogenation, 904

phosphine, 41
phosphine, polymer bound, 752
salen, 1005
light, and autoxidation, 832
and optical activity, 145
circularly polarized, 124
circularly polarized, and asymmetric synthesis, 154
plane polarized, 122, 138
plane polarized, rotation of, 123
limonylborane, 924
Lindlar catalyst, and hydrogenation of alkynes, 905
linear combination, MO, 6
linear free energy relationship (LFER), 355
linear polyacenes, 57
lipases, dihydroxylation of alkynes, 997
formation of lactams, 1217
transesterification, 1207
liquid chromatography see LC
liquids, and ultrasound, 308
ionic see ionic liquids
NBS, and halogenation of aromatic compounds, 604
literature searching, 1592–1604
online, 1594–1604
online, problems, 1593
literature, and Beilstein, 1578–1580
annual reviews, 1585
irregular publications, 1584, 1585
journals, 1570–1573
primary sources, 1569
secondary sources, 1569, 1574–1583
lithiated allylic carbamates, 1160
lithiated oximes, 1149
lithiation also see metalation
lithiation, of alkynes, 695
of amides, 696
of aromatic compounds, 784–787
of aromatic compounds, mechanism, 695
of carbamates, 555
of heterocycles, 696
of pyridine, 785
lithioalkynes, coupling with alkyl halides, 516
lithio-epoxides, rearrangement, 489
lithium (trimethylsilyl) diazomethane, 687
lithium aluminum hydride, 1434
and desulfurization, 1552
and dihalides, 1304
and reduction of acyl halides, 1544
and reduction of aldehydes or ketones, 1503
and reduction of amides, 1544
and reduction of imines, 1520
and reduction of nitro compounds, 1525
and reduction of sulfones, 1553
and sterically hindered ketones, 1504
lithium aluminum hydride, reactivity with azo and azoxy compounds, 1554
lithium aluminum hydride, reduction, of acetals or ketals, 1537
of aldehydes or ketones, mechanism, 1508
of alkyl halides, 1532, 1534
of amides to aldehydes, 1518
of amides, 1544
of amine oxides, 1549
of azides, 1529
of carboxylic acids, 1515
of conjugated alkenes, 916
of conjugated carbonyls, 1504
of disulfides, 1555
of epoxides, 1502
of esters to alcohols, 1516
of hydroperoxides, 1539
of imidazoles to aldehydes, 1519
of iodoazides, 990
of nitriles, 1522
of nitro compounds, 1562
of nitroso compounds, 1562
of oximes, 1527
of propargyl halides, 1533
of substituted cyclohexanones, 878
of thiols, 1551
of tosylates, 1537
lithium aluminum hydride, with chromic chloride, 1121
with aluminum chloride, reduction of alcohols, 1535
with aluminum chloride, reduction of ethers, 1537
with amides, 1519
with chiral additives, 1513
with crown ethers, 1511
with cyclopropanes, 911
with episulfides, 1288
with epoxides, 1435
with Lewis acids, reduction of ethers, 1543
with peroxides, 1540
with quaternary ammonium salts, 1548
with quaternary ammonium salts, 1548
with sulfonyl halides, 1552
lithium borohydride, borane and carbon monoxide, 1377
lithium diethylamide, 543
lithium diisopropylamide see LDA
lithium hexamethyldisilazide see LHMDS
lithium hydroxide, base, 481
lithium iodide, and collidine, 508
with carboxylic esters, 508
with lactones, 508
lithium ions, and ambident nucleophiles, 449
binding by crown ethers, 109
lithium metal, with alkyl halides, 1109
lithium naphthalenide, with thioethers, 852
lithium perchlorate, and S_N1 reactions, 438
as a Lewis acid, 331
in ether, and *Diels Alder reactions*, 1023
in ether, and formation of amino-alcohols, 489
special salt effects, 438
lithium tetrachlorocuprate, coupling with halides, 521
lithium tetramethylpiperidide see LTMP
lithium triethylborohydride see borohydride
lithium, and formation of enolate anions, 698
and hybridization of carbon, 696
in alcohols, 909
in amines, 909
in amines, reduction of aromatic compounds, 915
in amines, reductive cleavage of esters, 1538
in ammonia, and *Birch reduction*, 914
in ammonia, reduction of alkenes, 912
in ammonia, reduction of aromatic compounds, 913
in ammonia, with cyclopropanes, 920
with alkyl halides, 715
and ultrasound, 1232
lithium-halogen exchange, 953, 1230
lithium-hydrogen exchange, with aromatic compounds, 784
LiTMP-butyllithium mixed aggregates, 1146
local aromaticity, 59
lone pairs, and bond angle, 27
electrons, 26
long bonds, 23
long range rearrangements, 1331
Lossen rearrangement, 1324, 1362
enantioselectivity, 1363
mechanism, 1363
Lowest Unoccupied Molecular Orbital see LUMO

low-temperature matrix, 68
LTMP (lithium hexamethyldisilazide), 342
LTMP, 544
  and enolate anions, 544
  with epoxides, 489, 1287
LUMO, and *Diels-Alder reactions*, 1020
  and elimination, 1275
  and endo addition, 1036
  and frontier orbital method, 1031
  and tetraenes, 43
  of alkenes and the *Pauson-Khand reaction*, 978
  of ethylene, 9
lyase and cyanohydrin formation, 1181
lyonium ions, and solvent acidity, 326

MABR, as a catalyst, 1119
macrocycles, and gyroscanes, 121
  by the *Story synthesis*, 1319
  crown ethers, 109
macrocyclic compounds, and catenanes, 120
  by acyloin condensation, 1560
macrocyclic lactones, by metathesis reactions, 1421
  from hydroxy acids, 1204
magnesium alkoxides, from the *Grignard reaction*, 1107
magnesium halides, *Grignard reagents*, 229
magnesium imines, 549
magnesium monoperoxyphthalate see MMPP
magnesium, and elimination of halo ethers, 1306
  and the *Barbier reaction*, 1108
  and the *Boord reaction*, 1306
  and the *Grignard reaction*, 1107–1114
  dialkyl, 1108
  elimination with haloethers, 714
  enolate anions, 1148
  formation of *Grignard reagents*, 713
  powdered, 716
  with dihalides, 1109
magnetic anisotropy, and ESR, 236
  and NMR, 17
magnetic field, and ESR, 235
  and microwaves, 310
magnetic susceptibility, and the Étard reaction, 1479
maleic acid, 165
maleic anhydride, in the ene reaction, 942
malic acid, chlorination of, 375
malonate esters, and enantiotopic atoms, 170
  derivatives, with alkenes, 960
  with alkylsilanes, 930
  with sulfones, 779
malonic acid, 170
malonic acids, decarboxylation, 718, 1210
  decarboxylation versus anhydride formation, 1210
malonic acid esters see malonate esters
malonic ester synthesis, 540, 557, 559
  and decarboxylation, 540
  arylation, 616
mandelic acid, and asymmetric synthesis, 152
manganate esters, 993
manganese acetate, and ultrasound, 1013
  with alkenes, 1013
manganese dioxide oxidation of allylic and benzylic alcohols, 1445
  and halogenation, 826
  and oxidation of alcohols, 1445
  and oxidation of amines, 1455
manganese salen complex, and asymmetric epoxidation, 1004
manganese triacetate, 938
  and radical cyclization, 964
Mannich bases, 1100
  and amino leaving groups, 433
  and elimination-addition reactions, 416, 433, 487
  coupling with organometallics, 530
  from ketones, 1100
  with amines, 487
Mannich reactions, 631, 1100–1103
  acid catalyzed, 1101
  and *Eschenmoser's salt*, 1102
  and iminium ions, 1101, 1102
  and the *Robinson annulation*, 1150
  and the *Strecker synthesis*, 1182
  base catalyzed, 1101
  diastereoselectivity, 1102
  enantioselectivity, 1102, 1103
  in ionic liquids, 1103
  kinetics, 1101
  mechanism, 1101
  metal catalysts, 1103
  nitro, 1103
  regioselectivity, 1101
  vinylogous, 1101
  with more than equivalent of an amine, 1101
Marchantia polymorpha, and ester hydrolysis, 1192
Marcus equation, and base catalysis, 328
  and *Brønsted equation*, 329
Marcus theory, 273, 274
  and mechanism, 274
  and proton transfer, 329
  and rate constants, 279
  and S_N2 reaction, 274
  and the *Swain-Scott equation*, 429
Markovnikov addition, phosphines and alkynes, metal catalysts, 899
  alcohols to alkenes, 891
  vinyl phosphines, 899
  vinyl phosphonate esters, 899
Markovnikov, anti see *anti-Markovnikov*
Markovnikov's rule, acylation of alkenes, 685
  addition of alkyl halides to alkenes, 991
  addition of carboxylic acids to alkenes, 892
  addition of thiols to alkenes, 894
  alkenes, and *Friedel-Crafts alkylation*, 614
  and acyloxylation, 1012
  and addition of hypohalous acids to alkenes, 985
  and addition of silanes to alkynes, 929, 930
  and addition to alkynes, 884
  and addition to cyclopropanes, 880
  and alcohol addition to alkenes, 889
  and alkoxymercuration, 891
  and allenes, 876
  and amination of alkenes, 897
  and bromination, 875
  and cyclopropanes, 881
  and halolactonization, 987
  and hydration of alkenes, 885
  and hydroboration, 921
  and hydrocarboxylation, 973, 974
  and oxymercuration, 886
  and the Hammond postulate, 875
  and the Prins reaction, 1185
  and the *Wacker process*, 1488
  definition, 874
  hydroamination of alkenes, 897
  nitrosyl chloride with alkenes, 989
masked reagents, 1133
masochistic steric effects, in [2+2]-cycloadditions, 1045
mass spectrometry see MS
  and tautomerism, 89
  electrospray ionization, and *Suzuki-Miyaura coupling*, 773
  high pressure, and S_N2 reactions, 376
  of carbocations, 209

of catenanes, 119
of radicals, 235
of the methanonium ion, 660
mass-law effect, and rate of reaction, 381
matrix trapping, 258
oxirenes, 1003
argon, 202
trapping carbenes, 249
maximum coordination number, and bonding, 9
McFadden-Stevens reduction, 1519
m-chloroperoxybenzoic acid see mCPBA
McMurry coupling, 1559
cross coupling, 1559
formation of unsymmetrical alkenes, 1559
intramolecular, 1559
mechanism, 1559, 1560
reagents, 1559
mCPBA (*m*-chloroperoxybenzoic acid), 998
and α-hydroxylation of ketones, 1474
oxidation of boranes, 925
oxidation of sulfides, 1303
with aziridines, 1304
with imines, 1366
with nitrocyanamide, 497
mechanical separation, and resolution, 157
mechanics, molecular see molecular mechanics
mechanics, wave, 3
mechanism, 650
mechanism, (E1CB)ip, 1267
mechanism, [2+2]-cycloaddition, 1044, 1045
of enamines with ketenes, 1047
mechanism, [3+2]-cycloaddition, 1016
of allylic carbanions, 1020
mechanism, A2, and acetal hydrolysis, 456
mechanism, acetal and ketal formation, 1082
mechanism, acid catalyzed, aldol reaction, 1149
hydrolysis of isocyanides, 1246
rearrangement of hydroperoxides to ketones, 1371
mechanism, acyloin condensation, 1561
mechanism, addition, of alkanes to alkenes, 927
of amines to ketenes, 899
of *Grignard reagents* to aldehydes or ketones, 1111, 1112
of organolithium reagents to aldehydes or ketones, 1113
of thiols to alkenes, 894, 895
of water to carbonyls, 1076
to cyclopropanes, 879–881
mechanism, addition-elimination, 413, 685, 741, 784, 1196, 1197
and alkylation of aromatic compounds, 785
and oxidation-reduction, 1436
and quinones, 414
and rearrangement, 414
and the *Bucherer reaction*, 756
and the *Heck reaction*, 766, 767
and vinyl halides, 413
electrochemical substitution, 658
hydrolysis of carbamates, 1197
IUPAC nomenclature, 413
mechanism, $A_E + D_E$, 569
mechanism, alcohols, addition to alkenes, 889
deoxygenation, 1535
mechanism, aldehyde or ketone rearrangement, 1348
mechanism, aldehydes, with allylic trihalosilanes, 1126
mechanism, aldol condensation, 1143
computation study, 1146
mechanism, alkanes, cleavage, 726
mechanism, alkene metathesis, 1422, 1423
mechanism, alkenes, from halo ethers, 1306
with HOX, 985
with NOX, 989
with singlet oxygen, 834
with sodium nitrite, 1300
mechanism, alkenylboranes with iodine and NaOH, 1379
mechanism, allylic radical halogenation, 827
mechanism, ambiguity in elimination reactions, 1267
mechanism, amines, with anhydrides, 1215
with HONO, 790
mechanism, anchimeric assistance, 391
mechanism, and benzynes, 276
and bond cleavage, 261
and *Brønsted equation*, 1269
and catalysis, 277
and deuterium isotope effects, 285–287
and enols, 286
and flash photolysis, 306
and frequency factor, 284
and half-life, 282
and *Hofmann rearrangement*, 275
and intermediates, 275
and isotope effects, 285
and isotopic labeling, 277
and kinetics, 278, 284
and *Marcus theory*, 274, 279
and NMR, 283
and rate constants, 279, 284
and rate law, 278
and ReactIR, 276
and reduced mass, 286
and secondary isotope effects, 287
and solvent isotope effects, 288
and solvolysis, 384
and stereochemistry, 278
and steric hindrance, 349
and temperature, 284
and *von Richter reaction*, 275
and *Walden inversion*, 278
mechanism, arenium ion, 569, 570, 572
and decarboxylation, 644
and mercuration of aromatic compounds, 785
and reverse *Gatterman-Koch reaction*, 643
encounter complex, 575
evidence for, 571–575
rate, 571
mechanism, aromatization by quinones, 1439
arylation of aromatic compounds, 795, 796
aryldiazonium salt coupling, 675
aryne see benzyne
A-SE_2, 457, 863
Au catalyzed hydroamination, 897
autoxidation, 833
Baeyer-Villiger rearrangement, 1370
Bamberger rearrangement, 800
Bamford-Stevens reaction, 1294, 1295
Barton reaction, 1427, 1428
base induced elimination of sulfones, 1295
base induced elimination of ethers, 1285
Baylis-Hillman reaction, 1127
Beckmann rearrangement, 1366, 1367
benzidine rearrangement, 1415, 1416
benzil-benzylic acid rearrangement, 1350
benzoin condensation, 1187
mechanism, benzyne, 737–739, 743, 751
and coupling aryl halides with active methylene compounds, 779
and isotope labeling, 737
reactivity order of halides, 738

mechanism, *Birch reduction* of aromatic compounds, 914
bis(decarboxylation) of dicarboxylic acids, 1469
borane oxidation, 1375
borane with oxygen, 805
boranes with CO, 1376
boranes, with metal alkyne anions, 1380
borderline, 388
boron-to-carbon rearrangement, 1375
Boyland-Sims oxidation, 634
bromination of acetone, 285
bromination of alkenes, 983
Bucherer reaction, 756
C to N rearrangements, 1360
Cadiot-Chodkeiwicz reaction, 842
Cannizzaro reaction, 1563
carbanion, 866
carbanion, and elimination, 1262
carbene addition, 1055
carbene insertion, 693
carbenoid formation, 1052
mechanism, carbocation, addition of alkanes to alkenes, 927
formation, 875
mechanism, carboxylic acid decarboxylation, 1238
carboxylic esters with amines, 1220
catalytic hydrogenation of aldehydes or ketones, 1511
cationic isomerization of alkenes, 662
α-CH oxidation of ketones, with selenium dioxide, 1478
Chapman rearrangement, 1429
cheletropic reactions, 1303
Chichibabin reaction, 787
chromium (VI) oxidation of alcohols, 1444
Chugaev reaction, 1289
cis-trans isomerization, 276
Claisen condensation and *Dieckmann condensation*, 1235
Claisen rearrangement, 1407–1409
cleavage of alkanes with superacids, 726
Clemmensen reduction, 1543
combination, 264
concerted, 1372
conducted tour, 656, 662
conjugate addition of organometallics, 955
Cope elimination, 1293
Cope rearrangement, 1403
Criegee, ozonolysis, 1460–1462
Cu-quinoline decarboxylation, 644
Curtius rearrangement, 1362
cyanogen bromide with carboxylate salts, 1242
cyclic intermediate, 1457
mechanism, cyclic, 869, 1113
and addition to alkenes, 869
and electrophilic substitution, 658
decarboxylation, 720
deoxygenation of diols, 1301
diimide reduction of alkenes, 910
reduction of hydrazones, 1542
mechanism, cyclobutane ring opening, 1424
cyclobutane, ring closure, 1424
cyclopropane ring opening, 1347
cyclopropyl cation ring opening, 1389
Dakin-West reaction, 722
Darzens condensation, 1161
DCC esterification, 1205
DCC reaction of carboxylic acids and amines, 1217
$D_E + A_E$, 654
D_EA_E, 650
decarbonylation with *Wilkinson's catalyst*, 858
decarboxylation of aldehydes, 1300
mechanism, definition, 261
dehalogenation of dihalides, 1305
dehydrohalogenation of alkyl halides, 1298
deprotonation by organometallics, 696
determination of, 275–288
determination of, for elimination reactions, 1267
determining kinetic data, 281
diazoalkanes with aldehydes or ketones, 1177
diazotization of anilines, 790
Diels-Alder reaction, 1028–1030
diion, and [2+2]-cycloaddition, 1046, 1047
diionic, 1245
diionic, ketones with imines, 1245
dimer, and S_NAr reactions, 735
diol oxidative cleavage, 1457
mechanism, diradical, and [2+2]-cycloaddition, 1046
and carbenes, 1055
and *Cope rearrangement*, 1404
and photochemical[2+2]-cycloaddition, 1049
sigmatropic rearrangements, 1397
stepwise versus concerted, *Diels-Alder*, 1028–1030
mechanism, displacement, and oxidation-reduction, 1436
DMSO oxidation of alkyl halides, 1481
Duff reaction, 628, 1261, 1262
mechanism, E1 see E1
acid catalyzed dehydration of alcohols, 1284
and arenium ions, 569
IUPAC mechanism, 1261
mechanism, E1anion reactions, 1266
mechanism, E1cB, 1262–1267
mechanism, E2, 1254–1260
IUPAC mechanism, 1254
mechanism, E2C, 1268
Eglinton reaction, 842
mechanism, E^i, 1163, 1278
ammonium salts with organolithium reagents, 1292
and *Cope elimination*, 1293
pyrolysis of carboxylic acids, 1288
mechanism, electronic heterolytic, 1017
electronic transfer, 786
electrophilic addition, 859
mechanism, electrophilic, 786, 885, 991
halogenation of alkenes, 982
mechanism, elimination-addition, 416, 487, 530, 1249, 1534
and *Mannich bases*, 433
at saturated carbon, 416
at vinylic carbon, 416
mechanism, enamine hydrolysis, 1079
ene reaction, 942
enolization in *Grignard reactions*, 1113
Étard reaction, 1479
exchange, 660
Favorskii rearrangement, 1351, 1352
first-order reactions, 279
Fischer indole synthesis, 1413
Fischer-Hepp rearrangement, 639
mechanism, formation, of acyl cyanides, 1237
of azoxy compounds from oximes, 729
of gem-dihalides from aldehydes or ketones, 1105
of *Grignard reagents*, 715
mechanism, four-center, addition to alkenes, 869
and hydroboration, 922
mechanism, fragmentation, 1307
free-radical, 262
Friedel-Crafts acylation, 624
Friedel-Crafts alkylation, 613
Fries rearrangement, 636

Gatterman reaction with aryl halides, 847
Glaser reaction, 842
glycidic acid decarboxylation, 719
Grignard reactions, 1111–1113
Grignard reagents, with metal halides, 711, 849
Grignard reagents, with nitriles, 1140
Grob fragmentation, 1308
haloacylation of alkenes, 992
mechanism, halogenation, of alkenes, 982
of ketones, 671
of organometallics, 706
mechanism, haloketones with boranes, 559
Hay reaction, 842
heterogeneous organic catalysis, 906
Hoesch reaction, 633
Hofmann degradation, 1290
Hofmann rearrangement, 1361
Hofmann-Löffler reaction, 1427
homogeneous catalytic hydrogenation, 907, 908
homologation of aldehydes or ketones, with diazomethane, 1355
homolytic, 262
Hunsdiecker reaction, 855
hydration of aldehydes and ketones, 1076
hydride reduction of carbonyls, 1510
hydroboration, 922
hydrogen exchange, 660
mechanism, hydrolysis, 1078
of acyl halides, 1189
of alkyl halides, 451
of amides, 1198–1200
of anhydrides, 1190
of carbamates, 1196, 1197
of carboxylic acid esters, 356, 1192–1197
of enol esters, 1197
of iminium ions, 1078
of nitro compounds, 1079
mechanism, hydroperoxides, oxidation of sulfoxides, 1495
oxidation of thioethers, 1495
mechanism, α-hydroxylation of enolate anions with sulfonyloxaziridines, 1474
mechanism, identification of products, 275
insertion reactions, 690, 693
mechanism, interfacial, 443
intramolecular rearrangement, 643
inverse isotope effects, 286
iodo azide to alkenes, 990
mechanism, ion pair, 387, 656, 799, 1262
and E1 reactions, 1262
mechanism, isocyanates, with alcohols, 1085
with phosphine oxides, 1241
mechanism, IUPAC see IUPAC
amide hydrolysis, 1198, 1200
amines with esters, 1221
and carbenes, 435
and diazonium salts, 435
E1, 1261
E2, 1254
ester hydrolysis, 1192–1197
esterification, 1204–1206
nomenclature, 368–370
mechanism, ketenes cycloaddition to imines, 1245
keto-enol tautomerism, 666
Kolbe-Schmidt reaction, 629
mechanism, lead tetraacetate cleavage of diols, 1457
oxidation of alcohols to cyclic ethers, 831
oxidation of alcohols, 831
mechanism, $LiAlH_4$ reduction of aldehydes or ketones, 1508
lithiation of aromatic compounds, 695
Lossen rearrangement, 1363
Mannich reaction, 1101
McMurry coupling, 1559, 1560
Meerwein-Ponndorf-Verley reduction, 1508
Meisenheimer rearrangement, 1373
mercuric catalyzed hydration of alkynes, 888
mechanism, metal catalyzed, acyloxylation, 836
cycloadditions, 1064
cyclotrimerization, 1062
decarbonylation of aldehydes, 858
hydrocarboxylation, 974
mechanism, metal hydride addition-elimination, 663
mechanism, metal reduction of nitro compounds, 1525
metal-hydrogen exchange, 717
methyl transfer, 274
Michael addition, 866
mixed S_N1-S_N2, 387
Neber rearrangement, 1359
Nef reaction, 1079
mechanism, neighboring group also see neighboring groups
mechanism, neighboring group, 391
and anti-dihydroxylation, 994
and bromonium ions, 392
and epoxides, 392
and halonium ions, 394
and lactones, 392
and rearrangement, 392
and solvolysis, 393
solvolysis, 394
stereochemistry, 392
mechanism, nitration of alkanes, 677
nitrene insertion, 680
nitrogen extrusion reactions, 1317
mechanism, nitrosation, 597
of amines, 728
of aromatic compounds, 597
of ketones, 676
mechanism, nucleophilic, 865, 1341
addition, 865
and displacement of diazonium, 788
aromatic substitution, 732–734
rearrangements, 1322–1333
substitution at sulfonyl sulfur, 1248, 1249
mechanism, of ozonolysis of alkenes, 1460–1462
of substitution reactions, 373
of thallation, 786
of the *Kolbe reaction*, 853
of the *Wacker process*, 1488
organocuprate coupling, 527
oxa-di-π-methane rearrangement, 1426
mechanism, oxidation, of aldehydes to carboxylic acids, 1486
of aldehydes with chromic acid, 1486
of aldehydes with permanganate, 1487
of alkylboranes, 701
of amines to amine oxides, 1492
of anilines with *Caro's a*cid, 1490
of aromatics to phenols, 830
of phenols with sodium periodate, 1453
of thiols to disulfides, 1497
mechanism, oxidation-reduction, 1434
mechanism, oxidative cleavage of alkenes, 1464, 1465
mechanism, oxidative decarboxylation of carboxylic acids, 1468
oxime formation, 1094, 1095
oxygen insertion into alkanes, 1472
ozonolysis, 1460
palladium catalyzed arylation of amines, 752
Passerini reaction, 1247
Pauson-Khand reaction, 977
pericyclic and the *Prins reaction*, 1186

mechanism, pericyclic, 262
  pyrolysis of homoallylic alcohols, 1315
mechanism, periodic acid with diols, 1457
  peroxyacid epoxidation of alkenes, 999
  Petasis alkenylation, 1174
  Peterson alkenylation, 1163
mechanism, photochemical, 306
  actinometer, 307
  and emission, 306
  and fluorescence or phosphorescence, 306
  quantum yield, 306
  dimerization of ketones, 1557
mechanism, π-allyl complex, 663
mechanism, pinacol rearrangement, 1343
  polar transition state, and benzidine rearrangement, 1416
  Prins reaction, 1184
  proton-transfer reactions, 323
  Pschorr reaction, 796
  Pummerer rearrangement, 1565
  pyrolysis of esters to alkenes, 1288
  pyrolysis of homoallylic alcohols, 1315
  pyrolytic elimination, 1278–1281
  radial pairs, 1374
mechanism, radical addition, 867
  of aldehydes to alkenes, 972
  of alkanes to alkenes, 927
mechanism, radical alkylation, of aromatic compounds, 843
mechanism, radical arylation, of aromatic compounds, 844
mechanism, radical chain, 1468
  and $S_{RN}1$ reactions, 740
mechanism, radical cyclization, 962
mechanism, radical elimination, 1281
mechanism, radical halogenation, of alkenes, 824
mechanism, radical neighboring group effects, 810
mechanism, radical substitution, 808
mechanism, radical, 792, 803, 828, 829, 895, 1468
  and alcohol coupling, 532
  and coupling of boranes, 851
  and dehydrohalogenation, 1298
  and E^i reactions, 1280
  and fluorination of aryldiazonium salts, 792
  and $S_{RN}1$ reactions, 739, 740
  cyclopropane addition, 881
  deoxygenation of diols, 1301
  halogenation of allylic hydrogen, 827
  organometallic compounds with alkyl halides, 520
  oxidation of alcohols, 1445
  reduction of esters, 1539
  with aromatic compounds, 809
mechanism, *Ramberg-Bäcklund reaction*, 1302
  Raney nickel desulfurization, 852, 1552
  reaction of organocuprates, 521
mechanism, reduction, of carbonyls with sodium in ethanol, 1506
  of diazonium salts with sodium sulfite, 1530
  of hydrazones, 1542
  with *Grignard reagents*, 1113
mechanism, *Reed reaction*, 837
  reverse *Friedel-Crafts alkylation*, 642
  $S_{AL}2$, 462
  Schmidt reaction, 1364, 1365
  S_E1, 570, 576, 653, 654
  S_E1, and resonance, 654
  S_E2, 570, 650
  S_E2 and cyclopropanes, 880
  second-order reactions, 279
  S_Ei, 650, 651
  S_Ei', 657
  selenium dioxide allylic oxidation of alkenes, 1470
  semibenzilic, 1352
mechanism, SET, 389
  an aldol reaction, 1141
  and active methylene compounds, 542
  and arylation of enolate anions, 780
  and chain reactions, 389
  and CIDNP, 390
  and coupling, 531
  and electrophilic aromatic substitution, 590
  and ESR, 390
  and *Grignard reactions*, 1112, 1113
  and *Grignard reagents*, 715, 716
  and $LiAlH_4$ reduction of alkyl halides, 1534
  and oxidation-reduction, 1435
  and radical cyclization, 390
  and radical probes, 390
  and substitution reactions, 419
  and the *Williamson reaction*, 461
  organocalcium reagents, 233
  organometallic compounds with alkyl halides, 519
  versus S_N2, 390
mechanism, SF_4 with aldehydes or ketones, 1106
  Shapiro reaction, 1294
  Sharpless asymmetric dihydroxylation, 996
  Sharpless asymmetric epoxidation, 1004
  Simmons-Smith procedure, 1058
  Simonini reaction, 856
  six-center, and decarboxylation, 720
  six-center, *Cope rearrangement*, 1404
  S_N(ANRORC), 754
mechanism, σ-substitution, 599
mechanism, S_N1 or S_N2, and ester hydrolysis, 1195
mechanism, S_N1, 379
  acyl halides with alcohols, 1200
  and deuterium, 424
  and ion pairs, 383
  and primary carbocations, 419
  and secondary isotope effects, 424
  hydrolysis of acetals, 455
mechanism, S_N1cB, 453, 492
  carbenoid formation, 1052
mechanism, S_N2, 374–379
  acyl halides with alcohols, 1200
  and addition to dienes, 870
  and deuterium, 424
  and diol formation, 994
  and hydrolysis of acyl halides, 1189
  and secondary isotope effects, 424
mechanism, S_N2', 410
mechanism, S_N2-like, reaction at sulfur, 1249
mechanism, S_NAr, 732–735
  ortho metalation, 784
mechanism, *Sneen's ion pair*, 659
mechanism, S_Ni, 408, 1106
mechanism, S_Ni', 411
mechanism, solvolysis of alkyl halides, 287
mechanism, *Sommelet-Hauser rearrangement*, 799
mechanism, $S_{ON}2$, 749
mechanism, $S_{RN}1$, 739, 750, 754, 1113
  and arylation of enolate anions, 778
  and *Grignard reactions*, 1113
mechanism, $S_{RN}2$, 740
mechanism, stepwise, ene reaction, 943
  Stevens rearrangement, 1372
  Stille coupling, 683
  Stobbe condensation, 1154

substituent effects and the *Diels-Alder reaction*, 1030
substitution, IUPAC, 432
substitution at sulfur, 1249
sulfonation of aromatic compounds, 601
sulfoxide elimination, 1296
Suzuki-Miyaura coupling, 773
termolecular addition, 861
mechanism, tetrahedral, 413, 1069, 1190, 1226, 1248
acyl halides with alcohols, 1200
and base cleavage of ketones, 723
and conformation, 1072
and formation of aziridines, 415
and hyperconjugation, 415
and isotope labeling, 1071, 1072
and leaving groups, 1073, 1074
and MO calculations, 415
and substituent effects, 423
and vinyl halides, 413
ester hydrolysis, 1192–1197
evidence for, 1070–1072
hydrogen ion catalyst, 1070
hydrolysis of carboxylic esters, 1192–1197
in acid solution, 1070
isolation of intermediates, 1071
reactivity of carbonyl substrates, 1074
special detection of intermediates, 1071
stereoelectronic control, 1073
synthetic transformations, 1074
mechanism, the *Gatterman method*, 796
thermal cleavage of alkoxides, 722
thermal elimination of sulfoxides, 1296
transesterification, 1207
trapping intermediates, 276
types, 261
Ullmann reaction, 769
vicarious nucleophilic substitution of hydrogen, 787
Vilsmeier-Haack reaction, 626
vinyl ether hydrolysis, 457
vinylboranes, with NaOH and iodide to give alkenes, 1377
vinylcyclopropane rearrangement, 1400
von Braun reaction, 510
von Richter reaction, 276
von Richter rearrangement, 798
Wagner Meerwein rearrangement, 1341
Waits-Scheffer epoxidation, 1003
Walden inversion, 375
Wallach rearrangement, 1430
Wittig reaction, 1168
Wittig rearrangement, 1374
Wolff rearrangement, 1353
Wolff-Kishner reduction, 1542
Wurtz reaction, 514
mechanistic spectrum, elimination, 1267
mediated coupling conjugated ketones, 514
medium effects, on acids and bases, 343
medium rings, strain, 201
medium size rings, and I strain, 350
medium, and rate of reaction, 361
and reactivity, 361
and the *Diels-Alder reaction* in water, 363
supercritical carbon dioxide, 363
water, 363
Meerwein arylation, 794
mechanism, 794
Meerwein-Eschenmoser-Claisen rearrangement, 1409
Meerwein-Ponndorf-Verley reduction, aluminum free, 1507
and alumina, 1507
and enol content, 1507
and microwave irradiation, 1507, 1508
and the *Oppenauer oxidation*, 1447
cyclic transition state, 1507
enantioselectivity, 1508
mechanism, 1508
of carbonyls, 1507
transition state, 1508
Meinwald rearrangement, 1344
Meisenheimer rearrangement, 1373
Meisenheimer salts, 733
and NMR, 733
and X-ray crystallography, 733
Meisenheimer-Jackson salts, 733
Meldrum's acid, and acidity, 340
and conformation, 340, 341
melting points, and Beilstein, 1578
and hydrogen bonding, 101
MEM ethers, 460
memory effect, 1331
of migrating groups, rearrangements, 1330
Menshutkin reaction, 378, 481
and high pressure, 446
and S_N2, 377
Merck Index, 1582
mercpatides, as reducing agents, 1548
mercuration, benzene, rate and product distribution, 588
of aromatic compounds, 785
toluene, rate and product distribution, 588
mercuric acetate, and acyloxylation, 835
and oxymercuration, 885, 886
dehydrogenation of amines, 1440
with alkenes, 885
mercuric chloride, and orbitals, 7
linear, 8
with boranes, 1377
mercuric compounds, the *Corey-Seebach procedure*, 1088
mercuric oxide, oxidation of glyceraldehyde, 137
mercuric salts, and hydration of alkynes, 887
complex with alkynes, 888
mercuric trifluoroacetate, reaction with alkene-alcohols, 891
mercury compounds, and acetal cleavage, 457
mercury fulminate, with aromatic compounds, 633
mercury, sp orbitals, 7
Merrifield resin, and *Sonogashira coupling*, 777
scavenging PPh_3, 777
Merrifield synthesis, 1218
and HF, 1219
and separation of products, 1219
Merrifield, R.B., 1218
mesitylene, and isolable arenium ions, 572
aromatic substitution, 573
meso compounds, and diastereomers, 147
and monocyclic compounds, 166
definition, 147
mesoionic compounds, and aromaticity, 82
mesomeric effect also see resonance
mesomeric effect, 45
mesomeric ions, and tautomerism, 666
mesylates, as leaving groups, 432, 433
meta bromination, reagents, 606
meta directing groups, 579
and *Friedel-Crafts acylation*, 622
and *Friedel-Crafts alkylation*, 612
meta selectivity, and aryl radicals, 818
meta-carbene complex, and metathesis, 1422, 1423
metal acetates, and dihydroxylation of alkenes, 997
metal additives, and *Grignard reagents*, 1112

metal carbene complexes, 1017, 1053
addition to alkenes, enantioselectivity, 1054
metal carbenes see carbenes
metal carbenes, 1423
with carboxylic esters, 1174
Fischer carbene complexes, 1062
metal carbenes, insertion, 693
metal carbonyls and sonochemistry, 309
metal catalysts see catalysts
metal catalysts, acylation of carboxylic acids, 1209
addition of alkynes to alkenes, 931
metal catalysts, alkenes, coupling, 932
with alcohols, 889
with alkyl halides, 991
with tosylimines, 1136
metal catalysts, amides, from alcohols and amines, 494
metal catalysts, amines, with epoxides, 488
metal catalysts, and [3+2]-cycloaddition, 1018
and acetal formation, 1081
and *Claisen rearrangements*, 1410
and conjugate reduction, 917
and cyanohydrin formation, 1181
and diazonium salts, 788
and enolate anions, 1145
and epoxidation of alkenes, 1001
and forbidden electrocyclic reactions, 1388
and formation of thiophenols, 791
and *Friedel-Crafts acylation*, 622
and α-hydroxylation of ketones, 1473
and methylene cyclopropanes, 1346
and *Oppenauer oxidation*, 1447
and rearrangement of epoxides, 1343
and *Suzuki-Miyaura coupling*, 770
and the *Finkelstein reaction*, 498
and the *Grignard reaction*, 1108
and the *Mukaiyama aldol reaction*, 1151, 1152
and vinyl sulfide formation, 477
metal catalysts, aziridine ring opening, 491
boranes with aldehydes, 1124
boronates coupling, 620
carbonylation of alkenes and alkynes, 975
chiral, 1183
conjugate addition of amides, 966
Cope rearrangement, 1402
coupling alkenes to alkenes, 933
cyclotrimerization, 1060
epoxides with amines, 489
metal catalysts, for addition of silanes to alkenes, 928
for carbonylation, 973
for carboxylation of alkenes, 979
for conjugate addition of alkynes, 954
for cyclotrimerization of alkynes, 1060
for dehydrogenation, 1440
for hydroformylation, 979
for peroxide epoxidation of alkenes, 999, 1000
for the *Pauson-Khand reaction*, 976
metal catalysts, formation of cyclic amines, 560
Grignard reagents with acyl halides, 1227
Grignard reagents with imines, 1133
hydrataion of alkynes, 887
hydrolysis of nitriles, 1081
isomerization of allylic alcohols, 1357
isomerization of propargyl alcohols, 1358
lactones from alkenes, 978
Mannich reactions, 1103
organolanthanides, 1008
α-oxidation of ketones, 1477
reductive amination, 1097
silanes with alkynes, 929
thiols with alkynes, 895
with acyl halides, 1300
with allyltin compounds, 1118
metal catalyzed, [2+2]-cycloadditions, 1041
photochemical, 1043
metal catalyzed, [3+2]-cycloadditions, 1017
metal catalyzed, acyloxylation of hydrocarbons, 835
mechanism, 836
metal catalyzed, addition, of alcohols to alkenes, 890
of aldehydes to alkenes, 971
of alkanes to alkenes, 928
of alkenes to alkenes, 931
of alkynes to alkenes, 931
of boronic acids, to aldehydes, 1124
propargyl organometallics to carbonyls, 1114
metal catalyzed, alcoholysis of enol ethers, 891
metal catalyzed, alkylation, aryl halides, 545
vinyl halides, 545
metal catalyzed, alkyne coupling, 934
metal catalyzed, alkyne cyclotrimerization, 1060
amide formation, 631
amination, 707
amination, of alkenes, 679, 896, 897
metal catalyzed, arylation, of alkenes, 762
of alkenes, the *Heck reaction*, 763–768
of alkynes, 561
of amines, 753
of amines, and ionic liquids, 752
of amines, and microwaves, 752
of amines, and S_NAr mechanism, 754
of silanes, 783
of sulfonamides, 493
metal catalyzed, *aza-Claisen rearrangement*, 1410
aza-Cope rearrangement, 1410
Baeyer-Villiger rearrangement, 1369
carbene insertion, 692
metal catalyzed, carbonylation, 972, 973
of alkenes, 975
of alkyl halides, 566
of alkynes, 975
of amines, 730
of aryl halides, 781
metal catalyzed, carboxylation, of alkenes, 978
Carroll rearrangement, 1409
metal catalyzed, cleavage, of benzofurans, 535
of ethers, 505
metal catalyzed, conjugate addition, 945
of carbamates, 966
organolithium reagents, 969
to alkynes, 954
metal catalyzed, conversion of alkynyl ketones to furans, 1083
Cope rearrangement, 1402
metal catalyzed, coupling, alkynes with aryl halides also see Sonogashira
metal catalyzed, coupling, alkynes with aryl halides, 776
and *Grignard reagents*, 520
aryl halides and boronic acids, 770–775
azobenzenes, 598
boronic acids, 701
organometallics, 523–526

with allylic carbonates, 529
with organocuprates, 527
metal catalyzed, cyanation, 689
cyclization of enynes, 935
cycloadditions, 1063, 1066
cyclotrimerization of alkynes, 1060
decarbonylation, of acyl halides to alkenes, 1300
dehydration of alcohols, 1283
diazo transfer reactions, 1054
diazoalkanes, and cyclopropanation, 1051
Diels-Alder reaction, 1022
directed ortho metalation, 785
elimination of carboxylic acids, 1288
enamine formation, 1092
ene reactions, 942
enol carbonate alkylation, 545
enolate alkylation, 544
epoxidation of alkenes, with peroxides, 999, 1000
metal catalyzed, formation, of aryl nitriles, 633
of biaryls, 760–762
of boronic acids, 701
metal catalyzed, *Friedel-Crafts alkylation*, 610
halogenation of aromatic compounds, 604
hydration of alkenes, 886
Fries rearrangement, 636
halogenation of epoxides, 507
halogenation of ketones, enantioselectivity, 671
hydration of alkynes, 887
hydroamination, of alkenes, 1007
hydrocarboxylation, mechanisms, 974
hydroformylation, 979
hydrogen exchange, aromatic compounds, 592
imines and aryl halides, 599
intramolecular, alcohol-alkene, 890
ketones and silanes, 687
Knoevenagel reaction, 1158
Kolbe-Schmidt reaction, 630
lithiation of Boc-amines, 555
Mannich reactions, imines and enol ethers, 1102
methylation of aryldiazonium salts, 793
Michael reactions, 945
metal catalyzed, *Nazarov cyclization*, 946
nitration of aryldiazonium salts, 847
organolithium reagents with nitrogen, 754
organometallic coupling, 524
oxidation of hydrocarbons with hydroperoxides, 835
Pauson-Khand reaction, 976
preparation of enols, 663
Prins reaction, 1186, 1187
radical halogenation, 827
rearrangement of alkenes, 663
Rosenmund-von Braun reaction, 758
σ-bond rearrangement, 1423
Stille coupling, 682
sulfohalogenation of aryldiazonium salts, 848
metal cations, and crown ethers, 108
metal complexes also see complexes
metal complexes, and acyl addition of dialkylzinc, 1120
and alkyl halide coupling, 518
and allylic rearrangement, 663
and atropisomers, 132
and catalytic dehydrogenation, 1450
and cyclotrimerization, 1062
and enantioselective hydroboration, 926
and mechanism of catalytic hydrogenation, 908
and photooxygenation, 1006
chiral, 1148
with carbenes, 1053
metal compounds, and oxidation of alkynes to diketones, 1490
for catalysis of *Michael reactions*, 945
opening epoxides, 536
reaction with alkenes, 936
metal cyanides also see cyanide
metal cyanides, and formation of cyanohydrins, 1181
metal exchange, and electron transfer, 718
metal extrusion, and cyclotrimerization, 1062
metal free cyanation of aryl halides, 759
metal halides see halides
metal halides, diazotization, 509
metal hydrides, addition-elimination mechanism, 663
addition to alkenes, 926
and reduction of alkynes, 911
and reduction of conjugated alkenes, 916
metal induced dehalogenation of acyl halides to ketenes, 1306
metal induced elimination of halo ethers to alkenes, 1306
metal ions, and S_N1 reactions, 439
metal leaving groups, 659
metal mediated, acylation, of amines, 1213
addition, HCN to alkynes, 981
and the *Baylis-Hillman reaction*, 1128
arylation, of alkynes, 561
arylation, of amines, 754
carbonylation, 709
carbonylation, of alkyl halides, 564, 565
Claisen condensation, 1154
conjugate addition, 954
coupling, alkyl halides, 513, 518
coupling, allylic esters, 527
coupling, and *Grignard reagents*, 517
coupling, aryl halides, 768
coupling, of vinyl halides, 514
coupling, silylamines with alkynes, 562
deoxygenation of bis (alkoxides), 1301
enamine alkylation, 552
formation of biaryls, 760–762
halogenation, 826
halogenation, of allylsilanes, 829
halogenation, of aryl diazonium salts, 847
halogenation, of enol acetates, 672
halogenation, of ketones, 669
hydroxylation, of aryldiazonium salts, 790
oxidative decarboxylation, 1467
radical couplings, 810
reaction, thiols with arylboronic acids, 750
rearrangements, aniline ammonium salts, 640
Simmons Smith procedure, 1058
transesterification, 1208
unsymmetrical coupling, 514
metal oxides, and alcohol dehydration, 1283
and hydrogenation, 902
and pyrolysis of alkyl halides, 1298
metal particles, as catalysts, surface and particle types, 907
metal reduction of sulfonyl halides, 1252
metal salen complexes, *Michael reactions*, 947
metal salts, addition of organotin compounds to carbonyls, 1118, 1119
and *Grignard reagents*, radical cyclization, 962
for *Mukaiyama aldol*, 1151, 1152

metal salts, addition of organotin compounds to carbonyls (*Continued*)
formation of dithioacetals and dithioketals, 1087
reagents, for formation of acylals, 1084
metalated alkynes see alkynes, metallated
metalated alkynes, 561
metalation, and organolithium reagents, 695
aromatic compounds, 635
directed ortho, 517, 784
of alkynes, 695
of aromatic compounds, 784–787
of C-H, 694
with metals, 697
with organometallics, 694
metal-cyclobutadiene complex, and cyclotrimerization, 1062
metal-hydrogen exchange, 698
and CIDNP, 717
and radicals, 717
mechanism, 717
metallated imines, 1247
synthetic applications, 1248
metallocenes, 61, 105, 106
and 18 electron systems, 61
and a chiral axis, 140
and alkene metathesis, 1422
and aromatic substitution, 61
and chirality, 134
and cyclopentadiene, 61, 62
and transmetallation, 711
bonding, 61, 106
metallocyclobutanes, and metathesis, 1422
metalloids, hydrolysis, 699
metalloprophyrins, and epoxidation, 1003
metals, activated, 715
active, and organometallics, 695
acyl halides with alcohols, 1201
alkali, and radical ions, 249
allylic silanes with aldehydes, 1125
ammonia, reduction of aromatic compounds, 913
metals, and acid, deoxygenation of aldehydes or ketones, 1540
and acid, reduction of anhydrides, 1544
and acyl addition, 1116–1123
and alcohols, with alkenes, 909
and alkylation of amines, 485
and ammonia, decyanation of nitriles, 726
and aromatization, 1438
and boronic acid conjugate addition, 958
and catalysis of alkyne amination, 898
and conjugate addition of amines, 965
and conjugate reduction, 917
and decarboxylation, 644
and elimination of dihalides to alkenes, 1305
and elimination of halo ethers to alkenes, 1306
and enolate anions, 1145
and formation of enolate anions, 698
and hydrogenation, 903
and hydrosilation, 918
and organometallics, 695, 696
and oxidation of alkenes to aldehydes or ketones, 1488
and preformed enols, 1146
and reduction with silanes, 1509
and reductive coupling to diols, 1556
and the *Barbier reaction*, 1109
and the *Boord reaction*, 1306
and the *Michael reaction*, 945
and the *Reformatsky reaction*, 1129, 1130
and *Wurtz coupling*, 513, 515
metals, as catalysts in catalytic hydrogenation, 904
as catalysts for conjugate addition, 967
chiral, in the *Henry reaction*, 1156
deprotonation, 698
dimerization of alkenes, 931
dissolving metal reductions, 913
electromotive series, 710
metals, for alkene metathesis, 1417
for alkyne dimerization, 933
for catalytic dehydrogenation of alcohols, 1450
for oxidation of alcohols with TEMPO, 1448
for oxygen oxidation of alcohols, 1446
for pinacol coupling, 1555–1558
metals, formation of enolate anions, 778
hydrogenation of imines, 1521
hydrogen-metal exchange, 717
hydrolysis of C=N compounds, 1077
metals, in acid and reduction of nitro compounds, 1525
in acid, and reduction of nitro compounds, 1524
in alcohol, reduction of vinyl halides, 1534
in amines, reduction of aromatic compounds, 915
in ammonia, and *Birch reduction*, 914
in ammonia, and decyanation, 726
in ammonia, reduction of alkynes, 911
in aqueous alcohols, reduction of heterocycles, 915
metals, intramolecular hydroamination, 897
metalation, 698
powdered, reactivity, 715
reactivity with alkyl halides, 715
metals, reduction, of aldehydes or ketones, 1507
of alkyl halides, 1532
of azides, 1529
of nitro compounds, mechanism, 1525
metals, surface area, and the acyloin condensation, 1561
metals, transition, chiral catalyst, 1182
chiral catalysts, 1153
chiral, and reducing agents, 1514
promotion of radical reactions, 817
metals, transmetallation, 710
vapor phase, reactivity, 715
metals, with aldehydes, formation of acyl radicals, 805
with alkyl halides, 713, 715
with boranes, 957
with crown ethers, 726
with diazo compounds, 1053
with diazomethane, 1053
with imines, 1135
with silanes, reduction of amides, 1545
with $NaBH_4$, 911
with the *Reformatsky reaction*, 1129
metal-salen complexes, and epoxidation, 1005
and hydroxylamines, 1311
and Michael addition, 947
metathesis, alkane, 1421
metathesis, alkene, 1417–1423
and formation of lactones, 1421
and *Grubbs catalysts*, 1418, 1419
and metal carbene complex, 1422, 1423
and metallocyclobutanes, 1422
and Mo catalysts, 1417
and PEG, 1420
and Ru catalysts, 1417
and stability of alkenes, 1417
and the *Shrock catalyst*, 1418, 1419
chain metathesis, 1423

compatible functional groups, 1419
cross, 1420
cross, alkynes, 1422
domino, 1420
double, 1420
enantioselectivity, 1420
enyne, 1422
formation of cyclic dienes, 1421
functional group compatibility, 1419
homo-, 1420
in ionic liquids, 1420
in supercritical carbon dioxide, 1420
mechanism, 1422, 1423
metallocenes, 1422
of alkynes, 1422
polymer bound catalysts, 1420
polymerization, 1421
reactivity of alkenes, 1420
ring closing, 1417–1423
ring opening, 1420
structural changes in the reaction, 1417
synthetic importance, 1419
synthetic variations, 1419
tandem, 1420
triple, 1421
with dienes, 1421
with diynes, 1421
methane hydrate, 114
methane radical, electronic structure, 15
methane, and PES, 11–13
bond angles, 8
bond energy, 28
radical cation, 14
rate-determining state in radical halogenation, 824
spectroscopy, 12
methanoannulenes, 73, 74
and antiaromaticity, 79
methanoazaannulene, 73
methanol, as a guest, 114, 116
methanonium ion, 209, 660
mass spectrum, 661
Methods in Organic Synthesis, 1586
methoxide, potassium, and phenalene, 56
methoxy methyl amides see *Weinreb amides*
methoxyacetyl chloride, with aromatic compounds, 619
methoxyamines, cyclic, 965
from organolithium reagents, 706
methoxymethyl carbocation, 214
α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) see *Mosher's acid*
methyl aromatic compounds, and *Étard reaction*, 1479
α-CH oxidation to aldehydes, 1479
methyl carbanions, 227
methyl carbocation, X-ray of, 209
methyl compounds, from silylmethyl compounds, 1546
reduction of carboxylic esters, 1546
reduction of tosylates, reagents for, 1537
methyl groups, neighboring group participation, 407
methyl ketones see ketones
methyl radical, esr, 243
polarity, 816
methyl transfer, 274
methylalminum bi(4-bromo-2,6-di-tert-butylphenoxide) see MABR
methylation, aromatic amines, 612
of aryldiazonium salts, 793
methylene compounds, by reduction of ketones, 1540
CH oxidation to amines, 1475
oxidation to sulfonic acids, 1476
methylene groups, oxidation, 1473
methylene, active see active methylene
methylene, addition to benzene, 1056
and decomposition of diazomethane, 1056
by desulfurization, 1551
carbene, 249, 252
carbene, singlet, 254
from diazomethane, 691
insertion, 691
methylenecyclohexanes, and chirality, 133
methylenecyclopentanes, 1019
methylenecyclopropanes, rearrangement, 1346
methylene-pentadiene see dendralenes
methylids, sulfur, 1175
methyllithium also see organolithiums
methyllithium, with CH_2I_2, 1110
with enol acetates, 547
with silyl enol ethers, 547
X-ray crystallography, 229
methylmercaptide, as a reducing agent, 1548
methylpyrrolidinone see NMP
methylrhenium trioxide, and alcohol dehydration, 464
methylsulfinyl carbanions, 1086
with aryl nitro compounds, 786
with esters, 1236
methylthioalkynes see alkynes
methyltrioxorhenium, with ketones, 1175
Meyers aldehydes synthesis, 556
Meyer's V values, 360
Meyer-Schuster rearrangement, 1357
Mg, coordination with heteroatoms, 936
symmetrical coupling of allylic halides, 515
micellar catalysis see catalysis
micellar effects, and *Diels Alder reactions*, 1023
Michael addition, acidic conditions, 948
amines to conjugated carbonyl compounds, 896
Michael addition, and amino ketones, 1230
DABCO, 946
and electrochemistry, 948
and enamines, 552
and *Grignard reactions*, 1109
and *Nazarov cyclization*, 946
and radical initiators, 948
and radicals, 948
and the *Ramberg-Bäcklund reaction*, 1303
aza- see *aza-Michael*
double, 944
enantioselectivity, 947
hydroperoxide anion, 1003
intramolecular, 946, 947
mechanism, 866
of enolate anions, 947
organocatalysts, 945
phosphine catalysts, 944
with conjugated nitriles, 866
Michael alkenes, and the Wittig reaction, 1165
Michael reactions, acid conditions, 948
alkynes, 948
Michael reactions, and addition reactions, 884
and antibodies, 947
and enolate anions, 866, 867
and enzymes, 947
and organocuprates, 949
and phase transfer catalysis, 945
and *Robinson annulation*, 1150
and tautomerism, 95
and tautomers, 867
and the aldol reaction, 1146
and transition metals, 945
Michael reactions, aza-, 965
chiral additives, 947
chiral catalysts, 947
conjugated substrates, 943
cyanide ion, 946
double, 944
electrochemistry, 948
enamines, 947
enantioselectivity, 947

Michael reactions, aza- (*Continued*)
enolate anions, 945, 947, 948
in ionic liquids, 945
Michael reactions, intramolecular, 946, 0947
metal catalyzed, 945
metal-salen complexes, 947
nitrones, 945
organocatalysts, 947
oxy- see *oxy-Michael*
phase transfer catalysts, 945
proline derivatives, 947
radicals, 948
reversibility, 866
sparteine, 947
stereoselectivity, 947
substrates for, 944
sulfur ylids, 1178
to conjugated alkenes, 943–949
ultrasound, 947
vinylogous, 944
water promoted, 945
Michael substrates, 944
Michael type addition, 1265
Michael type alkenes, addition of HCN, 981
and enamines, 1042
Michael type mechanisms, and epoxidation, 1003
Michael type substrates, 866, 981
hydroamination, 897
microbeads, and *Sonogashira coupling*, 776
microencapsulated, OsO4, 997
microfiche, 1571
microfilm, 1571
microscopic reversibility, 273, 666, 1075, 1186, 1265
and alcohol dehydration, 1284
microwave irradiation, 309–355
acyl halides with alkynes, 1228
alcoholysis of anhydrides, 1202
aldehyde conjugate addition, 969
alkoxides with aryl halides, 747
amides to isocyanides, 1314
microwave irradiation, and acetal cleavage, 457
and acetal formation, 1082
and acetal hydrolysis, 457
and acylation of amines with esters, 1220
and acylation of amines, 1215
and alkene metathesis, 1420
and alkyl iodides, 501
and amide formation, 631
and amines, 481
and anhydride formation, 1210
and aromatic sulfonation, 603
and aryl halide coupling, 526
and arylation of amines, 752
and *aza-Michael reactions*, 966
and CH oxidation of aryl methyl, 1479
and chromate oxidation of alcohols, 1443
and conjugate addition, 967
and conjugate addition, of aldehydes, 969
and conversion of aldehydes to nitriles, 1095, 1096
and cyanation of aryl halides, 759
and dehalogenation of dihalides, 1305
and dehydration of amides to nitriles, 1313
and dehydration of oximes to nitriles, 1311
and dielectric heating, 310
and *Diels-Alder reactions*, 310, 1022
and dihydroxylation, 997
and enamine formation, 1091, 1092
and ester formation, 469
and ester hydrolysis, 1191, 1192
and esterification of carboxylic acids, 1203
and ether formation, 459
and formation of amino-alcohols, 488
and formation of phenols, 746
and *Friedel-Crafts acylation*, 622
and *Friedel-Crafts cyclization*, 617
and *Gibbs energy*, 311
and halide exchange in aryl halides, 757
and hydrolysis of C=N compounds, 1078
and hydrolysis of carboxylic esters, 1192
and hydrolysis of dithioketals, 1089
and hydrolysis of nitriles, 1080, 1081
and hypervalent iodine oxidation of alcohols, 1450
and inorganic esters, 473
and ketal hydrolysis, 457
and *Meerwein-Ponndorf-Verley reduction*, 1507
and metal catalyzed conjugate addition of amines, 966
and microwave ovens, 310, 311
and Montmorillonite clay, 445
and oxidation of benzylic alcohols, 1451
and α-oxidation of ketones to diketones, 1477
and oxidation of phenols, 1453
and ozonolysis, 1460
and peroxide epoxidation of alkenes, 1000
and phase transfer catalysis, 444
and phosphine reactions with alkyl halides, 1165
and polarization, 310
and rate acceleration, 311
and rate enhancement, 310
and rate of reaction, 446
and reactivity, 445
and reduction of conjugated aldehydes, 919
and reduction of imines, 1520
and reduction of nitro compounds, 1525
and reductive amination, 1098
and sodium borohydride reduction, 1504
and *Sonogashira coupling*, 776
and *Stille coupling*, 682, 683
and superheating, 310
and *Suzuki-Miyaura coupling*, 771, 772, 775
and synthesis, 311
and the *Baylis-Hillman reaction*, 1127
and the *Beckmann rearrangement*, 1366
and the *Claisen rearrangement*, 1408
and the *Doebner modification*, 1158
and the *Fischer indole synthesis*, 1412
and the *Fries rearrangement*, 636
and the *Heck reaction*, 764
and the *Huang-Minlon modification*, 1540
and the *Hunsdiecker reaction*, 856
and the *Krönke reaction*, 1482
and the *Mannich reaction*, 1101
and the *Pauson-Khand reaction*, 977
and the *Pechmann condensation*, 617
and the *Ritter reaction*, 1240
and the *Vilsmeier-Haack reaction*, 626
and the *Williamson reaction*, 459
and thioamide formation, 1212
and warming, 310
microwave irradiation, aromatic compounds with alkenes, 940
aryl halides with amines, 751, 752
aryl halides with phenoxides, 748
benzylic halides from alcohols, 445
carbonylation of aryl halides, 781

chlorosulfonyl isocyanate with alkenes, 1245
conversion of carboxylic acid to amines, 1216
cycloaddition reaction, 311
diazoketones with imines, 1245
dihydroxylation reaction, 311
diketones with acid, 1083
dry-reaction, 310
electric field component, 310
electromagnetic waves, 310
ene reactions, 310
epoxides and HX, 506
ethers with alkynes, 928
formation of acylals, 1084
formation of enamines, 1091
formation of imines, 1091
microwave irradiation, *Friedel-Crafts acylation*, 624
Fries-rearrangement, 636
halogenation of alcohols, 501
halogenation of ketones, 669
Heck reaction, 311
Hundiecker reaction, 855
in ionic liquids, 366
in reactions of amines with diketones, 1091
Knoevenagel reaction, 1158
magnetic field component, 310
Meerwein-Ponndorf-Verley reduction, 1508
metal catalyzed arylation of amines, 752
Mitsunobu reaction, 311
origins, 309
oxidation of alcohols, 1446
oxidation of hydrazines, 1455
oxidation of thiols, 1497
reactors, 311
reduction of alkyl halides, 1533
Rosenmund-von Braun reaction, 758
Sonogashira reaction, 311
Suzuki reaction, 311
thermal effects, 310
Ullmann reaction, 311
wavelength, 310
with dicarboxylic acids, 1235
with imines and diazo ketones, 1245
microwave ovens, and microwave chemistry, 310, 311
microwave reactors, 311
microwave spectroscopy, and bond distance, 22
and conformations, 174
Fries rearrangement, 637
migrating groups, hydrogen, in rearrangements, 1328
in radicals rearrangements, 1335
in rearrangement, 1321
rearrangements, memory effects, 1330
stereochemistry, in rearrangements, 1328
migration origin, and rearrangement, 1321
migration terminus, and rearrangement, 1321
migrations see rearrangements
migrations, [1,3]-, suprafacial, photochemistry, 1398
1,2-hydride, 687
alkenes, in hydration of alkynes, 887
and the ipso carbon, 582
antarafacial, 1392
of Mg in *Grignard reagents* with $TiCl_4$, 711
para, and *Fries rearrangement*, 636
suprafacial, 1392, 1394
migratory aptitudes, H versus alkyl versus aryl, 1329, 1330
in hydroperoxide rearrangement, 1370
in rearrangements, 1328
in the *Baeyer-Villiger rearrangement*, 1369
in the *Beckmann rearrangement*, 1366
in the *Schmidt reaction*, 1364
in the *Sommelet-Hauser rearrangement*, 1373
in the *Stevens' rearrangement*, 1371
in the *Wittig rearrangement*, 1374
of radicals, 1336
milling, ball, and oxidative amidation, 837
Mills reaction, 793
Mills-Nixon effect, 48
and electrophilic aromatic substitution, 586
mirror plane, and allenes, 132
Mislow-Evans rearrangement, 1415
Mitsunobu cyclodehydration, 469
Mitsunobu reaction, and alcohols dehydration, 464
and esterification, 1203
and ether formation, 460, 464
and microwave irradiation, 311
and P esters, 474
and *Williamson reactions*, 460
azide and epoxides, 489
esterification, 469
formation of alkyl azides from alcohols, 1364
formation of amines, 485
of amides, 494
mixed aggregate bases, and the aldol reaction, 1146
mixed aldol reaction, 1144
mxed anhydrides, 622, 623, 848
with DMAP, 1204
mixed benzoin condensation, 1188
mixed Claisen condensation also see Claisen
mixed halogenation also see halogenation
mixed halogens, in aromatic halogenation, 604
mixed organocuprates, 522, 950
mixed S_N1-S_N2 reactions, 387
Mizoroki-Heck reaction see *Heck*
MM3, and molecular mechanics, 191
MM4, 191
and molecular mechanics, 191
MM40 calculations and hyperconjugation, 87
MMFF, 191
and molecular mechanics, 191
MMPP (magnesium monoperoxyphthalate), 998
and oxidation of hydrazones, 1455
Mn complex, and dihydroxylation, 993
as a catalyst, 1005
Mn-salen complex, dehydration of hydroxylamines, 1311
MO calculations, 5
[2+2]-cycloaddition of alkenes and ketenes, 1045
ab initio, 34, 35
AM1, 34
and aromatic compounds, 33, 34
and azulene, 63
and bond angles, 35
and bond distances, 35
and conformation, 340
and cross conjugation, 42
and cyclopropane, 194
and cyclopropyl cation ring opening, 1389
and ferrocene, 61
and free energy for S_N2 reactions, 379
and fullerenes, 84
and *Hückel's rule*, 65
and ion pair formation, 386
and naphthalene, 55
and S_N1 reactions, 424
and strain, 194
and the tetrahedral mechanism, 415
antiaromaticity, 66
CNDO, 34
cyclobutadiene, 68
dipole moments, 35
energy barrier to rotation, 176
MINDO, 34
PM3, 35
semiempirical, 34

Mo catalysts, and metathesis, 1418, 1419
  polymer bound, alkene metathesis, 1420
MO energies, 54
Mo peroxide, α-hydroxylation of ester enolate anions, 1473
  α-hydroxylation of ketone enolate anions, 1473
MO studies, amide hydrolysis, 1198
MO theory, activation hardness, 587
  and electrophilic aromatic substitution, 587
  and resonance, 32
Möbius aromaticity, 81, 82
Möbius strip compounds, and chirality, 135
Möbius strip ligand exchange, and rotaxanes, 119
Möbius strip, and cycloadditions, 1034
Möbius system, [1,3]-sigmatropic rearrangement, 1394
Möbius systems, allowed reactions, 1033
Möbius systems, conrotatory processes, 1384
Möbius-Hückel method, 1031–1033, 1406
  and cyclopropane ring opening, 1346
  and *Diels-Alder reaction*, 1032, 1033
  and electrocyclic reactions, 1383–1385
  and orbital symmetry, 1388
modified neglect of diatomic overlap, 34
Moffatt oxidation, of alcohols, 1448
molar rotation, definition, 124
molecular belts, 118
molecular conformation, and geometry, 191
molecular dynamics, and ester hydrolysis, 1192
molecular knots, 120, 121, 135
molecular mechanics, 190–192
  and conformations, 174
  and thermochemical data, 192
molecular mechanisms, and torsion strain, 191
molecular necklaces, 118
molecular orbitals also see MO
molecular orbitals, 4, 5, 32
  alkene, 1031
  and [1,5-]-phenyl migration, 1396
  and hybridization, 8
  antarafacial shift, 1393
  benzene, 33
  diene, 1031
  suprafacial shift, 1393
molecular orbital method, 4
molecular propellers, and a chiral axis, 140
molecular recognition, 112
molecular refraction, and aromaticity, 59
  and hardness, 59
molecular ribbons, 118
molecular shuttle, 120
molecular sieves, and amine formation, 482
  and epoxidation, 1004
  and formation of imines, 1091
  and *Jones reagent*, 1442
  as a dehydrating agent, 1202
  formation of amides, 1217
molecular switches, 118
molecular threads, 118
molecularity, and rate law, 279
molecules, strained see strained molecules
molybdenum hexacarbonyl, with Pd catalyst, 753
MOM ethers, 460
monochloroborane see boranes
monohapto compounds, 106
monooxygenases, bacterial, oxidation of thioethers, 1494
monoperoxysulfate, with O_2, enantioselectivity, 1451
Montmorillonite clay, 473
  and acetal cleavage, 456
  and acylation of amines, 1215
  and addition of thiols to alkenes, 894
  and aromatic halogenation, 602
  and formation of phenols, 746
  and *Meerwein arylation*, 794
  and microwave irradiation, 445
  and the *Beckmann rearrangement*, 1366
  and the *Heck reaction*, 764
  and the *Hofmann rearrangement*, 1361
  and the *Pechmann condensation*, 617
  and the *Prins reaction*, 1186
  and the *Willgerodt reaction*, 1567
  aziridines with allylic alcohols, 538
  with $Bi(NO_3)_3$, 1451
MoOPH, α-hydroxylation of ester enolate anions, 1473
  of ketone enolate anions, 1473
  of nitrile enolate anions, 1474
Morita-Baylis-Hillman alkylation, 1129
Morita-Baylis-Hillman reaction see *Baylis-Hillman*
morphine, and resolution, 173
Mosher's acid: α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA)
  and absolute configuration, 142
Mosher's ester, and absolute configuration, 142
MTPA, see Mosher's acid
Mukaiyama aldol reaction, 1148
  ab initio study, 1152
  and transition metal catalysts, 1151, 1152
  chiral additives, 1153
  chiral auxiliaries, 1153
  chiral organocatalysts, 1153
  domino reaction, 1152
  in ionic liquids, 1152
  organocatalysts, 1152
Mukaiyama aldol also see aldol
Mukaiyama reagent, and lactonization, 1204
  dehydration of carboxylic acids, 1284
multiple bonds see bonds
  +M and –M effects, 348
  and field effects, 348
(–)-murtenal, and chiral Lewis acids, 340
myrtanylborane, 924

N,O-bis(trimethylsilyl)acetamide (BSA) see BSA
$NaBH_4$, see sodium borohydride
N-acylation, and Friedel-Crafts acylation, 622
Nafion, and alcohol dehydration, 464
  and the *Ritter reaction*, 1239
Nafion-H, 603
  and hydration of alkynes, 887
N-alkylation, enamines, 550, 551
named reactions, 368
Nametkin rearrangements, and *Wagner-Meerwein rearrangement*, 1340
nanoparticles, and catalytic hydrogenation, 903
  and Pd catalyzed coupling of allylic esters, 529
  and reduction of nitro compounds, 1524
  and *Sonogashira coupling*, 776, 777
  and the *Pauson-Khand reaction*, 976
  reduction of alkenes, 910
nanosecond time-resolved Raman spectroscopy, 637
naphthalene, alternant hydrocarbon, 63
  and aromaticity, 57
  and complex formation, 112
  and *Dewar structures*, 55
  and MO calculations, 55
  and partial bond fixation, 55

and resonance, 33
bond order, 55
canonical forms, 55
electrophilic aromatic substitution, 584
electrophilic aromatic substitution, 584
in *Friedel-Crafts alkylation*, 611
oxidation to naphthoquinones, 1480
oxidation to phthalic acid, 1465
resonance energy, 56
naphthoic acid, from 2-methylnaphthalene, 1466
naphthols, with ammonia, 756
naphthoquinones, by oxidation of naphthalenes, 1480
naphthoxide, alkylation, 449
naphthylamines, and the Bucherer reaction, 756
Natural Products Updates, 1586
Nazarov cyclization, 708, 946, 975
and *Michael addition*, 946
enantioselectivity, 946
Fe complex, 975
in ionic liquids, 946
metal catalyzed, 946
reductive, 946
retro-, 946
vinylogous, 946
with allenes, 946
with Lewis acids, 946
Nazarov, interrupted, 947
Nazarov-Wagner-Meerwein sequence, 947
N-bromodimethylsulfonium bromide, 605
N-bromosaccharin, halogenation of alcohols, 503
NBS (N-bromosuccinimide)
NBS, AIBN, ammonia, and aldehydes, 837
and acetal cleavage, 457
and Chloramine-T, 1011
and decarboxylation of amino acids, 721
and formation of alkyl halides from carboxylic acids, 1213
and formation of halohydrins, 985
and halogenation of carboxylic acids, 673
and oxidation of alcohols, 1451
and radical halogenation, 823
and the *Pummerer rearrangement*, 1565
and *Wohl-Ziegler bromination*, 826
as a source of bromine, 827, 828
bromination of aromatic compounds, 604
formation of haloamines, 729
halogenation of aldehydes or ketones, 672
halogenation of aromatic compounds, 604
halogenation of ketones, 669
in ionic liquids, 604
oxidation of diols, 1447
oxidative hydrolysis of dithianes, 1236
radical halogenation, 826
with alcohols and carbodiimides, 503
with DBU, 1360
with DBU, and carbamates, 1361
with enol borinates, 672
with sodium methoxide, and the Hofmann rearrangement, 1360
with sulfoxides, 674
with vinyl carboxylic acids, 856
with vinylboranes, 705
N-chlorodimethylsulfonium chloride, 605
N-containing radicals, 241
NCS (N-chlorosuccinimide)
and allylic chlorination, 827
and the *Pummerer rearrangement*, 1565
formation of haloamines, 729
halogenation of ketones, 668
oxidative hydrolysis of dithianes, 1236
radical chlorination, catalysts for, 827
with betaines, 1172
with sulfoxides, 674
with vinylboranes, 705
Neber rearrangement, 1359
and azirene intermediates, 276
and azirenes, 1359
and intermediate isolation, 275
mechanism, 1359
necklaces, molecular, 118
Nef reaction, 1079
alkyne anion with ketones, 1114
and the aci form of nitro compounds, 1079
and the *Knoevenagel reaction*, 1158
in connection with the Favorskii reaction, 1158
mechanism, 1079
negative enhancement, and NMR, 237
negative hyperconjugation, 187
Negishi coupling, 524
neighboring group effects, and rate, 399
deactivation, 811
neighboring group mechanism see mechanisms
neighboring group mechanism, 391
anti-dihydroxylation, 994
neighboring group participation, and nonclassical carbocations, 395
and rate, 392
neighboring groups, 393
alkenes, 396, 397
alkynes, 396
and cyclization, 394
and electron density, 397
and first order rates, 391
and halonium ions, 394
and NMR, 398
and nucleophiles, 397
and phenonium ions, 399
and radicals, 810
and rate enhancement, 400
and retention, 396
and S_N2 reactions, 391
and solvolysis, 394, 397, 398, 400
and the *Heck reaction*, 765
aromatic rings, 398, 399, 400
β- to leaving group, 391
β-aryl, 402
C=C, 396
C–C single bonds, 402
cyclobutyl or cyclopropyl, 398
hydrogen, 408
neighboring groups, methyl, 407
and NMR, 407
and Raman, 407
neighboring groups, participation by π bonds or σ bonds, 394
principle of increasing electron demand, 394
propargyl groups, 420
σ-bonds, 402
silyalkyl, 407
structural features, 393
neopentyl systems, 652
and S_N2 reactions, 419, 651
neophyl radicals, 1333
neophyl systems, rearrangement, 1339
neutron diffraction, and hydrogen bonds, 99
Newman projections, and conformations, 175
definition, 175
syn and anti elimination, 1259, 1260
N-haloamides see amides
N-hydroxysuccinimide (NHS), nitration of alkanes, 677
Ni catalysts, and coupling with cyanide ion, 563
and decarboxylation of amino acids, 721
and *Hiyama coupling*, 545
and *Negishi coupling*, 524
and the *Corey Winter reaction*, 1301
and the *Ullmann reaction*, 769

Ni catalysts, for [3+2]-cycloaddition, 1018
for alkyne cyclotrimerization, 1059
for allenes with aldehydes or ketones, 1122
for aryl triflates with *Grignard reagents*, 518
for carbonate coupling, 532
for coupling alkylboranes and alkyl halides, 526
for coupling of aryl halides, 760
for coupling of aryl or vinyl halides, 519
for cyanation of aryl halides, 759
for cyclotrimerization, 1060
for formation of aryl halides, 757
for *Grignard reagents* with acyl halides, 1226
for *Sonogashira coupling*, 777
for *Suzuki-Miyaura coupling*, 774
with *Grignard reagents*, 534
Ni complex, boranes with aldehydes, 1124
nickel boride, and hydrogenation, 902
nickel carbonyl and hydroformylation, 980
and hydrocarboxylation, 973, 974
with alkyl halides, 566, 567
with organometallics, 708
nickel chloride, with $NaBH_4$, 1551
nickel complexes, and coupling aryl halides, 769
nickel peroxide, 837
nickel, Raney see Raney
Nicotiana tabacum, reductase, 919
N-iodosaccharin, halogenation of alcohols, 503
N-iodosuccinimide see NIS
NIS, and formation of halohydrins, 985
in aqueous media, 985
with alcohols and carbodiimides, 503
nitosamines, 728
nitrate esters, and aromatic compounds, 593
from alcohols, 473
nitrate, ethyl see ethyl nitrate
nitrate, silver see silver nitrate
nitrates, see esters, nitrate
nitrating reagents, aromatic compounds, 594
nitration, and electrophilic aromatic substitution, 596
and radical intermediates, 596
electrophilic, 677
nitration, of active methylene compounds, 677
of alkanes, 676
of alkanes, and N-hydroxysuccinimide, 677
of alkanes, and nitronium salts, 677
of alkanes, and radicals, 677
of anilines, 594
nitration, of aromatic compounds, 576, 593, 594, 596, 664
and arylboronic acids, 596
and ethyl nitrate, 594
and Lewis acids, 594
and Raman spectroscopy, 595
in ionic liquids, 593
kinetics, 596
nitration, of benzene, and intermediates, 276
rate and product distribution, 588
nitration, of heterocycles, 594
of N-nitroanilines, 638
of toluene, rate and product distribution, 588
ortho selective, 593
with nitrate esters, 593
nitrene insertion, cyclization, 680
mechanism, 680
enantioselectivity, 680
nitrenes, 257–260, 1010
ab initio calculations, 258
acyl, 1323
addition to alkenes, 259
amino see aminonitrenes
and electric discharge, 258
and photolysis, 258
and rearrangements, 1323
aryl, 258
by elimination of *O*-sulfonylamines, 258
carbonyl see carbonyl nitrenes
definition, 257
dimerization, 259
enantioselective formation, 1010
enthalpy, 258
formation of amides, 679
from amines and nitrous acid, 435
from azides, 258
hydrogen abstraction, 259
insertion, 259, 679
insertion, formation of carbamates, 680
rearrangements, 259
singlet, 258
singlet also see singlet
trapping in a matrix, 258
triplet, 258
triplet also see triplet
with alkanes, 679
with aromatic compounds, 1011
nitrenium ions, 259, 800
singlet and triplet, 260
nitric acid, AIBN, and conjugated acids, 838
and nitration of aromatic compounds, 593
and nitration of aromatic compounds, 595
nitration of aryldiazonium salts, 848
nitrosation of amines, 727
with alkenes, 676
with vinyl carboxylic acids, 838
nitric oxide, radical inhibitor, 807
nitrilases, 1080
nitrile carbanions, 224
nitrile imines, [3+2]-cycloaddition, 1015
nitrile oxides, dyotropic rearrangement to isocyanates, 1431
nitrile ylids, [3+2]-cycloaddition, 1015
nitriles also see dinitriles
nitriles, acid catalyzed addition of alcohols, 1239
acid catalyzed reaction with alcohols, 1085
acidity of γ-protons, 549
acylation reactions, 632
addition of amines, 1104
addition of ammonia, 1104
addition of HCN, 1184
alcoholysis, 1085
alkenes and acylium ions, 1012
alkylation, 542
amino, 1182
nitriles, and chlorophosphates, 1096
and hydrazoic acid, 1095
and hypervalent iodine, 1096
and sulfinyl imines, 1096
and the *Blaise reaction*, 1131
and the *Diels-Alder reaction*, 1037
and the *Ehrlich-Sachs reaction*, 1164
and the *Hoesch reaction*, 632, 633
and the *Pinner synthesis*, 1086
and the *Ritter reaction*, 1239
and the *Stephen reduction*, 1523
and the *Thorpe reaction*, 1179
and trimethylsilyl amides, 1096
nitriles, aryl, and the *Rosenmund-von Braun reaction*, 758
by the *Sandmeyer reaction*, 847
from aryl diazonium salts, 847
from aryl halides, 758
from arylthallium compounds, 786
metal catalyzed, 633
nitriles, by addition of HCN to alkenes, 980
by an S_N2 reaction, 562

nitriles, by dehydration, of amides, and microwave irradiation, 1313
and phase transfer, 1313
and *Swern oxidation*, 1313
and thionyl chloride, 1313
reagents for, 1313
nitriles, by dehydrogenation of amines, 1453, 1454
of amines, reagents for, 1454
nitriles, by dehydration, of oximes, 1310
and microwave irradiation, 1311
nitriles, by elimination of hydrazonium salts, 1311
by fragmentation of oximes, 1312
by oxidation of amines, 1453, 1454
by oxidation of hydrazones, 1455
by oxidation of hydrazones, 1455
by rearrangement of *O*-tosyl oximes, 1312
by reduction, of dinitriles, 1547
by reduction, of nitro compounds, 1528
nitriles, catalytic hydrogenation, 1522
condensation with esters, 1236
condensation with nitriles, 1179
conjugate, cyanoethylation, 866
conjugated, proton acidity, 549
conjugated, reagent for conjugate reduction, 917
cyclotrimerization, 1061
decyanation, 726, 1546
nitriles, dehydration, of amides, 1313
of amides, and the *Burgess reagent*, 1313
of oximes, alternative methods, 1311
of oximes, reagents for, 1311
nitriles, enzymatic hydrolysis, 1080
nitriles, formation of aryl ketones, 632
nitriles, from aldehydes and hydroxylamine, 1095
from aldehydes, 1095, 1311
from aldehydes, reagents for, 1095, 1096
from alkyl halides, 562
from amides, 1313
from amides, by the *von Braun reaction*, 1313
from amines, 1454
from aromatic compounds, 633
from aryl triflates, 633
from carboxylate anion and cyanogen bromide, 1241
from cyanide ion, 562
from hydrazonium salts, 1311
from hydrosilanes, 1547
from hydroxylamine, 1095
from imines, 1312
from imines, and dehydrogenation, 1454
from iminium salts, 633
from isocyanides, 1373
from isocyanides, and *Schwartz's reagent*, 981
from nitro compounds, 1529
from organometallics, 709
from oximes, 1310
from oximes, and acids, 1312
from oximes, and the *Burgess reagent*, 1311
from phenylenediamine, 1465
nitriles, halo, with *Grignard reagents*, 1140
halo, with organolithium reagents, 1140
nitriles, hydrolysis, 563, 1080, 1081
and microwave irradiation, 1080, 1081
to amides, 1080
to thioamides, 1081
nitriles, metal catalyzed, addition of amines, 1104
addition of alkenes, 1239
nitriles, photochemical radiation with hydrocarbons, 838
nitriles, pK_a, 336
of the α-proton, 542
nitriles, radioactive, 277
reaction with carbocations, 1239
reagents for hydrolysis, 1080
reducing agents, 1523
nitriles, reduction, to aldehydes, reagents, 1523
to amines, reagents, 1522
to hydrocarbons, 1546
to methyl with terpenes, 1531
nitriles, reductive cleavage to ketones, 1539
substitution of H, 689
nitriles, vinyl, from vinyl triflates, 709
from vinylorganometallics, 709
nitriles, vinylidene, hydration and cleavage, 886
nitriles, with active methylene compounds, 1180
with allylic halides, 1140
with amines, 1483
with boronic acids, 1140
with esters, 1236
with *Grignard reagents*, 1139
with *Grignard reagents*, mechanism, 1140
with HCl and alcohols, 1086
with imines, 1136
with metal alkyne anions, 775
with metals in ammonia, 726
with Mo peroxide, α-hydroxylation of enolate anions, 1474
with organolithium reagents, 1140
with sodium borohydride, 726
nitrilium ions, 1312
and *Friedel-Crafts cyclization*, 618
and isoquinolines, 618
and the *Beckmann rearrangement*, 1367
and the *Schmidt reaction*, 1365
by reaction of nitriles with oxonium salts, 1523
reduction to amines, 1523
nitrite esters, from alcohols, 473
from alkyl halides, 496
nitrite ion, as an ambient nucleophile, 448, 474
with diazonium salts, 848
nitrite salts, with aryl halides, 838
nitrite, isoamyl, 789
nitrite, sodium see sodium nitrite
nitrites, alkyl, 675
and conversion of anilines to aryl halides, 847
and diazotization of amines, 792
and halogenation of aromatic compounds, 606
conversion to azides, 496
from amines, 474, 727
with acid, 789
with aromatic compounds, 795
with aromatic compounds, and radicals, 796
nitrites, in DMSO, 795
nitro aldol reaction, enantioselectivity, 1156, 1157
nitro compounds, aci form, 94, 1079
and the *Nef reaction*, 1079
nitro compounds, alkylation with *Katritzky pyrylium-pyridinium method*, 542
and nitric acid, 676
and tautomerism, 94
and the *Nef reaction*, 1079
and ultrasound, 1524
anion formation, 448
nitro compounds, aryl, alkylation, 786
and the *von Richter rearrangement*, 797
base induced elimination, 1315
from aryldiazonium salts, 847
replacement of nitro with alkyl, 797
vicarious nucleophilic substitution of hydrogen, 786
with carbanions, 786
with cyanide, 797

nitro compounds, aryl, alkylation (*Continued*)
with dimethyloxosulfoxonium methylid, 786
with methylsulfinyl carbonation, 786
nitro compounds, by dioxirane oxidation of isocyanates, 1491
by oxidation of amines, reagents, 1491
by oxidation of hydroxylamines, reagents, 1491
by oxidation of nitroso compounds, 1491, 1492
nitro compounds, canonical forms, 94
conjugated, with baker's yeast, 919
cyanation, 689
electrolytic reduction to hydroxylamines, 1526
enolate anions, reduction to hydroxylamines, 1526
from alkyl halides, 495, 496
from aryl halides, 838
from arylthallium compounds, 786
from isocyanates, 1491
from oximes, 1491
from silver nitrate, 496
from sodium nitrite, 496
in the *Henry reaction*, 1156
hydrolysis, 1079
photochemical rearrangement, 304
photolysis, 1526
reagents for reduction, 1528
reagents, for hydrolysis, 1079
rearrangement to carboxylic acids, 797
nitro compounds, reduction, 1528, 1562
and amination of alkenes, 897
and microwave irradiation, 1525
and UV light, 1526
enantioselectivity, 1524
on alumina, 1525
to amines, reagents, 1524–1526
to azo compounds, 1561
to azo compounds, reagents, 1562
to azoxy compounds, 1561
to azoxy compounds, reagents, 1562
to enamines, 897
to hydrazo compounds, 1562
to hydrocarbons, 1548
to hydrocarbons, reagents, 1548
to hydroxylamines, reagents, 1526
to oximes, reagents, 1528
with bakers yeast, 1525
with C*lostridium sporogenes*, 920
with Enzyme YNAR-1, NADP-H, 920
with $LiAlH_4$, 1525
with metals in acid, 1524, 1525
with metals, mechanism, 1525
nitro compounds, reductive alkylation, 1099, 1526
removal of nitro, reagents, 1548
nitro compounds, vinyl, 838
by decarboxylation of radicals, 838
from vinyl methyl, 677
nitro compounds, with aldehydes or ketones, 1156
with alkyl halides, 448
with enolate anions, 531
with *Grignard reagents*, 1137
with imines, 1137
with imines, enantioselectivity, 1137
with phosphorus ylids, 1173
nitro groups, deactivating groups, 594
rearrangement, 638
nitro-alcohols, by the *Henry reaction*, 1156
from epoxides, 490
nitroalkanes, with imines, 1157
nitroalkenes, *Michael addition*, 945
nitrobenzene, and dipole moment, 18, 19
nitrocyanimde, with mcpba, 497
nitrogen-15, 736, 1413
nitrogen fixation, and triketones, 1061
nitrogen ylids also see ylids
nitrogen, and argon, fluorination of alkenes, 982
and metal catalyzed reactions with organolithium reagents, 754
as a leaving group, 434, 788, 790, 1017, 1294, 1316, 1455, 1542
bond angles, 6
cleavable groups, 638
electron structure, 13
electrophiles, 674
extrusion from pyrazoles, 1316, 1317
extrusion from pyrazolines, 1316, 1317
extrusion from triazolines, 1316, 1317
insertion, 679
nucleophiles, 481
PES spectrum, 12
ylids, 50, 1173
nitro-Hunsdiecker reaction, 838
nitro-Mannich reaction, 1103
nitromethanes, pK_a, 224
nitronates, from nitro compounds, 1157
with aldehydes, 1157
nitrones, addition of organometallics, 1138
azulenyl, and radicals, 236
by oxidation of amines, 1455
by oxidation of hydroxylamines, 1455
from hydroxylamines and metal-salen complexes, 1311
from hydroxylamines, 1311, 1491
from oximes, 475
in [3+2]-cycloaddition reactions, 1015, 1018
in *Michael reactions*, 945
with boronates, 1136
with *Grignard reagents*, 1138
nitronic acids, 94
nitronic esters, O-alkylation, 448
nitronium ions, 575, 582, 596, 590, 677
and aromatic compounds, 664
and nitration of aromatic compounds, 594, 595
and X-ray, 595
as a leaving group, 591
electrophilic aromatic substitution, 582
migration from nitrogen, 638
nitronium salts, and nitration of alkanes, 677
and nitration of aromatic compounds, 595
nitration of amines, 728
nitronium tetrafluoroborate, 575
with alkenes, 989
nitrosation, 675
and arenium ions, 597
and enols, 676
and nitrosonium ion, 597
and steric inhibition of resonance, 597
and UV, 676
aromatic compounds, mechanism, 597
mechanism, 597
of amines, 727, 728
of amines, mechanism, 728
of ketones, mechanism, 676
photochemistry, 676
nitroso amides, base induced elimination, 1316
nitroso carbamates, base induced elimination, 1316
nitroso compounds, and formation of imines, 676
and tautomerism, 93
and the *Barton reaction*, 1427, 1428
and the *Ehrlich-Sachs reaction*, 1164

aromatic, 596
nitroso compounds, aryl and the *Mills reaction*, 793
Fischer-Hepp rearrangement, 639
N-nitroaniline rearrangements, 639
with anilines, 793
nitroso compounds, by oxidation of anilines with *Caro's acid*, and mechanism, 1490
of anilines, 1490
of hydroxylamines, 1455
nitroso compounds, from amines, 728, 1491
from nitro compounds, 304
from nitrous acids, 675
hydrolysis, 1428
in the *Diels-Alder reaction*, 1037, 1039
metal reduction to amines, 1526
N- versus C-, 596
oxidation to nitro compounds, 1491
oxidation, 1492
preparation of diazomethane, 1316
nitroso compounds, reduction, 1527, 1562
to amines, 1530
nitroso compounds, reductive alkylation, 1099
with nitriles, 1164
with oximes, 728
nitroso oximes, tautomerism see tautomerism
nitroso radicals, 1428
nitroso ureas, base induced elimination, 1316
nitrosoamides, rearrangement, 796
with aromatic compounds, 795
nitrosoamines, from amines, 727
nitroso-halogenation, of alkenes, 989
nitrosomethane, and tautomerism, 93
nitrosonium ion, 596, 639, 676
and diazotization, 790
and nitration of aromatic compounds, 597
nitrosyl chloride, with alkenes, 989
nitrosyl halides, with alkenes, 989
nitrotoluene, dipole moment, 18
nitrous acid, and amines, 434
and carbocation formation from amines, 219
and diazonium salts, 598
and formation of aryl diazonium salts, 788
and pH, with amines, 789
reaction with amines, 219
selectivity, 789
with amides, 1198
with amines, 727, 1346
with amines, kinetics, 789
with amines, mechanism, 790
with anilines, 788
with aziridines, 1304
with hydrazides, 1362
with hydrazines, 727
nitrous oxide, [3+2]-cycloaddition, 1015
nitrous oxide, oxidant, 635
nitroxide radicals, 245
asymmetric, 243
nitroxide, and TEMPO and radicals, 240
nitroxyl radicals, 240
and *Bobbitt's reagent*, 1449
compounds, and oxidation of alcohols, 1448, 1449
Fremy's salt, 1453
TEMPO, 240
X-ray, 241
nitryl chloride, addition to alkenes or alkynes, 989
with alkynes, 989
N-methylmorpholine-N-oxide see NMO
N-methylpyrrolidinone see NMP
NMO (N-morpholine-N-oxide), 993
and dihydroxylation of alkenes, 993
and nitrile formation, 1095
as a solvent, 1095
solvent, 1095
NMR (nuclear magnetic resonance), 1583
analysis, and stereochemistry, 144
and absolute configuration, 143, 144
and alkenes, 51
and amination of quinoline, 787
and annulenes, 72–75, 79
and antiaromaticity, 69, 81
and aromaticity, 54
and aryl carbanions, 915
and benzene, 51
and benzenonium ion, 573
and bond order, 55
and bullvalene, 1405
and carbocation stability, 1324
and carbocations, 209, 214, 216–218, 398, 401
and chemical shift, 17
and chiral compounds, 160
and chiral lactams, 142
and chiral shift reagents, 161
and chiral solvents, 161
and CIDNP, 237
and conformation of macrocycles, 189
and conformations, 174
and *Cope rearrangements*, 1405
and coupling constants, 17
and crown ethers guest-host interactions, 112
and cycloheptatrienyl anion derivatives, 71
and cyclopropylmethyl carbocations, 406
and cyclopropylmethyl cation, 406
and detection of hemiaminals, 1090
and determining absolute configuration, 142
and diamagnetic ring current, 51
and diastereotopic compounds, 172
and diatropic, 51
and dynamic nuclear polarization, 238
NMR, and electronegativity, 17
and emission, 237
and enantiomeric excess, 160
and enantiomeric purity, 162
and enol content, 91
and *Fischer indole synthesis*, 1413
and Grignard reagents, 230, 231
and homoaromatic compounds, 83
and hydrogen bonding, 100
and intermediates, 276
and isotope effects, 286
and isotopic labeling, 278
and kekulene, 78
and keto-enol tautomerism, 91
and kinetics, 283, 382
and mechanism, 283
and *Meisenheimer salts*, 733
and methane, 11
and methyl neighboring groups, 407
and *Mosher's acid*, 142
NMR, and nonclassical carbocations, 396, 398, 404, 1340
and norbornadienyl carbocations, 396
and norbornyl carbocation, 404
and organometallics, 229
and oxaphosphetanes, 1168
and oxime formation, 1095
and paramagnetic ring current, 53
and paratropic compounds, 53, 81
and phenonium ions, 401
NMR, and radicals, 236–238
and ring current, 51, 52
and rotaxanes, 120
and solvolysis of esters, 382
and spin traps, 236
and steric strain, 192
and structure of carbocations, 1390
and tetramethylsilane, 17

NMR, and radicals (*Continued*)
and the mechanism of conjugate addition of organometallics, 956
and the *Wittig reaction*, 1168, 1169
and valence tautomerism, 1406
NMR, anisotropy, and conformations, 174
annulenes, 78, 81
bicyclo[5.1.0]octadiene, 1404
C13, and ring current, 52
calixresorcarenes, 51
chiral solvating agents, 161
cyclobutadiene derivatives, 68
dynamic, 189
EtI + EtLi, 236
heptalene, 62
lanthanide shift reagents, 142
negative enhancement, 237
paracyclophanes, 47, 51
tri-*tert*-butylcyclobutene, 1406
tropone and tropolone, 60
N-nitroaniline also see anilines
N-nitroaniline, rearrangement, 638
N-nitroso compounds, 596
N-nitroso groups, rearrangement, 639
nodes, and electron density, 4
NOESY, and π-π-interactions, 104
nomenclature, *aa/ee/ae*, and conformations, 183
acid and base, IUPAC, 312
and the *Cahn-Ingold-Prelog rules*, 163
and diastereomers, 148
and IUPAC, 208
carbocations, 208
cis/trans, and dienes, 163
D/L, and stereogenic atoms, 137
dig, 270
nomenclature, E/Z, 163
and alkenes, 163
and azo compounds, 163
and dienes, 163
and imines, 163
and thiocarbonyls, 163
nomenclature, epi, 148
erythro/threo, 148
g transitions, 292
[i,i], and sigmatropic rearrangement, 1391, 1392
IUPAC, mechanisms, 370–371
IUPAC, transformations, 368–370
peri-, 148
"r" and "s", 147
R/S, and stereogenic atoms, 138–141
re/si, 172
syn/anti, 149
tet or trig, 270
u transitions, 292
nonadjacent π-bonds, stabilization of carbanions, 226
nonaflates, leaving groups, 432, 433
nonalternant hydrocarbons, 63
cyclopropenyl cation, 67
topological polarization, 65
nonaromatic rings, and arynes, 739
nonaromatic systems, and Hückel's rule, 66
nonbonded interactions, 193
nonbonding orbitals, 39
carbocation, 39
nonclassical carbocations also see carbocations
nonclassical carbocations, 218, 394
and neighboring group participation, 395
and superacids, 403
and temperature, 403
stable solutions, 403
nonconcerted *Cope rearrangement*s, 1404
nonconcertedness, 639
nonhomoaromatic compounds, 83
nonionic bases, 1207, 1297
nonplanar radical cations, 250
nonpolar solvents see solvents
norborandienone, metal complex, 107
norbornadienes, and photochemical [2+2]-cycloaddition, 1050
cycloaddition with alkenes, 1027
norbornadienone, irontricarbonyl complex, 106
norbornane, and twist conformation, 182
norbornenes, addition of DCl, 878
and strain, 203
stereochemistry of addition, 878
with thiols, 1334
norborneol, 168
norbornyl carbocations, ab initio calculations, 404
and NMR, 404
classical arguments, 403
in stable solutions, 403
stability, 404
norbornyl compounds, and S_N1 reactions, 382
norbornyl *Grignard reagents*, 653
norbornyl sulfonates, 421
norbornyl systems, and nonclassical carbocations, 395
and solvolysis, 402
norcamphor, 168
norcaradienes, 1056
from methylene and benzene, 1056
photochemical ring opening, 1380
norephedrine, benzoyl, and rearrangement, 351
normal acid, definition, 323
Normant reagents, addition to alkynes, 940
Norrish Type I cleavage, definition, 303
Norrish type I reactions, and radicals, 1318
photolysis of cyclobutanones, 1318
Norrish Type II cleavage, 303
and elimination, 1254
nortricyclane, and nonclassical carbocations, 404
nortricyclyl chloride, 257
nosylates, leaving groups, 432, 433
notes, as a publication, 1570
N-oxides, and spin traps, 236
Nozaki-Hiyama reaction, and acyl addition, 1121
nuclear magnetic resonance see NMR
Nuclear Overhauser effect spectroscopy see NOESY
nucleofugal ability, and E1 mechanism, 1265
and elimination, 1266
nucleofuges, 373
and *Zaitsev's rule*, 1271
nucleons, 123
nucleophiles, 426
nucleophiles, acyl addition, 1067
nucleophiles, ambident, 446
and basicity, 448
and counterions, 449
and crown ethers, 449
and *Kornblum's rule*, 449
and phenoxide ions, 448
and regioselectivity, 447
and steric effects, 450
and thermodynamic control, 448
cyanide, 448, 563
dianions, 447
enolate anions, 447
nitrite ion, 448, 474
nitro compounds, 448
solvent effects, 449
types, 447
nucleophiles, and catalysis of attack at carbonyls, 1073
and cation affinity, 427
and displacement of diazonium, 788
and ester hydrolysis, 1191
and HSAB, 428
and Lewis bases, 426, 427
and neighboring groups, 397
and nucleophilic aromatic substitution, 745
and nucleophilicity table, 430

and rate of reaction, 492
and S_N1 reactions, 382, 427
and substitutions, 373
and Umpolung, 549
nucleophiles, approach to carbonyl, 1071, 1072
attack at ipso carbon, 732
carbon, 510
carbon, with esters, 1236
carboxylic acids, 1189
catalysis of amide hydrolysis, 1198
catalysts for acyl addition, 1073
charged, and solvent effects, 437
counterions, 449
cyanide ion, 1182
definition, 262
dicarbonyl anions, 447
directionality of approach to carbonyls, 1072
enolate anions, 447
heteroatom, conjugate addition, 965
in S_N2 reactions, 427
nucleophiles, nitrogen, 481
on the arenium ion, 582
opening aziridines, 538
rate of reaction with carbocations, 427
reaction with carbocations, 220
reaction with epoxides, 466
reaction with halonium ions, 875
reactivity order in nucleophilic aromatic substitution, 745
strength of, 427
sulfur, 475
trajectory of approach to carbonyls, 1071, 1072
uncharged, 428
with allylic sulfones, 530
nucleophilic addition also see addition
nucleophilic addition, 263
nucleophilic allylic rearrangement, 663
nucleophilic assistance, and solvents, 441
nucleophilic catalysis, 1190
and pyridine, 1190
hydrolysis of anhydrides, 1190
nucleophilic catalyst, pyridine, 1202
nucleophilic mechanism, 865, 1341
diazonium salts, 788
nucleophilic radicals, 816, 874
nucleophilic reactions, 262
nucleophilic rearrangements, 263
mechanism, 1322–1333
nucleophilic strength also see nucleophilicity
nucleophilic strength, 427
electron repulsion and functional groups, 431
table, 430
nucleophilic substitution see substitution
nucleophilicity, ambident nucleophiles, 448
amides, 493
and basicity, 427
and Brønsted-plots, 430
and polarizability, 448
and rate of reaction, 492
and solvation, 428
and solvents, 427, 428, 438
and steric hindrance, 429
and supercritical carbon dioxide, 442
and *Swain-Scott equation*, 429
and the Periodic table, 427
and the α-effect, 431
and unshared electrons, 430
at carbonyl carbon, 430
in nucleophilic aromatic substitution, 745
in $S_{RN}1$ reaction, 745
indexes, 1029
of nucleophiles, table, 430
of silyl enol ethers, 1152
order, for S_N2 reactions, 429
order, toward sulfonyl sulfur, 1249
π-, 859
reaction at carbonyls, 430
scale, 431
silyl enol ethers, 1146
solvent, scale, 441
to sulfur, 1249
versus basicity, and elimination, 1276
with hetero multiple bonds, 1067
Nucleus Independent Chemical Shift (NICS), 53
Numerical Data and Functional Relationships in Science and Technology, 1581

O-acylation see acylation, *O*-acylation
observed rotation also see enantiomers, chiral compounds
observed rotation, α, definition, 124
octahydroannulene, 76
octatetraenes, cyclization to cyclooctatrienes, 1387
octylidenes, 252
Official Gazette of the Patent Office, 1573
oleanene, and *Wagner-Meerwein rearrangements*, 1340
olefin metathesis see metathesis, alkene
olefination, Peterson see *Peterson*
oligocatenanes, 118
oligomeric carbodiimides, 1241
onium salts, from amines, 331
with alcohols, 467
online literature searching, 1594–1604
problems, 1593
Oppenauer oxidation, 1445
and metal catalysts, 1447
and supercritical conditions, 1447
and the *Meerwein-Ponndorf-Verley reaction*, 1447
of alcohols, 1447
uncatalyzed, 1447
optical activity, 122
and allenes, 132
and biaryls, 130
and biphenyls, 130
and chiral atoms, 126
and chirality, 122
and circularly polarized light, 145
and light, 145
and paracyclophanes, 134
and polarizability, 126
and refractive index, 145
and restricted rotation, 134
and solvolysis, 402
and symmetry, 145
and *Tröger's base*, 129
cause of, 145
determining absolute configuration, 142
Grignard reagents, 652
N,P,As,Sb, 129
perpendicular dissymmetric planes, 130
optical inactivity, 122
optical purity, 160, 161
optical resolution see resolution
optical rotatory dispersion, 143
and conformations, 174
orbital coefficients, and [3+2]-cycloaddition, 1016
orbital interaction, and bond strength, 30
orbital movement, thermal [1,3]-sigmatropic migration, 1397
orbital movement, thermal [1,5]-sigmatropic migration, 1397
orbital overlap, [2+2]-cycloaddition, 1044
[2+2]-cycloaddition, ketene with cyclopentadiene, 1045, 1046
and *Diels-Alder reactions*, 1032, 1035
and photochemistry, 1032
and ring closing of dienes, 1383, 1384

orbital overlap, [2+2]-cycloaddition (*Continued*)
and sign inversion, 1032
cyclopropane, 195
orbital symmetry rules, and [2+2]-cycloaddition, 1044
and cyclobutene-butadiene, 1388
and cyclopropane ring opening, 1389
and endo addition, 1036
and photochemical [2+2]-cycloaddition, 1050
and stability of *Dewar benzenes*, 1387
and stereochemistry of electrocyclic rearrangements, 1388
and the *Diels-Alder reaction*, 1030
and the *Möbius-Hückel method*, 1388
and the *Woodward-Hoffmann rules*, 1030
conservation of, 1346
orbitals, 1s and 2p, 4
allylic carbocations, 39
alternant and nonalternant hydrocarbons, 63, 64
and allenes, 132
and benzene, 32, 33, 36
and bond angle, 25
and bond distance, 22
and conjugation, 39, 40
and cyclopropane, 195
and delocalization, 31
and disrotatory ring opening, 1385
and ethyne, 10
and ferrocene, 61
and hybridization, 7
and hyperconjugation, 87
and metallocenes, 61
and mutual repulsion, 7
and PES, 12, 13
and rearrangement, 1321
and resonance, 32
and thermal ring opening of cyclobutenes, 1383
and trienes, 42
and ylids, 49
orbitals, antarafacial overlap, 1035
antibonding, 4, 5, 9
antibonding, and S_NAr reactions, 743
antibonding, of butadiene, 37, 38
bonding, 5, 9
cyclohexadiene-trine interconversion, 1384, 1385
orbitals, d, 15
and carbanion stability, 225
orbitals, diagrams, 4
dienes-cyclobutene interconversion, 1384, 1385
five-membered ring heterocycles, 57
gerade, 5
hybrid, 9
hybrid, 2p, 8
linear combination of, 6
orbitals, molecular, 4, 5, 32
orbitals, molecular also see molecular orbitals and MO
nonbonding, 39
of alkenes, 1031–1037
of dienes, 1031–1037
of mercury, 7
of oxygen atom, 6
overlap, [2+2]-cycloaddition, 1044
orbitals, p, and vinyl carbocations, 415
conjugated with double or triple bonds, 39
orbitals, π, 9, 10
orbitals, sigma, 5
sigma, overlap, 85
orbitals, sp, 7
sp^2 hybrid and sp^3 hybrid, 8, 9
suprafacial overlap, 1035
ungerade, 5
ORD, see optical rotatory dispersion
organic compounds, and bond energy, 30
Organic Electronic Spectral Data, 1583
Organic Functional Group Preparations, 1591
Organic Reaction Mechanisms, 1585
Organic Syntheses Collective Volumes, 1590
Organic Syntheses Indexes, 1590
Organic Syntheses, 1589, 1590
Organic Syntheses, Reaction Guide, 1590
organoaluminum compounds, acyl addition, 1119
organoaluminum, trialkyl, reaction with alcohols, 533
with imines, 1136
organoantimony compounds, 777
organobases, and the aldol reaction, 1147
and the *Cannizzaro reaction*, 1563
organobismuth compounds, conjugate addition, 955
coupling, 760
organoboranes see boranes
organoborates see borates
organoboronates, metal catalyzed coupling, 620
organocadmium reagents, hydrolysis, 698
with acyl halides, 1227, 1229
organocalcium reagents, and radicals, 233
and SET mechanism, 233
organocatalysts, and cyclopropanation, 1054
and epoxidation, 1000
and the aldol reaction, 1147
and the *Grignard reaction*, 1108
and the *Mukaiyama aldol reaction*, 1152
aziridination of alkenes, 1011
organocatalysts, chiral, 1147, 1181, 1183
and the *Mukaiyama aldol reaction*, 1153
organocatalysts, for conjugate addition, 967
for cyclopropanation, 1179
for halogenation of epoxides, 506
for halogenation of ketones, 669
for halolactonization, 987
for silane reduction, 1514
for the *Diels-Alder reaction*, 1025, 1026
for the *Henry reaction*, 1157
for the *Michael reaction*, 945, 947
imidazolidones, 1025
N-heterocyclic carbenes, 1108
Pybox, 1102
with silanes and dienes, 929
organocerium compounds, with hydrazones, 1138
with acid derivatives, 1230
organochromium compounds, acyl addition, enantioselectivity, 1121
organocopper compounds, and the *Ullmann reaction*, 769
Lewis acids and alkyl halides, 523
organocopperzinc reagents, with allyl halides, 523
organocuprates, acyl addition, 1122
addition to alkynes, 941
aggregation states, 950
amido, 966
amino, 951
organocuprates, and coupling with alkyl halides, 520
and Cu(III) complexes, 950
and elimination, 521
and formation of enolate ions, 951
and inversion of configuration, 521
and racemization, 521
and the structure of alkyl halides, 521

organocuprates, complex formation, 956
organocuprates, conjugate addition, 949
1,2- versus 1,4-addition, 952
diastereoselectivity, 951
enantioselectivity, 951, 952
of conjugated aldehydes, 952
organocuprates, cyano, 950
diaminocyano, 536
dibutylphosphine complex, 522
dummy ligands, 950
enantioselectivity, 951, 952
excess reagent required, 950
from organolithium reagents, 711, 950
Gilman reagents, 520
halogen-metal exchange, 523
organocuprates, higher order mixed, 522
and conjugate addition, 949
organocuprates, higher order, 522
and transmetallation, 712
conjugate addition, 969, 1122
structure controversy, 522
organocuprates, in the *Michael addition*, 949
in the S_N2' reaction, 412, 537
limitations to conjugate addition, 950
limitations to reactivity, 521
lithium, 517
mechanism of reaction, 521
metal catalyzed coupling, 527
mixed, 522
mixed, and conjugate addition, 950
oxygen mediated coupling, 849
reaction with alkyl halides, 521
selectivity in transfer reactions, 950
solvent effects, 949
thermal instability, 521
tolerated functional groups, 950
organocuprates, with acyl halides, 1225, 1227
with aldehydes or ketones, 1122
with alkenes, 937
with alkyl halides, 520, 951
with alkyl halides, stereochemistry, 521
with allylic alcohols, 533
with allylic phosphonates, 530
with amines, 707
with aziridines, 538
with carbamoyl halides, 1214
with conjugated sulfoxides, 950
with cyclopropylcarbinyl halides, 412
with dihalides, 521
with dithiocarboxylic esters, 1132, 1133
with enol acetates, 527
with epoxides, 536
with epoxides, and Lewis acids, 536
with haloketones, 548
with organotellurium compounds, 1122
with propargyl esters, 527
with sulfonate esters, 521
with thioesters, 1231
with trialkylsilyl halides, 949
with vinylic epoxides, 537
organogallium reagents, and enolate anions, 696
organogermanium compounds, coupling, 760
with aryl halides, 767
organoindium compounds, carbonylation, 567
organolanthanide catalysts, hydroamination, 1008
organolanthanum compounds, 1231
organolead compounds, 757
with acyl halides, 1227
organolithium reagents, 1, 2- versus 1,4-addition, 1109
acyl addition, 1110
acyl addition, enantioselectivity, 1110
addition to aldehydes or ketones, mechanism, 1113
addition to alkenes or to alkynes, 936
addition to conjugated aldehydes, 952
aggregate formation, 1110
aggregates, 229, 695, 697
amination, 754
organolithium reagents, and aggregation state, 231, 232
and alkylation of aromatic compounds, 785
and alkylation of arylnitro compounds, 786
and amide bases, 751
and amines, 687
and based induced elimination of dihalo alkenes, 1298
and cleavage of ethers, 534
and deprotonation, 696
and deprotonation, of arylsilanes, 516
and directed ortho metalation, 784
and electron affinity, 232
and enolate anions, 1113
and formation of organocuprates, 711
and formylation, 628
and metalation, 695
and preparation of organometallics, 526
and solvation, 231
and stereochemistry, 717
and steric hindrance, 1112
and the *Shapiro reaction*, 1293
and TMEDA, 231, 232
and transmetallation, 712
and *Wurtz coupling*, 716
and X-ray crystallography, 231, 232
and *Ziegler alkylation*, 785
organolithium reagents, aryl, hydrolysis, 648
unsolvated, 232
organolithium reagents, arylation of amines, 751
as bases, 322
basicity, 1109
complexation, and conjugate addition, 953
configurational stability, 228
conjugate addition, 952, 953
organolithium reagents, coupling, alkenes to allylic thioethers, 935
with sulfones, 531
organolithium reagents, exchange, with alkyl halides, 222, 1109
with organolithium compounds, 516
organolithium reagents, from alkyl halides and lithium, 1109
from alkyl halides, 715
from organotin compounds, 938
from thioethers, 852
organolithium reagents, hydrolysis, 698
in DME, 231
in situ generation, 1230
Li-H exchange, 516
metal catalyzed conjugate addition, 969
metal catalyzed reaction with nitrogen, 754
metal halogen exchange, 516
precursors to organocuprates, 950
reactivity order, 697
safe-handling, 695
sonochemical preparation, 309
structural variation, 1110
structure, 231
structure, and rate of deprotonation, 696
sulfurization, 703
organolithium reagents, with aldehydes or ketones, 1108, 1160
with alkenes, 937
with alkoxides, and elimination of epoxides, 1287
with alkyl halides, 516
with alkyl halides, and CIDNP, 520
with alkyl halides, and ESR, 520
with alkynes, 937
with allylic ethers, 555

organolithium reagents, with aldehydes or ketones (*Continued*)
with amines, 1373
with amines, and amination of alkenes, 896
with ammonium salts, E^i mechanism, 1292
with aromatic compounds, 784–787
with aryl amines, rearrangement, 1373
with aryl halides, 516, 757, 759
with aziridines, 1019
with borates, 953
with boronic esters, 1377
with carbamoyl halides, 1231
with carbon disulfide, 1132
with carbon tetrachloride, 716, 717
with carboxylate salts, 1131, 1229
with carboxylic acids, 1131, 1229
with chiral alcohols, 1110
with CO_2, 708, 1132
with CO_2, enantioselectivity, 1132
with conjugated compounds, 1109
with copper compounds, 520
with cryptands, 1113
with cyclic ethers, 1285
with cyclic sulfones, 1319
organolithium reagents, with dienes and carbon dioxide, 978
with dihalocyclopropanes, 1347
with dithianes, 1432
with epoxides, 535, 537
with esters, 1229, 1232
with ethers, 1285, 1374
with ethers, *Wittig rearrangement*, 1373, 1374
with EtI, and NMR, 236
with fluorene, 695
with formamide, 709
with gem-dihalides, 1110
with halonitriles, 1140
with imines, 1133
with imines, and chiral additives, 1134
with iron pentacarbonyl, 782
with isocyanates, 1140
with isocyanides, 1247
with isothiocyanates, 1141
with lactams, 1230
with LIDAKOR, 1287
with metal halides, 711
with methoxyamine, 706
with nitriles, 1140
with organozirconium reagents, 933
with oxazines, 556
with oxazolines, 557
with oximes, 1138
with phenyl cyanate, 759
with phosphonium salts, 1165
with RI, radical intermediates, 237
with siloxanes, 783
with sparteine, 937, 1110
with sparteine, enantioselectivity, 516
with thioamides, 1230
with TMEDA, 1110
with transition metals, 938
with vinyl boronates, 533
with *Weinreb amides*, 1230
organolithium-TMEDA complex, 784
organomagnesium compounds also see Grignard reagents
organomagnesium compounds, and carbanions, 222
exchange with R_2Hg, 222
rearrangement, 711
organomanganese compounds, coupling reactions, 761
with alkenes or with allenes, 938
organomercury compounds, 653, 658
acetolysis, 659
exchange with R_2Mg, 222
rate of reaction with halogens, 659
organometallic compounds, addition to alkenes or alkynes, 938
and carbanions, 221
and NMR, 229
aryl, 648
structure, 228
with alkenes, 938
with alkyl halides, and radicals, 520
with alkyl halides, mechanisms, 519
with alkynes, 938
with imines, 1133–1138
organometallic reagents, and acyl substitution, 1231
conversion to carboxylic acids, 568
from organolithium reagents, 526
hydrolysis, 698
structural requirements, 526
various, with acid derivatives, 1231
with acyl halides, 1225–1227
with carbon dioxide, 1132
with halogens, 704
organometallics, addition, to aldehydes or ketones, 1114–1125
to aldehydes or ketones, metals used, 1114, 1115, 1116
to alkenes, 936–940
to C=N compounds, 1133–1138
to carbonyls, enantioselectivity, 1115
to carbonyls, in ionic liquids, 1115
to carbonyls, structural compatibility, 1115
to imines, enantioselectivity, 1134
organometallics, amination of, 706
organometallics, and active metals, 695
and alkylation of aromatic compounds, 785
and alkylation of pyridine or pyrrole, 785
and carbonylation of aryl halides, 782
and formation of biaryls, 761
and halogen replacement in alkyl halides, 716
and metalation, 694
and metals, 695, 696
and proton transfer, 695
and radical ions, 716
and S_E1 reactions, 659
and the *Heck reaction*, 763–768
and the *Stetter reaction*, 1123
and transmetallation, 712
organometallics, aryl, formation of biaryls, 620
aryl, hydrolysis, 648
arylation of alkenes, 762
as bases, 322
bis addition to alkynes, 940
carbonylation, 564, 708
cleavage of ethers, 534
conjugate addition, 949–956
conjugate addition, mechanism, 955
containing heteroatoms, 696
organometallics, coupling, with active methylene compounds, 780
with alcohols, 532
with allylic esters, 527
with malonate esters, 780
with *Mannich bases*, 530
and the *Stille reaction*, 524
organometallics, cross coupling, 850
deprotonation, 696
deprotonation, mechanism, 696
dimerization, 850
dimetallic compounds, 941
directed ortho metalation, 784
electrophilic substitution, 652
enantioselectivity, 697
from alkenes, 926, 936
from alkyl halides, 713, 715
from dihalides, 1109

from metals, 698, 713, 715
from organometallics, 694
organometallics, *Grignard reagents* with metal halides, 711
Group I, coupling with alkyl halides, 515, 516
Group II, coupling with alkyl halides, 515, 516
halogenation, mechanism, 706
oxygenation, 703
poor reactivity with water, 698
preparation of ketones, 564
propargyl, metal catalyzed addition to carbonyls, 1114
protonation of, 698
reagents, and acyl addition, 1117
reduction with sodium borohydride, 699
sulfuration, 703
transmetallation, 710
vinyl, and the *Heck reaction*, 767
vinyl, formation of dienes, 682
vinyl, formation of divinyl ketones, 564
organometallics, with acids, 698
with acyl halides, 1226
with aldehydes or ketones, 153
with alkyl halides, 523–526, 564, 565, 716
with amides, 1228, 1229
with anhydrides, 1228
with anhydrides, enantioselectivity, 1229
with anhydrides, or carboxylic esters, 1229
with aryl halides, 759
with aryldiazonium salts, 793
with aziridines, 538
with conjugated carbonyl compounds, 949–95
with cuprous cyanide, 709
with disulfides, 703
with epoxides, 535, 536
with esters, 1228
with imines, 1135
with imines, enantioselectivity, 1135
with metal sulfonates, 530
with oxygen, 699
with peroxides, 700
with sulfonic acid esters, 703
with sulfonyl halides, 1252
with sulfur dioxide, 703
organopotassium reagents, 695
with alkyl halides, 515
organosilanes see silanes
organosodium reagents, 520
with ethers, 1285
with alkyl halides, 515
organotellurium, coupling, 761
with organocuprates, 1122
organothallium compounds, and aryl iodides, 757
formation of phenols, 747
organotin compounds, 659
acyl addition, 1119
acyl addition, enantioselectivity, 1118, 1119
coupling, 760
metal catalyzed addition to carbonyls, 1118, 1119
with aryl halides, 767
with Selectfluor, 1119
with isocyanates, 1141
organotitanium compounds also see Petasis reagent
acyl addition, 1119
conjugate addition, 1120
reaction with tertiary alcohols, 533
organotrifluoroborates, with acetals, 700
organozinc compounds, and alkene formation, 1175
and alkynes, 940
and carbenoids, 1057
and conjugate addition, 953
and insertion reactions, 694
and the *Reformatsky reaction*, 525, 1130
and the *Simmons-Smith procedure*, 1057
enantioselectivity of conjugate addition, 953
hydrolysis, 698
with alkyl halides, 524
with chiral ligands, 953
with imines, 1134
with thioesters, 1231
X-ray crystallography, 1057
organozinc halides, 718
with thioesters, 1231
organozinc also see dialkylzinc
organozirconium compounds, with halogens, 704
with organolithium reagents, 933
orientation, and addition reactions, 874, 877
ortho chlorination, phenols, 605
ortho effect, 583
and rate of reaction, 361
ortho esters, and transacetalization, 1083
hydrolysis, 456
reduction to aldehydes, 1537
transetherification, 465
ortho methylation, of phenols, 612
ortho quinones, 581
ortho rearrangements, *Claisen rearrangement*, 1407
ortho selective nitration, 593
ortho/para ratio, *Fries rearrangement*, 636
ortho/para selectivity, and aryl radicals, 818, 819
orthoformates, with sulfonic acids, 1250
orthogonal conformations, 180
ortho-para directing groups, 578
ortho-para ratio, and electrophilic aromatic substitution, 580
Orton rearrangement, 640
and peroxides, 640
intramolecular, 640
photochemical, 640
and diamination of alkenes, 1009
osazones, and carbohydrates, 1093
from hydroxy aldehydes or hydroxy ketones, 1093
oscillation, carbanions, 227
in organocuprate complexation, 950
osmate esters, 993
osmium complex, and dihydroxylation, 993
osmium tetroxide, and catalysts, with *Cinchona* alkaloids, 993
and chiral additives, 995, 996
and diamination, X-ray structure, 1009
and dihydroxylation of alkenes, 992
and *Sharpless aminohydroxylation*, 1007
encapsulated, 993
ionic polymer supported, 997
microencapsulated, 997
polymer-bound, 993
toxicity, 993
with alkenes, 993
with *Jones reagent*, 1464
with Oxone, 1464
out-in isomers, 168
out-in isomers also see isomers
out-out isomers, 168
over oxidation, of alcohols, 1443
overall rate, 281
overlap of orbitals, in HOMO, 1381, 1382
oxacyclooctane, conformation, 189
oxa-di-π-methane rearrangement, 1425
mechanism, 1426
oxalacetic acid, 171
oxalates, and elimination of esters, 1289
oxalyl bromide, with carboxylic acids, 1224
oxalyl chloride, and DMSO, oxidation of alcohols, 1447
and *Friedel-Crafts acylation*, 622

oxalyl chloride, and DMSO, oxidation of alcohols (*Continued*)
with amides, 1223
with carboxylic acids, 1224
oxaphosphetanes, and NMR, 1168
and the *Wittig reaction*, 1168
oxathiazinanes, 679
oxathiolanones, extrusion to give alkenes, 1319, 1320
twofold extrusion, 1319, 1320
oxatriquinene, 219
oxazaborolidines, chiral in reductions, 1513
1,3-oxazine-2-ones, from isocyanates and oxetanes, 1085
oxazines, alkylation, 556
and epoxides, 556, 557
and iminium salts, 557
reduction, 556
with organolithium reagents, 556
oxaziridines, 128
and α-hydroxylation, 1474
chiral, α-hydroxylation, 1474
hydroxylation of hydrocarbons, 1471
photolysis, 1367
rearrangement to lactams, 1344
sulfonyl and α-hydroxylation of enolate anions, 1474
sulfonyl, and oxidation to thioethers, 1494
α-hydroxylation, enantioselectivity, 1474
oxaziridinium salts, and epoxidation of alkenes, 1002
from Oxone and iminium salts, 1002
oxazolidines, from acyl aziridines, 1399
from aziridines, 731
hydrolysis, 557
amides, with alcohols, 1209
oxazolidin-2-ones, alkylation, 493
oxazolidinones, 678
arylation, 755
as catalysts, 947
chiral, and enolate alkylation, 546
oxazolines, alkylation, 557
and carboxylic acids, 557
from ketones, 1159
with organolithium reagents, 557
and the *Dakin-West reaction*, 722
ene reactions, 942
oxepin, and the *Cope rearrangement*, 1406
oxetane, conformation, 188
oxetanes, and formation of isocyanides, 492
and photochemical [2+2]-cycloaddition, 1049
by the *Paterno-Büchi reaction*, 1049, 1243
carbene insertion, 692
cleavage with organolithium reagents, 534
formation of dinitrates, 474
from alkenes and halides or ketones, 1243
in the *Prins reaction*, 1185
with amines, 490
with isocyanates, 1085
oxidation number, 1433
oxidation, 264, 1437
oxidation, allylic see allylic oxidation
CH, enantioselectivity, 1471
with selenium dioxide, 1470, 1471
oxidation, and DMSO, 1481
Boyland-Sims, 634
by loss of hydrogen or gain of oxygen, 1433
oxidation, α-CH, and the *Étard reaction*, 1479
of cyclic ethers to lactones, 1478
of ethers to carboxylic esters, 1478
of ketones, with selenium dioxide, mechanism, 1478
of lactams to imides, 1478
of methyl aromatic compounds, 1479
oxidation, CH, aryl methyl, and microwave irradiation, 1479
by the *Gif system*, 1472
enantioselectivity, 1472
in ionic liquids, 1473
of lactams, 1478
remote, of hydrocarbons, 1478
to alcohols, with dioxiranes, 1474, 1475
with dioxirane, 1472
with enzymes, 1472
with hypervalent iodine, 1473
oxidation, definition, 1433
of acid sensitive compounds, 1443
of alcohols also see alcohols
oxidation, of alcohols, 1442–1452
and NBS, 1451
by catalytic dehydrogenation, 1450
metal catalyzed with oxygen, metals for, 1446
miscellaneous reagents, 1451, 1452
reagents, utilized with DMSO, 1448
to aldehydes, but not acids, reagents, 1443
to ketones, reagents for, 1446, 1447
with alternative hypervalent iodine reagents, 1450
with *Bobbitt's reagent*, 1449
with chromium (VI), 1442–1445
with chromium(VI), mechanism, 1444
with *Dess-Martin periodinane*, 1449
with DMSO and sulfur trioxide, 1448
with DMSO reagents, 1447
with enzymes, 1451
with *Fremy's salt*, 1452
with hypervalent iodine, 1449
with TEMPO, co-reagents, 1448
with TEMPO, in ionic liquids, 1448
with TPAP, 1446
oxidation, of aldehydes to carboxylic acids, 1484–1487
of aldehydes to carboxylic acids, reagents for, 1485
of alkanes, 1470, 1471
of alkenes to ketones, reagents, 1489
of alkenes, to allylic alcohols, 1470, 1471
oxidation, of alkyl halides, and the *Kornblum reaction*, 1481
to aldehydes, 1481
to aldehydes, *Sommelet reaction*, 1482
oxidation, of alkynes to diketones, reagents, 1490
oxidation, of amines to nitriles, 1454
reagents for, 1483
with manganese dioxide, 1455
oxidation, of anilines to azo compounds, 1455
of aromatic compounds, 1453
of aromatic hydrocarbons, to quinones, 1480
of aromatic side chains, 1465
of aromatic side chains, reagents for, 1466
of aromatic side chains, relative reactivity, 1466
of aromatic side chains, structural limitations, 1466
of arylhydrazines, 1454
of benzylic alcohols, and microwaves, 1451
of benzylic CH, and hypervalent iodine, 1471
of benzylic halides, and the *Krönke reaction*, 1482
of boranes, 701, 923

of boranes, to alcohols, 1375
of boronates, 1376
of boronic acids, 702
of diarylhydrazines, reagents for, 1455
of diols, 994
of hydrazines, to azo compounds, 1454
of hydrazones, to nitriles, 1455
of hydrocarbons, 1469–1473
of hydrocarbons, and hypervalent iodide, 1470
of hydrocarbons, to amines, 1476
of hydrocarbons, to sulfonic acids, 1476
of hydrocarbons, with Cr(VI), 1470
of hydrocarbons, with permanganate, 1470
of hydroxylamines, 1455
of iodide ion, 792
of methyl groups, by the *Barton reaction*, 1427
of methylene groups, 1473–1475
of 2-methylnaphthalene, 1466
of phenols, 1436
of propargylic CH, 1477
of sulfides or sulfoxides, reagents, 1494
of sulfoxides with hydroperoxides, mechanism, 1495
of thioethers with hydroperoxides, mechanism, 1495
of thioethers, reagents for, 1493
oxidation, *Oppenauer*, 1445, 1447
reagents, $KMnO_4$, 994
state, of functional groups, 1434
Swern, 1482
Swern also see *Swern Tamao-Fleming*, 468, 929
oxidative addition, catalytic hydrogenation, 908
Pd catalyst, 773
oxidative amidation, 837
and epoxides, 838
oxidative cleavage, of alkenes, 1459, 1460, 1463–1465
by the *Barbier-Wieland procedure*, 1464
reagents for, 1463, 1464
with the *Lemieux-von Rudloff reagent*, 1463
oxidative cleavage, of aromatic compounds, and the *Dakin reaction*, 1466
of aromatic compounds, reagents, 1465
of cyclic ketones to dicarboxylic acids, 1458
of cyclic ketones, reagent for, 1458
of diamines, 1456
of dihydrophenanthrenes, 1466
of diketones, and enols, 1458
of diols, 1456, 1457
of diols, by lead tetraacetate, cyclic transition state, 1457
of diols, by lead tetraacetate, mechanism, 1457
of diols, enantioselectivity, 1456
of diols, mechanism, 1457
of diols, with lead tetraacetate, 1456
of diols, with periodic acid, 1456
oxidative cleavage, phenylenediamine, 1465
with dimethyl dioxirane, 1457
with ozone see ozonolysis
oxidative coupling, and the *Suzuki-Miyaura coupling*, 773
of alkyl halides, with base, 1495
of silyl enol ethers, 1496
oxidative decarboxylation, with periodate, 1468
oxidative hydrolysis, with NBS or NCS, 1236
oxide, amine see amine oxides
oxides, metal catalyzed arylation, 848
α-oxidation, of alkenes to conjugated ketones, 1477
of amines to amides, 1477
of cyclic amines to lactams, reagents, 1477
of ketones, reagents for, 1476, 1477
of ketones, to diketones, and microwave irradiation, 1477
of ketones, to diketones, and ultrasound, 1477
oxides, phosphine see phosphine oxides
oxidizing agents, 1437
and iodination of aromatic compounds, 607
and *Jacobsen-Katsuki epoxidation*, 1005
for alcohols, 1442–452
for ozonides, 1459
hypervalent iodine, 1449, 1450
with alcohols and ylids, 1166
oxido phosphorus ylids, 1172
oxime alkenes, radical cyclization, 965
oxime ethers, from alkyl halides, 475
from oximes, 475
reduction, 1522
oxime formation, and high-pressure, 1094
and pH, 1094, 1095
base catalysis, 1095
rate-determining step, 1094
oxime sulfonates, rearrangement, 1367
oximes, acid catalyzed formation of nitriles, 1312
addition of HCN, 1183
addition of organometallics, 1138
alkylation, 475
and tautomerism, 93
and the *Barton reaction*, 1428
aryl, and the *Bamberger rearrangement*, 800
by reduction of nitro compounds, reagents, 1528
catalytic hydrogenation, 1520
conversion to gem-difluorides, 1106
cyclic, and *Beckman rearrangement*, 1366
oximes, dehydration, to nitriles, 1310
alternative methods, 1311
and microwave irradiation, 1311
reagents for, 1311
oximes, dehydration, with the *Burgess reagent*, 1311
E/Z isomers, 1325
esters, with acids, 1366
formation in ionic liquids, 1094
formation of, rate of reaction, 1094, 1095
formation, mechanism, 1094, 1095
fragmentation to nitriles, 1312
oximes, from aldehydes or ketones, 1094
from ketones, 675
from nitro compounds, 1137, 1528
from nitrones, 1138
from nitronic esters, 448
from nitrous acid, 675
hydrolysis, 800, 848, 1077, 1427
lithiated, 1149
metal catalyzed coupling to ketones, 1558
O-alkyl, from oximes, 463
O-tosyl, rearrangement to amides, 1312
O-tosyl, rearrangement to nitriles, 1312
oximes, oxidation, 1491
and the *Beckmann rearrangement*, 1455
to nitro compounds, reagents, 1491

oximes, photoisomerization, 304
radical addition, 1189
reaction with hydrazines, 1093
reagents, for *Beckmann rearrangement*, 1365
reducing agents, 1527
oximes, reduction, enantioselectivity, 1527
to amines, reagents, 1521
to aziridines, 1528
to imines, reagents, 1528
with bakers yeast, 1527
with borane, 1521
with Dibal, 1528
oximes, with alkyl halides, 475, 1189
with aryldiazonium salts, 848
with diazoalkane, 463
with *Grignard reagents*, 1138
with nitroso compounds, 728
with organolithium reagents, 1138
with phosphorus pentachloride, 1365
oxindole, fluorination, 670
oxiranes, divinyl, *Cope rearrangement*, 1402
oxirenes, stability, 1003
oxo process, 979
oxocarbenium ions, 214, 219, 1069
and the *Prins reaction*, 1185
formation, 1348
from aldehydes or ketones, 1149
lifetime, 219
with enolate anions, 1149
oxocarboxylic acids, tautomerism, 94
oxoglutaric acid, 171
Oxone (potassium peroxomonosulfate), 1001
and carbonylation of alkenes, 975
and dialkylalloxans, 1002
and formation of dioxiranes, 1001
and haloamines, 729
and KBr, halogenation of aromatic compounds, 605
and oxidation of alcohols, 1450, 1452
and oxidation of alcohols, to esters, 1484
and oxidation of amines to hydroxylamine, 1491
and oxidation of boranes, 923
and oxidation of boranes, to phenols, 747
and oxidation of hydrazones, 1455
and oxidation of oximes to nitro compounds, 1491
and oxidative amidation, 837
and oxidative cleavage of alkenes or alkynes, 1464
with iminium salts, 1002
with iodobenzenesufonic acids, 1450
with ketones, and epoxidation of alkenes, 1001
with osmium tetroxide, 994, 1464
oxonia-Cope rearrangement, 1401
diastereoselectivity, 1401
oxonin, 73
oxonium ions, 393, 458
and dioxane, 389
and hydration of alkenes, 885
and solvolysis, 389
fragmentation, 1308
X-ray crystallography, 219
oxonium salts, cleavage, 505
from alkyl halides, 472
from ethers, 472
with amides, 1209
with amines, 731
with ethers, 472
with nitriles, 1523
oxyamination, and carbamates, 1007
enantioselectivity, 1007
of alkenes, 1007
oxychlorocarbenes, 257
oxy-Cope rearrangement, 1401, 1410
anionic, 1401
antibody catalyzed, 1401
rate of reaction, 1401
silyloxy, 1401
oxygen atom, and orbitals, 6
oxygen electrophiles, 634
oxygen insertion reactions, 1355
oxygen insertion, into alkanes, mechanism, 1472
oxygen leaving groups, 646
[2,3]-oxygen-to-sulfur migrations, 1415
oxygen, and autoxidation, 832
and conjugate addition of boranes, 957
and coupling of organocuprates, 849
and coupling of organometallic, 850
and dehydrogenation of ketones, 1441
and epoxidation of alkenes, 1001
and formation of cyanoamines, 689
and α-hydroxylation of ketones, 1473
and lactone formation, 888
and metal catalyzed oxidation of alcohols, catalysts for, 1446
and oxidation of trimethylsilyl ethers, 1452
and oxidative cleavage of diketones, 1458
and photochemical oxidation of aromatic compounds, 1453
and radical conjugate addition, 959
and radicals, 805
and the *Glaser reaction*, 841
and the *Hay reaction*, 841
and the *Heck reaction*, 767
oxygen, as a diradical, 832
as a radical inhibitor, 807
cycloaddition to dienes, 1039
electronic structure, 15
in ene reactions, 834
in the *Diels-Alder reaction*, 1037
reaction with boranes, 699
reactivity in autoxidation, 832
singlet also see singlet oxygen
singlet, with alkenes, 1006
triplet also see triplet oxygen
oxygen, with alkenes, 886
with alkenes, enantioselectivity, 834
with alkenes, stereochemistry, 834
with *Bacillus megaterium*, CH oxidation, 1472
with boranes, 805
with boranes, mechanism, 805
with Chloramine-T, oxidation of amines, 1477
with *Grignard reagents*, 714, 936
with *Grignard reagents*, formation of alcohols, 699
with *Grignard reagents*, formation of hydroperoxide, 699
with heptalene, 62
with hydrocarbons, 832
with organolithium reagents, 747
with organometallics, 699
oxygenation, of organometallics, 703
oxymercuration, 899
and *Markovnikov's rule*, 886
and steric effects, 874
of alkenes, 874, 885, 886
of norbornene, 878
of vinyl halides, 452
with alcohols see alkoxymercuration
oxy-Michael reaction, 967
intramolecular, 967
oxytosylation, of ketones, 1475
ozone, and oxidation of aromatic compounds, 1465
and oxidation of hydrocarbons to alcohols, 1469

and oxidative cleavage see ozonolysis
and phenanthrene, 56
formation of ozonides, 1459
in [3+2]-cycloaddition reactions, 1015
ozonides, by photooxidation of diazo compounds, 1462
formation and reactivity, 1460, 1461
from ozone and alkenes, 1459
oxidation of, 1459
regiochemistry of formation, 1460, 1461
stereochemistry of formation, 1462
structural variation, 1461
trioxolanes, 1460, 1461
ozonolysis, 1459–1463
alkenes versus alkynes, 1460
and alkene structure, 1459
and carbonyl oxides, 1460
and diradicals, 1460
and ion pairs, 1460, 1461
and microwave irradiation, 1460
and trioxolanes, 1460
Criegee mechanism, 1460–1462
formation and reactivity of ozonides, 1460, 1461
gas phase, 1463
mechanism, 1460
of alkenes, 1459–1463
1,3-dipolar addition, 1460, 1462
and rearrangement, 1460
isotope labeling, 1462
mechanism, 1460–1462
of ethylene, formation of dioxirane, 1463
regiochemistry of ozonide formation, 1460, 1461
stereochemistry and the Criegee mechanism, 1462

p character, and bond angle, 26, 27
and hyperconjugation, 86
palladacycles, 692
palladium acetate, acyloxylation of alkenes, 835, 836
pancreatic porcine lipase, formation of lactams, 1217
para migration, and *Fries rearrangement*, 636
para quinones, 581
para rearrangements, and the *Wallach rearrangement*, 1430
para selectivity, arylazo compounds, 639
para/ortho ratio, *Fries rearrangement*, 636
para-Claisen rearrangement, 1407
paracyclophanes, 47
and chirality, 134
and planarity, 46
and resonance, 46, 47
and restricted rotation, 134
and spectroscopy, 47
and strain, 47
and X-ray crystallography, 46
heterocyclic, 47
paracyclophanes, NMR, 51
paradoxical selectivity, in *Friedel-Crafts alkylation*, 612
paraformaldehyde, and formylation, 628
and the *Eschweiler-Clarke procedure*, 1098
from formaldehyde, 1240
paraldehyde, and acetaldehyde, 1240
paramagnetic ring current, 53
and paratropic compounds, 53
paratropic compounds, 53, 80
antiaromaticity, 81
bridged annulenes, 80
dipleiadiene, 80
NMR, 81
pyracyclene, 80
partial bond fixation, 55
partial molar volume, and high pressure, 446
partial rate factors, aryl radicals, 818
definition, 586
ipso, 591
particle sites, heterogeneous catalysts, 907
partition factor, arenium ions, 571
partitioning effects, and S_NAr reactions, 734
with arenium ions, 571
Passerini reaction, 1247
mechanism, 1247
Pasteur, Louis, and resolution, 157
Patent Office, *Official Gazette*, 1573
patents, 1571
Paterno-Büchi reaction, 1049, 1243
and diradical intermediates, 1243
diastereoselectivity, 1243
intramolecular, 1243
Pauli exclusion principle, 4
Pauli principle, 291
and radicals, 235
Pauli repulsion, and bond energy, 30
Pauling resonance energies, and arynes, 739
and ring current, 51
Pauling scale of electronegativity, 16
Pauson-Khand reaction, 975, 976
and heteroatom components, 977
and microwave irradiation, 977
and ultrasound, 977
enantioselectivity, 977
functional group compatibility, 977
heterogeneous, 976
mechanism, 977
metal catalysts, 976
photochemical, 976
Payne rearrangement, 466
PCC (pyridinium chlorochromate), oxidation of alcohols, 1443
acidity of, 1443
Pd catalysts, acyl halides with boronic acids, 1226
alcohols and allylic esters, 460
alcohols with alkenes, 889
alkoxides with aryl halides, 748
alkyne cross coupling, 561
alkynes and amines, 910
alkynes with allenes, 935
allylic alcohols with dialkylzinc, 1117
allylic alcohols with imines, 1138
allylic amines from allylic alcohols, 485
amination reaction, 707
amines, with aryl halides, 599
amines, with ethers, 487
amines, with nitriles, 1104
Pd catalysts, and asymmetric *Heck reactions*, 766
and boronic acids, 770
and coupling aryl halides with boronic acids, 770–775
and coupling enolate anions with aryl halides, 780
and dehydrogenation of ketones, 1441
and *Hiyama cross coupling*, 545
and hydrogenation, 903
and *Lindlar catalysts*, 905
and oxidation of alkenes to aldehydes or ketones, 1488
and oxidative amidation, 837, 838
and *Rosenmund reduction*, 1517
and selenide formation, 479
and *Sonogashira coupling*, 776
and *Stille coupling*, 682
and *Suzuki-Miyaura coupling*, 770
and the *Heck reaction*, 763–768
and the *Stille reaction*, 524
and the *Tsuji-Trost reaction*, 528
and the *Wacker process*, 1488
and transesterification, 1208
and trifluoroborates, 775
and vinyl triflates, 461

Pd catalysts, anilines, with alkenes, 897
aromatic compounds with alkynes, 940
aryl aldehydes with aryltrifluoroborates, 1125
aryl halide with CO_2, 1132
aryl halides and KOH, 746
aryl halides with amines, 752
aryl halides with iodonium salts, 753
aryl iodides with alkynes, 939
aryl triflates with *Grignard reagents*, 518
arylation of amides, 755
arylation of diazonium salts, 795
arylation of sulfonamides, 493
arylboronic acids, *Friedel-Crafts acylation*, 624
Pd catalysts, aziridination, 1011
Pd catalysts, boranes, and alcohols, 701
and aryl iodides, 702
Pd catalysts, boronic acids, with allylic acetates, 560
with carboxylic acids, 1131
with diazonium salts, 793
with esters, 1231
with isocyanates, 1140
with nitriles, 1140
with O_2, 1485
Pd catalysts, carbonylation, of aryl halides, 781
of vinylmercury compounds, 709
Pd catalysts, chloroformates with alkynes, 1228
conjugate addition of amines, 966
Cope rearrangement, 1402
Pd catalysts, coupling, and *Sonogashira coupling*, 775–778
lithioalkynes, 516
of aryl halides, 760
of vinyl groups, 524
organolithium reagents, 516
vinyl triflates and phenols, 460
with organotin reagents, 527
with trialkylfluoroborates, 560
Pd catalysts, cyanation or aryl triflates, 633
cyanides with aryl halides, 758
cyclic amines from alkynes, 898
cyclization of carbamates, 901
cyclization of diene carboxylic acids, 892
cyclobutane ring openings, 1424
diacetoxylation, 997
dienes with diketones, 939
fluorination of oxindoles, 670
for coupling reactions, 526
formation of allenes from propargylic amines, 1305
formation of thioethers, 477
Heck reaction, 763–768
homocoupling of alkene-trifluoroborates, 843
homocoupling of alkyne-trifluoroborates, 843
hydration of alkynes, 887
hydrogenation of alkynes, 905
imidazolium ligands, 772
imines with boronic acids, 1136
isomerization of alkenes, 882
ketones with alkenes, 939
LiCN and vinyl triflates, 564
Pd catalysts, *Mannich reaction*, 1102
organometallic coupling, 524, 525
oxidation addition, 773
phosphines with alkynes, 899
polyene cyclization, 932
polymer supported, 752, 777
preparation of amines, 484
pyrolysis of carboxylic acids, 1288
pyrrole and vinyl triflates, 708
recyclable, 760
reductive elimination, 773
silanes with aryl halides, 783
silanes with dienes, 929
Stille coupling, aryl halides, 683
Stille coupling, heteroaryl halides, 683
thiocarbamate formation, 731
thiolates with aryl halides, 749, 750
thiophenes from en-ynes, 895
trifluoroborates with tosylimines, 1136
vinylation of ketones, 545
with alkyne carboxylic acids, 893
with $Mo(CO)_6$, 753
Pd complexes, 41
and *Eschenmoser-Claisen rearrangement*, 1409
and the *Stille reaction*, 683
aryl iodides with alkynes, 939
carbonylation of alkyl halides, 567
chiral, 1369, 1409
trans-, 683
Pd free cross coupling, 771
Pd hydride, 908
Pd migration, and the *Heck reaction*, 765
Pd, peroxo complexes, 773
Pd, π-allyl complex, 42
Pd, π-allylic, 528
Pd, transmetallation, 773
PDC (pyridinium dichromate), oxidation of alcohols, 1443
Pechmann condensation, 617
ionic liquids, 617
microwave irradiation, 617
PEG 400, 563
PEG (polyethylene glycol), and alkene metathesis, 1420
and conjugate addition, 967, 968
and nitrile hydrolysis, 1080
and recyclable hydrogenation catalysts, 905
and the *Baylis-Hillman reaction*, 1127
diketones with acid, 1083
solvent, 760
PEG-telluride, and the Reformatsky reaction, 1131
pentacoordinated ions, 209
pentadiene, with DCl, 870
pentadienyl radical, 239
pentaerythritol, by the *Tollen's reaction*, 1165
pentahelicene, and chirality, 134
and steric crowding, 134
pentalene derivatives, 68
pentalene, and aromaticity, 62
pentasulfides, 479
peptide synthesis, 1219
and DCC, 1217
and the *Ugi reaction*, 1247
Peptides, and the Merrifield synthesis, 1218
Peptides, tagging amino end, 752
perborate, oxidation of boranes, 701
perborate, sodium see sodium
perbromides, with Chloramine-T, 990
perchlorate, lithium TMSCN with aldehydes, 1181
perdeuteration, alkenes, 661
perepoxides, 834
pericyclic addition, 263
pericyclic mechanism, 262
and the *Prins reaction*, 1186
pyrolysis of homoallylic alcohols, 1315
pericyclic reactions, *Cope rearrangements*, 1403
pericyclic sigmatropic rearrangement, 1407
periodate, and oxidation of alcohols, 1452
and $RuCl_3$, with amines, 1477
oxidative decarboxylation, 1468
periodic acid, and oxidative cleavage of diols, 1456
and the *Lemieux-von Rudloff reagent*, 1463
with diols, mechanism, 1457
periodic readings, and kinetics, 281
periodic table, and acidity, 337
and bond energy, 30

and electronic structure, 14
and Lewis acids, 330, 337
and nucleophilicity, 427
periodinane, *Dess-Martin* see *Dess-Martin*
Perkin condensation, 1142
Perkin reaction, 1161
permanganate, in [3+2]-cycloaddition reactions, 1014
oxidation of hydrocarbons, 1470
oxidization of catechol, 1453
potassium and oxidation of sulfoxides, 1493
potassium and the *Lemieux-von Rudloff reagent*, 1463
potassium, oxidation of alcohols, 1445
with alkenes, 993
with crown ethers, 1463
Permuterm Subject Index, 1599
peroxide anions, conjugate addition, 967
peroxide, diperoxohydrate, calcium, 833
peroxide, hydrogen, alkenes and formic acid, 994
with NaOH, and boranes, 923
with thiols, 1496
peroxide, *tert*-butyl, and *Sharpless asymmetric epoxidation*, 1004
peroxides also see hydroperoxides
peroxides, 834
peroxides, acyl, from acyl halides, 472
with aldehydes, 835
with aromatic compounds, 843
with *Grignard reagents*, 700
with hydrocarbons, 835
from alcohols, 1370
peroxides, and addition of aldehydes to alkenes, 971
and addition of polyhalo compounds to alkenes, 991
peroxides, and *anti-Markovnikov addition*, 883
and conjugate addition of boranes, 957
and decarbonylation, 857
and epoxidation of alkenes, 999, 1001
and *Fenton's reagent*, 830
and ferrous sulfate, 830
and halogenation, 826
and hydroxylation of aromatic compounds, 830
and oxidation of thioethers, 1493
and radical coupling of alkanes, 839
and radical rearrangements, 1333
and radicals, 803, 804
and the *Orton rearrangement*, 640
and the *Baeyer-Villiger reaction*, 1004
and the *Glaser reaction*, 841
and the *Prins reaction*, 1186
and the *Story synthesis*, 1319
peroxides, cleavage, 246
co-reagents for epoxidation of alkenes, 999, 1000
cyclic, 1040
cyclic, preparation of, 1319
decomposition, 804
decomposition, temperatures, 804
peroxides, diacyl, 245
and peroxide, 245
from acyl halides, 472
peroxides, diffusion rate of radicals, 804
formation of radicals, 804
peroxides, from alkyl halides, 472
from alkynes, 892
from cycloaddition of singlet oxygen to dienes, 1040
from *Grignard reagents*, 699
from hydrocarbons, 832, 835
from hydroperoxides, 804
from organometallics, 699
peroxides, oxidation of thiols, 1497
reduction with $P(OEt)_3$, 1540
silyl see silylperoxides
peroxides, with alkenes and bromine, 1336
with alkenes, 883, 994
with alkylboranes, 700
with amides, 1198
with base, with boranes or boronates, 1376
with HBr and alkenes, 883
with HOCl, 985
with $LiAlH_4$, 1540
with organometallics, 700
with sulfuryl chloride, 817
peroxo complexes, of Pd, 773
peroxomonosulfate, 1001
peroxy radicals, 807
peroxyacetic acid, and iodination of aromatic compounds, 608
peroxyacids, and *Baeyer-Villiger rearrangement*, 1368
and dihydroxylation of alkenes, 993
and epoxidation of alkenes, 998
and hydroxylation of aromatic compounds, 634
by oxidation of carboxylic acids, 1487
of alkenes, mechanism, 999
oxidation of amines to amine oxides, 1492
preparation, 832
with alkenes, 1488
with alkenes, stereochemistry, 878
with aromatic compounds, 634
with epoxides, and hydride shifts, 1428
with ketones, 1368
peroxydisulfates, with formation ion, 1538
peroxyesters also see peroxides, acyl
peroxyesters, 835
labeling, 836
peroxyimidic acid, and dioxiranes, 1002
with alkenes, 1002
peroxymercuration, 892
peroxynitrous acid, 830
persistent radicals, 236
persulfate, potassium see potassium
PES (photoelectron spectroscopy), and methane, 11, 12, 13
and alkenes, 14
and bond fixation, 69
and carbocation stability, 216
and conformations, 174
and hybridization, 14
and ionization potential, 200
and multiple bonds, 13
and nitrogen, 12
and orbitals, 12, 13
and radical cations, 15
and strain, 200
and the captodative effect, 69
cyclobutadiene, 68
pentalene derivatives, 63
Petasis alkenylation, 1174
mechanism, 1174
Petasis reagent (dimethyltitanocene), 1174
reactivity, 1174
structural variations, 1174
with aldehydes or ketones, 1174
with lactones, 1174
Peterson alkenylation, 1162
and the *silyl-Wittig reaction*, 1163
mechanism, 1163
modified, epoxide formation, 1163
structural modifications, 1163
Peterson olefination see *Peterson alkenylation*
Peterson reaction, 1142
pH and diazonium salts, 597
and oxime formation, 1094, 1095
and solvent acidity, 325
and tautomerism, 89
nitrous acid and amines, 789

phase transfer agents, and tetracarbonylferrate alkylation, 565
phase transfer catalysis, 442, 468, 470
  and acyl cyanides, 1238
  and ammonium salts, 442
  and carboxylate salt alkylation, 468
  and crown ethers, 443
  and cryptands, 443
  and interfacial mechanism, 443
  and ion pairs, 444
  and microwave irradiation, 444
  and nucleophilic substitution, 444
  and polar solvents, 442
  and preparation of carbonates, 470
  and the *Michael reaction*, 945
  and the *Williamson reaction*, 460
  and water, 443
  Cinchona alkaloids, 1001
  cleavage of ethers, 504
  ether formation, 460
  fluorination of alkyl halides, 499
  phosphonium salts, 442
  quaternary ammonium salts, 442
  triphase catalysts, 445
phase transfer, and alcohols, 501
  and *Cinchona* alkaloids, 1003
  and cleavage of ethers, 504
  and formation of alkyl halides, 499
  and halide ions, 499
  and sulfur ylids, 1176
  and the *Ullmann reaction*, 769
phase transfer, for amine formation, 483
  for anhydride formation, 1209
  for carbonylation of vinyl halides, 568
  for catalytic dehydrogenation, 1450
  for dehydration of amides to nitriles, 1313
  for formation of alkyl azides, 496
  for halide exchange with aryl halides, 757
  for hydrolysis of carboxylic esters, 1192
  for α-hydroxylation of ketones, 1473
  for hydroxylation of aromatic compounds, 830
  for oxidation of amines, 1483
  for thioether formation, 476
phase transfer, reagents, and dihydroxylation, 994
phase transfer, with acyl halides with alcohols, 1201
  with alcohols with HCl, 501
  with alkenes with HX, 884
  with aryl halides with alkoxides, 747
  with base induced elimination of alkyl halides, 1297
  with catalytic hydrogenation of aromatic compounds, 913
  with diazonium coupling, 598
  with enolate alkylation, 543
  with *Julia-Colonna epoxidation*, 1004
  with permanganate oxidation of alcohols, 1445
  with the *Finkelstein reaction*, 499
  with the *Gomberg-Bachmann reaction*, 795
  with the *Michael reaction*, 945
  with the *Mills reaction*, 793
  with the *Rosenmund-von Braun reaction*, 758
phenacenes, and aromaticity, 78
phenalene cation, resonance energy, 56
phenalene radical, resonance energy, 56
phenalene, acidity of, 56
phenalene, and aromaticity, 56
phenanthrenes, alkylation of, with organometallics, 785
  and aromaticity, 55
  and bromine, 56
  and *Dewar benzene structures*, 55
  and ozone, 56
  and partial bond fixation, 55
  bay region, 56
  canonical forms, 56
  cyclization with singlet oxygen, 1039
  electrophilic aromatic substitution, 584
  from stilbenes, 1390
  resonance energy, 56
phenathroline, 755
phenol and tautomerism, 93
  and hydrogn bonding, 100
  and the enol form, 93
  from phenylallyl ethers, Pd catalyst, 487
  iodination, 608
phenol-dienone rearrangement, 1349
phenolic esters, 636
phenol-keto tautomerism also see tautomerism
phenol-quinone tautomerism, 1408
phenols, 2-allyl, by *Claisen rearrangement*, 1407
  acid catalyzed rearrangement of dienone, 1349
  acyl, *Fries-rearrangement*, 635, 636
  addition to ketenes, 892
  alkali fusion of arylsulfonic acids, 747
phenols, and ether formation, 462
  and ethers formation, 464
  and *Fenton's reagent*, 830
  and microwave irradiation, 746
  and the *Bucherer reaction*, 746
phenols, aromatization of cyclic ketones, 1438
  by electrolysis, 635
  by *Fries rearrangement*, 635, 636
  by oxidation of aromatic compounds, 1453
  by the *Reimer-Tiemann reaction*, 627
  catalytic hydrogenation, 1536
  conversion to sulfonate esters, and reduction, 1536
  dihydroxylation, 1535
  formation of vinyl ethers, 460
  formylation, 628
Phenols, from allylic aryl ethers, 1407
  from aromatic compounds, 634, 830
  from aryl halides, 746
  from aryldiazonium salts, 790
  from arylthallium compounds, 786
  from boranes and Oxone, 747
  from esters, 635
  from ethers, 485
  from organolithium reagents, 747
  from peroxyacids, 634
  hydrogenation to cyclohexanones, 913
  hydroxymethylation, 616
  ortho chlorination, 605
  ortho methylation, 612
phenols, oxidation, 1436
  and microwaves, 1453
  to quinones, reagents, 1453
  with *Fremy's salt*, 1453
  with sodium periodate, 1453
phenols, quenching in photochemistry, 301
  reagents for dihydroxylation, 1536
  reduction to aromatic compounds, 1535
  Tl salts, and ester formation, 1201
  with alkenes, 889
  with ketenes, 892
  with keto-esters, 617
  with phosphorus oxychloride, 757
phenonium ions, 399
  and electrophilic aromatic substitution, 401
  and isotope effects, 402

and labeling, 402
and NMR, 401
and rate, 399
and solvolysis, 401
stable, 401
phenoxide ion, carboxylation, 630
with alkyl halides, 448
phenoxides, as bases, 1164
with aryl halides, 748
with aryl halides, and microwaves, 748
with chloroform, 627
phenyl carbocations, 215
phenyl cyanate see cyanate
phenyl radicals also see radicals
phenyl radicals, 246, 816
phenylenediamine, oxidative cleavage, 1465
phenylenes, as twisted compounds, 48
phenylhydrazine, with aldehydes or ketones, 1412
phenyllithium, 106
aggregation state, 232
phenylmagnesium bromide, and X-ray crystallography, 230
phosgene, and dehydration of amides to isonitriles, 1314
and formation of carboxylic acids, 629
and the *Vilsmeier-Haack reaction*, 625
reaction with alcohols, 1086
with amides, 1314
with amines, 1213
with aromatic compounds, 629
with carboxylic acid salts, 1210
phosphate esters, 474
phosphate, triaryl, with aryl halides, 748
phosphates, and chirality, 127
aryl, amination, 756
from phenols, 757
vinyl, 704
phosphazene bases, 1286
phosphazene base, and anionic *oxy-Cope rearrangement*, 1401
phosphazides, and reduction of azides, 1529
phosphazine bases, formation of thioethers, 750
phosphine free Heck reaction, 763
phosphine oxide ylids, 1171
phosphine oxides, and chiral calixarenes, 155
and resonance, 49
and ylids, 49
by oxidation of phosphines, 1492
chiral reduction, enantioselectivity, 1549
chiral, 1492
enantioselectivity, 1549
from phosphorus ylids, 1165
from the *Wittig reaction*, 1166
reduction to phosphines, 1549
with alkenes, 899
with alkynes, 899
with isocyanates, 1241
with isocyanates, isotopic labeling, 1241
with isocyanates, mechanism, 1241
phosphine sulfide, with epoxides, 478
phosphine-free *Heck reactions*, 763
phosphines, alkylation, 483
and [3+2]-cycloaddition, 1019
and decarbonylation of aldehydes, 1300
and elimination of epoxides, 1286
and esterification, 1203
and the *Mitsunobu reaction*, 469, 1203
and the *Reformatsky reaction*, 1130
aryl, 755
as chiral ligands in catalytic hydrogenation, 904
as ligands, 41
by reduction of phosphine oxides, 1549
by reduction of phosphonium salts, 1548
catalyst for *Michael addition*, 944
chiral, 904
conjugate addition, 967
from alkyl halides, 484
from metal catalyzed addition of phosphines to alkenes, 899
α-hydrogens and ylid formation, 1166
ligands, chiral, 780
metal catalyzed, addition to alkenes, 899
metal catalyzed, arylation, 755
metals, and elimination of epoxides, 1286
oxidation to phosphine oxides, 1492
polymer-bound, and *Mitsunobu reaction*, 469
polymer-bound, metal catalyzed arylation of amines, 752
polymer-supported, as ligands, 530
silyl see silylphosphines
silyl, addition to ynones, 930
with alkyl halides, 1165
with aryl halides, 755
with epoxides, 1169
phosphino alkynes, 707
phosphinyl imines, reduction, 1521
phosphiranes, divinyl, *Cope rearrangement*, 1402
phosphites, and the *Corey-Winter reaction*, 1301
conjugate addition, 967
reduction of peroxides, 1540
trialkyl, with sulfonic acids, 1250
trimethyl, and Mislow-Evans rearrangement, 1415
with alkenes, 900
with alkyl halides, 1170
with amines, 1105
with cyclic thionocarbonates, 1301
with halogens, 1105
phospholene-1-oxides, with isocyanates, 1241
phospholes, and circumambulatory rearrangement, 1395
phosphonate esters see esters
phosphonate esters, 474, 484
by the *Arbuzov reaction*, 1170
from alcohols, 473
vinyl, and the *Heck reaction*, 765
vinyl, conjugate addition, 968
phosphonates, allylic, coupling reactions, 530
allylic, with organocuprates, 530
ylid formation, 1169
phosphonium halochromates, 1443
phosphonium salts, 697
by the *Arbuzov reaction*, 1170
conversion to ylids, 1165
deprotonation, 1166
from alcohols, 560
from alkyl halides and phosphines, 1165
phase transfer catalysis, 442
reduction, 1548
suitable bases for ylid formation, 1165
with bases, 1165
with organolithium reagents, 1165
phosphonium ylids, 697
phosphonothionates, and formation of ylids, 1170
phosphoramide bases, and the aldol reaction, 1143
phosphoramides, and determining absolute configuration, 142
as catalysts, 1143, 1152
from amines, 555
with carboxylic acids, 1218
phosphoranes se ylids, phosphorus
cleavage of ethers, 505
vinyl, rearrangement, 1399
with butyllithium, 1172
with sulfur, 838
phosphorescence, 298, 299

phosphoric acid catalysts, chiral, 1136
phosphoric acid, and dehydration of alcohols, 1283
phosphoric acid anhydrides, 1211
phosphorous oxychloride, with DMAP, 507
phosphorous, stabilization of carbanions, 225
phosphorus oxychloride, 501
and DMF, 626
and from amides, 685
Friedel-Crafts cyclization, 617
with aryl halides, 757
phosphorus pentabromide, with aldehydes or ketones, 1105
phosphorus pentachloride, 501
and dehydration of amides, 1313
and electronic structure, 15
with aldehydes or ketones, 1105
with amides, 1429
with amides, *Sonn-Müller method*, 1523
with aryl halides, 757
phosphorus pentoxide and silica gel, and the Ritter reaction, 1239
phosphorus tribromide, 501
phosphorus trichloride, with sulfonic acids, 1251
phosphorus ylids see ylid
phosphorus, and carbanions stabilization, 228
and optical activity, 129
and stereogenic atoms, 169
chirality at P, 169
inversion of configuration, 169
photochemical [2+2]-cycloaddition, 1043
photochemical [4+2]-cycloaddition, 1036
photochemical *Beckmann rearrangement*, 1367
photochemical conjugate addition, 966
photochemical decarbonylation, 303
photochemical decarboxylation, of carboxylic acids, 845
photochemical decomposition, 302
of diazomethane, 1056
photochemical *Diels-Alder reaction*, 1022
photochemical dimerization of ketones, mechanism, 1557
photochemical isomerization, 882
photochemical mechanism, 306
photochemical nitrosation, 676
photochemical reactions, 289
table, 302
photochemical *Wallach rearrangement*, 1430
photochemistry also see excited states
photochemistry also see photolytic cleavage
photochemistry also see photosensitization
photochemistry, 151, 338
photochemistry, and [1,7]-hydrogen shifts, 1395
and [2+2]-cycloadditions, 1041, 1043, 1047
and [2+2]-cycloaddition, and *Wigner spin conservation rule*, 1049
and *Woodward-Hoffmann rules*, 1050
catalysts for, 1043
photochemistry, and actinometers, 307
and addition of alcohols to alkenes, 891
and addition of aldehydes to alkenes, 972
and addition of thiols to alkenes, 895
and auxochromes, 293
and chlorosulfenation, 837
and chromophore absorption, 293
and chromophore, 291
and cleavage, 302
and cleavage, and radicals, 246
and cleavage, to radicals, 302
and conjugated bonds, 293
and cyclization, 303
and cycloaddition of alkenes to carbonyls, 1243
and cycloaddition, of oxygen to dienes, 1039
and decarbonylation, 857
and electromagnetic spectrum, 290
and electron spectrum, 290
and electronic excitation, 292
and electronic transitions, 290
and elimination, 1254
and esterification of carboxylic acids, 1203
and exciplex formation, 301
and excited states, 294
and extinction coefficient, 291
and extrusion of nitrogen, 1316, 1317
and frontier orbital method, 1032
and HOMO of cyclobutenes, 1383
and *Hund's rule*, 292
and hydrogen atom abstraction, 302, 306
and hypsochromic shift, 293
and intramolecular [2+2]-cycloadditions, 1048
and intramolecular rearrangements, 304
photochemistry, and isomerization, 304
of azacrown ethers, 305
of azo compounds, 305
of boranes, 664
of oximes, 304
photochemistry, and *Jablonski diagrams*, 297
and *Norrish Type I cleavage*, 303
and *Norrish Type II cleavage*, 303
and orbital overlap, 1032
and oxidation of aromatic compounds with O_2, 1453
and photolysis of ketenes, 304
and photolytic cleavage, 296
and photosensitization, 299, 300
and properties of excited states, 294
and protonated quinoline, 845
and quantum yield, 306
and quenching by phenols, 301
and radicals, 804
and singlets, 292
and spectrophotometers, 290
and spin forbidden transitions, 292
and the acetylene excited state, 295
and the *Orton rearrangement*, 640
and the *Wallach rearrangement*, 1430
and the *Wigner spin-conservation rule*, 300
and triplets, 292
and UV light, 290, 293
and vinylcyclopropane rearrangement, 1399
and visible light, 290, 293
and wavelengths of light, 290
photochemistry, bathochromic shifts, 293
choice of photosensitizer, 300
deactivation, 301
energy cascade, 297
energy of light, 290
excited states, 289
excited states, of formaldehyde, 295
fluorescence, 298
for arylation of active methylene compounds, 778
for arylation of enolate anion, 780
for coupling hydrocarbons and nitriles, 838
for coupling of acyl halides, 1232
for coupling of dialdehydes, 1557

for decarboxylation, 721
for decomposition of diazomethane, 250
for dimerization, 302, 306
for dimerization, of ketones, 1557
for radical addition, 1189
for radical cyclization, 962
forbidden transitions, 292, 296, 298
formation of biaryls, 762
formation of carbocations, 382
g and *u* transitions, 292
ground state, 289
internal conversion, 297
intersystem crossing, 298, 1426
photochemistry, mechanism see mechanisms
n → π^* transitions, 293
n → σ^* transitions, 292, 293
NBS and aromatic halogenation, 604
photochemistry, of aromatic ketones, 301
of aryl alkenes, 1390
of arylthallium compounds, 845
of azo compounds, 1391
of biaryls, 1390
of bicycloheptadienes, 305
of carvone, 1049
of dienes, 293, 1380, 1425
of dienes, ring closure, 1424
of ethers, 292
of ketones, 293
of sulfonyl-halo addition to alkenes, 987
of thiols with alkynes, 894
phosphorescence, 298, 299
photoisomerization, 302
photoreduction, 306
photosensitizer definition, 299, 300
$\pi \rightarrow \pi^*$ transitions, 293
promotion, 298
promotion, to a dissociative state, 296
quenching, 301
reactions, 302
rearrangements, 302
rearrangements, of alkenes, 663
sensitization, 302
$\sigma \rightarrow \sigma^*$ transitions, 292, 293
singlet and triplet excited states, 294
suprafacial [1,3]-migrations, 1398
symmetry-forbidden transitions, 292
triplet state, 1049
photochemistry, with alcohols, 292
with aldehydes, 293
with alkanes, 292
with alkenes, 293
with alkenes, and geometry, 305
with amines, 292
with amines, with cyclopropane, 492
with halogens, and halogenation of alkanes, 821
with indoles and aldehydes, 1123
with reduction of cyclopropanes, 920
with reduction with silanes, 1510
with side chain halogenation, 605
with $S_{RN}1$ reactions, 740
with steroid derivatives, 1394
with the *Frank-Condon principle*, 296
with the *Pauson-Khand reaction*, 976
with the *Prins reaction*, 1187
with the *Reed reaction*, 837
Wolff rearrangement, 1354
photodimerization, 302
cyclopentenone, 306
photoelectron spectroscopy see PES
photo-Fries rearrangement, 637
and CIDNP, 637
and flash photolysis, 637
photoisomerization, 302, 304
azacrown ethers, 305
azo compounds, 305
of alkenes, 882
of cyclooctene, 305
oximes, 304
photolysis also see photolytic cleavage
photolysis, and conjugate addition, 960
aniline ammonium salts, 641
aromatic compounds with aryl halides, 844
benzenes and *Dewar benzenes*, 1387
photolysis, flash, 306
of bromoform, 252
photolysis, haloammonium salts, 1427
ketone and diazomethane, 694
laser flash, 209
NBS and tosylamines, 509
photolysis, of carboxylic acids, 854
of conjugated esters, 882
of cyclic sulfones, 1318
of cyclobutanones, 1317
of diazomethane, 691
of dienones, 1426
of halo amides, 1427
of ketene, 304
of lactones, 1318
of oxaziridines, 1367
of pyrazoles, 1316, 1317
of pyrazolines, 1316, 1317
of triazolines, 1017, 1316, 1317
photolysis, oxa-di-π-methane rearrangement, 1426
pyrocalciferols, 1386
reduction of nitro compounds, 1526
ring contraction of diazoketones, 1353
silanes and amines, 511
solid state, 1244
photolytic cleavage, 295
and the *Franck-Condon principle*, 296
energy cascade, 297
formation of radicals, 296, 302
Norrish type I, 303
Norrish Type II, 303
of aldehydes, 303
promotion to a dissociative state, 296
photolytic halogenation, 810
photolytic hydroxylation, 635
photonic devices, 118
photooxidation, of diazo compounds, 1462
photooxygenation, of alkenes, 1006
of alkenes, with singlet oxygen, 1005
photoreduction, of ketones, 306
photosensitization, 299, 300, 302, 1243
and electron transfer, 301
and the *Paterno-Büchi reaction*, 1243
of alkanes, 839
of oxygen, with alkenes, 833, 834
photosensitizer, definition, 299, 300
photosensitizers, and singlet oxygen, 833, 834
choice of, 300
cycloaddition of singlet oxygen to dienes, 1039
eosin, 1039
in [2+2]-cycloadditions, 1047–1049
phthalamic acid, hydrolysis, 1073
phthalate ion, rearrangement, 645
phthalazines, and asymmetric dihydroxylation, 996
and dihydroxylation, 996
phthalic acid, by oxidation of naphthalene, 1465
phthalides, *Ing-Manske procedure*, 494
phthalimides, conjugate addition, 966
formation of amines, 494
from amides, 1198
hydrolysis, 494
hydrolysis, reagents for, 494

phthalimides, conjugate addition (*Continued*)
in the *Gabriel synthesis*, 494
with hydrazine, 494
phthalocyanines, oxidation of aromatic compounds, 1453
Physical Constants of Organic Compounds, 1581
physical data, tables, 1581–1583
Physical Properties of Chemical Compounds, 1581
physical properties, and Beilstein, 1578
of diastereomers, 146
piancolone and the H_2S clathrate, 114
picene, 78
picolinium halochromates, 1443
picosecond absorption spectroscopy, and solvolysis, 385
picosecond optical grating calorimetry, 1056
picrates, 107
picric acid, and arenium ions, 573
and complex formation, 107
picryl iodide, and resonance, 46
Pictet-Spengler reaction, 618
enantioselective, 618
pig liver esterase, and hydrolysis of esters, 1191
and resolution, 157
pinacol coupling, 1555–1558
and electrochemistry, 1557
and *Grignard reactions*, 1113
and imines, 1558
and ultrasound, 1556
crossed, 1556, 1557
enantioselectivity, 1556
intramolecular, 1557
reagents, 1556
syn or anti selective, 1556
titanium mediated, 1560
pinacol rearrangement, 1342, 1352
and carbocation stability, 1343
and tosyl aziridines, 1344
in supercritical water, 1342
mechanism, 1343
migratory aptitudes, 1328, 1329, 1342
of epoxides, 1344
solid state, 1343
stereodifferentiation, 1342
pinacolone, formation, 1342
X-ray as guest molecule, 114
pinacols see diols
pinene, enantiomers, 924
α-pinene, with borane, 924
Pinner synthesis, 1086
piperidine, and cyclopropylcarbinyl halides, 413
pi-stacking, 104
π bonds, neighboring group participation, 394
π orbitals, 9
π route, to nonclassical carbocations, 395
π-interactions, with cations, 104
with CH, 104
π-nucleophilicity, 859
π-orbital, and addition reactions of alkynes, 873
π-orbitals, 10
π-π-interactions, 103
and catenanes, 119
Pisum sativum, CH oxidation, 1472
α-hydroxylation, 1472
Pitzer strain see strain
pK, and bases, table, 321
and carbocation formation, 215
and conformation, 340
and hydrogen bonding, 338
and indicators, 325
and proton transfer, 323
and resonance, 337
and superbases, 322
and UV, 339
bases, table, 321
pK_a, and acids, 314–318
and field effects, 334
and formation of enolate anions, 539
aniline, 338
benzoic acids, 335
carboxylic acids, table, 335
cyanomethanes, 336
cyclopentadiene, 58
diketones, 336
fluorene, 59
in DMSO, 319
indene, 59
measurements, 319
naphthol, ground vs. excited state, 295
nitriles, 336
nitromethanes, 224
of conjugate base in enolate anion reactions, 542
α-proton of carbonyl compounds, 542
α-proton of nitrile compounds, 542
resonance effects in carboxylic acids, 336
squaric acid, 82
substituted benzoic acids, 334
table, type of acid, 314–318
planar conformation, cyclopropane, 188
planarity, and annulenes, 73, 74
and aromaticity, 66, 76
and benzene, 46, 47
and C=C bonds, 206
and carbocations, 382, 383
and cyclobutadiene complexes, 69
and heptalene, 62
and methanoannulenes, 73
and paracyclophanes, 46
and resonance contributors, 44
and resonance, 46
annulenes, 81
distortion from, 74
Planck's constant, 3, 290
plane polarized light also see light
plane polarized light, 145
and enantiomers, 138
plane, of symmetry, and chirality, 125
mirror plane, and chirality, 125
platinum oxide (*Adam's catalyst*), 920
PMHS (polymethylhydrosiloxane), 1517
podands, 111
poisoning, and catalytic hydrogenation, 903
chiral, in asymmetric catalysis, 904
chiral, in hydrogenation, 904
poisons, catalytic hydrogenation, 903
polar *Diels-Alder reactions*, 1029
polar nucleophilic aromatic substitution, 741
polar protic solvents, and keto-enol tautomerism, 665
polar solvents also see solvents and reactivity, 361
polar transition state mechanism, and benzidine rearrangement, 1416
polarity, and cyclooctatetraene, 71
inductive and field effects, 19, 20
methyl radical, 816
solvent see solvent polarity
polarizability, and conformation, 177
and HSAB, 448
and nucleophilicity, 448
and optical activity, 126
polarization, and microwaves, 310
inductive and field effects, 19, 20
topological, 65
polarized bonds, 16
polarized light, circularly, 145
circularly, and asymmetric synthesis, 154
plane, 145
polarized transition state, 378
polyacenes, and annellation, 57
and *Kekulé structures*, 57
and UV, 57
angular and linear, 57
anthracene or phenanthrene, 57
triphenylene, 57

polyaromatic compounds see aromatic compounds
polyenes, cyclization, 932
  by coupling alkynes, 934
  UV, 293
polyethylene glycol, as a solvent, 1292
polyhalo compounds, addition to alkenes, 991
polyhalogenation, and radical halogenation, 823
polyhydrogen fluoride-pyridine, and nitration of alkenes, 989
  fluorination, 1225
  with alkenes, 883
polyleucine, and epoxidation, 1003
polymer bound, amide bases, 1143
  borates, with aldehydes, 1124
  Mo catalyst, alkene metathesis, 1420
  osmium tetroxide, 993
  phosphine ligands, 752
  pyridinium salt, 1244
  quaternary ammonium salts, 1003
  reagents, 473
  reagents, conversion of acids to amides, 1216
  Ru catalyst, alkene metathesis, 1420
  siloxanes, and transesterification, 1207
  sulfoxide, and *Swern oxidation*, 1447
  sulfurization reagent, with amides, 1212
  urea, and esterification, 1203
polymer supported, acid catalyst, conjugate addition of carbamates, 966
  azides, 1053
  azides, diazo transfer reagents, 1054
  carbodiimides, 1217
  carbodiimides, and formation of amides from acids, 1217
  catalysts, 777
  catalysts, for the *Heck reaction*, 763
  catalysts, with malonate anions, 540
  dienes, in the *Diels-Alder reaction*, 1038
  formate, reduction of conjugated aldehydes, 919
  Heck reaction, 763
  ligands, and dialkylzinc, 1121
  oxidizing agents, 1443
  Pd catalysts, 752
  peroxy acids, and *Baeyer-Villiger rearrangement*, 1369
  phosphine ligands, and coupling, 530
  reactants, and *Sonogashira coupling*, 777
  sulfur ylids, 1176
  Suzuki-Miyaura, 771
  synthesis, 1218
  synthesis, and separation of products, 1219
  ylids, in the *Wittig reaction*, 1166
polymer-bound, amide bases, and the aldol reaction, 1143
  and acylation of amines, 1215
  Beckmann rearrangement, 1366
  carbodiimides, 1205
  catalysts, for hydrogenation, 903
  Cinchona alkaloids, 996
  Claisen rearrangement, 1408
  conversion of carboxylic acids to amides, 1216
  hypervalent iodine, oxidation of aldehydes to acids, 1485
  ion catalyst, and radical cyclization, 963
  osmium tetroxide, and dihydroxylation of alkenes, 993
  oxazaborolidine, and reduction, 1513
  phosphine ligands, 752
  phosphonate esters, and *Wittig-Horner reaction*, 1170
  phosphoramide bases, and the aldol reaction, 1143
  pyridinium salts, and β-lactams formation, 1244
  substrates, reduction, 1524
  TPAP, oxidation of alcohols, 1446
  trialkyltin hydride, reduction of alkyl halides, 1532
polymerization, 221
  and boronic acids, 702
  and haloacylation of alkenes, 992
  and hydroformylation, 979
  and metathesis, 1421
  and photochemical [2+2]-cycloaddition, 1049
  and radicals, 247
  and the *Kolbe reaction*, 853
  halo-haloacylation of alkenes, 992
  of heptalene, 62
  of methyl vinyl ketone, 1150
  ring opening metathesis, 1421
polymers, and aldehydes addition to alkenes, 972
  and hydroxyalkylation, 616
  and supercritical carbon dioxide, 364
  and the *Pauson-Khand reaction*, 976
  and the *Suzuki-Miyaura coupling*, 771
  from ammonia with alkynyl halides, 898
  metathesis with dienes, 1421
  paraformaldehyde, 1240
  siloxane, 956
polymethylhydrosiloxane, reduction, 1517
polyphosphoric acid, 617, 631
  and *Friedel-Crafts acylation*, 624
  with arylsulfonic acids, 602
polystyrene, and the *Merrifield synthesis*, 1218
poly-yne-diene, metathesis, 1422
porphycenes, tautomerism, 94
porphyrins, and rotaxanes, 118
  CH amination, 1475
  tautomerism, 94
positional isomers, aromatic, stability, 584
postulate, *Hammond*, 272
potassium alkyls or aryls, 228
potassium cyanide, with Lewis acids, 563
potassium ferricyanate, 689
potassium ferricyanide, and dihydroxylation of alkenes, 993
potassium fluoride, in acetic acid, formation of acyl fluorides, 1225
potassium hydride, with silyl-thiols, 476
potassium hydroxide see KOH
potassium ions, and ambident nucleophiles, 449
  and crown ethers, 111
  binding by crown ethers, 108
potassium permanganate also see permanganate
potassium permanganate, and oxidation of diols, 994
  and oxidative cleavage of alkenes, 1463
  dihydroxylation of alkenes, 992
  dihydroxylation of alkenes, ultrasound, 994
potassium peroxomonosulfate see Oxone
potassium persulfate, and *Boyland-Sims oxidation*, 634
  and hydroxylation of aromatic compounds, 634
potassium superoxide see superoxide
potassium trifluoroborates see trifluoroborates

potassium, and formation of enolate anions, 698, 778
and sodium, 1561
and $S_{RN}1$ reactions, 740
and the acyloin condensation, 1561
in ammonia, and *Birch reduction*, 914
in ammonia, reduction of aromatic compounds, 913
potential energy, and reactions, 264
potential, ionization see ionization potential
P-P bonding, 169
preformed enols see enols
preparative LC, and diastereomers, 156
and resolution, 156
pressure, and hydroamination of alkenes, 896
and kinetics, 282
and substitution reactions, 388
and the *Heck reaction*, 764
and the *Strecker synthesis*, 1182
pressure, high also see high pressure
and dipolar transition states, 446
and *Knoevenagel condensation*, 446
and partial molal volume, 446
and reactivity, 362, 446
and steric hindrance, 446
and the *Claisen condensation*, 446
and the *Diels-Alder reactions*, 446
and the *Menshutkin reaction*, 446
and transition states, 446
and volume of activation, 446
in catalytic hydrogenation, 904
pressure, versus rate constant, 388
Prevost reaction, 994
Woodward modification, 994
primary quantum yield, 306
primary sources, literature, 1569
principle of conservation of orbital symmetry, and *Diels-Alder reaction*, 1030
principle of imperfect synchronization, 324
principle of increasing electron demand, 394
principle of least motion, 915
principle of microscopic reversibility, 273
Prins cyclization, and *oxonia Cope rearrangements*, 1401
Prins reaction, 1013, 1184
and alkene structure, 1186
and Lewis acid catalysts, 1185
and Lewis acids used as catalysts, 1186
and Lewis acids, 1186
and *Markovnikov's rule*, 1185
and oxocarbenium ions, 1185
and photochemistry, 1187
and radicals, 1185, 1187
and Sm compounds, 1185
and the ene reaction, 1186
and transition metals, 1186, 1187
enantioselectivity, 1186
formation of dioxanes, 1185
halogenation of alkenes, 991
mechanism, 1184
promotion by iodine, 1185
reversible, 1186
structural variations, 1186
with dienes, 1185
with enynes, 1185
with oxetanes, 1185
with peroxides, 1185
priority rules, *Cahn-Ingold-Prelog rules*, 139
prismane, 1406
and strain, 198
prismanes, Ladenburg formula, 1051
valence isomers, 1051
proazaphosphatranes, catalysts, 1126
process, SET, 236
prochiral ketones, reduction of, 1511
prochiral, definition, 171
product identification, and mechanism, 275
product quantum yield, 307
product spread, 410
proline derivatives, and *Michael reactions*, 947
proline, and addition of organometallics to imines, 1137
and cyanation of aryl halides, 758
and enantioselective *Mannich reactions*, 1102
and the aldol reaction, 1147
as a chiral additive, 1474
with enamines, 552
promotion, and fluorescence, 299
of electrons, 8
propane, and dipole moment, 19
bond energy, 28
2-propanol, supercritical, as a solvent, 1508
propargyl acetates see acetates
propargyl acetates, with alkynes, 935
propargyl carbocations, 213
propargyl groups, as neighboring groups, 420
propargyl rearrangement, 412
propargyl sulfides, 1115
propargyl systems, and allylic rearrangement, 412
propargyl, lithio, and silyl protecting groups, 517
with alkyl halides, 517
propargylamines, cyclotrimerization, 1061
propargylic carbonates, 477
propargylic radicals, 239
propargyllithium reagents, 516
propellanes, and geometry, 198
and S_N2 reactions, 424
and strain, 198
X-ray crystallography, 198
propeller shaped carbocations, 217
propene, from cyclopropane, and entropy, 268
protecting groups, acetals and ketals, 1082
dithioacetals and dithioketals, 1087, 1088
silyl, and lithiopropargyl compounds, 517
protection, aldehydes and ketones, 457
of alcohols, 460
protic solvents, 437
protic solvents, and enolate anions, 1143
proton abstraction, *Heck reaction*, 767
proton acceptor, bases, 312
proton affinity, and basicity, 320
and basicity, of proton sponges, 339
proton donors, acids, 312
proton exchange, and E1cB mechanism, 1263
proton NMR see NMR
proton sponges, 322, 339
and base strength, 339
and *Friedel-Crafts alkylation*, 611, 612
and helicene, 133
and proton affinity, 339
basicity of, 339
bis(amino)fluorenes, 339
bis(amino)naphthalenes, 339
bis(amino)phenanthrenes, 339
quinoquinolines, 339
vinamidine, 322
with tosylimines and ketenes, 1244
proton transfer, and acidity, 323
and alkynes, 324
and amides or amines, 324
and chloroform, 324
and HCN, 324
and keto-enol tautomerism, 665
and lactams, 324
and *Marcus theory*, 329
and organometallics, 695
and pK, 323

and principle of imperfect synchronization, 324
and resonance, 324
and solvents, 324
hydroxypropanoic acid, 323
transition state, 329
proton, as a leaving group, 569
as an electrophile, 863
protonated cyclopropanes, 880, 1326, 1327
protonation, alkyne-boranes, 1380
protonation, allylic carbocations, 1390
enantioselective, 458
enantioselective, enolate anions, 668
gas phase, alkylbenzenes, 575
of benzene, 580
of carbonyls, 1069
of diazo compounds, 434
of enolate anions, 698, 867
of *Grignard reagents*, 698
of organometallics, 698
of radical ions, 914
vinylboranes, 1379
protonic acids, and *Friedel-Crafts alkylation*, 610
and reverse *Friedel-Crafts alkylation*, 641
protonolysis, of alcohols, 219
of alkenes, 219
of boranes, with carboxylic acids, 911
of iminium ions, 219
protons, addition to alkenes, 863
α-protons, and enolate anions, 539
and the *Sommelet-Hauser reaction*, 799
reaction with alkenes, 863
proton-shift tautomerism, 92
proton-transfer reactions, and diffusion control, 323
mechanism, 323
proton-transfer, and hydrogen bonding, 323
and in-in isomers, 323
and out-in isomers, 323
intramolecular, 323
to carbon, 324
prototropic rearrangement, 662, 1321
prototropy, keto-enol tautomerism, 665
proximity effect, complex-induced, and directed ortho metalation, 784
Pschorr reaction, 844
mechanism, 796
Pschorr ring closure, 795
and the *Gomberg-Bachmann reaction*, 795
pseudo first order kinetics, S_N2, 375
pseudo first order rate constant, and solvent acidity, 327
pseudo first-order reactions, 281
pseudoasymmetric carbon, 147
pseudo-equatorial, 190
Pseudomonas oleovorans, α-hydroxylation of amines, 1476
Pseudomonas putida, and dihydroxylation of aromatic compounds, 998
pseudorotation, 180
and conformations, 189
and cyclophanes, 48
and equilibrium, 180
psuedo-axial, 190
Pt catalyst, and hydrogenation, 903
isomerization of alkenes, 882
Pt complex, and cycloalkynes, 202
resolution alkenes, 174
Pt compounds, and atropisomers, 131
publications: notes and communications, 1570
puckered conformations, 189
pulsed ultrasound, 308
Pummerer rearrangement, 1338, 1565
enantioselectivity, 1565
isotopic labeling, 1566
mechanism, 1565
Pummerer-sila, 1566
purity, optical, 160, 161
push-pull effect, 69
and radicals, 239, 240
pyracyclene, and *Stones-Wales rearrangement*, 1391
paratropic, 80
pyramidal inversion also see inversion
pyramidal inversion, 127, 128
pyranose compounds, and tautomerism, 94
pyrans, and aromaticity, 54
dihydro, metathesis, 1421
Friedel-Crafts acylation, 623
from alkynes, 891
from diketones, 1083
pyrazoles, and diradicals, 1317
extrusion of nitrogen, 1316, 1317
from diketones, 1093
pyrazolines, by [3+2]-cycloaddition, 1017
extrusion of nitrogen, 1316, 1317
from [3+2]-cycloaddition, 1017
stability, 1017
thermolysis, 1017
from keto esters, 1093
pyrenes, and aromaticity, 75
and complex formation, 112
pyrenophanes, 47
pyrenyl radicals, 241
pyridine N-oxide, from pyridine, 1492
pyridine, alkylation, and organometallics, 785
amination, 787
pyridine, and acyl halides with alcohols, 1200
and anhydride hydrolysis, 1190
and aromaticity, 54
and chlorination of alcohols, 409
and *Collins reagent*, 1443
and diazonium coupling reactions, 598
and nucleophilic catalysis, 1190
and resonance, 33
and the *Doebner modification*, 1158
pyridine, as a catalyst, 1200, 1202
basicity, 58
catalyst for hydrolysis of anhydrides, 1190
electrophilic aromatic substitution, 584
in rotaxanes, 120
ortho lithiation, 785
with carboxylic acids, 845
pyridine-2-thione, and tautomerism, 93
pyridine-HF, and acetals or ketals, 457
pyridines, and *Suzuki-Miyaura coupling*, 772
Birch reduction, 914
by cyclotrimerization of nitriles and alkynes, 1061
Friedel-Crafts acylation, 623
from dihydropyridines, 1439
from diynes and heterocyclic carbenes, 1061
hydroxymethyl, by *Boekelheide reaction*, 1373
pyridinethiol, and tautomerism, 93
pyridinium bromochromate, halogenation of aromatic compounds, 605
pyridinium chlorochromate see PCC
pyridinium compounds, leaving groups, 433
pyridinium dichlorochromate, 606
pyridinium dichromate see PDC
pyridinium ions, and elimination, 1266
electrophilic substitution, 584
from pyrylium ions and amines, 1091
pyridinium phenolbetaine, 441
pyridinium polyhydrogen fluoride, 1106
pyridinium salts, and radical cyclization, 963
in ionic liquids, 365

pyridinophanes, 47
pyridones, and tautomerism, 93
by cyclotrimerization, 1061
pyridyl leaving groups, and elimination, 1266
pyrocalciferols, electrocyclic reagents, 1385
photolysis, 1386
pyrolysis also see flash vacuum pyrolysis
pyrolysis, of alkyl halides, 1298
of amine oxides, 1292
of ammonium carboxylates, 1216
of ammonium salts, 1290
of biphenylenes, 1391
of carboxylic acids also see decarboxylation
of carboxylic acids, 1238
of carboxylic acids, E^i mechanism, 1288
of cyclic peroxides, 1319
of cyclobutane, 195
of cyclopropane, 194
of cyclopropanes, 1347
of *Dewar benzenes*, 1387
of enol ethers, 1286
of homoallylic alcohols, 1314
of hydrazonium salts, 1311
of lactones, 1288
of xanthate esters, 1289
pyrolytic elimination, 1254
pyrolytic eliminations also see elimination
pyrophosphate, synthesis of, 112
pyrroles, addition of carbenes, 1056
alkylation, 482
alkylation, and organometallics, 785
and aromaticity, 57, 58
and atropisomers, 131
and circumambulatory rearrangement, 1395
basicity, 58
Birch reduction, 914
B-substituted, 805
by amination of alkenes, 896
by cyclotrimerization, 1061
by hydroamination, 897
canonical forms, 58
electron potential map, 57, 58
electrophilic aromatic substitution, 584
Friedel-Crafts acylation, 623
Friedel-Crafts alkylation, 611
from alkynes, 898
from alkynyl imines, 898
from allene-amines, 898
from diketones and amines, 1091
from metal catalyzed amination of diynes, 898
from metal catalyzed amination of diynes, 898
halogenation, 607
in the *Reimer-Tiemann reaction*, 627
metal catalyzed coupling with aryl halides, 760
resonance energy, 58
pyrrolidines, and [3+2]-cycloadditions, 1018
and the *Hofmann-Löffler reaction*, 1426
by hydroamination, 897
from aziridines, 1018
from haloamines, 482, 483, 1426
vinyl, from alkene-amides, 900
2-pyrrolidinone, alkylation, 493
pyrrolidinones, 755
N-methyl see NMP
N-alkylation, 445
pyrrolines, by amination of alkenes, 896
from cyclopropyl tosylimines, 1399
from cyclopropylimines, 1399
via *aza-Wittig reaction*, 1173
pyrylium ions, 54
with amines, 1091
leaving groups, 433

quadricyclane, by photochemical [2+2]-cycloaddition, 1048, 1050
quadrivalent stereogenic atoms, 126
quantum mechanics, and hyperconjugation, 88
and molecular mechanics, 191
quantum yield, and radicals, 807
definition, 306
primary, 306
product, 307
quasiadiabatic collapse, 308
quasiclassical electrostatic attraction, 30
quasi-Favorskii rearrangement, 1352
quaternary ammonium salts see ammonium salts
quaternary ammonium salts, phase transfer catalysis, 442
polymer bound, 1003
thermal stability, 443
quenching, and kinetics, 282
in photochemistry, 301
quinazolines, and tautomerism, 94
quinidine, as a catalyst, 1242
quinolines, alkylation of, with organometallics, 787
amination, 787
and decarboxylation, 645
and *Friedel-Crafts acylation*, 623
and the *Friedländer quinoline synthesis*, 1091
as a poison in the *Rosenmund catalyst*, 905
by reaction of aldehydes or ketones with amines, 1091
catalytic hydrogenation, 913
from carbene addition to indoles, 1056
metal catalyzed coupling with aryl halides, 760
photochemical alkylation, 845
tetrahyro see tetrahydroisoquinoline
with carboxylic acids, 845
quinolino-quinolines, bases, 322
quinoloquinolines, 322
quinone-phenol tautomerism, 1408
quinones, 623
and addition-elimination mechanism, 414
and aromatization, 1439
and hydroxylation of aromatic compounds, 634
aromatization, mechanism, 1439
by dyotropic rearrangement, 1431
by oxidation of aromatic compounds, 1453
by oxidation of aromatic hydrocarbons, 1480
by oxidation of catechol, 1453
by oxidation of hydroquinone, 1452
by oxidation of phenols, reagents, 1453
from naphthalene or anthracene, 1480
reduction to hydroquinones, 1505
stability of ortho and para, 581
via *Bergman cyclization*, 1387
quinoquinolines, as proton sponges, 339
quinoxalines, acylation, 845
quinuclidines, catalyst, chiral, 1128

R and F values, table, 359
R values, and σ values, 359
racemates, 124
and resolution, 124
and substituted cyclohexanes, 184
racemic mixtures see racemates
racemic mixtures, 136
racemization, and amines, 129
and carbanions, 226
and enolate anions, 667
and first order reactions, 383
and organocuprates, 521
and pyramidal carbanions, 654

and radicals, 808
and rearrangement, 1325
and S_N1 reactions, 383
and S_N2 reactions, 377
and solvolysis, 386
and the S_E1 mechanism, 654
and the *Wittig rearrangement*, 1374
of configuration, of migrating group during rearrangement, 1325
out-in isomers, 168
radical anions, and *Birch reduction*, 249
and $S_{RN}1$ reactions, 739, 740
energy levels, 740
radical cations also see radical ions
radical cations, 810, 814, 824
and the *Diels-Alder reaction*, 1022
and nucleophilic aromatic substitution, 749
and PES, 14
and the *Diels-Alder reaction*, 1029
methane, 14
radical cyclization, 868, 876, 961–965
allenyl radicals, 963
and [1,4]-hydrogen transfer, 1395
and acyl radicals, 964
and aldehyde-alkenes, 964
and aryl radicals, 963
and *Baldwin's rules*, 876, 961
and boranes, 959, 963
and electrochemistry, 963
and exo/endo isomers, 963
and heterocycles, 965
and hydrogen transfer, 961
and iodolactonization, 964
and lactams, 964
and manganese triacetate, 964
and photochemistry, 962
and ring size, 962
and seleno esters, 964
and silanes, 963
and Sm compounds, 964
and TEMPO, 965
and tributyltin dimer, 961, 962
and tributyltin hydride, 961
radical cyclization, diastereoselectivity, 963
enantioselectivity, 963
formation of lactams, 963
formation of lactones, 964
functional group compatibility, 963
Grignard reagents and metal salts, 962
influence of the halogen, 963
kinetics, 962
mechanism, 962
oxime-alkenes, 965
polyenes, 932
ring expansion, 963
to aldehydes, 1188
vinyl radicals, 963
with haloaldehydes or ketones, 964
with imines, 1188
with sulfur or selenium groups, 963
radical halogenation see halogenation
radical halogenation, methane, rate determining state, 824
radical induced isomerization, E/Z, 882
radical inhibitors, 807
radical initiators, 894, 971
addition of sulfonyl halides to alkenes, 988
addition to *Michael substrates*, 884
and E^i reactions, 1279
and halogenation of alkenes, 982
and *Michael addition*, 948
triethylborane, 960
radical ions, 248, 390
acepentalenes, 248
aminium, 599
and alkali metals, 249
and *Birch reduction*, 914
and organometallics, 716
and semiquinones, 248
and solvent cage, 390
cation, 249
cation, azulenes, 249
cation, nonplanar, 250
from Na, 914
ketyls, 248
silylenes, 248
radical mechanism, 792, 803, 828, 829, 895, 1468
addition of alkanes to alkenes, 927
and alcohol oxidation, 1445
and dehydrohalogenation, 1298
and E^i reactions, 1280
coupling of boranes, 851
deoxygenation of diols, 1301
halogenation of allylic hydrogen, 827
organometallic compounds with alkyl halides, 520
reduction of esters, 1539
radical pair mechanism, 1374
radical probes, 390
radical reactions, and cumene, 520
and σρ relationship, 361
initiation, 805
stereocontrol, 963
transition metal promotion, 817
radical substitution see substitution
radicals, 1, 2-migration, 1347
radicals, 1, 2-shift, 1334
radicals, abstraction, 694
of atoms, 247
transition state, 808
radicals, activity, 820
radicals, acyl, 805, 964, 970
and radical cyclization, 964
conjugated, rearrangement, 805
from aldehydes with transition metals, 805
radicals, acyloxy, 246
radicals, acyloxylation, 836
radicals, addition reactions, 867, 874
steric effects, 875
radicals, addition also see addition
radicals, addition, 263, 876, 910
aldehydes to alkenes mechanism, 972
and photochemistry, 1189
enantioselectivity, 960, 1189
mechanism, 867
of carbonyls, 1188
polyhalo compounds to alkenes, 991
to alkenes, 247, 867, 960
to alkenes, rate of reaction, 961
to alkenes, stereoselectivity, 868
to alkynes, 961
to C=N compounds, 1188
to conjugated compounds, 870
to dienes, 876
to imines, 1138, 1188, 1189
to oximes, 1189
to thiocarbonyls, 1188
radicals, aldehydes with conjugated ketones, 1188
alkoxy, 254, 804, 817
alkyl nitrites with aromatic compounds, 796
alkylation of heterocycles, 845
allenyl, and radical cyclization, 963
radicals, allylic, 238, 239, 826, 877
and electron diffraction, 238
and resonance, 815
rearrangement, 815
stereoisomers, 239
radicals, alternant hydrocarbons, 64
amidyl, and radical cyclization, 965
aminoxyl, 241
aminyl, and radical cyclization, 965
radicals, and abstraction, 867
and addition of aldehydes to alkenes, 971
and addition of silanes to alkenes, 930
and addition of thiols to alkenes, 894
and addition to alkenes, 970
and AIBN, 804

radicals, and abstraction (*Continued*)
and alkylation, 445
and aminium salts, 1400
and aromatic H, 815
and arylation of aromatic compounds, 795, 796
and arylation of enolate anions, 780
and arylation, 620
and atom transfer, 867
and autoxidation, 833
and azoxy compounds, 729
and azulenyl nitrones, 236
and *Baldwin's rules*, 868, 1427
and bis(decarboxylation) of dicarboxylic acids, 1469
and bond energy for atom abstraction, 812
and bond energy, 30
and bond rotation, 244
and boranes, 805, 960
and bridged intermediates, 868
and captodative effect, 240
and carbene insertion, 693
and carbenes, 245, 693
and carboxylic acid decarboxylation, 1238
and chromotropic spin traps, 236
and CIDNP, 236, 237, 390
and conformation, 816
and conjugate addition of organometallics, 956
and conjugate addition, 956, 959
and coupling, 808
and coupling, of dialdehydes, 1557
and cyclization, 991
and cyclopropyl alkynes, 240
and decarbonylation, 857, 845
and decarboxylative halogenation, 855
and decomposition of peroxides, 804
and dehydrohalogenation of alkyl halides, 1298
and diazonium salts, 788
and dienes, 868
and disproportionation, 806, 816
and dithiocarbonates, 960
radicals, and E^i reactions, 1280
and electron withdrawing substituents, 816
and electrophilic aromatic substitution, 590
and elimination, 1280
and enantioselectivity, 809
and ENDOR, 236
and ESR, 240, 390, 729
and ESR/EPR, 235, 236
and extrusion of carbon monoxide from ketones, 1318
and fluorination of aryldiazonium salts, 792
and *Grignard reagent* formation, 715
and *Grignard reactions*, 241, 1113
and halo-alkenes, cyclization, 961–965
and halogenation of boranes, 705
and halo-ketones, 1347
and *Hofmann-Löffler reaction*, 1427
and hybridization, 243
and hydrogen bonding, 240
and hydrogen-metal exchange, 717
and hydroxylation of aryldiazonium salts, 790
and hyperconjugation, 86, 238, 238
and inhibitors, 807
and inorganic molecules, 235
and insertion, 694
and *Jacobsen-Katsuki epoxidation*, 1005
and mass spectrometry, 235
and *Meerwein arylation*, 794
and metal catalyzed acyloxylation, 836
and *Michael addition*, 948
and NCS, 827
and nitration of alkanes, 677
and nitration of aromatic compounds, 597
and NMR emission, 237
and NMR, 236–238
and *Norrish type I reactions*, 1318
radicals, and organocalcium reagents, 233
and organometallic compounds, coupling with alkyl halides, 520
and oxidation of thiols to disulfides, 1497
and oxidation-reduction, 1435
and oxidative decarboxylation of carboxylic acids, 1468
and oxygen autoxidation, 833
and oxygen, 805
and peroxide formation, 835
and peroxides, 803, 804
and photochemistry, 804
and photolytic cleavage, 296
and photoreduction, 306
and polyene cyclization, 932
and push-pull effect, 240
and quantum yield, 807
and racemization, 808
and radical clocks, 814
and rearrangement of N-nitroaniline, 638
and resonance, 238, 239
and ring closure, 991
and ring expansion, 815
and SET mechanisms, 389
and SET process, 236
and silanes, 826
and sodium borohydride reduction, 699
and solvation, 807
and spin states, 235
and spin trapping, 236
and $S_{RN}1$ mechanism, 739, 740
and stability, 240
and step-scan time-resolved infrared, 235
and strain, 812
and symproportionation, 927
and telomers, 867
and the *Gatterman method*, 796
and the *Gatterman reaction*, 847
and the *Hammett equation*, 817
and the *Hunsdiecker reaction*, 811, 855
and the *Kolbe reaction*, 853
and the *Orton rearrangement*, 640
and the *Pauli principle*, 235
and the *Prins reaction*, 1185, 1187
and the *Schmidt reaction*, 1364
and the *Stone-Wales rearrangement*, 1391
and the *Strecker synthesis*, 1183
and the *Wittig rearrangement*, 1374
and thiols addition to alkynes, 894
and triethylboranes, 960, 964
and ultrasound, 445
and unpaired electrons, 235
and UV, 238
and α-heteroatoms, 817
radicals, anomeric effect, 243
anti-Markovnikov addition to alkenes, 960
radicals, aryl, 790, 818, 847, 1550
and CIDNP, 810
and disproportionation, 809
and radical cyclization, 963
canonical forms, 809
coupling, 809
ipso attack, 818
meta selectivity, 818
ortho/para selectivity, 818, 819
partial rate factors, 818
resonance, 809
radicals, arylation, 844
of aromatic compounds, 844
radicals, as intermediates, 276
atom abstraction, 808
atom transfer, 806

azo compounds, 245
benzylic σ scales, 816
benzylic, 238, 815, 826
bond dissociation energy and reactivity, 819, 820
boranes and oxygen, 964
radicals, bridged, 811
and ESR, 811
and stereochemistry, 811
bromine, and ESR, 869
isotope effects, 811
radicals, bridgehead, 243
reactivity, 817
radicals, bromine, 808
butenyl, 814
by hydrogen atom abstraction, 306
by photochemical cleavage, 302
by photo-decarboxylation of carboxylic acids, 845
captodative, 239
chain mechanism, 1468
chain mechanism, and $S_{RN}1$ reactions, 740
chain reaction, 806
characterization, 235
chiral, 243
chlorine, 804
cleavage of, 246, 806
clocks, 248, 814
clocks, conformational, 937
complex with solvent, 821
concentration of, 235
conjugate addition, 870, 959
radicals, coupling, 246
and the *Kolbe reaction*, 853
with allylic silanes, 511
cubylcarbinyl, 1334, 1335
cyanation, 563
cyclization reactions, 868
cyclization, 390
cyclobutylcarbinyl, rearrangement, 814
cyclohexyl, formation, 879
cyclopropyl, 244
radicals, cyclopropylcarbinyl, 247, 248, 814
rate of rearrangement, 814
rate of rearrangements, ab initio study, 814
radicals, decarboxylation, 838
decomposition, 247
delocalization of migrating aryl groups, 1335
detection of intermediates, 276
diffusion rate, 804
dimerization, 238, 844
diphenylpicrylhydrazyl, 240
disproportionation, 247, 844
dissociation energy, 242
dissociation energy, table, 242
dissociation, and photo-Fires rearrangement, 637
E/Z isomers, 239
electrophilic, 808, 874
elimination, 246
elimination, and sulfoxides, 1296
elimination, mechanism, 1281
equilibration, 962
fast radical reaction, 814
fate of, 245
fluorine, 822
formation by cleavage, 808
fragmentation of carbenes, 257
free, 208
free, from carbanions, 234
radicals, from aldehydes, 246
from alkyl halides, 817
from alkyl hypochlorites, 804
from azo compounds, 804
from carbenes, 257
from ketones, 246
from radicals, 246
radicals, general reactivity, 808
generation of radicals for addition to alkenes, 960
generation of, 245
geometry, 243, 244
Grignard reagents and oxygen, 700
radicals, H abstraction, 810
H abstraction, and rearrangements, 1333
H abstraction, from alkanes, 813
H abstraction, from alkenes, 815
H abstraction, rate, 812
H abstraction, stereoselectivity, 816
H abstraction, transition state, 812
radicals, H transfer, 806
halogen abstraction, 817
radicals, halogen, 246
rate of H abstraction, 815
with allylic and benzylic hydrogens, 826
radicals, heteroatom, 965
heterolysis, 810
homocubyl, 1334, 1335
hydrazyl, 240
hydroxide, 810
imidoyl, 805
in aqueous media, 241
in nitration of aromatic compounds, 596
inhibitors, galvinoxyl, 959
initiation, 803, 805
intermediates, and dehalogenation of dihalides, 1305
intramolecular addition to alkenes, 868
iodine, and light, 822
ion, and cyanation, 689
ion, to cyclopropanes, 881
ion-radical pair, and S_NAr reaction, 735
isotope effects, 810
ketenyl, 805
ketyls, 1113
kinetics of radicals chain reactions, 807
lifetimes, 235, 236, 814, 1335
metal mediated, 810
methane, 15
radicals, methyl, 243
and ESR, 243
IR, 243, 244
polarity, 816
radicals, *Michael reactions*, 948
migrating groups in rearrangements, 1335
migratory aptitudes, 1336
N-containing, 241
neighboring group assistance, 810
neophyl, 1333
nitroso, 1428
nitroxide, 240, 243, 245
nitroxyl, 240
nucleophilic, 816, 874
of aryl groups, 1334
oxidation to carbocations, 248
ozone and hydrocarbons, 1469
pentadienyl, 239
pentenyl, 814
peroxy, 807
persistent, 236
phenyl, 246, 811, 816
photochemical cleavage, 246
planar versus pyramidal, 243
polar transition states, 816
polymerization, 247
propagation steps, 806
propargylic, 239
pulsed radiolysis, 820
push-pull, 239
pyrenyl, 241
radical clock reactions, 248
radical cyclization see radical cyclization
rate of H abstraction and structure, 815
rate of rearrangement, 248
radicals, reactivity, 819, 820
and steric hindrance, 814
and structure, 813
and substrates, 812
in aromatic solvents, complex formation, 820
with aromatic compounds, 818
radicals, rearrangements, 247, 248, 263, 815, 1333–1336
and CIDNP, 1335
and ESR, 1335
and isotopic labeling, 1334
and stability, 1336
radicals, reduction, 807
of alkyl halides, 1532
of thiocarbonates, 1538
to carbanions, 248

radicals, resonance stabilized, 809
reversible addition to alkenes, 869
ring expansion of halo-ketones, 1347
rotation barrier, 244
Schiemann reaction, 793
radicals, selectivity, 819
of hydrogen abstraction, 813
radicals, silyl, 871, 964
singlet, 245
solid, 240, 241
solvents and reactivity, 820
SOMO-LUMO, 964
spectroscopic analysis, 235
spin traps, 241
radicals, stability, 235, 238, 0239, 876
and conjugation, 240
and steric hindrance, 239
and substitution, 238
radicals, stable, 241
stereoelectronic effects, 817
steric effects, 239
strain and reactivity, 817
Strecker synthesis, 1183
structure, 235
structure, and reactivity, 813
β-substituents, and rearrangements, 1334
succinimidyl, 829
TEMPO, 240
termination state, 806
thermal cleavage, 245
trimethylenemethane, 245
radicals, triphenylmethyl, 238
stability, 819
radicals, triplet, 245
radicals, vinyl, and radical cyclization, 963
E/Z inversion barrier, 239
radicals, with alkanes, 811–813
with alkenes, 806, 810, 815, 879
with alkyl halides, 811
with alkylsilanes, 807
with allenes, 877
with aromatic compounds, mechanisms, 809
with benzylic hydrogens of aromatic compounds, 815
with tributyltin hydride, 806
radii, hydrogen bonds, 99
radioactive carboxylates, 277
radioactive iodide, and S_N2, 377
radioactive nitriles, 277
radiolysis, pulsed of radicals solutions, 820
Raman spectroscopy, and carbocations, 216
and conformations, 174
and hydrogen bonding, 110
and intermediates, 276
and methyl neighboring groups, 407
and the *Fries rearrangement*, 637
laser, and nonclassical carbocations, 404
nanosecond time resolved, 637
nitration of aromatic compounds, 595
Ramberg-Bäcklund reaction, 1302
and episulfones, 1302
and *Michael addition*, 1303
extrusion reactions, 1304
mechanism, 1302
order of halogen reactivity, 1302
with halo sulfides, 1303
Raney nickel also see nickel
and desulfurization of dithioketals, 1089
and dithianes, 554
and hydrogenation, 902
and the *Zinin reduction*, 1524
and transamination, 487
desulfurization, 852, 1088, 1552
hydrogenation of thioethers, 851
hydrogenation of thiols, 851
reduction of alkyl halides, 1532
reduction of sulfo groups, 646
reduction of sulfur compounds, 1524
with dithioacetals and dithioketals, 554
rate of reaction, S_N2, and allylic substrates, 420
rate acceleration, and microwave chemistry, 311
electrophilic addition to alkenes, 864
rate constants also see kinetics
rate constants, 267
addition carbenes, to alkenes, 1052
amide hydrolysis, 1199
and cyclopropylcarbinyl radicals, 248
and *Marcus theory*, 279
and mechanism, 279, 284
and phenonium ions, 399
and ring-closing reactions, table, 269
and the *Hammett equation*, 352
rate constants, decarboxylation, 720
ester hydrolysis, 356
first order, 283
pseudo first order, and solvent acidity, 327
radical conjugate addition, 870
Sandmeyer reaction, 847
second-order, 283
versus pressure, 388
rate determining step, 279
acetal hydrolysis, 456
alkane halogenation, 824
amide hydrolysis, 1199
and arenium ions, 663
and E1 mechanism, 1261
and E2 mechanism, 1255
benzidine rearrangement, 1416
carboxylic esters with amines, 1220, 1221
haloform reaction, 724
multi-step reactions, 280
oxime formation, 1094
protonation of alkynes, 888
radical halogenation of methane, 824
Stille coupling, 683
sulfonation of aromatic compounds, 601
rate enchantment, and neighboring groups, 400
and cyclopropylmethyl groups, 404, 405
of the *oxy-Cope rearrangement*, 1401
solvolysis, 404, 405
solvolysis, of cyclobutyl, 406
solvolysis, of cyclopropylmethyl, 406
rate law, 280
and frequency factor, 284
and half-life, 282
and kinetics, 278
and mechanism, 278
and molecularity, 279
and solvent isotope effects, 288
and steady state, 280
E1cB and E2, 1263
first-order, 282
methods for determining kinetics, 281
pseudo first-order, 281
rate-determining step, 279
rate of diffusion, and high pressure, 362
and reactivity, 362
rate of H abstraction, halogen radicals, 815
rate of ionization, sulfonate esters, 438
sulfonate esters, solvent effects, 438
rate of reaction, alkyl halides with ethanol, 349
rate of reaction, and chiral compounds, 123
and enantiomers, 146
and ionic strength, 381
and mass-law effect, 381
and medium, 361
and microwave irradiation, 310, 446
and nucleophiles, 429
and nucleophilicity, 492
and radical clock reactions, 248
and resolution, 158
and resonance, 420
and salt effect, 381

and S_N1 reactions, 380, 381, 419
and S_N2 reactions, 375, 417, 418
and solvation, 429
and solvents, 438
and solvolysis, 400, 401
and steroids, 351
and structure, 417, 418
and the ortho effect, 361
and the *Smiles rearrangement*, 801
rate of reaction, common-ion effects, 381
Diels-Alder reaction, 1026, 1028, 1029
E2 reactions, 1256
E^i reactions, 1280
formation of oximes, 1094, 1095
hydrolysis of alkyl halides, 350
hydrolysis of esters, 350
ionization and B strain, 350
radical addition to alkenes, 961
radicals, and inhibitors, 807
selectivity in aromatic substitution, 590
S_N1 with aryldiazonium salts, 736
S_N1, and alkyl tosylates, 420
S_N1, and B strain, 419
S_N2 reactions, 417, 418, 420
S_N2, and allylic substrates, 420
S_N2, and solvent effects, 437
S_NAr reactions, 742
solvolysis of alkyl bromides, 419
tritium exchange in aromatic substitution, 592
rate retarding substituents, 421
rate, alkyl halide hydrolysis, table, 350
amide hydrolysis, 348
rate, and cyclopropanation, 1055
and cyclopropane solvolysis, 1390
and elimination, 1265
and leaving groups, 1074
and neighboring group effects, 399
and neighboring group participation, 392
and phenonium ions, 399
and S_N1, 379
and S_N2 reaction, 377
and temperature, 284
rate, arenium ion mechanism, 571
Cope elimination, 1292
decarboxylation, 720
electrophilic aromatic substitution, 581, 586
H abstraction by radicals, 812
halogenation of ketones, 671
hydration of alkenes, 873
in [2+2]-cycloaddition reactions, 1045
in [3+2]-cycloaddition reactions, 1016
isotope exchange with carbanions, 655
nucleophilic aromatic substitution, 733, 734
organomercury compounds with halogens, 659
ortho/para/meta substitution, aryl radicals, 818, 819
oxy-Cope rearrangement, 1401
partition factor, 571
ratios, electrophilic aromatic substitution, 588
salt effects, and electrophilic substitution, 653
solvolysis, 351
substituent effects on solvolysis, 398
vinylcyclopropane rearrangements, and aminium salts, 1400
rate-controlling step, 279
ratio of para and meta factors, 589
Rauhut-Currier cyclization, 1128
R-camp, chiral ligand, 904
re/si nomenclature, 172
reaction coordinate, 265
Reaction Index of Organic Syntheses, 1590
reaction intermediates, 268
reaction parameters, toluene, 589
reactions, and *Hammond postulate*, 272
and molecularity, 279
and steady state, 280
by type of compounds synthesized, 1605–1629
diffusion-controlled, 267
electrophilic, 262
enantioselective, 153
first-order, 279
gas-phase, and kinetics, 282
gas-phase, kinetics, 282
homodesmotic, 36
isodesmic, 36
kinetically controlled, 271, 272
kinetics of fast reactions, 282
multi-step, rate determining step, 280
nucleophilic, 262
photochemical, 289, 302
photochemical, table, 302
proton-transfer, 323
pseudo first-order, 281
second-order, 279
thermodynamically controlled, 272
very fast, kinetics, 282
ReactIR, 276
reactivity, and cavitation, 445
and conformation, 351
and conformational transmission, 351
and electrical effects or field effects, 347
and high pressure, 362, 446
and ionic solvents, 364
and medium, 361
and microwave irradiation, 445
and rate of diffusion, 362
and resonance, 347
and solvent polarity, 361
and steric effects, 349
and substrate structure, 417
and the *Hammett equation*, 352
and ultrasound, 445
and ρ values, 352
and σ values, 352–354
reactivity, in supercritical carbon dioxide, 363
in water, 363
reactivity, of alkyl groups in *Friedel-Crafts alkylation*, 611
of alkyl halides with ethanol, 349
of aromatic compounds, 576–588
of groups, in S_N1 reactions or S_N2 reactions, 424
of organolithium reagents, 697
of radicals, 819, 820
of radicals, and structure, 813
of radicals, substrate variation, 812
of tetrahedral intermediates, 348
reactivity, quantitative treatments, 352
reactors, microwave, 311
Reagents for Organic Synthesis, 1590
reagents, bromination of alkenes, 983
by reduction of oximes, 1527
chlorination of alkenes, 983
deoxygenation of alcohols, 1535
elimination of dihalides to alkenes, 1304
episulfides to alkenes, 1288
fluorination of alkenes, 982
reagents, for acylation of amines, 1217
for aromatization, 1438, 1439
for *Beckman rearrangement*, 1365
for benzylic oxidation to aldehydes, 1479
for dehydration of amides to isonitriles, 1314
for dehydration of amides to nitriles, 1313
for dehydration of oximes to nitriles, 1311
for dehydrogenation of amines to nitriles, 1454

reagents, for acylation of amines (*Continued*)
for elimination of epoxides, 1287
for epoxidation of alkenes, 998, 999
for formation of acylals, 1084
for halogenation of ketones, 668, 672
for hydrolysis of C=N compounds, 1077, 1078
for hydrolysis of dithioacetals and dithioketals, 1088
for hydroxylation of hydrocarbons, 1470
for *McMurry coupling*, 1559
reagents, for oxidation, of alcohols to carboxylic acids, 1483
of alcohols without over oxidation, 1443
of aldehydes to carboxylic acids, 1485
of amines, 1483
of aromatic side chains, 1466
of thioethers, 1493
reagents, for oxidative cleavage, of alkenes, 1463, 1464
of aromatic compounds, 1465
of diols, 1456
reagents, for α-hydroxylation of carbonyl compounds, 1473
for α-oxidation of ketones, 1476
for pinacol coupling, 1555–1558
for preparation of thiocarbonyls, 1088
for reduction of aldehydes or ketones to alcohols, 1503–1515
for reduction of alkenes to alkanes, 909
for reduction of conjugated alkenes, 916
for reduction of conjugated carbonyls, 1504
for reduction of nitriles, 1523
for reductive alkylation of aldehydes or ketones, 1097
for remote CH oxidation of hydrocarbons, 1478
reagents, oxidation of alkenes to ketones, 1489
oxidation of alkynes to diketones, 1490
reduction of diazonium salts, 1550
reduction of esters to alcohols, 1516
reduction of sulfoxides to sulfones, 1553
self-immolative, 152
silane reduction agents, 1514
rearrangements, [1,2]-sigmatropic hydrogen shift, 1345
rearrangements, [2,3]-sigmatropic, 799, 1375, 1375, 1413
rearrangements, [2,3]-Wittig, 1413
rearrangements, 1, 2, 3-trioxolanes, 1461
rearrangements, 1, 2-alkyl, of alkyne anions, ab initio study, 1337
rearrangements, 1, 3-, and greater, 1332
rearrangements, 1, 4-, 1336
rearrangements, 1, 5-, 1336
rearrangements, 1, 6-, 1336
rearrangements, acid catalyzed of epoxides, 1343
rearrangements, alkyl, from ammonium salts, 640
from aniline ammonium salts, 640
in *Friedel-Crafts reactions*, 640
in the *Hofmann-Martius reaction*, 640
in the photolysis of aniline ammonium salts, 641
rearrangements, allylic, 409, 657
and acyl addition of allylic boranes, 1124
and allylic oxidation, 1470, 1471
and formation of allenes, 412
and metal complexes, 663
and reduction of allylic alcohol, 1535
and S_N1' reactions, 411
in halogenation reactions, 827
in propargyl systems, 412
in S_N2' reactions, 410
in the *Stille coupling*, 683
in the *Wurtz reaction*, 514
of allylic radicals, 815
of carbenes, 691
with allylic alcohols, 532
with ammonium salts, 1414
with vinyl epoxides, 537
rearrangements, *amino-Cope*, 1401
rearrangements, and addition of alkyl halides to alkenes, 991
and addition-elimination mechanism, 414
and anchimeric assistance in migrating group, 1326
and carbene addition to aromatic compounds, 1056
and diazotization of amines, 1327
and diradicals, 1335
and formation of carbocations, 1322
and formation of nitrenes, 1323
and *Friedel-Crafts acylation*, 621
and halogenation of alcohols, 500, 501
and ion pairing, 1331
and ions, 1331
and isotope effects, 1326, 1329
and memory effects of migrating groups, 1330
and methyl group participation, 407
and migratory aptitudes, 1328
and migratory aptitudes, H versus alkyl versus aryl, 1329, 1330
and neighboring group mechanisms, 392
and racemization, 1325
and S_N1 mechanisms, 1326
and S_N1-type processes, 1325
and solvolysis, 407
and the conducted tour mechanism, 662
and the ipso carbon, 582
and *Whitmore 1,2-shifts*, 1322
rearrangements, *aza-Cope*, 1401
aza-Payne, 467
aza-Wittig, 1375
B to O, 1375
Baeyer-Villiger, 1368
Bamberger, 800
Beckmann, 1312, 1325, 1359, 1365
Beckmann, migratory aptitudes of groups, 1328
benzidine, 635, 1415
benzil-benzylic acid, 1350
boron-to-carbon, 1375
Brook, 1431
C to N, 1359
carbene to carbene, 1354
Carroll, 1409
catalytic *Wagner-Meerwein*, 1340
cationotropic, 1321
Chapman, 1428
circuambulatory, 220, 1394
Claisen, 635, 1407–1413
Cope also see *Cope*
Cope, 1400–1406
Curtius, 1354, 1361
cyclopropylcarbinyl, in ionic liquids, 1345
cyclopropylcarbinyl, with Ag, au, Ru or In, 1345
Dakin reaction, 1370
degenerate, 1324
Demyanov, 1345
dienone-phenol, 1349
di-π-methane, 1425
dyotropic, 1430
rearrangements, electrocyclic, 1380–1391
and carbenes, 1056
and orbital symmetry, 1388
electrophilic, 264, 1321, 1337

electrophilic allylic, geometry of, 658
enolene, 1412
Favorskii, 1350
Fischer-Hepp, 639
Fries, 635, 636, 637
Grovenstein-Zimmerman, 1342
halogen from N-haloamides, 640
hiscotropic, 1345
Hofmann, 1360
Hofmann, mechanism, 275
hydride, 1331
hydride, 1, 3- and greater, 1332
hydrogen as a migrating group, 1328
rearrangements, in *Friedel-Crafts alkylation*, 615
in oxidations with PCC, 1443
in the Dibal reduction of oximes, 1528
in the *Diels-Alder reaction*, 1023
in the *Heck reaction*, 766
in the *Jacobsen reaction*, 645
in the ozonolysis of alkenes, 1460
rearrangements, intermolecular, definition, 1322
internal abstraction, 1336
intramolecular, 1360
intramolecular, definition, 1322
intramolecular, photochemical, 304
α-ketol, 1349
long range, 1331
Lossen, 1362
Meinwald, 1344
Meisenheimer, 1373
Meyer-Schuster, 412, 1357
migration origin, 1321
migration terminus, 1321
Mislow-Evans, 1415
multiple 1,2-shifts, 1340
nature of the migrating group, 1321
nature of the migration, 1324
rearrangements, *Neber*, 1359
and intermediate isolation, 275
rearrangements, non-carbocation mechanism, 614
nucleophilic allylic, 663
nucleophilic, 264
nucleophilic, mechanism, 1322–1333
rearrangements, of acyl aziridines, 1399
of acyl phosphorus ylids, 1293
of aldehydes, acid catalyzed, 1348
rearrangements, of alkenes and photosensitized oxygen, 833, 834
and π-allyl complexes, 663
carbocation, 662
metal catalyzed, 663
photochemical, 663
with alcohols, 889
rearrangements, of alkylcarbenes, 691
of alkynes, 664
of allylic carbocations, 420
of amino acids, and nitrous acid, 1343
of ammonium salts, 799
of ammonium salts, base induced, 1371
of aryl carboxylate ions, 645
of aryl groups, transition state, 1335
of aryl halides, 647
of aryl oximes, 800
of aryl triazenes, 639
of benzoylnorephedrine, 351
of benzyl ammonium salts, 798
of biphenylene, 1391
of boranes, 664
of carbanions, 234
rearrangements, hydrogen shifts, 1337
of carbenes, 256, 257, 1051, 1337
rearrangements, of carbocations, 210, 220, 566, 690, 726, 885, 889, 928
and deuterium labeling, 1327
and *Friedel-Crafts alkylation*, 613
direction of rearrangement, 1323
rearrangements, of cubane, 1423
cyclohexadienones, 1349
of cyclopropyl propargylic alcohols, 1345
of cyclopropylmethyl groups, 406
of diazo alkoxides, 1355
of diene-alcohols, 1396
of diols, migratory aptitudes, 1329
of divinylcyclobutanes, 1402
of divinylcyclopropanes, 1402
of double bonds, 661
of epoxides, 1343
of epoxy-alcohols, 466
of esters, 635
of haloamines, 1367, 1368
of haloammonium salts, 1427
of hydroperoxides to ketones, 1370
of ketones, acid catalyzed, 1348
of lithio ethers, 1374
of lithio-epoxides, 489
rearrangements, of methylenecyclopropanes, 1346
of neopentyl carbocations, 1326
of neophyl systems, 1339
of nitrenes, 259
of nitro groups, 638
of nitroso amides, 796
of N-nitroso groups, 739
of N-nitrosoanilines, 639
of norbornyl carbocations, 1338
of *O*-tosyl nitriles, 1312
of *O*-tosyl oximes, 1312
of oxime sulfonates, 1367
of phenonium ions, 399
of protonated cyclopropanes, 1326
rearrangements, of radicals, 247, 248
of radicals, and β-substituents, 1334
rearrangements, of sulfur ylids, 799
of *tert*-pentyl carbocation, 1324
of vinyl epoxides, 1344
organomagnesium compounds, 711
rearrangements, *Orton*, 640
and peroxides, 640
photochemical, 640
rearrangements, oxa-di-π-methane, 1425, 1426
oxonia-Cope, 1401
oxy-Cope, 1401
para-Claisen, 1407
Payne, 466
pericyclic sigmatropic, 1407
phenol-dienone, 1349
pinacol see pinacol
pinacol, migratory aptitudes of groups, 1328, 1329
propargyl, 412
prototropic, 662, 1338, 1565
quasi-Favorskii, 1352
rearrangements, radical, 264, 815, 1333–1336
and hydrogen abstraction, 1333
and isotopic labeling, 1334
and stability, 1336
migrating groups, 1335
of aryl groups, 1334
rearrangements, *Reilly-Hickenbottom*, 641
resonance in migrating groups, 1326
retro-Claisen, 1407
Schleyer adamantization, 1341
Schmidt, 1366
semipinacol, 1343
sequential 1,2-shifts, 1332
σ-bond, metal catalyzed, 1423
rearrangements, sigmatropic also see sigmatropic
rearrangements, sigmatropic, 1391–1417
configuration of migrating groups, 1396, 1397
definition, 1391

rearrangements, *sila-Pummerer*, 1566
Smiles, 800
Sommelet-Hauser, 798, 1373
stereochemistry of migrating group, 1324, 1325, 1328
rearrangements, *Stevens'*, 798, 799, 1371, 1414
Stieglitz, 1367
Stone-Wales, 1391
rearrangements, transannular, 1332
and alkyl groups, 1333
hydrogen shift, 1336
rearrangements, *Truce-Smiles*, 802
vinylcyclopropane, 1399
vinylcyclopropane, rate and aminium salts, 1400
von Richter, 797
rearrangements, *Wagner-Meerwein* also see *Wagner-Meerwein*
rearrangements, *Wagner Meerwein*, 1368
Wallach, 1429, 1562
Willgerodt, 1338
with σ-participation, 1340
Wittig, 555, 1373, 1414
Wolff, 1244, 1353
"wrong way", 1336
Reaxys, 1580, 1601–1604
recognition, molecular, 112
recoverable catalysts, and the *Heck reaction*, 764
recrystallization, fractional, and diastereomers, 156
and resolution, 156
rectus, and stereogenic centers, 172
recyclable catalysts, for alkene metathesis, 1420
for *Suzuki-Miyaura coupling*, 771
Red-Al, 1502
reduced mass, and mechanism, 286
reducing agents, and chiral transition metals, 1514
and dehalogenation, 647
for ozonides, 1459
reductase, for reduction of conjugated ketones, 919
of *Nicotiana tabacum*, 919
reduction, 264
reduction, and chiral additives or chiral catalysts, 1513
and chiral ligands, 1513
and ease of reduction of functional groups, 1499–1501
and gain of hydrogen or loss of oxygen, 1433
and selectivity, 1498
reduction, asymmetric, 1511–1515
benzoylformates, 152
reduction, by the *Barton-McCombie reaction*, 1538
by the *Katritzky pyrylium-pyridinium method*, 1547
reduction, conjugate, enantioselective hydrogenation, 918, 919
reagents for, 917
with silanes, 917
reduction, conjugated carbonyls, reagents, 1504
reduction, definition, 1433
dissolving metal, 913
enantioselective, 1513
in *Grignard reactions*, 1111
in supercritical 2-propanol, 1508
in the *Cannizzaro reaction*, 1509
influence of steric hindrance, 1505
reduction, of acyl halides, reagents, 1517
of aldehydes or ketones, 1503–1515
of aldehydes or ketones, steric hindrance, 1505, 1506
of alkyl halides, reagents, 1531–1534
of allenes, 912
of amides, reagents for, 1545
of carbonyls with sodium in ethanol, mechanism, 1506
of conjugated alkenes, reagents for, 916
of dithianes, 554
of enamines, 911
of epoxides, enantioselectivity, 1502
of esters, reagents for, 1516
of ketones, diastereoselectivity, 1515
of nitriles to methyl, with terpenes, 1531
of nitro compounds, reagents, 1528
of prochiral ketones, 1511
of radicals, 807
of selenides, 1551
of sulfonate esters of phenols, 1536
of sulfonate esters, from alcohols, 1535
of sulfones or sulfoxides, 540
reduction, oxazines, 556
type of, 1497
reduction, with alanes, 1509
with ammonium formates, 1510
with borane reagents, 1509
with boranes, enantioselectivity, 1509
with hydrides, mechanism, 1510
with $LiAlH_4$, with aldehydes or ketones, mechanism, 1508
with metals, 1507
with PMHS, 1517
with silanes, 1509
with siloxanes, 918
Wolff-Kishner, 1540, 1547
reductive alkylation, 1096–1099
and formic acid, 1098
and the *Wallach reaction*, 1098
azo compounds, 1099
enantioselectivity, 1099
in ionic liquids, 1099
nitro compounds, 1099
nitroso compounds, 1099
of alcohols, 1084
of nitro compounds, 1526
with *Hantzsch dihydropyridines*, 1098
reductive amination, 1096–1099
and *Hantzsch esters*, 1099
and hydrogenolysis, 1097
and microwaves, 1098
and the *Eschweiler-Clarke procedure*, 1098
enantioselectivity, 1099
metal catalysts, 1097
of aldehydes or ketones, reagents for, 1097
reductive amination, reagents, 1097, 1098
reductive cleavage, of amides, 1554
of amines, 1553
of cyclopropanes, 920
sulfonamides, 1554
reductive coupling also see coupling
of aldehydes or ketones, reagents, 1558
reductive dimerization, 1085
reductive elimination, Pd catalyst, 773
reductive hydrogenation, 1097
reductive *Nazarov cyclization*, 946
Reed reaction, 837
Reed reaction, mechanism, 837
Referativnyi Zhurnal, Khimiya, 1575
references from *Organic Syntheses*, 372
Reformatsky conditions, and β-lactam formation, 1244
Reformatsky reaction, 525, 1129, 1244
Reformatsky reaction, and activated zinc, 1129
and dialkylzinc reagents, 1130
and hydrolysis, 1130
and PEF-telluride, 1131
and phosphines, 1130
and solvents, 1130
and sonochemistry, 309
and the *Claisen condensation*, 1154
and the *Grignard reaction*, 1130

and the *Wittig reaction*, 1130
and transition metals, 1129, 1130
and ultrasound, 1129
and zinc, 1130
intermediates, 1130
with carboxylic esters, 1328
with metals, 1129
X-ray of intermediates, 1130
Reformatsky-type zinc derivatives, 526
refractive index, and optical activity, 145
regiochemistry, and ozonide formation, 1460, 1461
E2 reactions, 1270
in the *Heck reaction*, 764
of elimination, 1269
regioisomers, and the *Diels-Alder reaction*, 1023, 1024
regioselective, definition, 447
regioselectivity, and ambident nucleophiles, 447
and benzyne formation, 738
and enolate anions, 546
and formation of arynes, 743, 744
and halogen radicals, 822
and *Hofmann's rule*, 1270
and hydroboration, 922
and steric effects, 449
and *Stille coupling*, 682
and unsymmetrical ketones, 546
and *Zaitsev's rule*, 1270
regioselectivity, condensation of esters and ketones, 1236
conjugated dienes, 876
crossed aldol reaction, 1145
cyclotrimerization, 1062
definition, 874
epoxide halogenation, 506
regioselectivity, for alkenes with alcohols, 889
for dihydroxylation of alkenes, 995
for halogenation of alkanes, 822, 823
for halogenation of alkanes, 823
for halogenation of ketones, 670, 672
for hydroformylation of alkenes, 980
for organometallic reactions with heteroatoms, 696
regioselectivity, in [3+2]-cycloaddition reactions, 1016
in [3+2]-cycloaddition reactions, and FMO, 1016
in pyrolytic elimination, 1281
in the *Dieckmann condensation*, 1235
in the *Diels-Alder reaction*, 1023–1026
in the *Heck reaction*, 765
in the intramolecular aldol reaction, 1150
in the *Mannich reaction*, 1101
in transesterification, 1207
Registry Number, *Chemical Abstracts*, 1578
Reilly-Hickenbottom rearrangement, 641
Reimer-Tiemann reaction, 627, 629
Reissert compounds, with sulfuric acid to give aldehydes, 1519
relative rate ratios, aromatic substitution, 590
remote CH oxidation of hydrocarbons, 1478
remote dehydrogenation, 1441
Reppe carbonylation, 973
residual dipolar coupling, 148
resins, polystyrene, 445
resolution, 129
resolution, and chiral additives, 158
and chiral recognition, 156
and chromatography, 156
and crown ethers, 156, 157
and cryptands, 157
and cyclodextrins, 157
and differential absorption, 156
and fractional crystallization, 154–157
and fractional distillation, 156
and GC, 156
and metal complexes, 134
and preparative LC, 156
and rate of reaction, 158
and sublimation, 158
and synthesis, 149
resolution, biochemical processes, 157
conversion to diastereomers, 154
deracemization, 159
resolution, kinetic see kinetic
resolution, kinetic, 136, 156, 158
and alkenes, 158
and dihydroxylation of alkenes, 159
and epoxidation of alkenes, 159
and epoxidation, 1005
resolution, mechanical, 157
and heptahelicene, 158
resolution, methods of, 154–159
resolution, of alkenes, 174
of amine salts, 156
of amino acids-boric acid, 173
of crystals, 157
of enantiomers, 124
of sulfoxides, 1494
of sulfur compounds, 129
of trans-cyclooctene, 155
resolution, organomercury compounds, 652
spontaneous, 158
resolution, with brucine, 173
with cholic acid, 157
with ephedrine, 173
with esterases, 157
with morphine, 173
with pig liver esterase, 157
with *Sphingomonas pauchimobilis*, 159
with strychnine, 173
resonance contributors, and planarity, 44
resonance effects, 45
and acidity, 336
and substituent effects, 421
and σ values, 359
electrostatic scale, 35
resonance energy also see energy
resonance energy, 32, 193
ab initio calculations, 36
acenes, 78
and aromatic compounds, 56
and aromaticity, 58
and cross conjugation, 42
and dendralenes, 42
and fused aromatic compounds, 56
and hybridization, 38
bond, 59
of benzene, 35, 36
of butadiene, 37, 38
of cyclopentadienide ion, 58
of furan, 58
of phenalene radical and cation, 56
of pyrrole, 58
of thiophene, 58
resonance, 31
resonance, allylic carbanion/cation/radical, 40
allylic carbocation, 409
amine oxides, 49
resonance, and 1,3-dipoles, 1014
and allylic carbanions, 657
and allylic carbocations, 420, 869
and allylic radicals, 815
and amines, 337
and aniline, 45
and anthracene, 46
and arenium ions, 570
and aromatic compounds, 33, 34, 46
and aryl halides, 44
and benzene, 32, 32
and bond angles, 45
and bond distance, 45
and bond order, 31
and calculations, 34
and canonical forms, 31
and captodative effect, 240
and carbanions, 223, 227, 654

resonance, and 1,3-dipoles (*Continued*)
and carbenes, 693
and carbocations, 219, 420, 875
and charge separation, 44
and conjugate addition, 870
and *Dewar structures*, 31
and dimethyloxosulfonium methylid, 1175
and dimethylsulfonium methylid, 1175
and diradicals, 44
and electron density, 45
and electronegativity, 45
and electrons, 43
and enolate anions, 224
and hyperconjugation, 211
and hyperconjugative stretching, 87
and hypophosphorus acid, 49
resonance, and MO theory, 32
and nonequivalent canonical forms, 44
and orbitals, 32
and paracyclophanes, 46
and phosphine oxides, 49
and phosphorus ylids, 1165
and π-bonds, 44
and pK, 337
and planarity, 44, 46
and proton transfer, 324
and push-pull effect, 240
and radicals, 238, 239, 809
and rate of reaction, 420
and reactivity, 347
and steric effects, 46
and strain, 46
and sulfones or sulfoxides, 49
and the *Hammett equation*, 352
and the mesomeric effect, 45
and unpaired elections, 44
and vinyl chloride, 40
and wave equations, 32
and ylids, 49
resonance, energy and canonical forms, 44
in migrating groups, in rearrangements, 1326
integral, 36
resonance, of carbonate, 40
of carboxylate anion, 644
of *Dewar structures*, 46
of keto-ylids, 1167
of naphthalene, 33
of pyridine, 33
of substituted arenium ions, 577
resonance, rules of stability, 44
rules of, 43
σ bond, 33
steric inhibition, 597
structures, of fulvalenes, 63
stabilization, and the captodative effect, 69
retention of configuration, and chlorination of alcohols, 409
and elimination-addition reactions, 416
and hydrolysis of esters, 1195
and neighboring group participation, 396
and phenonium ions, 399
and radicals, 809
and S_Ei mechanisms, 651
and S_N1 reactions, 386
and S_N2 reactions, 376
and S_Ni reactions, 409
retention of migrating group during rearrangement, 1324
retro ene reaction, and pyrolysis of homoallylic alcohols, 1315
retro-aldol condensation, 718, 1143
retro-Barbier reaction, 1109
retro-Claisen condensation also see *Claisen*
retro-Claisen rearrangement, 1407
retro-*Diels-Alder reaction*, 1023
and thermal extrusion of carbon monoxide from ketones, 1309
retro-ene reaction, 942
retrograde aldol see retro aldol or aldol
retro-Nazarov, 946
retropinacol rearrangements, and *Wagner-Meerwein rearrangement*, 1340
reverse *Brook rearrangement*, 1431
reverse *Claisen condensation*, 723
reverse *Friedel-Crafts alkylation* see *Friedel-Crafts*
reverse *Gatterman-Koch reaction*, 643
reversibility, *Diels-Alder reaction*, 1028
reversibility, microscopic, 273, 1075, 1186
reversible reactions, *Michael reactions*, 866
radicals to alkenes, 869
reviews, annual, literature, 1585
reviews, of the literature, 1583, 1584
ρ values, and reactivity, 352
ρ values, E1 versus E2, 1276
Rh catalysts, and formation of silyl enol ethers, 688
chiral, and cyclopropanation, 1054
DOSP ligands, 1054
Rh catalysts, for 1,6-addition, 954
for alkyne cyclotrimerization, 1059
for aromatic compounds with alkenes, 940
for arylation of imines, 1135
for boronic acids with isocyanates, 1140
for cyclization of enynes, 934
for cycloaddition, 1066
for decomposition of diazoalkanes, 255
for diazoalkane cyclopropanation, 1051
for haloacylation of alkenes, 992
for hydroformylation of alkynes, 979
for hydrogenation of enamines, 905
for hydrogenation, 903
for imines with boronic acids, 1136
for insertion reactions, 692
for isothiocyanate formation from isonitriles, 498
for nitroso compounds and isocyanates, 731
for the *Cannizzaro reaction*, 1563
for the deuteration of aromatic compounds, 592
Rh catalysts, in [2+2]-cycloaddition reactions, 1041, 1043
Rh catalysts, in the [3+2]-cycloaddition of diazoalkanes, 1017
in the *Reformatsky reaction*, 1130
in the *Scholl reaction*, 620
Rh catalysts, with acyl halides, 1300
with alcohols and alkyl halides, 460
with asymmetric cyclopropanation, 1055
with diazoalkanes, 1051
with nitrosamides, 1295
with vinyltetrafluoroborates, 958, 959
ribbons, molecular, 118
ring bond order, 59
ring closing metathesis, 1417–1423
ring closing reactions, and rate constants, table, 269
and *Baldwin's rules*, 270–271
and dithiane chemistry, 553
and entropy of activation, 268
and *Friedel-Crafts acylation*, 623
and hydroboration of trienes, 925
dig nomenclature, 270
disfavored or favored, 270, 271

tet nomenclature, 270
trig nomenclature, 270
ring contraction, acid catalyzed, 1345
Favorskii rearrangement, 1351
photolysis of diazoketones, 1353
ring current, 51
and alkenes, 51
and anisotropy, 51, 52
and annulenes, 76
and benzene, 51, 52
and C13 NMR, 52
and cyclophanes, 51, 52
and *Pauling resonance energy*, 51
antiaromatic systems, 53
benzocyclobutene, 49
paramagnetic, 53
ring expansion, acid catalyzed, 1345
and metathesis, 1421
and radicals, 815
and the *Stevens' rearrangement*, 1371
aryl azides, 1362
carbene addition, and strain, 1057
carbene insertion, 692
carbenes with aromatic compounds, 1056
cyclopropylmethyl carbenes, 1347
halo ketones, 1347
lactones, 1431
of alkyl azides, 1362
of aromatic rings, 1011
of cyclic ketones, 1355
Tiffeneau-Demyanov, 1346
ring opening metathesis, 1420
polymerization, 1421
ring opening, cyclopropyl cations, 1389
ring size, and entropy, 268
and lactone formation, 269
ring strain energy and hyperconjugation, 89
and bond energy, 30
Ring Systems Handbook, 1582
ring-chain tautomerism see tautomerism
ring-closing metathesis see metathesis
ring-in-ring complexes, 118
rings, and the *Hofmann rule*, 1291
common, strain, 201
large, strain, 201
medium, strain, 201
small, strain, 201
Ritter reaction, 1239
and alcohols, 1239
and HCN, 1239
and hydroxysuccinimide, 1240
and Nafion, 1239
and the *Beckmann rearrangement*, 1367
microwave irradiation, 1240
steric hindrance in nitriles, 1239
with cyanamides, 1240
Robinson annulation, 1150
and ammonium ketones, 1150
and intramolecular aldol reaction, 1150
and polymerization of substrates, 1150
and silyl ketones, 1150
and *Stryker's reagent*, 1150
and the *Claisen reaction*, 1155
and the *Mannich reaction*, 1150
and the *Michael reaction*, 1150
enantioselectivity, 1150
in ionic liquids, 1150
solventless, 1150
Rodd's Chemistry of Carbon Compounds, 1586
ROESY, and π-π-interactions, 104
Rosenmund catalyst, and hydrogenation of alkynes, 905
Rosenmund reduction, of acyl halides, 1517
Rosenmund-von Braun reaction, 745, 758
rotamers, and conformer, 174
definition, 174
rotating-frame nOe spectroscopy see ROESY
rotation barrier also see barrier
of radicals, 244
strained aromatic compounds, 205
rotation, and catenanes, 119
and α, 124
bond, and carbocations, 863
bond, carbocations, 861
C-S, and chirality, 228
in ethane, energy barrier, 175
molar see molar rotation
observed see observed rotation
rotation, restricted, and atropisomers, 132
and chirality, 134
and cis/trans isomers, 205
rotation, specific see specific rotation
rotaxanes, 118
and chirality, 135
and fullerenes, 118, 120
and isomers, 118
and ligand exchange, 119
and *Möbius strip mechanisms*, 119
and NMR, 120
and porphyrins, 118
and tronsitional isomers, 118
as inclusion compounds, 120
as molecular shuttles, 120
as molecular switches, 118
as photonic devices, 118
as stoppers, 120
beads and stations, 120
chiral, 120
synthesis of, 119
Ru catalysts, and decarboxylation, 721
and hydrogenation, 903
and metathesis, 1418, 1419
and oxidative amidation, 838
Ru catalysts, and amide formation, 495
for alcohol coupling, 532
for alkynes with allylic alcohols, 938
for allylic silanes with aldehydes, 1126
for amines with nitriles, 1104
for boronic acids with esters, 1231
for cycloisomerization of enynes, 1395
for formylation of alkenes, 975
for hydration of alkynes, 887
for oxidative cleavage of alkenes, 1464
for oxidative cleavage of alkynes, 1464
for the alkylation of amines, 483, 485
in the *Scholl reaction*, 620
in the *Suzuki-Miyaura coupling*, 774
in the vinylcyclopropane rearrangement, 1399
polymer bound, and alkene metathesis, 1420
with alkyne carboxylic acids, 893
with oximes, 1311
with propargylic ethers, 1285
Ru complexes, and Tischenko reaction, 1564
rubidium alkyls or aryls, 229
rules, of resonance, 43
stability of resonance forms, 44
ruthenium tetroxide, oxidation of alkenes, 1471
ruthenium trichloride, and Bromamine-T, 1492
with $NaIO_4$, with amines, 1477
Ruzicka cyclization, 1238

s character, and acidity, 341
and bond angle, 26
and bond distance, 24
and bond energy, 28, 30
and bond length, 30
and carbanion stability, 222, 225
and hyperconjugation, 88
and strain, 194

sacrificial hyperconjugation, 88
Sadtler Research Laboratories, spectra, 1582
Sakurai reaction, 956
  catalytic, 956
salen catalysts, and catalytic hydrogenation, 905
  and epoxidation, 1005
  cobalt, 458
salen complex, and nitrile formation, 564
salen ligands, 1005
salen metal complexes, and epoxidation, 1005
S-alkylation, with thiocyanate ion, 497
salt effects, and kinetics, 381
  and S_N1 reactions, 438
  of lithium perchlorate, 438
  rate of electrophilic substitution, 653
salt free phosphonium ylids, 1165
salts, and S_N1 reactions, 438
  enamine, 551
  enamine, and alkylation, 550
  Meisenheimer, 733
samarium catalysts, and radical cyclization, 964
  and the *Prins reaction*, 1185
  coupling with alkynes, 562
samarium catalyst,
samarium iodide, and acyl halide coupling, 1232
  coupling of iminium salts, 1558
  reduction of pyridine, 916
  ring expansion of cyclic ketones, 1356
  with dinitriles, 1547
  with epoxy ketones, 1287
  with triamines, reduction of alkenes, 910
samarium metal, and acyl addition of allylic halides, 1116
  and dehalogenation of dihalides, 1305
  dehydration of halohydrins, 1284
  in acetic acid, and desulfurization, 852
Sanderson scale of electronegativity, 17
Sandmeyer reaction, 605, 788, 792, 846
  formation of aryl nitriles, 847
  rate constants, 847
  with copper cyanide, 847
sandwich compounds see metallocenes
Sanger's reagent, 752
saponification, 1190
scales, of electronegativity, 17
  of nucleophilicity, 431
  of reactivity, electrophilic aromatic substitution, 587
  solvent nucleophilicity, 441
scandium catalyst, with allylic boranes, 537
scandium, and fullerenes, 85
SCF method, and aromaticity, 54
Schiemann reaction, 608, 792
  radical intermediates, 793
Schiff bases, addition of HCN, 1183
  chiral, epoxides with organometallics, 535
  formation of, 1091
  hydrolysis, 1077
  reduction to amines, 1520
Schlenk equilibrium, 229–231
Schleyer adamantization, 1341
Schmidt reaction, 1363
  acid catalysis, 1363
  and acylium ions, 1364
  and hydrazoic acid, 1095
  and nitrilium ions, 1365
  intramolecular, 1364
  IUPAC mechanism, 1364
  mechanism, 1364, 1365
  migratory aptitude, 1364
  of azide ketones under radical conditions, 1364
  synthetic variation, 1364
Schmidt rearrangement, 1324, 1366
Scholl reaction, 619
  intramolecular, 620
Schotten-Baumann procedure, 1200
  acylation of amines, 1213
Schrödinger equation, 3, 4, 8
Schwartz's reagent, 926
  and *anti-Markovnikov* addition, 981
  with alkynes, 933
  with isocyanides, 981
Schwesinger proton sponges, see bases
Schwesinger proton sponges see proton sponge
SCI, see *Science Citation Index*
Science Citation Index (SCI), 1575, 1586, 1597, 1599
SciFinder, 1569, 1574, 1595–1598
  drawing tools, 1577
α-scission, 254
scoopy reaction, 1172
screening effects, in solvents, 437
SDS, and hydrolysis of C=N compounds, 1077
S_E1 mechanism, 570, 576
  and decarbonylation, 643
  and decarboxylation, 644, 645, 719, 720
  and the halogen dance, 647
  halogenation with organometallics, 706
S_E2, see substitution
S_E2 mechanism, 570
  and decarboxylation, 719, 720
  and *Stille coupling*, 683
  halogenation with organometallics, 706
searching the literature, 1592–1604
SEC, 653
seco acids, 1204
second order, *Beckmann rearrangements*, 1312
  rate constants, 283
  reaction, kinetics, 280
secondary isotope effects, 287, 1268
  in substitution reactions, 424
secondary orbital interactions, for *Diels-Alder reactions*, 1025
secondary sources, literature, 1569, 1574–1583
second-order reactions, 279
seeding method, 158
S_E, see substitution
Selectfluor, 822
  fluorination of aldehydes or ketones, 670
  with organotin compounds, 1119
selective pinacol coupling, 1556
selectivity relationships, 588
selectivity, and reduction, 1498
  bromine versus chlorine radicals, 822
  catalytic hydrogenation of alkenes, 904
  dialkylzinc with propargylic acetates, 1121
  endo/exo, [2+2]-cycloaddition, 1045
  facial, for reactions at carbonyls, 1068
  homogeneous catalysts in hydrogenation, 903
  of radicals, 819
  of nitrous acid, 789
  paradoxical, in *Friedel-Crafts alkylation*, 612
  torquoselectivity, 1381
Selectride, diastereoselectivity of reduction, 1505
  reduction of aldehydes or ketones, 1505, 1506
  stereoselectivity of reduction, 1505
selenenyl chlorides, catalysts from radical chlorination, 827
selenides, aryl, from aryl halides, 478, 750
  aryl, reduction with triaryltin hydride, 852
  by reduction of selenoxides, 1553
  catalysts from radical chlorination, 827

cleavage, 477
from alkyl halides, 478
from selenol addition to alkenes, 895
hydroxyalkyl, and semipinacol rearrangement, 1343
oxidation to selenones, 1494
oxidation to selenoxides, 1494
reduction, 1551
selenium, and carbonylation of amines, 730
selenium compounds, 475
selenium dioxide oxidation, and [2,3]-sigmatropic rearrangement, 1470
allylic hydroxylation, 1471
allylic oxidation of alkenes, mechanism, 1470
and allylic oxidation, 1470, 1471
and dehydrogenation, 1441
and ene reaction, 1470
and *Sharpless method* for allylic oxidation, 1471
aromatization of dihydropyridine, 1439
α-CH oxidation of ketones, mechanism, 1478
α-oxidation of ketones, 1476
selenium groups, and radical cyclization, 963
selenium tetrafluoride, 1106
with aldehydes or ketones, 1106
selenium ylids, 50
chiral, 1176
selenium, and aromatization, 1438
with *Grignard reagents*, 703
seleno esters, 1201
and radical cyclization, 964
by carbonylation, 781
from diselenides and acyl halides, 1201
selenoalkynes, hydration, 887
selenoamides, 1104
and transamidation, 1212
from amides, 1212
selenocarbonates, 1085
selenoethers see selenides
selenoketones, 681
selenols (RSeH), addition to alkenes, 895
by reaction of diselenides, 1555
organolithium reagents, conjugate addition, 968
selenones, by oxidation of selenides, 1494
selenosilanes, with epoxides, 466
selenoxides, alkylation, 554
by oxidation of selenides, 1494
elimination reactions, 1296
keto, 1296
reduction to selenides, 1553
thermal elimination to alkenes, 1296
self condensation, and the *Claisen condensation*, 1234
self-consistent field theory (SCF), 34, 35
self-immolative reagents, 152
semibenzilic mechanism, 1352
semibullvalene, 1425
and *Cope rearrangements*, 1406
semicarbazide, with aldehydes or ketones, 1093
semicarbazones, and *Wolf-Kishner reduction*, 1540
from aldehydes or ketones, 1093
hydrolysis, 1077
reduction to amines, 1528
semidines, 1415
and [1,5]-sigmatropic rearrangements, 1417
semiempirical calculations, 34
semipinacol rearrangement, 1343
substrates, 1343
semiquinones, radical ions, 248
semirubin, and hydrogen bonding, 102
sensitizers, triplet, 972
sequence rules, absolute configuration, 138–141
serine derivatives, and dehydration, 1283
SET (single electron transfer)
SET, and organocalcium reagents, 233
SET, mechanisms also see mechanism
SET, mechanisms, 389
and active methylene compounds, 542
and aldol reaction, 1141
and arylation of enolate anions, 780
and chain reactions, 389
and conjugate addition of organometallics, 956
and electrophilic aromatic substitution, 590
and *Grignard reagents*, 1112, 1113
and $LiAlH_4$ reduction of alkyl halides, 1534
and oxidation-reduction, 1435
and radicals, 389
conjugate addition, 956
organometallic compounds with alkyl halides, 519
SET, probes, 236
SET, processes, and radicals, 236
shape, and guest-host interactions, 113
of cyclodextrins, 117
Shapiro reaction, 1293
and deuterium labeling, 1294
formation of dienes, 1294
mechanism, 1294
Sharpless asymmetric aminohydroxylation, 1007
Sharpless asymmetric dihydroxylation, 996
mechanism, 996
Sharpless asymmetric epoxidation, 1004
and allylic alcohols, 1004, 1005
mechanism, 1004
Sharpless method, allylic oxidation with selenium dioxide, 1471
Shi epoxidation, 1002
[1,5]-shifts, homodienyl, 1395
3,2-shifts, and *Wagner-Meerwein rearrangements*, 1339
Shrock catalyst, for metathesis, 1418, 1419
shuttle, molecular, 120
side chain oxidation, aromatic compounds, 635
side chains, on aromatic compounds, oxidation, 1465
oxidation, side chain reactivity, 1466
oxidation, structural imitations, 1466
sigma bonds, overlap, 87
sigma orbitals, overlap, 85
σ route, to nonclassical carbocations, 395
σ values, and field effects, 357, 358
and reactivity, 352–354
and resonance and field effects, 359
F and R values, 359
Swain-Lupton, 359
σ∗ values, and field effects, 357
σ-complexes, and arenium ions, 570
σ-orbitals, shape, 10
σ-participation, and rearrangement, 1340
σ-substitution mechanism, 599
σρ relationships, and radical reactions, 361
sigmatropic rearrangements, 663, 1391–1417
and the [i,j] nomenclature, 1391, 1392
and σ-bond migration, 1392
antarafacial rearrangement, 1392, 1393
carbon migrations, 1396
configuration of migrating groups, 1396, 1397
definition, 1391
diradical mechanism, 1397
suprafacial migration, 1392, 1393
vinylcyclopropanes, 1398

[1,2]-sigmatropic hydrogen shift, 1345
[1,3]-sigmatropic alkyl migration, 1396–1398
[1,3]-sigmatropic migration, orbital movement, 1397
[1,3]-sigmatropic rearrangements, HOMO, 1393
  imaginary transition state, 1392, 1393
  migration of hydrogen, 1393
  Möbius-Hückel method, 1394
  of carbon, vinylcyclopropanes, 1398
  photochemical, suprafacial, 1393, 1394
  thermal, 1394
  thermal, antarafacial, 1393
[1,5]-sigmatropic alkyl migration, 1396–1398
[1,5]-sigmatropic migration, orbital movement, 1397
[1,5]-sigmatropic rearrangements, and semidines, 1417
  homodienyl, 1412
  Möbius-Hückel method, 1394
  of alkyl, 1398
  of hydrogen, 1392
  of hydrogen, and ene reactions, 1392
  photochemical, antarafacial, 1393, 1394
  thermal, 1394
  thermal, suprafacial, 1393, 1394
[2,3]-sigmatropic rearrangements, 799, 1413
  and SeO_2 oxidation, 1470
  and the *Mislow-Evans rearrangement*, 1415
  and the *Sommelet-Hauser rearrangement*, 799, 1415
[3,3]-sigmatropic rearrangements, and the *amino Cope rearrangement*, 1401
  and the *Fischer indole synthesis*, 1413
  Claisen rearrangement, 1407–1413
  Cope, 1400–1406
  enantioselectivity, 1403, 1410
  of allyl vinyl ethers, 1398
  oxy-Cope, 1401
[5,5]-sigmatropic rearrangements, and benzidine rearrangement, 1416
sigmatropic shifts, and cyclopropanes, 1395
sign inversion, and orbital overlap, 1032
sila-Baylis-Hillman reaction, 1128
silane-alkenes, cyclization, 930
silanes, acyl, 1155
silanes, alkyl, radicals and hydrogen transfer, 807
  with alkenes, 704
  with radicals, 807
silanes, allylic, and proazaphosphatranes, 1126
  and the *Sakurai reaction*, 956
  by silylene insertion, 692
  chiral, 1137
  conjugate addition, 956
  coupling, 840
  coupling, with AIBN, 511
  electrolytic coupling, 511
  Lewis acid catalyzed addition to aldehydes, 1125
  metal catalyzed addition to imines, 1180
  metal catalyzed coupling with alcohols, 533
  metal mediated halogenation, 829
  radical coupling, 511
  with acetals, 534
  with acyl halides, 1180
  with aldehydes, 1180
  with aldehydes, and carbamates, 1099
  with aldehydes, and transition metals, 1125
  with alkyl halides, 510
  with epoxides, 511
  with imines, 1137
silanes, and cleavage of ethers, 504
  and conjugate reduction, 917
  and enantioselective reduction, 1514
  and formation of acylals, 1084
  and radical cyclization, 963
  and TBAF, 783
  and the acyloin condensation, 1560
  and the Brook rearrangement, 1431
silanes, aryl, 511
  deprotonation with organolithium reagents, 516
silanes, arylation, and Suzuki-Miyaura coupling, 783
  benzyl, 511
  conjugate addition, 968
  coupling with alkynes, 562
  cyclic, by addition of silanes to alkynes, 929
  desilylation, 1531
  from anhydrides, 1546
  from metal catalyzed addition of silanes to alkenes, 928
  halo, with enolate anions, 686
  halogenation of, 826
  hydro see hydrosilanes
  hydroxylation, 467
  intramolecular addition to alkynes, 929
  Lewis acid catalyzed addition to alkenes, 929
  Lewis acid catalyzed addition to alkynes, 929
  lithio, with aldehydes or ketones, 1162
  metal catalyzed addition to alkenes, 928
  metal catalyzed arylation, 782
  metal catalyzed coupling, 511
  metals and reduction, 918
  radical halogenation, 826
  reaction with hydroxide, 223
  reducing agents, 1514
silanes, reduction, enantioselectivity, 1514
  of aldehydes or ketones, 1509
  of amides to amines, 1545
  of carboxylic esters, 1517
  of imines, 1520, 1521
  organocatalysts, 1514
  to hydrocarbons, 1531
silanes, trialkoxy, with aryl halides, 783
  trialkyl, and acids, with alkenes, 909
  trihaloallyl, acyl addition, 1126
silanes, vinyl, 705, 1163
  addition to conjugated carbonyl compounds, 930
  and *Stille coupling*, 684
  by addition of silanes to alkynes, 929
  coupling with aryl halides, 783
  from vinyl iodides, 513
  with allylic carbonates, 511
silanes, with acyl halides, 1539
  with AIBN, 1538
  with AIBN, reduction, 1543
  with alkyne aldehydes, 1123
  with alkynes, metal catalyzed, 562
  with aryl halides, metal catalyzed, 782
  with boranes, 1538
  with chloroformates, 1539
  with dienes, organocatalyst, 929
  with dienes, Pd catalyst, 929
  with dienes, Zr catalyst, 929
  with enamides, 929
  with fluoride ion, 956
  with ketones, metal catalyzed, 687
  with metals, reduction of amides, 1545
sila-Pummerer rearrangement, 1566
siletanes, 468
silica bound *Cinchona* alkaloids, 996
silica gel, 445
  and acetal cleavage, 456
  and addition of HCl to alkenes, 883
  and ceric ammonium nitrate, 593

and CrO_3 oxidation, 1442
and dehydration of oximes to nitriles, 1311
and ester hydrolysis, 1191, 1192
and formation of oximes, 1094
and nitrosation of amines, 728
and P_2O_5, and the *Ritter reaction*, 1239
and ring opening of aziridines, 491
and the *Claisen rearrangement*, 1408
and the *Knoevenagel reaction*, 1158
and the *Wittig reaction*, 1166
as a dehydrating agent, 1202
sulfuric acid impregnated, 1311
silica immobilized chiral ligands, and dialkylzinc, 1121
silica supported, *Heck reaction*, 763
phosphine Pd complex, 518
silicon tethered *Heck reaction*, 763
silicon, and cis/trans isomers, 11
and double bonds, 11
bond distance with carbon, 22
siloxane polymers, 956
siloxanes, addition to enamines, 930
and reduction, 918
with alkynes, 912, 929
with aryllithium reagents, 783
with enamines, 930
silver acetate, and decarboxylation, 645
silver carboxylates, and dihydroxylation of alkenes, 994
silver compounds, and alkyl halides, 439
and coupling of boranes, 850
with alkyl halides, 472
silver cyanide, 449
silver nitrate, and alkyl halides, 439, 496
and alkyl halides, 439
silver oxide, hydrolysis of alkyl halides, 451
oxidation of benzylic or allylic halides, 1481
silver perchlorate, reaction with iodocyclopentane, 70
silver salts, with trimethylsilyl cyanide, and alkenes, 981
silver, complex with ethylene, 105
silyl alkenes, as a protecting group, 842
silyl dichloride, with sodium tetraphenylborate, 784
silyl enol esters, from vinyl halides, 700
silyl enol ethers see enol ethers
silyl enol ethers also see ethers
silyl ethers, 461
silyl ethers see ethers
silyl ketene acetals see acetals
silyl ketones, and *Robinson annulation*, 1150
silyl radicals, 871, 964
silyl substituents, and conformation, 184
silyl sulfonate esters, 688
silylalkyl groups, neighboring groups, 407
participation in solvolysis, 407
silylalkylamines, 484
silylalkynes, halogenation, 706
silylamines, with alkynes, metal mediated, 562
with aryl halides, 752
silylated carbocations, 219
silylazides, formation of azidoamines, 491
silylcarbenes, 252
silylene insertion, 692
silylenes, radical ions, 248
silyloxy-Cope rearrangement, 1401, 1660
silylperoxides, with vinyllithium reagents, 700
silylphosphines, with alkenes, 899
with ynones, 930
silylthiols, 894
addition to alkenes, 894
silyl-Wittig reaction, 1163
Simmons-Smith procedure, and carbenes, 1051
and density functional theory, 1057
and dienes, 1058
and α-methylation of ketones, 1058
enantioselectivity, 1058
mechanism, 1058
metal mediated, 1058
with alkenes, 1057
with allenes, 1058
with diethylzinc, 1058
X-ray of intermediates, 1057
Simonini reaction, 855
and the *Hunsdiecker reaction*, 855
mechanism, 856
simultaneous addition, 263
simultaneous reactions, 861
single electron transfer (SET) mechanisms see SET
single electron transfer see SET
singlet carbenes see carbenes
singlet carbenes, 250, 1055
singlet carbonyls, 1243
singlet methylene, 254
singlet nitrenes, 258, 1010
singlet nitrenium ions, 260
singlet oxygen, and autoxidation, 833
and diradicals, 834
and formation of dioxetanes, 1040
and hydroperoxides, 833
and photooxygenation of alkenes, 1005
and photosensitizers, 833, 834
and the ene reaction, 942
cycloaddition to dienes, 1039
cycloaddition with alkenes, 1040
cycloaddition with phenanthrene, 1039
in the *Diels-Alder reaction*, 1040
reagents for preparation, 833
with alkenes, 833, 1006
with alkenes, mechanism, 834
singlet radicals, 245
singlets, in photochemistry, 292
sinister, and stereogenic centers, 172
six-center mechanism, *Cope rearrangement*, 1404
six-center transition states, 1428
Sm, see samarium
small ring compounds, table, 196, 197
Smiles rearrangement, 800
and sulfenic acids, 801
and disulfides, 801
and *Truce-Smiles rearrangement*, 802
S_N' reaction see substitution, SN'
S_N(ANRORC) mechanism, 754
S_N1 conditions, and isoborneol, 1338
S_N1 mechanism, alcohols with acyl halides, 1200
alkylation of active methylene compounds, 542
alkylation of alcohols, 533
and carbocations, 1323
and ester hydrolysis, 1195
and hydride reduction of alkyl halides, 1534
and rearrangements, 1326
diazonium salts, 788
S_N1 reactions see substitution
S_N1 reactions, 379–387
IUPAC system, 380
alkyl halides hydrolysis, 349
alkyl halides with alcohols, 460
and hardness, 379
and ion pairs, 383
and IUPAC system, 380
and leaving groups, 1074
and nucleophiles, 382
and proton transfer, 592
and silyl enol ether alkylation, 544
and the E1 reaction, 1262

S_N1 reactions (*Continued*)
ion-molecule pairs, 385
kinetics, 382
rate determining step, 379
S_N1 substitution see substitution
S_N1cB mechanisms, 453, 492
S_N2 character, of the transition state, 449
S_N2 mechanisms, alcohols with acyl halides, 1200
and ester hydrolysis, 1195
S_N2 reactions see substitution
S_N2' reactions see substitution
S_N2 reactions, 861
ab initio study, 378
and ester formation, 468
and leaving groups, 1074
and the *Hofmann-Martius reaction*, 640
and the *Menshutktin reaction*, 378
and vinyl halides, 416
cyanide with alkyl halides, 562
gas phase, 376
gas phase, free energy profile, 378
in the *Williamson ethers synthesis*, 461
intrinsic barriers and strain energy, 392
ion pair destruction or formation, 387
S_N2-like mechanism, at sulfur, 1249
S_N2 versus E2, 1261
S_N2(intermediate) reactions see substitution
S_N2' reactions, and higher order cuprates, 522
with organocuprates, 521
S_NAr mechanism, 732–735
ortho metalation, 784
S_NAr reactions, isotope effects, 735
Sneen formulation, 387
Sneen's ion-pair mechanism, 659
S_Ni reactions see substitution
S_Ni reactions, 1106
chloroformates, 409
intimate ion pairs, 409
snoutane, 1424
sodium alkyls, 228
sodium amide also see amides
sodium amide, and the *Haller Bauer reaction*, 725
as a base, 539
rearrangement of alkynes, 664
sodium ammonium tartrate, 157
sodium aryls, 228
sodium azide, and potassium iodide, 990
sodium bisulfite, reaction with aldehydes or ketones, 1090
sodium borohydride see borohydride
and decyanation, 726
and in situ hydrogenation, 904
and isoquinolines, 618
and nickel, hydrogenation, 902
and oxymercuration, 885, 886
and radicals, 699
and reduction of alkynes, 911
and the *Pictet-Spengler reaction*, 618
disproportionation, 1511
reduction of conjugated alkenes, 916
reduction of imine nitrates, 1239
reduction of organometallics, 699
solvent effects, 1503
with iodine, 1515
with metal compounds, reduction of alkenes, 911
with metal salts, reduction of conjugated alkenes, 917
with metals, 911
with $NiCl_2$, 1551
with nitriles, 726
sodium bromite, with amines, 729
sodium carbonate, base, 481
sodium cation, from sodium, 914
sodium chloride, as a host, 115
sodium cyanide, and the *Rosenmund-von Braun reaction*, 758
in HMPA, 564
with Lewis acids, 563
sodium cyanoborohydride see cyanoborohydride
sodium hydride, and hydrogen peroxides, with boranes, 923
with lactams, 493
sodium hydroxide, and the *Cannizzaro reaction*, 1563
sodium hypochlorite see hypochlorites
sodium hypochlorite, and epoxidation of alkenes, 1004
sodium hypochlorite, and *Jacobsen-Katsuki epoxidation*, 1005
sodium in ammonia, reduction of quaternary salts, 1548
sodium in ethanol, and reduction of aldehydes or ketones, 1506
sodium in ethanol, and reduction of imines, 1520
sodium iodide see iodide
sodium ions, and crown ethers, 111
sodium metal, and acyloin condensation, 1561
and the *Bamford-Stevens reaction*, 1294
surface area and reactivity, 1561
sodium nitrate, and epoxides, 490
sodium nitrite, with acid, 727
with alkenes, 1300
preparation of carboxylic acids, 566
with alkenes, formation of alkynes, 1300
with alkyl halides, 496
with aryl diazonium salts, 847
sodium nitrocyanamide, 497
sodium perborate, and hydroxylation of aromatic compounds, 634
sodium peroxide, and hydroperoxide formation, 472
sodium persulfate, and dimerization of carboxylate salts, 854
sodium sulfhydride see sulfhydride
sodium sulfite, with osmate esters, 993
sodium tetracarbonylferrate (*Collman's reagent*), 564
carbonylation of alkyl halides, 566
with alkyl halides, 564
sodium,
amalgam, and the *Gomberg-Bachmann pinacol synthesis*, 1555
amalgam, reduction of quaternary ammonium salts, 1548
ammonia, reduction of aromatic compounds, 913
and ammonia, reduction of allenes, 911
and coupling of alkyl halides, 513
and decyanation, 726
and formation of acyloins, 1560
and formation of enolate anions, 698, 778
and potassium, 1561
and reductive coupling of esters, 1560
and the *Wurtz coupling*, 513
and the *Wurtz-Fittig reaction*, 513
formation of radical ions, 914
in alcohols, 909
in amines, 909
in ammonia, and *Birch reduction*, 914
in ammonia, reduction of alkynes, 911
in ammonia, with cyclopropanes, 920

in ethanol, reduction of carbonyls, mechanism, 1506
soft acids, and covalent bonds, 332
definition, 331
soft and hard acids, table, 332
soft bases, and covalent bonds, 332
definition, 331
softness, 331
softness, and Lewis acids, 331
solid phase, and *Grignard reactions*, 1107
anhydride formation, 1209
Claisen rearrangement, 1408
Fischer indole synthesis, 1412
synthesis, 1218
solid radicals, 240, 241
solid state, amide bases, and the aldol reaction, 1143
and *Diels Alder reactions*, 1023
conformations, 205
esterification, 1203
photolysis, 1244
pinacol rearrangement, 1343
reactions, 468
solubility, and cyclodextrins, 116
and ester hydrolysis, 1192
and hydrogen bonding, 101
differential, 154
solvated electrons, 740
solvating agent, chiral, for NMR, 161
solvating power of solvents, table, 440
solvation energy, and Baker-Nathan effect, 86
solvation rule, and S_N2 reactions, 437
solvation, and anomeric effect, 187
and cryptands, 429
and *Grignard reagents*, 230
and nucleophilicity, 428
and organolithium reagents, 231
and rate of reaction, 429
by leaving groups, 655
carbanions, 227
counterions, 428
of radicals, 807
solvent acidity, and activity of proton, 325
and dielectric constant, 325
and equilibrium constant, 327
and lyonium ions, 326
and pH, 325
and the *Bunnett-Olsen equation*, 326, 0327
solvent cages, and radical ions, 390
and rearrangement of N-nitroaniline, 638
and the *Wittig rearrangement*, 1374
in the *Stevens rearrangement*, 1372
organometallic coupling, 519
solvent effects, and acidity, 343, 344
and ambident nucleophiles, 449
and basicity, 343, 344
and bond energy, 29
and carbenes, 254, 255
and carboxylic ester formation, 468
and charged nucleophiles, 437
and conformations, 178
and gauche conformations, 178
and Lewis acids, 343, 344
and limiting S_N1 mchanisms, 380
and rate of reactions, 437
and reactions, 1269
and S_N2 reactions, 377
and S_NAr reactions, 734
and substitution reactions, 438
and syn elimination, 1260
and the *Grunwald-Winstein equation*, 439
and the rate of ionization of sulfonate esters, 438
and unsymmetrical metal mediated coupling, 514
solvent effects, aryl halides with sulfur nucleophiles, 749
for E1 versus E2 reactions, 1277
for elimination versus substitution, 1277
for the halogenation of ketones, 670
in electrophilic substitutions, 660
in enolate alkylation reactions, 539
in $NaBH_4$ reductions, 1503
in S_N2 reactions, 437
in $S_{RN}1$ reactions, 740
in the aldol condensation, 1143, 1144
in the *Bamford-Stevens reaction*, 1294
in the *Claisen rearrangement*, 1409
in the *Cope elimination*, 1293
in the E1 reaction, 1262
in the *Gabriel synthesis*, 494
in the *Hofmann degradation*, 1290
in the isocyanide rearrangement, 1373
in the *Wurtz coupling*, 515
solvent effects, on the base, in elimination reactions, 1274
on the selectivity in the *Diels-Alder reaction*, 1025
with organocuprates, 949
solvent free, acylation of amines, and DABCO, 1213
addition of organometallics to aldehydes or ketones, 1114
[2+2]-cycloadditions, 1043
cyclopropylcarbinyl rearrangement, 1346
formation of cyanohydrins from trimethylsilyl cyanide, 1181
iodination, 607
oxidation of thiols to disulfides, 1497
solvent free, reactions, 366
acyl addition, 1114
aldehydes with TMSCN, 1181
conjugate addition of amines, 966
Friedel-Crafts acylation, 622
halogenation of alcohols, 502
oxidation of alcohols, 1442
thiols with vinyl ethers, 894
amines with epoxides, 488
Baeyer-Villiger rearrangement, 1369
Beckmann rearrangement, 1366
Claisen condensation, 1234
dehydration of oximes to nitriles, 1311
Diels Alder reactions, 1023
Henry reaction, 1156
Knoevenagel reaction, 1158
Robinson annulation, 1150
Sonogashira coupling, 776
Suzuki-Miyaura, 771
the *Heck reaction*, 764
sulfur ylid reaction, 1176
solvent isotope effects, 288
solvent nucleophilicity, scale, 441
solvent polarity, and electrophilic substitution, 653
and S_N1 reactions, 436
and transition states, 435, 437
solvent separated ion pairs, 386
solvent, and acidity, 345
and *Grignard reagents*, 231
DME, 1162
ionizing power and leaving groups, 441
sulfur dioxide, 382
supercritical CO_2, 841
solventless see solvent free
solvents also see ionic liquids
solvents, achiral, CD of chiral molecules, 145
acidic, 326
solvents, acidity, 324
and free energy, 327
solvents, alcohols, 909
amines, 909
ammonia, 747, 1292
solvents, and [2+2]-cycloaddition, 1043
and acid strength, 320
and base strength, 322
and bond energy, 30
and cleavage of ketones, 724

solvents, and [2+2]-cycloaddition (*Continued*)
and enolate anion formation, 1143
and *Grignard reagents*, 713
and *Hammett acidity function*, 325
and hydride reduction, 1510
and keto-enol tautomerism, 665
and nucleophilic assistance, 441
and nucleophilicity, 427, 428, 438
and proton transfer, 324
and rate of reaction, 438
and sonochemistry, 308
and the *Reformatsky reaction*, 1130
solvents, aprotic, 437, 1143
aromatic, complex formation and radicals, reactivity, 820
asymmetric, and synthesis, 153
basic, 326
benzene or toluene, 714
chiral, and NMR, 161
decane, 1319
dielectric screening effects, 437
dimethyl sulfone, 757
DME, 1159
DMF, 757, 1464, 1550
DMSO, 749, 757, 1293, 1303
solvents, effect, and free energy, 439
on ion pairs, 210
radicals, and reactivity, 820
ylid reactions, 1171
solvents, enolate condensations, 543
ethanolamines, 488
solvents, ether, and *Grignard reagents*, 229, 230, 1107
and hydroboration, 921
solvents, ethylene glycol, 1294, 1376
for enolate alkylation, 544
solvents, HMPA, 749, 1172, 1229, 1432
in cyanide-alkyl halide reactions, 563
induced chirality, 146
ionic, 364
ionizing power, 439
NMP, 1095
nonpolar, and reactivity, 361
polar and nonpolar, 361
solvents, polar, [2+2]-cycloaddition acceleration, 1045
and ionic transition states, 435
and phase transfer catalysis, 442
and reactivity, 361
aprotic, and enolate alkylation, 539
aprotic, and enolate condensations, 543
isocyanide rearrangement, 1373
solvents, polyethylene glycol, 1292
solvents, protic, 437, 1143
verses aprotic, and S_N2 reactions, 437
solvents, radical complex, 821
screening effects, 437
solvating power, table, 440
sulfolane, 1127, 1534
solvents, supercritical, alcohol, 1542
ammonia, 364
carbon dioxide, 363, 442, 1510
2-propanol, 1508
water, 1342
solvents, tetramethylenediamine, 1294
THF, 1550
UV of charge transfer complex, 441
water, 363, 1408
solvolysis, 451
and alkene neighboring groups, 396
and anchimeric assistance, 396, 397
and aromatic ring participation, 398, 399
and B strain, 350
and borderline mechanisms, 388
and carbocation stability, 383
and destabilizing groups, 421
and dioxane, 389
and I strain, 350, 424
and inversion, 389
and ionizing power of solvents, 439
and mechanism, 384
and methyl group participation, 407
and neighboring group mechanisms, 393
and neighboring groups, 394, 397, 398, 400
and nonclassical carbocations, 396, 397
and oxonium ions, 389
and participation of hydrogen, 408
and phenonium ions, 401
and picosecond absorption spectroscopy, 385
and racemization, 386
and rate enhancement, 404, 405
and rate of reaction, 400, 401
and rearrangement, 407
and σ-bond participation, 402
and silylalkyl group participation, 407
and special salt effects, 385
and stereochemistry, 399, 402
and structural effects, 419
and substituent effects on rate, 398
and substitution, 373
and the *Grunwald-Winstein equation*, 420
solvolysis, of alcohols, 1330
solvolysis, of alkyl halides, 659
and carbocations, 287
and mechanism, 287
solvolysis, of alkyl tosylates, rate of reaction, 420
of benzylic halides, 423
of brosylates, 385, 396
of cyclobutyl compounds, 405
of cyclopropanes, 1390
of cyclopropanes, rate, 1390
of cyclopropyl groups, 423
of cyclopropyl ring opening stereochemistry, 423
of cyclopropylmethyl groups, 404, 405
of esters, and NMR, 382
of iodocyclopentadiene, 70
of iodocyclopentane, 70
of norbornyl systems, 402
of optically active compounds, 402
of sulfonate esters, 385, 389, 395, 396, 408, 421
of tosylates, 385, 395
rates, 351
rates, and azide ions, 388
rates, for alkyl bromides, 419
Sommelet reaction, oxidation of alkyl halides to aldehydes, 1482
Sommelet-Hauser rearrangement, 798, 1373
[2,3]-sigmatropic rearrangement, 1415
and *Hofmann elimination*, 798
and *Stephens' rearrangement*, 798, 1373
mechanism, 799
SOMO-LUMO and radicals, 964
$S_{ON}2$ mechanism, 749
sonication, and cyclotrimerization, 1061
halogenation of alcohols, 502
Sonn-Müller method, from amides, 1523
sonochemistry also see cavitation
sonochemistry, 307–309
and carbohydrates, 309
and cavitation, 307
and emission of light, 307
and gas vacuoles, 307
and hot spots, 307
and hydrostannation, 309
and organic solvents, 308
and quasiadiabatic collapse, 308
and sonoluminescence, 307
commercial instruments, 308

origin of, 307
reproducibility, 308
sonochemistry, with arylation reactions, 309
with carbene formation, 309
with colloids, 308
with metal carbonyls, 309
with nucleophilic aromatic substitution, 309
with organolithium formation, 309
with $S_{RN}1$ reactions, 309
with the *Diels-Alder reaction*, 309
with the Reformatsky reaction, 309
with the *Weissler reaction*, 309
Sonogashira coupling, 776
and alkyne coupling, 842
and boronic acids, 778
and heterocycles, 776
and iodonium salts, 778
and microwave irradiation, 311, 776
and trifluoroborates, 778
Au catalysts, 777
copper free, 776
Fe catalysts, 777
in aqueous media, 776
in ionic liquids, 776
ligand free, 776
Ni catalysts, 777
other metal catalysts, 777
polymer supported catalysts, 777
problems, 777
reaction conditions, 776
sulfonate esters, 778
transition metal free, 776
variations, 777
with diazonium salts, 777
Sonogashira cross coupling, 842
sonoluminescence, 307
Sorenson method, amino acid synthesis, 541
Source Index, 1599
Soxhlet extractor, and the aldol reaction, 1144
sp hybridization, 10
sp orbitals, 7
sp^2 hybrid orbitals, 8, 9
sp^3 hybrid orbitals, 8, 9
sparteine, and *Michael addition*, 947
chiral additive, 1110
enantioselectivity with organolithium compounds, 516
Michael reactions, 947
with organolithium reagents, 937, 1110, 1132
special salt effects, and solvolysis, 385
Specialist Periodical Reports of the Royal Society, 1585
specific acid catalysis, 328
specific rotation also see enantiomers, chiral compounds
specific rotation, definition, 124
specific rotation, and concentration, 124
and enantiomeric excess, 160
and enantiomers, 124
and molar rotation, 124, 143
and temperature, 125
and wavelength of light, 125, 143
of aspartic acid, 125
spectra, *Aldrich Library*, 1583
spectra, Sadtler Research Laboratories, 1582
spectral readings, kinetics, 281
spectrophotometer, definition, 290
spectrophotometric measurements, and solvent acidity, 325
spectroscopic analysis, radicals, 235
spectroscopy, and bond distance, 22
and cyclic allenes, 203
and kinetics, 282
deuterium quadrupole echo, 113
diradicals in the *Paterno-Büchi reaction*, 1243
IUPAC classification, 12
of carbanions, 224
photoelectron, 11
electromagnetic, 290
electronic, 290
spherands, 110
spherical aromaticity, 84
spherical homoaromaticity, 84
sphericity, 173
Sphingomonas pauchimobilis, and deracemization, 159
and resolution, 159
Sphingomonas sp HXN-200, α-hydroxylation of amines, 1476
spin forbidden transitions, 292
spin states, and radicals, 235
spin trapping, and carbenes, 251
and radicals, 236
spin traps, 241
and NMR, 236
and N-oxides, 236
chromotropic, 236
spin, and the Pauli principle, 291
electron, 4
spin-conservation, Wigner rule, 300
spiranes, and atropisomers, 133
and chirality, 133, 134
and enantiomers, 133
spiro compounds, 43
spiroborate esters, 1509
reducing agents, 1522
spirocycles, and the *Nazarov cyclization*, 947
cyclization of enynes, 934
spirocyclic amides, 600
spirodienes, 48
spirooxathianes, and tautomerism, 94
spiropentanes, by carbene addition, 1053
spirotetraenes, 43
splitting, and esr, 235
sponge, proton see proton sponge
spontaneous reactions, and free energy, 264
spontaneous resolution, 158
spontaneous trimerization, 1059
squalene 2,3-oxide, and steroids, 932
squaric acid, 52
dianion and aromaticity, 82
pK_a, 82
$S_{RN}1$ mechanism, 739, 740, 750, 754
$S_{RN}1$ mechanism, arylation of active methylene compounds, 778
$S_{RN}1$ reactions see substitution
$S_{RN}1$ reactions, and radical anions, 739, 740
ferrous chloride catalysis, 417
mechanism, 1113
$S_{RN}2$ reactions, 740, 741
stability, and antiaromaticity, 67
and aromaticity, 66
and hyperconjugation, 86
and keto-enol tautomerism, 90
conformational see conformation
stability, of alkynyl carbocations, 415
of arenium ions, 574
of aromatic positional isomers, 584
of carbanions, 222, 223
of carbocations, 215
of diazonium salts, 788
of dienes in the *Cope rearrangement*, 1401
of mixed anhydrides, 1211
of norbornyl carbocations, 404
of phenonium ions, 401
of π-complexes, 575
of radicals, 238, 239, 240
of radicals, and conjugation, 240
of radicals, and steric hindrance, 239
of radicals, and substitution, 238
of radicals, substituents effects, 816

stability, of alkynyl carbocations (*Continued*)
open versus bridged carbocations, 862
stabilization, and delocalization, 44
of carbanions, 226
stabilizing groups, electrophilic aromatic substitution, 578
for carbanions, 720
stabilomers, 1341
stable carbenes, 255
stable radicals, 241
starands, 111
states, transition see transition
statistical effects, and acidity, 338
Staudinger reaction, 1529
steady state, and kinetics, 280
steering wheel model, 140
Steiglitz rearrangements, and carbocations, 1368
Stephen reduction, 1523
Stephens-Castro coupling, 775
and electrolysis, 775
step-type atoms, catalytic hydrogenation, 907
stereochemistry, and addition to cyclopropanes, 880
and bridged radicals, 811
and electrophilic addition, 860
and electrophilic substitution, 652
and *Grignard reagents*, 716
and mechanism, 278
and neighboring group mechanisms, 392
and NMR analysis, 144
and organolithium reagents, 717
and ozonide formation, 1462
and solvolysis, 399, 402
and substitution at vinyl carbon, 414
and the *Criegee mechanism* of ozonolysis, 1462
and the S_E2 mechanism, 650
and the S_E1 mechanism, 651
and vinyl boranes, 705
and vinyl boronic acids, 705
and vinylic halides, 705
and Zaitsev's rule, 1273
stereochemistry, for ion pairs and internal return, 386
for S_N1 reactions at vinylic carbon, 415
for S_N2' reactions, 411
in [2+2]-cycloadditions, 1045
in the *Cope rearrangement*, 1403
in the *Diels-Alder reaction*, 1024
in the *Diels-Alder reaction*, disrotatory motion, 1024
in the *Diels-Alder reaction*, endo/exo addition, 1025
in the oxidation of boranes, 701
in the *Stevens' rearrangement*, 1372
stereochemistry, of alkenes, from epoxides, 1286
of alkenes, with oxygen, 834
of alkyl migrating groups in sigmatropic migrations, 1396
of carbanions, solvent effects, 655
of carbocations, 217
of cyclohexanes, 148
of cyclopropyl ring opening in solvolysis, 423
of deamination of amines, 1548
of E1 reactions, 1273
of E2 reactions, 1259, 1273
of E^i reactions, 1279
of electrocyclic rearrangements, 1381
of epoxidation of cyclic alkenes, 877
of epoxides during halogenation, 506
of halogenation of alkenes, 982
of lactone alkylation, 544
of migrating groups, in rearrangement, 1324, 1325
of organocuprates with alkyl halides, 521
of S_E2 reactions, 652, 653
of S_E1 reactions, 653
of the migrating group, in rearrangements, 1328
of the migrating group, in the *Stevens' rearrangement*, 1372
of vinylic carbons in S_E1 reactions, 656
stereochemistry, with addition to alkenes, 878
stereocontrol, in radical reactions, 963
stereodifferentiation, 1342
stereoelectronic control, tetrahedral mechanism, 1073
stereoelectronic effects, and radicals, 817
stereogenic atoms also see chiral
stereogenic atoms, absolute configuration, 137
and chemical reactions, 141
and diastereomers, 146
and *Fischer projections*, 136
and glyceraldehyde, 137
and heteroatoms, 127
and molar rotation, 143
and monocyclic compounds, 166
and optical activity, 126
and pyramidal inversion, 127, 128
and specific rotation, 143
and symmetry, 126
and the S_N2 reaction, 141
at phosphorus, 169
by reduction of prochiral ketones, 1511
Cahn-Ingold-Prelog rules, 138–141
creation of, 136
D/L nomenclature, 137
formed by *Michael reaction*, 947
multiple centers, 146
NMR and absolute configuration, 142
quadrivalent, 126
R/S nomenclature, 138–141
tervalent, 127
α to a carbonyl, 667
stereogenic centers see stereogenic atom
stereoisomerism, 122
stereoisomers, and allylic radicals, 239
and cyclohexane derivatives, 184
meso compounds, 166
out-in, 168
radical, 239
topological, and catenanes, 119
stereoselective ene reaction, 942
stereoselective synthesis see synthesis
stereoselective synthesis, 150, 173
stereoselectivity, and hydrogenation of alkynes, 906
and hydrogenation of alkynes, and steric strain, 906
E/Z, and enolate anions, 1146
for addition of bromine to alkenes, 862
in [2+2]-cycloadditions, 1046
in [3+2]-cycloadditions, 1017
in cyclopropanation, 1056
in *Michael reactions*, 947
in nucleophilic substitutions at sulfonyl sulfur, 1248, 1249
in the aldol condensation, 1146, 1147
in the *Stille coupling*, 682
in the *Wittig-Horner reaction*, 1170
stereoselectivity, of alkyne-boranes with Bu_3SnCl, 1379
of H abstraction by radicals, 816
of hydroformylation, 980
of radical addition to alkenes, 868
of radical hydrogen abstraction, 817
of reduction with Selectride, 1505

of thiols with alkynes, 895
of *Wagner-Meerwein shifts*, 1341
stereoselectivity, with 9-BBN reactions, 922
stereospecific synthesis, 173
stereospecificity, and the *Heck reaction*, 766
in the *Diels-Alder reaction*, 1025–1029
in the E2 reaction, 1255
in the *Wittig rearrangement*, 1374
steric acceleration, and the ene reaction, 942
steric crowding, and *Dewar benzenes*, 55
and pentahelicene, 134
steric effects, and acidity, 338
and ambident nucleophiles, 450
and basicity, 338
and bond energy, 28
and borane addition to alkenes, 921
and catalytic hydrogenation, 904
and elimination, 1271
and Lewis acidity, 340
and Lewis acids/bases, 338
and radials, 239
and reactivity, 349
and regioselectivity, 449
and resonance, 46
and the *Taft equation*, 360
base cleavage of ketones, 725
electrophilic aromatic substitution, 587
in [2+2]-cycloaddition, 1045
in radical addition reactions, 875
regioselectivity in the Heck reaction, 765
steric factors, and catalytic hydrogenation, 904
and cleavage of alkanes, 726
steric hindrance, and arenium ion deprotonation, 572
and carbene addition to alkenes, 1053
and conformations, 179
and cyclobutadienes, 68
and dihydroxylation, 997
and enol content, 91
and esterification, 1204
and *Grignard reactions*, 1111
and high pressure, 446
and hydrolysis of esters, 1191
and mechanism, 349
and nucleophiles, 429
and organolithium reagents, 1112
and propeller carbocations, 217
and radical reactivity, 814
and radical stability, 239
and reactivity of alkyl halides, 349
cis/trans isomers, 165
electrophilic aromatic substitution, 581
esterification of carboxylic acids, 349
in nitriles, and the *Ritter reaction*, 1239
ortho/para ratio, 581
steric inhibition, of resonance, 597
steric interactions, and pyrolytic elimination, 1282
steric requirements, electrons, 26
steric stabilization, of enols, 666
steric strain see strain
and stereoselectivity n hydrogenation of alkynes, 906
and substitution, 417
steroids, 148
and catalytic hydrogenation, 904
and conformational transmission, 351
and dammaradienol, 931
and *Johnson polyene cyclization*, 932
and rate of reaction, 351
and remote dehydrogenation, 1441
and *Robinson annulation*, 1150
and the *Barton reaction*, 1427
and the *Stork-Eschenmoser hypothesis*, 932
biosynthesis, 931
photochemistry, 1394
radical halogenation, 824
Stetter reaction, 971
Stetter reaction, 1123
Steven's rearrangement, 798, 799, 1371, 1414
and CIDNP, 1372
and concerted mechanisms, 1372
and *Hofmann elimination*, 1373
and isotopic labeling, 1372
and ring expansion, 1372
and *Sommelet-Hauser rearrangement*, 798
and Sommelet-Hauser, 1373
and sulfur ylids, 1373
enantioselectivity, 1372
isotopic labeling, 1372
mechanism, 1372
migratory aptitudes, 1371
radical versus ion pairs, 1372
ring expansion of cyclic amines, 1371
stereochemistry of the migration group, 1372
suitable bases, 1371
ylid formation, 1372
Stieglitz rearrangement, 1367
with hydroxylamines, 1368
stilbenes, photochemical conversion to phenanthrenes, 1390
stilbines, triaryl, metal catalyzed coupling with alkynes, 777
Stille coupling, 682
and alkylboronic acids, 683
and allylic rearrangement, 683
and cine substitution, 682
and metal catalyzed carbonylation, 975
and microwave irradiation, 682, 683
and supercritical carbon dioxide, 682
and vinyl halides, 682
and vinyl silanes, 684
enantioselectivity, 684
formation of en-ynes, 684
in aqueous KOH, 682
intramolecular, 682
mechanism, 683
metal catalyzed, 682
regioselectivity, 682
stereoselectivity, 682
with alkynes, 682
with enols, 683, 684
Stille reaction, 524
STN, 1595
Stobbe condensation, 1154
mechanism, 1154
Stone-Wales rearrangement, 1391
stoppers, and rotaxanes, 120
Stork enamine reaction, 448, 550
and hydrolysis of iminium ions, 1078
and hydrolysis, 551
and N-alkylation, 550
enantioselectivity, 550, 552
intramolecular, 552
Stork-Eschenmoser hypothesis, 932
Story synthesis, 1319
strain energy see energy
strain energy, 193
and fused ring aromatic compounds, 48
and S_N2 intrinsic barriers, 392
annulenes, 73
strain, $A^{1,3}$, 182, 184
and adamantanes, 199
and addition to alkenes, 351
and annelation, 48
and azaadamantanone, 199
and base cleavage of ketones, 725
and bent benzene rings, 206
and benzocyclopropene, 201
and betweenanenes, 202
and bicyclic dienes, 203
and bond distance, 206
and *Bredt's rule*, 203
and carbanion stability, 225

strain, $A^{1,3}$ (*Continued*)
and carbocation formation, 350
and centrohexacyclines, 198
and conformation, 351
and crowded alkenes, 206
and cubane, 198, 207
and cyclic allenes, 203
and cycloalkanes, 199, 200
and cycloalkenes, 202
and cycloalkynes, 202
and cyclobutadienes, 69
and cyclobutane, 195
and cyclobutanes, 194
and cyclononyne, 202
and cyclooctyne, 202
and cyclopentyne, 202
and cyclopropene, 201
and dioxiranes, 194
and E2 reactions, 351
and electrophilic aromatic substitution, 586
and epoxides, 194
and formal steric enthalpy, 206
and fused ring aromatic compounds, 48
strain, and geared molecules, 205
and hexahelicene, 206
and homocubene, 207
and lactams, 199
and leaving groups, 432
and MO calculations, 194
and molecular mechanics, 190
and nonbonded atoms, 193
and nonbonded interactions, 193
and norbornene, 203
and paracyclophanes, 47
and PES, 200
and prismane, 198
and propellanes, 198
and radicals, 812
and reactivity of radicals, 817
and resonance, 46
and ring size, 200
and s character, 194
and S_N1 reactions of alkyl halides, 350
and S_N1 reactions, 424
and substituted aromatic compounds, 204
and tetrahedranes, 198
and the E2 reaction, 1258
and tricyclododecadiene, 207
and unsaturated rings, 200
and X-ray diffraction, 199
strain, B, and rate of ionization, 350
B, and solvolysis of alkyl halides, 350
B, S_N1 rate of reaction, 419
strain, *Baeyer*, 192, 193
bicyclic alkenes, 203
carbene addition and ring expansion, 1057
cyclopropane, 193
double bond, 206
due to unavoidable crowding, 204
I, and acyl addition, 351
I, and cyclic ketones, 351
I, and hydrate formation, 1076
I, and reactivity, 350
I, and solvolysis, 350, 424
in ethylene oxide, 193
in small rings, 193
intramolecular crowding, 206
strain, large angle, 199
large, strain, 201
medium rings, 201
Pitzer, 199
small angle, 201
small ring compounds, table, 196, 197
small rings, 201
small-angle, 192
steric, 192–207
steric, and bond angles, 192
steric, and NMR, 192
transannular, 199, 200
unavoidable, 183
strained compounds, and bond angle, 26
by [2+2]-cycloadditions, 1044
by the *Wurtz reaction*, 514
Strecker synthesis, 1182
and pressure, 1182
enantioselectivity, 1182
in aqueous media, 1182
radical, 1183
structural effects, and solvolysis, 419
structure, and acid-base strength, 334
and carbanions stability, 227
and concentration of *Grignard reagents*, 231
and halonium in formation, 864
and rate of H abstraction by radicals, 815
and reactivity, 347
Lewis see Lewis structures
of alkyl halides, effect on elimination, 1275
of alkyl halides, effect on rate of elimination, 1275
of *Grignard reagents*, 229, 230
of organolithium reagents, 231
of organometallic compounds, 228
of substrates, and S_NAr reactions, 741
strychnine, and resolution, 173
Stryker's reagent, and *Robinson annulation*, 1150
styrenes, via *Suzuki-Miyaura coupling*, 772
sublimation, and resolution, 158
substituent effects, and acidity, 334
and field effects, 421
and *Hammett $\sigma\rho$ relationships*, 422
and mechanism of the *Diels-Alder reaction*, 1030
and radicals, 816
and resonance effects, 421, 420
and the tetrahedral mechanism, 423
in enolate anion formation, 667
in the *Heck reaction*, 767
of alkyl halides, in E2 reactions, 1274
of electron donating groups, 422
of electron withdrawing groups, 422
of thiols with alkynes, 894
of β- and γ-substituents, 422
on rate of solvolysis, 398
S_N1 on vinylic carbon, 419
S_N2 reactions, 417, 418
with benzoic acid, 335
with electrocyclic ring opening, 1381
with halonium ions, 864
β-substituents, and substitution reactions, 422
γ-substituents, and substitution reactions, 422
substituents, and carbocations, 218
and radical stability, 238
cyclohexane, energy, 183
substitution reactions, and entropy of activation, 391
and pressure, 388
and solvent effects, 438
and supercritical carbon dioxide, 442
groups, table, 425
IUPAC mechanism, 432
IUPAC nomenclature, 368
leaving group ability, table, 436
leaving group effects, 432
secondary isotope effects, 424
β-substituent effects, 422
γ-substituent effects, 422
substitution, aliphatic, 373
electrophilic, 793
and alkylation, 373
and allylic substrates, 420
and benzylic substrates, 420
and borderline mechanisms, 388
and bromine, 652
and carbenes, 257
and E1 reactions, 1261
and solvolysis, 373
and steric strain, 417
and the SET mechanism, 419
and the *Sneen formulation*, 387
and β-branching, 417
substitution, aromatic compounds, halogenation, 603

substitution, aromatic, activating groups, 741
and aromaticity, 66
and hyperconjugation, 580
and metallocenes, 61
and tropolones, 60
annulenes, 73
Baker-Nathan order, 580
deactivating groups, 742
destabilizing groups, 579
meta directing, 579
of annulenes, 75
of azulene, 63
ortho-para directing, 578
stabilizing groups, 578
substitution, at acyl carbon, 420
at sulfur, inversion of configuration, 1248
at sulfur, isotopic labeling, 1249
at sulfur, mechanism, 1249
at sulfur, S_N2 mechanism, 1249
at vinyl carbon, and electron withdrawing groups, 414
at vinyl carbon, and UV, 414
at vinylic carbon, and stereochemistry, 414
bimolecular see substitution, S_N2
substitution, cine, 738, 751
and *Stille coupling*, 682
substitution, electrophilic aromatic, HSAB, 587
multiple substituents, 583
naphthalene, 584
resonance between groups, 587
scale of reactivity, 587
selectivity relationship, 588
activation hardness, 587
alternant hydrocarbons, 585
amination see amination
and arenium ions, 571
and bond length, 586
and diazonium ions, 597
and EPR, 586
and neighboring groups, 400
and phenonium ions, 401
and π-complexes, 573
and radicals, 590
and SET mechanism, 590
and strain, 586
and the *Hammett equation*, 588
and the *Mills -Nixon effect*, 586
substitution, electrophilic aromatic, anthracene, 584
azo compounds, 597
benzoylation, 588
bromination, 588
Brown $\sigma*$ values, 588
chlorination, 588
encounter complex, 589
Friedel-Crafts alkylation, 609
furan, 584
halogenation, metal catalyzed, 604
Hammett σ values, 588
heterocycles, 584
hydrogen exchange, 592
in fused rings, 584
ipso attack, 581, 587
ipso position, 582
isomer distributions, 586, 587
isopropylation, 588
leaving group ability, 591
leaving groups, 591
mercuration, 588
naphthalenes, 584
nitration, 588, 594, 596
substitution, electrophilic aromatic, nitration also see nitration
nitronium in leaving groups, 591
substitution, electrophilic aromatic, nitronium ions, 582
orientation, 576
ortho effect, 583
ortho-para ratio, 580
partial rate factor, 586
phenanthrene, 584
pyridine or pyrrole, 584
rate, 581, 586
reactivity of substrates, 587
relative rate ratios, 588
Schiemann reaction, 608
selectivity relationship, 588
steric effects, 587
sulfonation see sulfonation
sulfones or sulfoxides, 602
sulfur electrophiles, 600
thiophene, 584
substitution, electrophilic, 262, 263, 793
addition-elimination mechanism, 658
and allylic carbanions, 657
and bridgehead carbons, 651
and double bond shifts, 657
and organometallics, 652
and solvent polarity, 653
and stereochemistry, 652
cyclic mechanisms, 658
electron donor-acceptor complexes, 653
rate, and salt effects, 653
solvent effects, 660
substrate effects, 658
unimolecular see substitution, S_E1
substitution, first order reactions, 380, 381
substitution, free radical, 262
substitution, nucleophilic aromatic, and *Chapman rearrangement*, 1429
and leaving group order, 744, 745
and leaving groups, 744, 745
and *Meisenheimer salts*, 733
and nucleophiles, 745
and radical cations, 749
and S_N1, 735
and $S_{ON}2$ reactions, 749
and sonochemistry, 309
arynes, and substrate structure, 743
benzyne mechanism, 737–739
cine substitution, 738
intermediates, 733, 734
mechanism, 732–734
nucleophile reactivity order, 745
one-stage versus two-stage, 740
other mechanism, 740
rate, 733, 734
S_NAr, 732–735
substrate structure, 741
substitution, nucleophilic internal see substitution, S_Ni
substitution, nucleophilic, 262
and alkynyl carbon, 419
and aryl substrates, 419
and leaving groups, 419
and phase transfer catalysis, 444
and vinylic carbon, 413, 419
at sulfonyl sulfur, 1248
at vinyl carbon, and the element effect, 414
intramolecular, 801
with allylic substitution, 409
substitution, polar nucleophilic aromatic, 741
substitution, radical, mechanism, 808
substitution, reactions, and HSAB, 448
substitution, S_E1, 576
and organometallics, 659
and pyramidal carbanions, 654
and resonance, 654
and vinylic carbons, 656
first order kinetics, 654
leaving group effects, 659
mechanism, 653, 654
solvent effects, 660
substrate effects, 658
substitution, S_E2', 650, 657
substitution, S_E2, and stereochemistry, 650, 652, 653
mechanism, 650
solvent effects, 660
substrate effects, 658
substitution, S_Ei', 657
substitution, S_Ei, and stereochemistry, 651, 653
mechanism, 650
solvent effects, 660
substitution, $S_{N'}$, 411
substitution, S_N1', 410
substitution, S_N1 also see S_N1

substitution, S_N1 mechanism with alkyl halides, 349
alkyl halides in sulfur dioxide, 382
and alcohol dehydration, 463
and allylic substrates, 420
and ambident substrates, 450
and aryldiazonium salts, 735
and aryliodonium salts, 736
and the *Baker-Nathan order*, 423
and bicyclic compounds, 382
and bridgehead carbons, 382
and carbocations, 379, 382
and conjugating substituents, 382
and contact ion pairs, 384
and cubyl compounds, 382
and diazonium salts, 434
and electrophilic addition, 860
and electrophilicity, 379
and equilibria, 383
and I strain, 350
and internal return, 384
and intimate ion pairs, 384
and ion pair mechanism, 387
and ion pairs, 384, 410
and ionic strength, 381
and ionization, 379
and leaving groups, 380
and limiting S_N1, 380
and lithium perchlorate, 438
and mixed S_N2, 387
and MO calculations, 424
and norbornyl compounds, 382
and nucleophiles, 427
and partial retention, 386
and pseudo first-order, 381
and racemization, 383
and rate of reaction, 380, 381, 419
and rearrangement, 1325
and salt effects, 438
and S_N2, 381
and solvent polarity, 436
and solvents, 380
and special salt effects, 385
and stereochemistry, 386
and strain, 424
and substituent effects, 419, 420, 422
and tight ion pairs, 384
substitution, S_N1, aromatic compounds, and isotope labeling, 736
aromatic, 736
substitution, S_N1, at vinyl carbon, 415
alkynyl groups, 415
allene groups, 415
cyclopropyl groups, 415
substituent effects, 419
vinyl groups, 415
at vinylic carbon, 419
substitution, S_N1, carboxylate salt alkylation, 468
formation of nitrite esters, 496
mechanism, 379
mechanism, and ion pairs, 383
nucleophilic aromatic, 735
primary halides and metal ions, 439
rate of reaction, and B strain, 419
reactivity of groups, 424
stereochemistry at vinylic carbon, 415
transition states, 437
trichloroamine with alkenes, 492
with allylic rearrangement, 409
substitution, S_N1', IUPAC nomenclature, 410, 411
kinetics and leaving groups, 380
substitution, S_N2 (intermediate), 388
substitution, S_N2 see S_N2
substitution, S_N2, ab initio study, 377
alkylation of carboxylate salts, 468
ambident substrates, 450
substitution, S_N2, and active methylene compounds, 542
and alcohol dehydration, 463
and anchimeric assistance, 391
and aziridine formation, 560
and backside attack, 374
and the *Baker-Nathan order*, 423
and bicyclic compounds, 424
and bridgehead carbons, 376, 424
and Brønsted plot, 379
and carboxylic esters, 437
and crossover experiments, 377
and diol formation, 994
and epoxides with organometallics, 535
and free energy, 379
and *Friedel-Crafts alkylation*, 614
and high pressure mass spectrometry, 376
and hybridization, 374
and inversion, 376
and ion pair mechanism, 387
and ion-dipole complexes, 377
and isotope effects, 288
and *Marcus theory*, 274
and mixed S_N1, 387
and neighboring groups, 391
and neopentyl systems, 419, 651
and nucleophiles, 427
and nucleophilicity order, 429
and propellanes, 424
and racemization, 377
and rate of reaction, 375, 417, 418, 420
and retention, 376
and solvent effects, 377
and stereogenic atoms, 141
and substituent effects, 417, 418
and sulfonyl halides, 473
and the *Finkelstein reaction*, 498
and the *Hammond postulate*, 272
and the *Mentshutkin reaction*, 377
and the *Williamson reaction*, 459
and transition state geometry, 420
and *Walden inversion*, 375
substitution, S_N2, chlorination of malic acid, 375
formation of alkyl halides, 498
gas phase, 376
intramolecular, 377
mechanism, 374–379
protic versus aprotic solvents, 437
pseudo first-order kinetics, 375
rate of reaction, 417, 418
reactivity of groups, 424
solvation rule, 437
solvent effects, 437
solvolysis of benzylic halides, 423
synthetic reactions, table, 425, 426
tight transition state, 421
transition state, 377, 418, 437
transition state, and neopentyl systems, 651
versus S_N2', 410
substitution, S_N2' also see S_N2'
substitution, S_N2', 410, 411
and concerted reactions, 411
and cyclopropylcarbinyl halides, 413
and organocuprates, 412
formation of cyclic amines, 483
stereochemistry, 411
with organocuprates, 537
with vinyl epoxides, 537
substitution, S_NAr also see S_NAr
substitution, S_NAr, activating ability of attached groups, 741, 742
and ion-radical pairs, 735
and *Meisenheimer salts*, 733
and solvent effects, 734
and π-complexes, 735
dimer mechanism, 735
effect of substrate structure, 741
Hammett relationships, 743
mechanism, 732–735
partitioning effects, 734
rate of reactions, 742

substitution, S_Ni also see S_Ni
substitution, S_Ni, and retention of configuration, 409
IUPAC nomenclature, 408
mechanism, 408
substitution, S_Ni', 411
and ion pairs, 412
substitution, $S_{RN}1$ also see, $S_{RN}1$
substitution, $S_{RN}1$, and aryl halides, 739, 740
and arylation of enolate anions, 778
and nucleophilicity, 745
and potassium metal, 740
and radical anions, 740
and sonochemistry, 309
and ultrasound, 740
and vinylic halides, 417
mechanism, 739, 740
mechanism, and radicals, 739, 740
mechanism, radical chain, 740
solvent effects, 740
substitution, versus elimination, 1261, 1274, 1275
and base strength, 1276
and leaving groups, 1276
charge dispersal, 1277
solvent effects, 1277
substitution, vicarious nucleophilic substitution of hydrogen, 786
vicarious, and amination of heterocycles, 787
substrates, ambident, allylic compounds, 450
and cyclic sulfates, 451
and S_N1 reactions, 450
aziridines, 450
definition, 450
epoxides, 450
S_N2 reactions, 450
substrates, and electrophilic substitution, 658
definition, 261
for the *Mukaiyama aldol reaction*, 1152
Michael type, 866
succinates, and the Stobbe condensation, 1154
succinimide, from NBS, 827, 828
succinimidyl radical, 829
sugars, aldehyde form, 94
and tautomerism, 94
suitanes, 121
sulfamate esters see esters
sulfamates, and ortho metalation, 785
Suzuki-Miyaura, 771
sulfanilic acids, and diazonium salts, 789
sulfates, alkyl, formation of ethers, 462
with alkoxides, 462
with halides ions, 500
sulfates, and formation of aldehydes, 886
cyclic, and ambident sulfates, 451
cyclic, from diols, 451
sulfenates, formation of, 681
sulfene intermediates, 1249, 1299
sulfenes, by base induced elimination of sulfonyl halides, 1299
from sulfonyl halides, 1178, 1299
from sulfonyl halides, and amines, 1249
with diazo compounds, 1178
sulfenic acids, and Smiles rearrangement, 801
sulfenylation, carboxylic esters, 681
of ketones, 681
of lactams, 681
of lactones, 681
of silyl enol ethers, 681
sulfhydride, sodium, with alkyl halides, 475
sulfides also see thioethers
sulfides, and the *Zinin reduction*, 1524
dimethyl, and borane, 702
dimethyl, as a leaving group, 1481
from disulfides, 703
halo, and the *Ramberg-Bäcklund reaction*, 1303
halo, *Pummerer rearrangement* of sulfoxides, 1565
halo, *Ramberg-Bäcklund reaction*, 1303
norbornyl, 1334
oxidation with mcpba, 1303
propargyl, 1115
reagents for oxidation of, 1494
vinyl from alkynes, 895
vinyl, alkylation, 554
vinyl, from alkynes, 894
vinyl, with epoxides, 554
sulfilimines, vinyl in *Diels-Alder reactions*, 1039
sulfimides, diaryl, and formation of aziridines, 1010
sulfinate esters see esters
sulfinic acid salts, with aryl halides, 603
sulfiny lamines, allylic, 1136
sulfinyl halides see halides
sulfinyl imines, 1096
chiral, 1134
sulfite, sodium, reduction of diazonium salts, mechanism, 1530
sulfolane, and the *Baylis-Hillman reaction*, 1127
and the *Diels-Alder reaction*, 1028
as a solvent, 1127, 1534
sulfolene, thermolysis, 1028
sulfonamides, alkylated, from imines, 1136
alkylation of, 495
and the *Hinsberg test*, 1251
arylation of, Pd catalyst, 493
as catalysts, 1152
by reduction of sulfonyl azides, 1530
dealkylation, 1554
from sulfinylimines, 1136
from sulfonamides, 1215
from sulfonyl halides and ammonia or amines, 1251
homoallylic, 1135
hydrolysis, 1250
hydroxy, by *Knoevenagel reaction*, 1159
metal catalyzed arylation, 493
reduction to amines, 1547
reductive cleavage, 1554
with alcohols, 1250
with aldehydes, 1100
with alkenes, 900
with alkyl halides, 495
with amines, 1222
with anhydrides, 1215
with carboxylic acids, 1218
with hypervalent iodine, 1554
sulfonate esters, and solvolysis, 389
and *Sonogashira coupling*, 778
aryl, coupling, 761
aryl, metal catalyzed coupling to aryl triflates, 770
aryl, reduction, 1536
aryl, with trifluoroborates, 890
as leaving groups, 432, 433
coupling with *Grignard reagents*, 513
coupling with trialkylfluoroborates, 560
cyanation, 759
cyclic, from allylic sulfonate salts, 893
decomposition to alkenes, 1289
DMSO oxidation, 1481
with azide ion, 496
sulfonate esters, from alcohol, and reduction, 1535
from alcohols, 473
from alkyl halides, 474
from aryl sulfones, 801
from ethers, 474
from *Smiles rearrangement*, 801
from sulfonamides and alcohols, 1250
from sulfonic acids, 474
from sulfonyl halides, 473

sulfonate esters, from alcohol, and reduction (*Continued*)
from sulfonyl halides, and alcohols, 1250
sulfonate esters, keto, 1475
mechanism of formation, 473
metal catalyzed coupling, 526
metal with organometallics, 530
migration, 1356
of phenols, and reduction, 1536
rate of ionization, solvent effects, 438
reagents for preparation, 473
reduction to methyl compounds, reagents for, 1537
reduction, 1537
silyl, 688
solvolysis, 385, 395, 396, 408, 421
sulfonate esters, with amide bases, 493
with *Grignard reagents*, 1248
with halide ions, 500
with organocuprates, 521
sulfonate esters, vinyl, and *Stille coupling*, 682
and the *Suzuki-Miyaura reaction*, 771, 772
by sulfonic acid addition to alkynes, 893
formation of dienes, 682
from alkynes, 894
with organometallics, 709
sulfonate salts, alkali fusion, 747
sulfonation, and sulfur trioxide, 601
and sulfuric acid, 601
and the *Jacobsen reaction*, 646
sulfonation, aromatic, and arylboronic acids, 603
and temperature, 601
in ionic liquids, 601
microwave irradiation, 603
sulfonation, of aromatic compounds, 600
mechanism, 601
sulfonation, of ketones, 680
sulfones, alkylation, 554
allylic, with nucleophiles, 530
allylic vinyl, and *thio-Claisen rearrangement*, 1411
and lack of chirality, 127
and resonance, 49
and ylids, 49
antarafacial elimination of sulfur dioxide, 1303
sulfones, aryl, and ionic liquids, 602
and the *Smiles rearrangement*, 801
by *Friedel-Crafts acylation*, 602
from aromatic compounds, 602
from sulfonyl halides, 602
sulfones, by oxidation of sulfoxides, 1493
by oxidation of thioethers, 1493
by reduction of sulfoxides, reagents, 1553
sulfones, coupling with organolithium reagents, 531
cyclic, cheletropic reactions, 1303
cyclic, with organolithium reagents, 1319
desulfurization, reagents, 1551
dimethyl, solvent, 757
extrusion of sulfur dioxide, 1318
sulfones, from alkyl halides, 480
from aryl halides, 750
from *Grignard reagents* and sulfonyl halides, 1252
from organometallics and sulfonyl halides, 1252
from sulfonate esters, 1248
from sulfonic acid salts, 480
from sulfonyl chlorides and alkynes, 988
from sulfonyl halides, 480
from sulfonyl halides, and boronic acids, 1252
sulfones, halo with ketones, 1177
and *Ramberg-Bäcklund reaction*, 1302
base induced elimination to dienes, 1302
based induced elimination to alkenes, 1302
with alkoxide bases, 1177
sulfones, pyrolysis to alkenes, 1295
sulfones, reduction, 540
to thioethers, 1552
substitution via elimination-addition, 416
suprafacial elimination of sulfur dioxide, 1303
tetraions, 1302
sulfones, vinyl, 866, 1163
sulfones, with *Grignard reagents*, 762
with ketones, 1159
with malonate esters, 779
sulfonic acid anhydrides, 1211
sulfonic acid salts, alkylation, 480
with aryl halides, 750
sulfonic acid, esters, with organometallics, 703
sulfonic acids, addition to alkenes or alkynes, 893
alkyl, with thionyl chloride to give an acyl l chloride, 856
sulfonic acids, aryl, alkali fusion, 747
and sulfuric acid, 645
and the *Jacobsen reaction*, 645
metal catalyzed reaction with arylboronic acids, 770
thermolysis, 646
with polyphosphoric acid, 602
with *Raney nickel*, 646
sulfonic acids, by hydrolysis of sulfonamides, 1250
by hydrolysis of sulfonate esters, 1250
by hydrolysis of sulfonyl halides, 1250
by oxidation of hydrocarbons, 1476
by oxidation of methylene compounds, 1476
by oxidation of thiols, 1493
by reduction of sulfonyl halides, 1252
sulfonic acids, desulfonation, 646
esters, hydrolysis, 454
reduction to thiols, 1552
sulfonic acids, with acyl halides, 1211
with alkynes, 894
with ethers, 474
with halogenating agents, 1251
with $SOCl_2$ or PCl_3, 1251
with thionyl chloride, 856
sulfonium salts, and *Hofmann's rule*, 1271
and *Swern oxidation*, 1447
from thioethers, 478
with nucleophiles, 1012
sulfonyl acids, by hydrolysis of sulfonic acid derivatives, 1249, 1250
sulfonyl azides, with active methylene compounds, 678
sulfonyl esters, hydrolysis, 1250
O-sulfonylamines, elimination to nitrenes, 258
sulfonyl fluoride, 603
sulfonyl groups, as leaving groups, 1249
stabilization of carbanions, 225
sulfonyl halides, and aromatic substitution, 602
sulfonyl oxaziridines, α-hydroxylation of enolate anions, 1474
sulfonyl sulfur, nucleophilic substitution, 1248
order of nucleophilicity, 1249
sulfonyl-amino-alkenes, with NBS, 987
sulfonylhydrazides, acyl, and *McFadden-Stevens reduction*, 1519
acyl, base cleavage to aldehydes, 1519
sulfonyloxaziridines, and oxidation of thioethers, 1494

sulfoxides, allylic, and [2,3]-*Wittig rearrangement*, 1414
and 1,4-elimination, 1296
sulfoxides, and atropisomers, 131
and chirality, 129
and conformation, 189
and NCS, 674
and radical elimination, 1296
and resonance, 49
and tetrahedral intermediates, 129
and Umpolung, 553
and ylids, 49
sulfoxides, aryl, from aromatic compounds, 602
by oxidation of sulfides, 1303
by oxidation of thioethers, 1493
by oxidation of thioethers, enantioselectivity, 1494
catalytic hydrogenation, 851
conjugated with organocuprates, 950
conversion to aldehydes, 553
desulfurization, reagents, 1551
elimination, *Hofmann's rule* and *Zaitsev's rule*, 1296
elimination, mechanism, 1296
from organometallics, 703
from sulfonic acid esters, 703
sulfoxides, halogenation, 674
halogenation, reagents for, 674
inversion, 129
keto, 1296
oxidation with hydroperoxide, mechanism, 1495
pyrolysis to alkenes, 1295
reagents for oxidation, 1494
rearrangement to acetoxy sulfides, 1565
sulfoxides, reduction, 540
and isotope labeling, 1553
to sulfones, reagents, 1553
to thioethers, reagents, 1552
sulfoxides, resolution of, 1494
thermal elimination, mechanism, 1296
treatment with anhydrides, 1565
with aromatic compounds, 632
with aryl halides, 890
with DAST, 674
with NBS, 674
sulfoxonium compounds, pyrolysis to alkenes, 1295
sulfur compounds, and optical activity, 129
sulfur dichloride, and chlorosulfenation, 837
sulfur dioxide, and superacids, 210
and the *Reed reaction*, 837
as a guest, 114
as a leaving group, 1302, 1303, 1318
as solvent, 382
liquid, 428
with alkenes and halogen, 837
with organometallics, 703
with silyl enol ethers, 1251
sulfur electrophiles, 600, 680, 703
sulfur groups, and radical cyclization, 963
sulfur hexafluoride, and electronic structure, 15
sulfur monochloride, with alkynes, 1006
sulfur nucleophiles, 475, 1087
sulfur reagents, chiral, 1494
sulfur tetrafluoride, with aldehydes or ketones, 1106
sulfur trioxide, and DMSO, for oxidation of alcohols, 1448
and sulfonation, 601
as an electrophile, 601, 602
sulfonation of carbonyl compounds, 681
sulfonation of ketones, 680
with aromatic compounds, 601
with trihalides to give acyl halides, 453
sulfur ylids see ylids
sulfur ylids, 50, 799
in ionic liquids, 1179
phase transfer conditions, 1176
sulfur-35, 1553
sulfur,
and aromatization, 1438
and carbanions stabilization, 228
and carbonylation of amines, 730
and hydrogen bonds, 101
as a poison in catalytic hydrogenation, 903
chiral, 541
inversion, of configuration, 129, 1248
reactivity with nucleophiles, 1249
stabilization of carbanions, 225
stabilization of organolithium reagents, 232
substitution, isotopic labeling, 1248, 1249
substitution, kinetics, 1249
substitution, S_N2 mechanism, 1249
sulfonyl see sulfonyl sulfur
with diazo compounds, 1178
with diazonium salts, 1178
with *Grignard reagents*, 703
with organometallics, 703
with phosphoranes, 838
sulfuric acid, and arylsulfonic acids, 645
and dehydration of alcohols, 1283
and esterification, 1204
and nitration of aromatic compounds, 595
and sulfonation, 601
and the *Jacobsen reaction*, 645
and ylids, 49
catalyst for the *Schmidt reaction*, 1363
electronic structure, 15
for cleavage of ethers, 454
fuming, with aromatic compounds, 600
with aromatic compounds, 600
with diols, 1343
sulfurization, organolithium reagents, 703
reagents for, 1089
sulfuryl chloride, 823
halogenation of aromatic compounds, 605
radical halogenation, 823
with *Grignard reagents*, 703
with peroxides, 817
sultones, from alkenes and sulfonate halides, 893
super hydride, 1502
reduction of alkyl halides, 1531
superacids see acids
superacids, 214, 319, 660
and benzenonium ions, 573
and carbocation structure, 1390
and carbocations, 379, 407, 1332
and cleavage of alkanes, 725
and coupling of alkenes, 690
and diazonium salts, 434
and halogenation of aromatic compounds, 605
and hydration of alkynes, 887
and hydrogen exchange, 661
and ionization, 382
and isomerization of biphenyls, 646
and nonclassical carbocations, 403, 1340
and the *Gatterman reaction*, 627
formation of carbocations, 661
with alkenes, 690
superaromatic, 78
superbases, 322, 695
and transesterification, 1207
supercritical, alcohol, reduction of ketones, 1542
ammonia, 364
supercritical, carbon dioxide also see carbon dioxide
supercritical, carbon dioxide, and oxidation of alcohols, 1442
and the *Heck reaction*, 766
aryl halides with amines, 751
carbonylation of aryl halides, 781
ethane, hydrogenation of aromatic compounds, 913

supercritical, carbon dioxide, and oxidation of alcohols (*Continued*)
for alkene isomerization and the *Heck reaction*, 766
for enzymatic carboxylation, 630
for enzymatic reductions, 1510
in the *Kolbe-Schmidt reaction*, 629
2-propanol, and reduction, 1508
water, and pinacol rearrangement, 1342
water, and the *Beckmann rearrangement*, 1366
superelectrophilicity, 379
superheating, and microwaves, 310
superimposability, and chirality, 122, 126
and enantiomers, 136
and optical activity, 122
superoxide, potassium, with alkyl halides, 472
superoxides, with alkyl halides or sulfonate esters, 473
superphane, 82
supersonic molecular jet spectroscopy, and conformations, 174
supplementary information, journals, 1571
supplements, of Beilstein, 1579
suprafacial concerted cycloaddition, 1064
suprafacial migration, 1392, 1394
in sigmatropic rearrangement, 1392, 1393
suprafacial overlap, 1035
suprafacial rearrangements, configuration of migrating groups, 1396, 1397
supramolecular forms, 121
surface sites, heterogeneous catalysts, 907, 908
surfactants, cleavage of ethers, 504
surrogates, amino acid, 548
Survey of Organic Synthesis, 1591
Suzuki coupling see *Suzuki-Miyaura*
Suzuki coupling, 560
Suzuki reaction, 795, 889
and microwave irradiation, 311
Suzuki-Miyaura coupling, 701, 770
additives, 770
alternative metal catalysts, 773
alternative reagents, 773
Suzuki-Miyaura coupling, and acyl halides, 774
and aryl boronic acids, 774
and aryl sulfonate esters, 770
and aryl triflates, 770
and arylation of silanes, 783
and arylborates, 774
and diazonium salts, 788
and electrospray mass spectrometry, 773
and ionic liquids, 771
and microwave irradiation, 771, 775
and trifluoroborates, 775
Suzuki-Miyaura coupling, base free, 774
biaryls, atropisomers, 773
catalysts for deactivated halides, 771
chiral catalysts, 773
compatible functional groups, 772
double coupling, 772
enantioselectivity, and biaryls, 773
in aqueous media, 771
in supercritical carbon dioxide, 771
ligand free, 771
mechanism, 773
on alumina, 771
oxidative addition, 773
Pd free cross coupling, 771
polymer supported, 771
polymer-tethered reagents, 771
reaction conditions, 770
recyclable catalysts, 771
solvent effects, 770
solvent free, 771
structural variations, 772
Suzuki-Miyaura coupling, with aryldiazonium salts, 793
with carbamates, 771
with carbonates, 771
with heterocycles, 771, 772
with sulfamates, 771
with vinyl substrates, 771
Swain-Lupton σ values, 359
Swain-Scott equation, 429
and *Marcus theory*, 429
Swern oxidation, 1482
and dehydration of amides to nitriles, 1313
and dehydration of amides, 1313
and polymer bound sulfoxide, 1447
and sulfonium salts, 1447
and sulfur substituents, 1448
of alcohols, 1447
temperature dependence, 1447
switches, molecular, 118
SYBYL, 191
sydnones, and aromaticity, 82
symmetry and chirality, 135
and aromaticity, 66
and atropisomers, 131
and biaryls, 131
and chiral compounds, 123
and chirality, 126
and circularly polarized light, 145
and dipole moment, 19
and electronegativity, 16
and enantiomers, 123
and hydrogen bonds, 99
and monocyclic compounds, 167
and orbitals, 5
and stereogenic atoms, 126
axis, and chirality, 125
of orbitals in dienes, 1381–1386
orbital see orbital symmetry
perpendicular dissymmetric planes, 130
plane, and chirality, 125
plane, and enantiomers, 125
symmetry-forbidden transitions, 292
symproportionation, addition of alkanes to alkenes, 927
syn addition, 860
bromine to alkenes, 864
dihydroxylation of alkenes, 992
of carbenes, 1055
syn elimination also see elimination, E^i
syn elimination see elimination, syn
syn nomenclature, 149
syn stereochemistry, in catalytic hydrogenation, 906
syn-anti dichotomy, and E2 reactions, 1258
synclinal conformation, 176, 177
synperiplanar conformation, 177
synthesis, and carbene insertion, 693
and carbenes, 255
and chiral pool, 149
and crown ethers, 109
and dediazoniation, 1550
and diastereoselectivity, 150
and microwave irradiation, 311
and reduction of aryldiazonium salts, 1550
and resolution, 149
and *Robinson annulation*, 1150
and sulfonate ester leaving groups, 433
and supercritical carbon dioxide, 364
and the *Diels-Alder reaction*, 1027
and the tetrahedral mechanism, 1074
and the *Wittig reaction*, 1172
synthesis, asymmetric, 143, 149–154
and active catalysts, 153
and active reagents, 152
and active solvents, 153
and active substrates, 150
and asymmetric induction, 153

and chiral auxiliaries, 151, 152
and *Cram's rule*, 150
and reduction of carbonyls, 152
and self-immolative reagents, 152
and the aldol condensation, 154
and the *Cornforth model*, 151
and the *Felkin-Anh model*, 151
and UV analysis, 151
chiral from achiral compounds, 151
double asymmetric synthesis, 153
with circularly polarized light, 154
with enantioselective reactions, 153
synthesis, azapagodanes, 198
by functional group type, 1605–1629
catenanes, 119
double asymmetric, 924, 1148
enantioselective, with hydroboration, 924
Merrifield, 1218
of pyrophosphate, 112
rotaxanes, 119
stereoisomeric catenanes, 120
synthesis, stereoselective, 150, 173
and active catalysts, 153
and active reagents, 152
and active solvents, 153
and active substrates, 150
and chiral auxiliaries, 151, 152
and chiral circularly polarized light, 154
and *Cram's rule*, 150
and self-immolative reagents, 152
and the aldol condensation, 154
and the *Cornforth model*, 151
and the *Felkin-Anh model*, 151
and UV analysis, 151
asymmetric induction, 153
double asymmetric synthesis, 153
enantioselective reactions, 153
reduction of carbonyls, 152
synthesis, stereospecific, 173
with alkene metathesis, 1421
with the *Brook rearrangement*, 1432
synthetic importance, alkene metathesis, 1419
Synthetic Methods of Organic Chemistry, 1585
synthetic targets, and the *Diels-Alder reaction*, 1027
synthon, definition, 553
4n systems, and electrocyclic rearrangements, 1388
conrotatory versus disrotatory, 1388
4n+2 systems, and electrocyclic rearrangements, 1388
conrotatory versus disrotatory, 1388

table, electronegativity, 17
Tables of Experimental Dipole Moments, 1582
Tables of Interatomic Distances and Configurations in Molecules and Ions, 1582
tables, of physical data, 1581–1583
Taft equation, 356, 360
Tamao-Fleming oxidation, 468, 929
tandem metathesis, 1420
tandem vicinal difunctionalization, 951
and organocuprates, 951
tartaric acid, and enantiomers, 124
diastereomers, 147
mechanism resolution, 157
tartrates, diethyl, and *Sharpless asymmetric epoxidation*, 1004
tartrates, epoxidation, 1004, 1005
sodium ammonium, 157
tautomeric forms, of bullvalene, 1405
tautomerism, 89
aci form of nitro compounds, 94
and bromination of acetone, 285
and carboxylic acids, 95
and deuterium isotope effects, 666
and enamines, 94
and hydrogen bonding, 90
and hydroxypyridine, 93
and imines, 94
and mass spectrometry, 89
and microscopic reversibility, 666
and nitrosomethane, 93
and oximes, 93
and pH, 89
and pyridones, 93
and quinazolines, 94
and spirooxathianes, 94
and sugars, 94
and the *Bucherer reaction*, 756
and the *Michael reaction*, 95
tautomerism, benzoxazine, 94
decahydroquianazolines, 94
enamine-imine, 898
enol-keto, 866
imine-enamine, 94, 1180
tautomerism, keto-enol, 89, 664, 887
amides, 91
and bond energy, 91
and conformation, 665
and conjugation, 91
and enol content, 91
and fluorine, 91
and NMR, 91
and solvent effects, 92
and steric hindrance, 91
and torsion strain, 666
fusion type enols, 91
mechanism, 90, 666
proton transfer, 665
solvent effects, 665
steric stabilization, 666
tautomerism, nitro compounds, 94
nitroso-oxime, 93
of enols, 664
oxocarboxylic acids, 94
phenol-keto, 93
phenol-quinone, 1408
porphycenes, 94
porphyrins, 94
proton-shift, 92, 95
ring-chain, 94
theoretical calculations, 92
tautomerism, valence, and *Cope rearrangement*, 1404
cycloheptatrienes-norcaradiene, 1406
oxepin-benzene oxide, 1406
tri-*tert*-butylcyclobutene, 1406
tautomerization, allene-alcohols, 412
amide-enol, 1239
and rate determining state, 285
tautomers, and *Cope rearrangements*, 1405
and hyperconjugation, 88
and mesomeric ions, 666
and *Michael reactions*, 867
oxime-imine, 1427
TBAF, with aziridines, 538
with silanes, 783
Tebbe's reagent, 1173
and titanium methylene complex, 1173
with aldehydes or ketones, 1174
with lactones, 1174
Techniques of Chemistry, 1587
teflon, and microwave chemistry, 310
tellurides, from alkyl halides, 478
tellurium salts, with hexamethyldisilazide, 1177
tellurium ylids, 1169, 1177
tellurium, with *Grignard reagents*, 703
telomers, 867
temperature dependence, reversal of *Friedel-Crafts alkylation*, 641
temperature effects, and amination of alkenes, 896

temperature, and enantiomers, 125
and enolate anion formation, 1144
and enthalpy or entropy, 265
and hyperconjugation, 287
and isotope effects, 288
and mechanism, 284
and rate, 284
and specific rotation, 125
influence of elimination, 1278
TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl free radical)
and conversion of aldehydes to nitriles, 1096
and co-reagents used for oxidation of alcohols, 1448
and metal catalyzed oxidation of alcohols, 1448
and oxidation of aldehydes to acids, 1485
and radical cyclization, 965
metals utilized for oxidation of alcohols, 1448
oxidation in water, 1449
oxidation of alcohols in ionic liquids, 1448, 1449
polymer bound hypervalent iodine, 1449
stable radical, 240
termolecular addition, mechanism, 861
terpenes, and *Robinson annulation*, 1150
reduction of nitriles to methyl, 1531
terrace-type atoms, catalytic hydrogenation, 907
tervalent carbocations, 661
tervalent stereogenic atoms, 127
tetaalkylammonium halochromates, 1443
tethered *Diels-Alder reactions*, 1028
tethered reagents, to polymers, 771
tethers, in the *Diels-Alder reaction*, 1028
tetrabutylammonium fluoride (TBAF) see TBAF
tetracarbonylferrate, 648
and the *Tischenko reaction*, 1565
sodium see sodium
2,3,5,6-tetrachloro-1,4-benzoquinone see chloranil
tetraenes, and homoconjugation, 43
tetrafluoroborate salts, thermolysis, 704
tetrafluoroborates, vinyl, Rh catalyst, 958, 959
tetrahydropyridines, via aza-Wittig reaction, 1173
tetrahedral intermediates, 348
and base cleavage of ketones, 723
and I strain, 350
and reactivity, 348
and sulfoxides, 129
isotope labeling, 1072
tetrahedral mechanism see mechanism
tetrahedral mechanism, 1069, 1190, 1226, 1248
alcohols with acyl halides, 1200
and conformation, 1072
and isotope labeling, 1071, 1072
and leaving groups, 1073, 1074
evidence for, 1070–1072
hydrogen in catalysts, 1070
hydrolysis of carboxylic esters, 1192–1197
in acid solution, 1070
isolation of intermediates, 1071
IUPAC designation, 1070
reactivity of carbonyl substrates, 1074
spectral detection of intermediates, 1071
stereoelectronic control, 1073
synthesis transformations, 1074
tetrahedranes, 198, 1318
and strain, 198
tetrahydrofurans, by catalytic hydrogenation of furan, 913
conformation, 189
from alcohol-alkenes, 890
from allenes and alcohols, 890
from halogenation of homoallylic alcohols, 986
from oxetanes, 692
tetrahydroisoquinolines, preparation, 618
tetrahydropyrans, from alcohol alkenes, 890
tetrahydroquinolines, by cyclotrimerization, 1061
tetraions, 1302
tetrakis-triphenylphosphinopalladium(0), 41
tetramerization, of alkynes, 1059
tetramethylenediamine, as a solvent, 1294
tetramethylethylenediamine, and the *Glaser reaction*, 841
tetramethylpiperidine-1-oxy free radial see TEMPO
tetramethylsilane, 17
tetraphenylborate, with silyl dichloride, 784
tetrapropyl perruthenate see TPAP
tetrasulfides, 479
textbooks, of Organic Chemistry, 1589
thallation, mechanism, 786
thallium carboxylates, and dihydroxylation of alkenes, 995
thallium, aryl see arylthallium
The Alkaloids, 1587
The Chemistry of Functional Groups, 1588
*The Physico-chemical Constants of Binary Systems in Concentrated Solution*s, 1582
theory, *Marcus*, 273, 274
thermal [2+2]-cycloaddition, 1043
thermal cycloreversion, cyclobutenes, 1047
thermal effects, microwave chemistry, 310
thermal extrusion of nitrogen, 1316, 1317
thermal reactions, of alkenes, 1041
thermal stability, quaternary ammonium salts, 443
thermochemical data, and molecular mechanics, 192
thermochemistry, and frontier orbitals method, 1032
cyclotrimerization of alkynes, 1060
thermodynamic acidity see acidity
thermodynamic and kinetic control, arenium ions, 576
thermodynamic conditions, enolate condensation, 543
thermodynamic control, and ambident nucleophiles, 448
and sulfur ylids, 1176
thermodynamic reactions, free energy, 272
thermodynamic stability, and alkyne isomerization, 664
and rearrangement of alkenes, 661
and rearrangement of alkenes, 664
of alkenes, 664
thermodynamically controlled reactions, 272
thermolysis, alkenes and nitric acid, 676
of alkoxides, 722
of cyclobutenes, 1380
of esters to give alkenes, 1288
of metal alkoxides, 1285
of organoboranes, 1358
of tetrafluoroborate salts, 704
of trienes, 1380
thexylborane, 921
THF, see tetrahydrofuran
THF, and *Grignard reagents*, 231
as a solvent, 1550
complex with borane, with alkenes, 921
hydroxylation, 1476
thiacarbenium ions, 219

thiacrown ethers see ethers, thiacrown
thia-Fries rearrangement, 637
thiazoles, aldehydes synthesis, 557
thiazolines, aldehyde synthesis, 557
thiazolium salts, and conjugate addition, 969
  catalysts, 971, 1188
thiiranes, and ionic liquids, 478
  and leaving groups, 432
  divinyl, *Cope rearrangement*, 1402
  elimination to alkenes, 1288
  from alkenes, 1006
  from alkynes and sulfur monochloride, 1006
  from diazo compounds and sulfur, 1178
  from epoxides, 478, 1178
  from halo disulfides, 988
  from halo-thioethers, 988
  from thioketones and diazo compounds, 1178
  from thioketones, and carbenes, 1178
  halogenation of, 507
  reduction to alkenes, 1502
  trans-thiiration, 1006
  with amines, 490
thiiranium ions, with alkenes, 1012
thiiren dioxides, 1303
thio esters, by hydration of alkynes, 888
  from acyl halides and thiols, 1201
  from thioacids, 1211
thioacetalization, 1088
thioacetals, from acetals, 478
  hydrolysis, 457
thioacids, from carboxylic acids, 1211
  with alcohols, 1211
thioaldehydes also see thioketones
thioaldehydes, from aldehydes, 1088
  stability, 1087, 1088
thioalkyl ketones, from enolate anions, 680
thioalkylation, of aromatic compounds, 632
thioamides, and conformation, 179
  atropisomerism, 164
  by hydrolysis of nitriles, 1081
  catalytic hydrogenation, 851
  conversion to amides, 1087
  from amides, 1212
  from chlorothioformates and amines, 1251
  from isothiocyanates, 630, 1141
  from ketones, 1566
  from thioaldehydes and amines, 838
  torsional barrier, 180
  transamidation, 1212
  with organolithium reagents, 1230
thioanisole, with butyllithium, 554
thiobenzilic acid, with aldehydes or ketones, 1320
thiocarbamates, 731
  by hydrolysis of thiocyanates, 1081
  conjugate addition, 968
  from isothiocyanates, 1085
thiocarbonates, and the *Barton-McCombie reaction*, 1538
  reduction to hydrocarbons, 1538
  thiol surrogates, 894
  with alkenes, 894, 970
thiocarbonyl compounds, from *Lawesson's reagent*, 1089
thiocarbonyl ylids, [3+2]-cycloaddition, 1016
thiocarbonyls, and bonding, 11
thiocarbonyls, and E/Z nomenclature, 163
  reagents for preparation, 1088
thiocarboxylic acids, from thiols and triflic acids, 1206
thio-Claisen rearrangement, 1411
thiocyanate ion, and S-alkylation, 497
  with alkyl halides, 480
thiocyanates, alkenes with isothiocyanates, 988
  and the *Hoesch reaction*, 633
  and ultrasound, 480
  aryl, from aryl diazonium salts, 791
  by the *Katritzky pyrylium-pyridinium method*, 480
  from alkyl halides, 480
  from amines, 480
  from aryl halides, 750
  from thiocyanate ion, 480
  hydrolysis, 1081
thioesters with aldehydes, 1155
  conjugate addition, 968
  from carboxylic acids, and thiols, 1206
  from thiocyanates, 633
  hydrolysis, 1072
  hydrolysis, kinetics, 1072
  reductive desulfurization, 1552
  transesterification, 1207
  with boronic acids, 1231
  with organocuprates, 1231
  with organometallic reagents, 1231
thioether-esters, 1006
thioethers also see sulfides
thioethers, alkylation, 554
thioethers, allylic vinyl, and *thio-Claisen rearrangement*, 1411
  by [2,3]-*Wittig rearrangement*, 1413
  from allylic sulfur ylids, 1413
thioethers, and DBU, 476
  and phase transfer, 476
  and the *Williamson reaction*, 476
  by reduction of sulfones, 1552
  by *Stevens' rearrangement* of sulfur ylids, 1373
  cleavage, 853
  cyclic, from alkyl halides, 477, 478
  desulfurization, reagents, 1551
thioethers, from addition of thiols to alkenes, 893
  from alcohols, 477
  from alkyl halides, 475, 476
  from aromatic compounds, 632
  from aryldiazonium salts, 791
  from carbonates, 477
  from organometallics, 703
  from thiols, 475, 476
  from thiophenols, 750
  from thioureas, 477
thioethers, hydration of, 888
  lithio, and *Peterson alkenylation*, 1162
thioethers, oxidation, to sulfones or sulfoxides, 1493
  to sulfoxides, enantioselectivity, 1494
  with hydroperoxide, mechanism, 1495
  with sulfonyloxaziridines, 1494
  with TPAP, 1494
thioethers, poisons in catalytic hydrogenation, 903
  reagents for oxidation, 1493
  reduction of sulfoxides, reagents, 1552
  sodium sulfide and alkyl halides, 477
  vinyl, from thiols addition to alkynes, 894
  with alkyl halides, 478
  with lithium naphthalenide, 852
thioformamides, by reduction of isothiocyanates, 1522
tiohydroxamic esters, 854, 855
thioketals, hydrolysis, 457
thioketenes, cycloaddition with imines, 1244
  from ketones, 1088
  from ketones, and hydrogen sulfide, 1087
  from Lawesson's reagent, 1089
  high yield synthesis, 1088
  in *Diels-Alder reactions*, 1038
  stability, 1088
  stability, and trimerization, 1087
  trimerization, 1088
  with boranes, 1231
  with carbenes, 1178

thioketenes, cycloaddition with imines (*Continued*)
with diazo compounds, 1178
thiol acids, for acyl halides and hydrogen sulfide, 1211
thiol anions see mercaptides
thiol anions, as reducing agents, 1548
thiol esters, from acyl halides and thiols, 1211
from esters, 1211
thiolactams, conjugate addition of amines, 966
from isothiocyanates, 1245
from thioketenes, 1244
β-thiolactams, from thioketenes and imines, 1244
thiolate anions, conjugate addition, 968
thiolate anions, with aryl halides, 749
thiolate ions, demethylation, 477
thiols, addition, to aldehydes, 1087
to alkenes, 893
to alkenes, mechanism, 895
to alkynes, 894
to ketones, 1087
thiols, and the *Chugaev reaction*, 1289
anions, reaction with vinyl halides, 413
thiols, aryl see thiophenols
thiols, aryl, from aryl halides, 749
by addition of hydrogen sulfide to alkenes, 894
by reduction of sulfonyl halides, 1552
catalytic hydrogenation, 851
conjugate addition, 895, 967, 968
desulfurization, reagents, 1551
from alcohols, 476, 1289
thiols, from alkyl halides, 475
from disulfides, 1555
from hydrogen sulfide, 475
from isothiouronium salts, 476
from *Lawesson's reagent*, 476
from organocopper reagents, and dithiocarboxylic acids, 1132, 1133
from organometallics, 703
from silylthiols and alkenes, 894
from silyl-thiols, 476
from sodium sulfhydride, 475
from sulfonic acids, 1552
from thiourea, 476
halogenating agents, 503
internal cyclization, 478
metal mediated reaction with arylboronic acids, 750
thiols, oxidation, of disulfides, and microwaves, 1497
to disulfides, 1493
to disulfides, mechanism, 1497
to disulfides, reagents, 1497
to sulfonic acids, 1493
with chlorine and water, 1493
thiols, photochemical addition to alkenes, 895
poisons in catalytic hydrogenation, 903
reaction with alcohols, 477
reduction of disulfides, reagents, 1555
silyl, 894
solventless oxidation to disulfides, 1497
with acyl halides, 1201, 1211
with alkenes, 894, 1006
with alkyl halides, 476
with alkynes, 894
with alkynes, metal catalyzed, 895
with alkynes, photochemical, 894
with amines and alkenes, 1012
with carboxylic acids, 1206, 1211
with hydrogen peroxide, 1496
with ketenes, 895
with $LiAlH_4$, 1551
with norbornene, 1334
with phosphoric acid esters, 1211
with triflic acid, 1206
with vinyl ethers, 894
thionitrites, and conversion of anilines to aryl halides, 847
thiono esters, catalytic hydrogenation, 851
thionocarbonates, and the *Corey-Winter reaction*, 1301
cyclic, cleavage to alkenes, 1301
from diols and thiophosgene, 1301
thionoesters, reduction to ethers, 1543
thionolactones, formation of cyclic ethers, and organolithium reagents, 1133
thionyl chloride, 500
and dehydration of amides to nitriles, 1313
and the Sni mechanism, 409
formation of aryl sulfoxides, 602
with alcohols, 409
with alkylsulfinic acids, 856
with carboxylate anions, 1210
with carboxylic acids, 1224
with sulfinic acids, 1251
thiophenes,
and aromaticity, 57, 58
and *Friedel-Crafts acylation*, 623
and *Friedel-Crafts alkylation*, 611
arylation, 755
by metal catalyzed addition of thiols to alkenes, 895
desulfurization, 852, 1551
desulfurization, to alkenes, 852
electrophilic aromatic substitution, 584
halogenation, 607, 703
metal catalyzed coupling with aryl halides, 760
reduction, 1551
resonance energy, 58
thiophenols, formation of thioethers, 750
from aryldiazonium salts, 791
organolithium reagents, conjugate addition, 968
with alkenes, 894
thiophilic addition, 1067
thiophosgene, with amines, 1214
with diols, 1301
with DMAP and diols, 1302
thiosulfate ion, with alkyl halides, 479
thioureas, and alkenes, metal catalyzed formation of thiiranes, 1006
and E/Z isomerization of conjugated aldehydes, 882
and inclusion compounds, 114
chiral, 1103
formation of thioethers, 477
from isothiocyanates and amines, 1103
with alkyl halides, 476
thio-Wittig see *Wittig*
thorium oxide, and decarboxylation of carboxylic acids, 1238
and dehydration of alcohols, 1283
Thorpe condensation, 1142
Thorpe reaction, 1179
intramolecular, 1179
Thorpe-Ziegler reaction, 1179
threads, molecular, 118
three-center hydrogen bond, 99
threo nomenclature, 148
thujones, 815
Ti catalyst, acyl addition, 1120
and epoxidation, 1004
diamination of alkenes, 1008
imino esters with aldehydes, 541
Ti complex, and acyl addition, 1118
Ti compounds see organotitanium
Ti, low valent, 1556
$TiCl_3$ and $LiAlH_4$, coupling alcohols, 532
$TiCl_4$, rearrangement of epoxy alcohols, 1344
Tiffeneau-Demyanov ring expansion, 1346

tight ion pair, 384
tight ion pair, and *Friedel-Crafts alkylation*, 614
tiglic acids, 657
tin compounds see organotin
tin hydrides see hydrides
tin, see organotin
tin, acyl see acylation
tin, allylic, acyl addition, 1119
  compounds, acyl addition, in ionic liquids, 1118
  with aldehydes or ketones, 1118
  with transition metal catalysts, 1118
tin, propargylic, 1118
Tischenko reaction, 1564
  and aldol reaction, 1564
  and hydroformylation, 979
  catalysts, 1564
  crossed, 1564
Tischenko-aldol transfer reaction, 1565
titanium cyclopentadienide-dimethylaluminum complex see Tebbe's reagent
titanium mediated coupling of aldehydes or ketones, 1558
titanium pinacoloate, 1560
titanium tetrachloride chiral amides with aldehydes, 1120
titanium tetraisopropoxide, and Sharpless asymmetric epoxidation, 1004
titanium, coupling of dialdehydes, 1557
  low valent, 1306, 1559
titanocene dichloride, and reduction of esters, 1546
titanocene, dimethyl, 1174
TMEDA, and organolithium reagents, 231, 232, 1110
TMEDA-butyllithium, 784
tolanes also see alkynes
tolanes, by oxidative coupling of dihalotoluenes, 1495
Tollen's condensation, 1562
  and the *Cannizzaro reaction*, 1563
  and the *crossed Cannizzaro reaction*, 1563
Tollen's reaction, 1142, 1164
  and crossed *Cannizzaro reaction*, 1164
  and mixed aldol reaction, 1164
toluene, as a solvent, 714
  dipole moment, 18
  electrophilic aromatic substitution, 588
  reaction parameters, 589
tolylnapthalenes, and strain, 206
topological polarization, 65
topological stereoisomers, and catenanes, 119
tormented aromatic compounds, 48
torquoselectivity, 1381
torsion angle also see angle
torsion angle, and specific rotation, 125
  and keto-enol tautomerism, 666
  and molecular mechanics, 191
torsional barrier, of amides, 179
  of carbamates, 180
torsional diastereomers, 132
ToSMIC, amide formation, 495
tosyl aziridines, 990
tosylamines, conversion to alkyl halides, 509
  halo, 989
  with epoxides, 490
tosylates also see sulfonate esters
tosylates, acetyl, formation of carboxylic esters, 471
  alkyl, rate of S_N1, 420
  and solvolysis, 385
  decomposition to alkenes, 1289
  leaving groups, 432, 433
  reduction to methyl compounds, reagents for, 1537
  solvolysis, 395
tosylazides see azides
tosylazides, with active methylene compounds, 678
tosylaziridines, from epoxides, 490
  with alkenes, 1011
tosylcyanide, 563
tosylcyanide see cyanides
tosylhydrazine, formation of allenes, 664
tosylhydrazones see hydrazones
O-tosyl imines, and the *Neber rearrangement*, 1359
tosylimines see imines, tosyl
tosylisocyanides, Knoevenagel reaction, 1159
toxicity, of cyclodextrins, 117
TPAP (tetrapropyl perruthenate), oxidation of alcohols, 1446
  and oxidation of amines, 1483
  and oxidation of thioethers, 1494
  catalytic oxidations, 1446
  polymer-bound, 1446
  recovery of catalysts, 1446
  the *Ley reagent*, 1446
transacetalization, 1083
transamidation, 1212
  and the zip reaction, 1222
  and thioamides, 1212
transamination, 487
transannular hydride shift, 1428
transannular hydrogen atom shifts, 1336
transannular interactions, 200
transannular rearrangements, 1332
  and alkyl groups, 1333
transannular shifts, of hydrogen atoms, 1336
transannular strain, 199
transannular strain also see strain
trans-cis isomers, 167
transesterification, 1206
  and boiling point, 1206
  and enol esters, 1208
  and lipases, 1207
  and polymer bound siloxanes, 1207
  and superbases, 1207
  and vinyl acetate, 1207
  enzymatic, 1207
  in ionic liquids, 1207
  Lewis acid catalysts, 1207
  mechanism, 1207
  metal mediated, 1208
  of lactones, 1207
  regioselectivity, 1207
  thioesters, 1207
transetherification, 464
  and acetals, 465
  and enol ethers, 465
  and ortho esters, 465
  internal, 464
transfer hydrogenation, 910, 912, 1510, 1513
  and *Hantzch esters*, 917
  and organocatalysts, 917
transformation, IUPAC nomenclature, 368
transient grating spectroscopy, and carbenes, 254
transition energies, 441
transition metal catalysts, and *Friedel-Crafts acylation*, 622
  diazonium salts, 788
transition metal complexes, 786
transition metals, chiral catalysts, 1153
  chiral complexes, 1148
transition state geometry, aldol reaction, 1145
  and rate of S_N2, 420
transition state, 265
  ab initio study, radical hydrogen abstraction, 812
  aldol reaction, 1145
  amide hydrolysis, 348
  and activation volume, 362
  and calculations, 35
  and ester hydrolysis, 1196
  and H abstraction by radicals, 812
  and high pressure, 362, 446
  and intermediates, 270
  and proton transfer, 329
  and solvent polarity, 435, 437

transition state (*Continued*)
and the *Hammond postulate*, 418
aryl migration, 1335
carbocations, and elimination, 1274
transition state, cyclic, and *Meerwein-Ponndorf-Verley reduction*, 1507
elimination, 1278
lead tetraacetate cleavage of diols, 1457
oxidative cleavage of diols, 1457
transition state, dipolar, and high pressure, 446
E2 reaction, 1269
E2C mechanism, 1268
E2C reactions, 1269
E^i reactions, 1280
elimination of epoxides with phosphines, 1286
epoxidation of alkenes, 999
for [2+2]-cycloadditions, 1033
for [4+2]-cycloadditions, 1033
for *Grignard reactions*, 1112
for the *Barton reaction*, 1427, 1428
for the *Claisen rearrangement*, 1407
for the *Cope rearrangement*, 1403, 1404
for the *Diels-Alder reaction*, 1024
for the *Meerwein-Ponndorf-Verley reduction*, 1508
imaginary, for [1,3]-sigmatropic rearrangement, 1392, 1393
ionic, and polar solvents, 435
lifetimes, 272
nucleophilic substitution at sulfonyl sulfur, 1248
peroxyacid epoxidation of alkenes, 999
polarized, 378
pyrolysis of keto-ylids, 1293
pyrolytic elimination, 1278
radical abstraction, 808
radical formation, 808
radicals, 816
six-center, 1428
six-center, and *Diels-Alder reactions*, 869
S_N2 character, 449
S_N2, 377, 418
S_N2, and neopentyl systems, 651
substitution reactions, 437
syn elimination, 1269
tight, and S_N2 reactions, 422
transitional isomers, rotaxanes, 118
transitions, in photochemistry, 292
transitions, in photochemistry also see photochemistry
transition-state theory, 267
transmetallation, and carbanion stability, 712
and higher order cuprates, 712
and metallocenes, 711
and organocuprate formation, 711
and organolithium reagents, 712
electromotive series, 710
Pd catalysts, 773
with metal halides, 710
with metals, 710
with organometallics, 712
transoid dienes, in the *Diels-Alder reaction*, 1021
trans-Pd complex, 683
trans-thiiration, 1006
trapping intermediates, 276
tresylates, leaving groups, 432, 433
triacylamines, 1214
trialkoxysilanes, with aryl halides, 783
trialkylaluminums, 533
trialkylboranes see boranes
trialkylfluoroborates, coupling reactions, Pd catalyzed, 560
from boronic acids, 560
stability, 560
triarylamines, and chirality, 135
triarylmethyl carbocations, 217
triazenes, 728
and azides, 707
aryl, isomerization, 597
aryl, rearrangement, 639
cis-trans isomerization, 882
with aromatic compounds, 795
with HF, 792
by trimerization of nitriles, 1240
triazoles, and amination, 787
from azides, 1018
triazolines, by [3+2]-cycloaddition, 1017
by 1,3-dipolar addition of alkyl azides, 1009, 1010
extrusion of nitrogen, 1316, 1317
from alkyl azides and alkenes, 1009, 1010
photolysis, 1009, 1010, 1017
thermolysis, 1009, 1010
tribromides, and bromination of alkenes, 983
tributyltin chloride, with alkyne-boranes, 1379
tributyltin dimer, and radical cyclization, 961, 962
tributyltin hydride also see hydride
and radical cyclization, 961
and reduction of conjugated esters, 918
and sulfoxide elimination, 1296
preparation, 959
reduction of isocyanides, 1548
with AIBN, 1296
tributyltin oxide, with vinyl halides, 452
tricarbonates, with amines, 731
tricarboxylates, aryllead, arylation of aromatic compounds, 844
trications, 213
trichloroacetimidates, and aza-Claisen rearrangement, 1411
trichloroacetonitrile, with aromatic compounds, 633
trichloroamine, and amination of aromatic compounds, 599
with alkanes, 491
trichloroisocyanuric acid, and conversion of aldehydes to nitriles, 1096
and N-haloamines, 730
and PPh_3 with alcohols, 501
chlorination of alkynes, 706
with alkenes, 884
with carboxylic acids, 1216
tricyclododecadiene, 206
trienes,
and cross conjugation, 42, 43
and interconversion with cyclohexadiene, 1402
and orbitals, 42
and the valence bond method, 43
by cheletropic reactions, 1303
cyclohexadiene interconversion, orbital requirements, 1384, 1385
from cyclic dienes, 1380
from thiepin-1,1-dioxides, 1303
hydroboration, 925, 1376
thermal ring closure to cyclic dienes, 1380
triethylamine, and *Grignard reagents*, 231
triethylborane, and radicals, 960, 964
radical initiator, 960
triethylborohydride, lithium, 915
with ammonium salts, 1548
triflates, aryl, and *Suzuki-Miyaura coupling*, 770
coupling with phenols, 460
coupling with trialkylfluoroborates, 560
formation of aryl nitriles, 633
from aryldiazonium salts, 791
leaving groups, 432, 433
vinyl, and palladium catalyst, 461
vinyl, and *Stille coupling*, 682
vinyl, with LiCN, 563

vinyl, with vinyltin reagents, 682
with amines, 751
with trifluoroborates, 890
triflic acid, with thiols, 1206
triflic anhydride see anhydride
with amides, 1208
triflimide, as an acid, 888
trifluoride ions, 1106
trifluorides, from carboxylic esters, 1106
trifluoroacetic anhydride, 1084
trifluoroacetic anhydride see anhydrides
trifluoroarylboronates, with amines, 754
trifluoroborates, alkene, Pd catalyzed coupling, 843
alkyl, with aryl halides, 768
alkyne, Pd catalyzed coupling, 843
alkynyl, 778
and *Sonogashira coupling*, 778
aryl, and *Suzuki-Miyaura coupling*, 775
aryl, conjugate addition, 958
aryl, with aryldiazonium salts, 794
formation of boronic acids, 701
potassium, from KHF_2, 703
potassium, stability of, 703
vinyl, and the *Heck reaction*, 768
vinyl, with aryl halides, 768
trifluoroborates, with alcohols, 462
with aldehydes, 1125
with aryl halides, 775, 890
with aryl sulfonate esters, 890
with aryliodonium salts, 890
with imines, 1136
trifluoromethanesulfonate esters, 1083
trifluoromethanesulfonic acid see triflic acid
with aryldiazonium salts, 791
trifluoromethanesulfonic anhydride, *Vilsmeier-Haack reaction*, 626
trifluoroperoxyacetic acid, 830
trigonal hybridization, 8
trihalides, formation of esters, 452
from CCl_4 and alkenes, 452
hydrolysis of, 452
trihomoaromatic, 83
trihomobarrelyl carbocations, 217
triiodide, and iodination of aryldiazonium salts, 792
triketones, cyclotrimerization, 1061
from diketone dianions, 1237
nitrogen fixation, 1061
trimerization, of aldehydes, 1240
of alkynes, 1059
spontaneous, 1059
trimethylaluminum, metalation of tertiary alcohols, 533
trimethylamine N-oxide, 15, 16
trimethylamine oxide, oxidation of boranes, 701
trimethylenemethane radicals, 245
trimethylenemethane, [3+2]-cycloaddition, 1019
with alkenes, 1019
trimethyloxonium salts, 1209
trimethylsilyl amides, and nitrile formation, 1096
trimethylsilyl chloride, trapping acyloins, 1561
trimethylsilyl cyanide see cyanide
trimethylsilyl cyanide, 564
with alkyl halides, 563
trimethylsilyl halides, and acyloin condensation, 1561
2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate, 1019
trinitrobenzenes, and complex formation, 107
trioxane, and cross coupling of alkanes, 840
from formaldehyde, 1240
trioxolanes, and ozonolysis, 1460
from aldehydes, 1240
hydrolysis, 1461
ozonides, 1460, 1461
triphase catalysts, 445
triphenylenes, 57, 85
and aromaticity, 57
and electron distribution, 57
solubility, 57
triphenylmethyl carbanion, 223
triphenylmethyl carbocation, 213, 217
triphenylmethyl radical, 238
canonical forms, 238
stability, 819
triphenylphosphine oxide, by oxidation of triphenylphosphine, 1492
triphenylphosphine, and dehydration of alkyne-alcohols, 1284
and phosphorus ylids, 1168–1173
and tetracarbonylferrate, 564
elimination with epoxides, 1286
oxidation to triphenylphosphine oxide, 1492
reduction of amine oxides, 1549
reduction of azoxy compounds, 1549
scavenging by Merrifield resin, 777
with alcohols and carbon tetrachloride, 502
with allylic alcohols and carbon tetrachloride, 503
with carbon tetrachloride, and carboxylic acids, 1224
triple bonds, and delocalization, 37
conjugated with p orbitals, 39
triple metathesis, 1421
triple-decker sandwiches, 61
triplet carbenes also see carbenes
triplet carbenes, 250, 257, 1055
persistent, 251
triplet carbonyls, 1243
triplet nitrenes, 258, 1010
triplet nitrenium ions, 260
triplet oxygen, with alkenes, 833, 834
triplet radicals, 245
triplet sensitizers, 972
triplet state, [2+2]-cycloaddition, 1049
photochemistry, 1049
triplets, in photochemistry, 292, 295
tris(trimethylsilyl)silane, 960, 964
and radical cyclization, 963
tri-*sec*-butylborohydride see Selectride
tri-*tert*-butylcyclobutadiene, and valence tautomerism, 1406
tritiation, aromatic compounds, 593
tritium labeling, 416
and diradicals, rearrangements, 1335
tritium, isotope effects, 286
tritium-decay, for generation carbocations, 416
tritium-hydrogen exchange, 660
trityl carbocations, 213
triynes, cyclotrimerization, 1060–1062
Tröger's base, and chirality, 129
tropane, 79
tropolones, and NMR, 60
and X-ray, 60
aromatic character, 60
bond alternation, 60
tropones, and cyclopropenyl cations, 67
and NMR, 60
and X-ray, 60
aromatic character, 60
bond alternation, 60
stability, 67
tropylium bromide, 60
tropylium ion, and aromaticity, 62
and *Friedel-Crafts alkylation*, 614
formation and stability, 60
Truce-Smiles rearrangement, 802
truxilic acid, and chirality, 125
Tsuji-Trost reaction, 528
tub conformation, 134
cyclooctatetraene, 134
tungsten reagents, deoxygenation of diols, 1301

twist conformation, 181
azaannulenes, 74
annulenes, 72
twistane, and twist conformation, 182
twisted amide bonds, and hydrolysis, 1197
twisted amides, 199
twisted aromatic compounds, 48
twisted aromatics, 48
twisted carbocations, 1331
twisted compounds, 199
twisted *Diels-Alder reaction*, 1035
twisted double bonds, 206
twisting, and chirality, 133

Udenfriend's reagent, hydroxylation of aromatic compounds, 830
Ugi four-component reaction, 1247
Ugi reaction, 1247
and imines, 1247
isocyanide free, 1247
Ugi three-component reaction, 1247
Ullmann biaryl synthesis, 748
Ullmann coupling, heterocyclic compounds, 769
Ullmann ether synthesis, 748
Ullmann reaction, 514, 768
alternatives, 769
and microwaves, 311
and the *Wurtz reaction*, 769
asymmetric, 769
mechanism, 769
ultracentrifuge, and *Diels Alder reactions*, 1023
ultrasonic waves, and acoustic cavitation, 307
and sonochemistry, 307
ultrasound also see cavitation
ultrasound also see sonication
ultrasound also see sonochemistry
ultrasound, 307–309
ultrasound, alkylation and alkyl halides, 445
and acyl cyanides, 1238
and acylation of carboxylic acids, 1209
and aromatic halogenation, 604
and carbene generation, 691
and carbene insertion, 692
and cavitation, 445
and DDQ, oxidation of alcohols, 1452
and *Diels Alder reactions*, 1022
and dihydroxylation, 994
and heteroatom *Diels-Alder reactions*, 1038
and hydrolysis of carboxylic esters, 1192
and lactonization, 1013
and liquids, 307
and lithium, 1232
and *Michael reactions*, 947
and α-oxidation of ketones to diketones, 1477
and permanganate oxidation of alcohols, 1445
and radicals, 445
and reactivity, 445
and reduction of nitro compounds, 1524
and $S_{RN}1$ reactions, 740
and the acyloin condensation, 1561
and the *Baylis-Hillman reaction*, 1127
and the *Knoevenagel reaction*, 1158
and the *Pauson-Khand reaction*, 977
and the *Reformatsky reaction*, 1129
and thiocyanates, 480
and zinc, 1129
aryl halides with amines, 751
formation of alkyl azides, 496
halogenation of aromatic compounds, 604
lactonization of alkenes, 1013
metals and pinacol coupling, 1556
pulsed, 308
with potassium permanganate, dihydroxylation, 994
ultraviolet see UV
Umpolung, acyl anion equivalent, 549
and aldehydes, 553
and dithianes, 553
and sulfoxides, 553
definition, 549
unavoidable strain, 183
ungerade orbitals, 5
unimolecular substitution see substitution, S_N1
universal NMR database, and absolute configuration, 143, 144
unshared electrons, and nucleophilicity, 430
unsolvated aryllithium reagents, 232
unsymmetrical coupling see coupling
ppfield shift, 51, 68
uranium complex, alkynes with isonitriles, 1141
urea complex, 113
urea, 114
and cage structures, 155
and *Fischer-Hepp rearrangement*, 639
and guest-host interactions, 113
arylation, 755
as a guest, 113
as an inclusion compounds, 113
carbonylation of amines, 730
with acyl halides, 1223
urea-hydrogen peroxide, 1003
and epoxidation, 1003
in formic acid, oxidizing agent, 1492
ureas, and the *Baylis-Hillman reaction*, 1128
and the *Hoffmann rearrangement*, 1360
by carbonylation of amines, 730
by the *Ritter reaction* with cyanamides, 1240
dehydration reagents, 1314
dehydration to carbodiimides, 1314
dehydration to cyanides, 1313
dehydration, 1314
diazotization, 790
from addition of amines to carbon dioxide, 1105
from amines and carbon dioxide, 731
from dicarboxylic esters, with urea, 1223
from isocyanates and amines, 1103
with dienes, 1009
urethanes, substituted see carbamates
UV (ultraviolet), 1583
absorption peak, 291
addition of halogens to cyclopropanes, 881
alkenes with haloamines, 988
and addition of aldehydes to alkenes, 971
and addition of sulfonyl halides to alkenes, 988
and addition reactions of alkynes, 873
and annellation, 57
and asymmetric synthesis, 151
and auxochromes, 293
and bromine or chlorine, 982
and carbanions, 662
and conformations, 174
and cyclopropane, 195
and detection of carbocations, 382
and dimerization of ketones, 1557
and EDA complexes, 105
and electrocyclic reactions of stilbenes, 1390
and electrocyclic ring opening, 1380
and enolate anion formation, 778
and halogenation of alkanes, 821
and halogenation of alkenes, 982

and halogenation, 826
and hyperconjugation, 85
and methane, 11
and nitrosation, 676
and nitrosyl halide, 676
and photochemistry, 290, 293
and pK, 339
and polyhalo addition to alkenes, 991
and quinone substitution, 414
and radicals, 238
and reactions, 151
and strained aromatic compounds, 204
and substitution at vinyl carbon, 414
and the *Fries rearrangement*, 637
arylation of active methylene compounds, 778
nitriles and alkanes, 838
reduction of nitro compounds, 1526
UV, dienes, 293
far UV, 293
far UV, and photochemistry, 290
isotropic, 143
paracyclophanes, 47
polyenes, 293
substituted benzenes, table, 294

valence bond isomers, 166
valence bond method, 4, 6
and trienes, 43
valence bond order, 915
valence bond theory, and benzene, 35
valence electrons, 14
valence isomers, 1051
valence isomers also see isomers
valence tautomerism, and *Cope rearrangement*, 1404
cycloheptatrienes-norcaradiene, 1406
oxepin-benzene oxide, 1406
tri-*tert*-butylcyclobutene, 1406
valence, and electronic structure, 15
multiple, 6
of boron, 8
valence-bond bond order, and principle of least motion, 915
van der Waals forces, 96
and guest-host interactions, 113
and inclusion compounds, 113
and molecular mechanics, 190, 191
van der Waals radii, and *Charton's ν values*, 360
vanadium complexes, 41
very fast reactions, kinetics, 282
very weak acids, 319
vibrational circular dichroism, 143
vibrational levels, and photochemistry, 295
vicarious nucleophilic substitution of hydrogen, 786
vic-diiodides, stability, 982
Vilsmeier reaction, aliphatic, 685
and haloacylation of alkenes, 992
formation of keto-aldehydes, 685
Vilsmeier-Haack reaction, 625
Vilsmeier-Haack reaction, and *Beckmann rearrangement*, 626
and microwave irradiation, 626
sulfonic anhydrides, 626
mechanism, 626
vinamidine proton sponges see proton sponge
vinamidine proton sponges, 322
vinyl acetate, and transesterification, 1207
vinyl alcohol, 91
vinyl boranes see boranes
vinyl boranes see boranes, alkenyl
vinyl carbanions, and configurational stability, 228
vinyl carbenes, 252
vinyl carbocations, 215
vinyl carbocations see carbocations
vinyl carbons, retention of configuration, 227
vinyl chloride, 171
orbitals, 40
vinyl compounds, and nucleophilic substitution, 419
and S_E1 reactions, 656
hydrolysis, 453
vinyl cyanides see cyanides
from vinyl bromides, 563
vinyl esters, from vinyl halides, 469
from vinyliodonium salts, 703
vinyl ethers, deprotonation of, 696
vinyl halides see halides, vinyl
vinyl halides, formation of vinyl esters, 469
formation of vinyl sulfides, 477
vinyl iodonium salts, with sodium sulfonate, 480
vinyl organometallics, and *Stille coupling*, 682
formation of dienes, 682
vinyl phosphates, 704
vinyl phosphines, *Markovnikov addition*, 899
vinyl radicals see radicals
vinyl silanes, 705
vinyl silanes see silanes
vinyl substrates, *Suzuki-Miyaura coupling*, 771
vinyl sulfides see sulfides
vinyl sulfides, from vinyl halides, 477
vinyl sulfones, from vinyl iodonium salts, 480
vinyl triflates see triflates
vinylation, of ketones, 545
vinylboranes, from alkynylboranes and alkylating agents, 1380
vinylcyclobutanes, rearrangement to cyclohexenes, 1399
vinylcyclopropane rearrangement, 1399
and cleavage of cyclopropane, 1399
and homodienyl [1,5]-shift, 1399
heteroatom, 1399
mechanism, 1400
vinylcyclopropanes, by carbene addition to dienes, 1053
from dienes, 1425
sigmatropic rearrangement, 1398
with acids HX, 884
vinylhalonium ions, 214
vinylic carbocations, 865
vinylic carbon, addition-elimination mechanism, 413
and S_N1 reactions, 415
nucleophilic substitution, 413
vinylic compounds, and S_N1 reactions, 419
elimination-addition mechanism, 416
vinyllithium reagents, by deprotonation, 696
with silyl peroxides, 700
vinylogous chiral aldol reactions, 1148
vinylogous conjugate addition, 944
vinylogous *Mannich reactions*, 1101
vinylogous *Michael reactions*, 944
vinylogous *Nazarov cyclization*, 946
vinylogy, and enolate anions, 549
and the aldol reaction, 1143, 1144
and the E2 reaction, 1258
enantioselective aldol reactions, 1148
vinylsilanes see silanes
vinyltellurium with alkynes, 939
vinyltin reagents, with vinyl triflates, 682
visible absorption peak, 291
visible spectrum, 143
Vitride, 1502
Vocabulary of Organic Chemistry, 1591

volume of activation, and high pressure, 446
volume, activation see activation volume
von Braun reaction, 509, 1313
  mechanism, 510
  counterattack reagent, 510
von Richter reaction, 745
  and mechanism, 275
  mechanism, 276
von Richter rearrangement, 797
  and labeling, 798
  mechanism, 798
  N_2 leaving group, 797

Wacker process, 1488
  and *Markovnikov's rule*, 1488
  aza-, 1489
  mechanism, 1488
Wadsworth-Emmons see *Wittig-Horner*
Wagner-Meerwein rearrangements, 1338–1342, 1368
  and 3,2-shifts, 1339
  and alkanes, 1341
  and elimination, 1339
  and equilibrium, 1341
  and friedelin, 1340
  and *Nametkin rearrangement*, 1340
  and *Nazarov cyclization*, 947
  and nonclassical carbocations, 1340
  and oleanene, 1340
  and retropinacol rearrangement, 1340
  and *Zaitsev's rule*, 1338
  catalytic, 1340
  enantioselectivity, 1340
  hydride shifts, 1339
  isotopic labeling, 1341
  leaving groups, 1339
  mechanism, 1341
  migratory aptitudes, 1328
  stereoselectivity, 1341
Waits-Scheffer epoxidation, 1003
  mechanism, 1003
Walden inversion, and hydride reduction of alkyl halides, 1534
  and mechanism, 278
  in S_N2 reactions, 375
Wallach reaction, 1098
  and the *Leuckart reaction*, 1098
  with formamides, 1098
Wallach rearrangement, 1429, 1562
  and isotopic labeling, 1430
  and para rearrangement, 1430
  mechanism, 1430
  photochemical, 1430
warming, and microwaves, 310
water promoted amide hydrolysis, 1197
water promoted *Michael reactions*, 945
water, acyl addition to carbonyls, 1075
  acyl addition, 1076
  addition to carbonyls, mechanism, 1076
  and acceleration of the Claisen rearrangement, 1408
  and alkyl, halides, 451
  and cage compounds, 114
  and carbon monoxide, with alkenes, 972
  and *Diels Alder reactions*, 363, 1023
  and *Hofmann elimination*, 1291
  and phase transfer catalysis, 443
  and reactivity, 363
  and the *Mukaiyama aldol*, 1152
water, angular, 8
  as a solvent, 1408
  basicity of amines, 320
  bond angles, 6
  catalysts, for sulfonation of alkenes, 893
  heteroatom *Diels-Alder reactions*, 1038
  labeling, 798
  supercritical, and *Diels Alder reactions*, 1023
  supercritical, as a solvent, 1342
water, with acyl halides, 1189
  with alkynes, 887
  with amine halides, 1356
  with aziridinium salts, 1357
  with azirines, 1359
  with carbocations, 1184
  with chlorine, 985
  with *Grignard reagents*, 714
  with isocyanates, 1362, 1363
  with isocyanides, 1246
  with ketenes, 1353
wave equations, 6
  and resonance, 32
wave function, 3
wave mechanical calculations, 4
wave mechanics, 3
wavelength of light, and bond energy, 295
  and conjugation, 293
  and microwave irradiation, 310
  and photochemical [2+2]-cycloaddition, 1048
  and photochemistry, 290
  and photolysis of dienes, 1380
  and specific rotation, 125, 143
weak hydrogen bonding, 102
weak interactions, 123
Web of Science, 1575
weighting factor, and wave equations, 6
Weinreb amides, 1147
  and the *Wittig reaction*, 1167
  from carboxylic acids, 1216
  intramolecular displacement, 1230
  preparation, 1217
  reduction to aldehydes, 1520
  with *Grignard reagents*, 1230
  with organolithium reagents, 1230
Weissler reaction, and sonochemistry, 309
Weitz-Scheffer epoxidation, 1000
Wheland intermediates, 570
Whitmore 1,2-shifts, 1322
Wigner spin-conservation rule, 300
  and photochemical [2+2]-cycloaddition, 1049
Wilkinson's catalyst, 41
  and decarbonylation of aldehydes, 856, 857
  and enantioselectivity in catalytic hydrogenation, 904
  and hydroboration, 926
  and hydrogenation, 903
  decarbonylation mechanism, 858
  mechanism of homogenous hydrogenation, 908
Willgerodt reaction, 1566
  and Montmorillonite, 1567
  Kindler modification, 1566
Willgerodt rearrangement, 1338
Williamson ether synthesis see *Williamson reaction*
Williamson ether synthesis, an S_N2 reaction, 461
Williamson reaction, 459
  and epoxides, 461
  and ionic liquids, 459
  and micellar catalysis, 460
  and microwave irradiation, 459
  and the *Mitsunobu reaction*, 460
  and phase transfer catalysis, 460
  and SET mechanism, 461
  and thioether formation, 476
Wittig reaction, 1142, 1165–1173
  and amides, 199
  and arsine ylids, 1169
  and azaadamantanone, 199
  and betaines, 1168
  and epoxides, 490
  and *Michael alkenes*, 1165
  and NMR, 1168, 1169
  and oxaphosphetanes, 1168
  and *Peterson alkeneylation reaction*, 1162
  and *Reformatsky reaction*, 1130
  and scoopy reactions, 1172
  and synthesis, 1172
  and the *Knoevenagel reaction*, 1159, 1160

betaine-lithium halide intermediate, 1172
compatible functional groups, 1166
E/Z-selectivity, 1171
energetics of ylid formation, 1168
E-selectivity, 1171
formation of *anti-Bredt alkenes*, 1168
formation of exocyclic alkenes, 1167
in aqueous media, 1166
intramolecular, 1172
mechanism, 1168
on silica gel, 1166
structural requirements of the carbonyl, 1166
with *Weinreb amides*, 1167
Z-selectivity, 1171
Wittig reagents see ylids, phosphorus
Wittig rearrangement, 555, 1373, 1414
formation of ketyls, 1374
mechanism, 1374
migratory aptitudes, 1374
stereospecificity, 1374
with vinyl ethers, 1374
[2,3]-Wittig rearrangement, 1413
and chirality transfer, 1414
and deformation of the molecule, 1413
enantioselectivity, 1414
structural requirements, 1414
structural variations, 1414
Wittig type reactions, and *Grignard reactions*, 1109
Wittig, aza- also see aza-Wittig
Wittig, thio-, 1168
Wittig-Horner reaction, 1169
electronic effects on the ylid, 1169
intramolecular, 1170
stereoselectivity, 1170
Wohl-Ziegler bromination, 821, 826
Wolff rearrangement, 256, 1244, 1353
and diazoketones, 1244
and the *Arndt-Eistert synthesis*, 1353
formation of ketones, 1353
isotopic labeling, 1354
mechanism, 1353
photochemical, 1354
Wolff-Kishner reduction, 1540, 1547
and semicarbazones, 1540
carbanion intermediates, 1542
Huang-Minlon modification, 1540
mechanism, 1542
Woodward modification, of the Prevost reaction, 994
Woodward-Hoffmann rules, 1030, 1064
and metal catalyzed cycloadditions, 1064
and photochemical [2+2]-cycloaddition, 1050
and E^i reactions, 1280
and electrocyclic reactions, 1388
"wrong way" rearrangements, 1336
Wurtz coupling, 520, 713
and organolithium reagents, 716
different metals, 515
of conjugated ketones, 514
solvent effects, 515
Wurtz reaction, 513, 769
and allylic rearrangement, 514
and coupling of acyl halides, 1232
and *Grignard reagents*, 849
and the *Ullmann reaction*, 769
cyclization, 513, 514
formation of bicyclic compounds, 514
intramolecular, 514
mechanism, 514
Wurtz type coupling, and *Grignard reactions*, 1111
Wurtz-Fittig reaction, 513

xanthate esters see esters
xanthates, and the *Chugaev reaction*, 1289
from alcohols and carbon disulfide, 1086
pyrolysis to alkenes, 1288
xanthine dye, photosensitizer, 1039
X-ray crystallography, and hydrogen bonds, 99
and annulenes, 75, 80
and Bijvoet, 139, 142
and bond distance, 23
and carbanions, 224
and carbenes, 255
and conformations, 174, 178
and cyclobutadiene complexes, 69
and D/L nomenclature, 138, 142
and diastereomers, 148
and enolate anions, 232
and homoazulenes, 74, 75
and hydrogen bonds, 99
and hyperconjugation, 87
and isopropyllithium, 231
and LDA, 341
and *Meisenheimer salts*, 733
and organolithium reagents, 231, 232
and osmium tetroxide-diamination, 1009
and *Simmons-Smith intermediates*, 1057
and twisted alkenes, 206
biphenylenes, 48
tert-butyl carbocation, 211
cyclobutadienes, 69
intermediate of the *Reformatsky reaction*, 1130
methyllithium, 229
nitronium ions, 595
nitroxyl radicals, 241
of the methyl carbocation, 209
osmium catalyst, 1054
oxonium ion, 219
propellanes, 198
X-ray diffraction, and bond distance, 21
and *Grignard reagents*, 230
and paracyclophanes, 46
and strain in medium rings, 199
pentalene derivatives, 63
tropones and tropolones, 60
X-ray electron spectroscopy, and nonclassical carbocations, 404
X-ray photoelectron spectroscopy see ESCA
X-ray structure, of betaines, 1168

Yamaguchi protocol, 1204
Y-aromaticity, 38
Yb, amines with oxetanes, 490
ylid formation, energetics, 1168
ylid reactions, solvent effects, 1171
ylid, dimethyloxosulfonium methylid, with aromatic nitro compounds, 786
ylides, see ylids
ylids, and acyl addition, 1179
and bonding, 49
and carbene insertion, 693
and carbenes, 693
and field effects, 225
and *Hofmann degradation*, 1290
and orbitals, 49
and resonance, 49
and sulfuric acid, 49
ylids, arsine, 1169
arsonium, with tosylimines, 1177
as intermediates, 1292
carbonyl, [3+2]-cycloaddition, 1015
dimerization, 1173
dimethyloxosulfonium methylid, 1175
dimethylsulfonium methylid, 1175
in *the Steven's rearrangement*, 1372
nitrile, in [3+2]-cycloadditions, 1015

ylids, nitrogen, 50, 1173
and field effects, 225
and organolithium reagents, 697
formation of alkenes, 1292
from ammonium salts, 697, 1292
ylids, oxido phosphorous, 1172
ylids, phosphine oxide, 1171
ylids, phosphonate, 1169
and *Wittig-Horner reaction*, 1169
electronic effects, 1169
ylids, phosphonium, 697
ylids, phosphorus, acyl, pyrolysis to alkynes, 1293
alkoxy, 1171
alkoxy, and scoopy reactions, 1172
and [2+2]-cycloadditions, 1171
and resonance, 1165
and triphenylphosphine, 1168–1173
from phosphonium salts and base, 1165
functional group capability, 1167
in the *Wittig reaction*, 1165
reactions with functional groups, 1173
reactivity with aldehydes and ketones, 1167
salt free, 1165
stability and reactivity, 1167
stabilized, 1167, 1170
structural requirements, 1167
suitable bases for formation of ylids, 1165
versus sulfur, 1177
with aldehydes or ketones, 1165
with carbon dioxide, 1173
ylids, polymer supported, in the *Wittig reaction*, 1166
reaction with alcohols and an oxidizing agent, 1166
reactivity, 1169
selenium, 50
selenium, and formation of epoxides, 1176
selenium, chiral, 1176
structural types, 1169
sulfonium, 1176
sulfoxonium, 1176
ylids, sulfur, 50, 799
and [2,3]-sigmatropic rearrangements, 1413
and formation of cyclopropanes, 1176
and sigmatropic rearrangements, 799
and *Stevens' rearrangement*, 1373
and the *Sommelet-Hauser rearrangement*, 799
chiral, 1176
diastereoselectivity, 1176
epoxide formation, enantioselectivity, 1176
in ionic liquids, 1178
kinetic versus thermodynamic control, 1176
polymer-supported, 1176
reaction with epoxides, 1176
rearrangement, 799
solvent free, 1176
with aldehydes or ketones, 1175–1177
with allylic alcohols, 1179
with conjugated compounds, 1178
with epoxides, 1287
ylids, tellurium, 1169, 1177
with imines, 1177
ylids, thiocarbonyl, in [3+2]-cycloadditions, 1016
ylids, with aldehydes or ketones, 1165–1173
with carbon dioxide, 1173
with lactams, 1166
with lactones, 1166
ynamides, 777
ynamines also see alkyne amines
ynamines, hydration of, 888
yn-dienes, and the *Pauson-Khand reaction*, 976
ynolates, with dienes, 1232
ynones, addition of silyl phosphines, 930
with silylphosphines, 930

Z/E nomenclature, definition, 163
Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik, 1581
Zaitsev orientation, and thermodynamic alkene, 1271
Zaitsev products, elimination, 1281
Zaitsev's rule, and alkene stability, 1270
and carbocations, 1339
and dehydration of alcohols, 1283
and E1 reactions, 1262
and E2 reactions, 1256
and E2C reactions, 1273
and *Hofmann degradation*, 1290
and nucleofuges, 1271
and pyrolytic elimination, 1281
and rearrangement of alkenes, 662
and stereochemistry, 1273
and sulfoxide elimination, 1296
and *Wagner-Meerwein* rearrangements, 1338
elimination of boranes, 1299
elimination reactions, failure of, 1270
zeolite Y, 215
zeolites, and addition of thiols to alkenes, 894
and carbocation formation, 215
and catalytic hydrogenation, 905
and conversion of aldehydes to nitriles, 1095
and dehydration, 1283
and *Diels Alder reactions*, 1023
and esterification, 1203
and *Friedel-Crafts acylation*, 622
and *Friedel-Crafts acylation*, 622
and halogenation of aromatic compounds, 607
and *Meerwein-Ponndorf-Verley reduction*, 1507
and oxidation of alcohols, 1446
and oxidation of tetrahydropyranyl ethers, 1452
and the *Knoevenagel reaction*, 1158
Ziegler alkylation, 785
Ziegler catalysts, coupling alkenes to alkenes, 933
zigzag acenes, 78
zinc chloride, and the *Fischer indole synthesis*, 1412
zinc cyanide, and the *Gatterman reaction*, 626
zinc,
activated, and the *Reformatsky reaction*, 1129
allyl, reagents, with alkynes, 938
and cleavage of esters, 470
and dehalogenation of acyl halides to ketenes, 1306
and electrochemistry, 718
and elimination of dihalides to alkenes, 1304
and reduction of disulfides, 1555
and reduction of nitro compounds to hydroxylamines, 1526
and reduction of nitro compounds, 1528
and reduction of phenols the aromatic compounds, 1535
and ultrasound, 1129
as a complex, 1134
compounds, imines with ketene silyl acetals, 1137
in acid, and reduction of nitro compounds, 1524
zinc-amalgam and *Wolff-Kishner reduction*, 1540

zincates, dianion, 929
Zinin reduction, 1524
zip reaction, 1222
zirconium catalyst, silanes with dienes, 929
  acyl, with allylic halides, 565
  and *Schwartz's reagent*, 926
Zn metal,
  and dehalogenation of propargylic halides, 1305
  and conjugate addition reactions, 713
  and elimination of halo ethers to alkenes, 1306
  and selenide formation, 479
  in acetic acid, reduction of conjugated systems, 916
  in the *Reformatsky reaction*, 1130
  with alcohols and acyl chlorides, 1201
  with allylic halides with nitriles, 1140
Zn-Cu, carbonylation, 565
Zr-Cr reagents, and alkynes, 933
zusammen, and alkene nomenclature, 163
zwitterion intermediates, and elimination of hydroxy acids, 1308
zwitterions, and oxime formation, 1095